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**DISABILITY
RELATED TO WORKPLACE
INDOOR AIR**

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ACADEMIC DISSERTATION

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following articles, referred to in the text by Roman numerals I to IV. The original articles have been reprinted with the permission of the copyright holders.

- I Vuokko A, Selinheimo S, Sainio M, Suojalehto H, Järnefelt H, Virtanen M, Kallio E, Hublin C, Karvala K (2015). Decreased work ability associated to indoor air problems – an intervention (RCT) to promote health behavior. *Neurotoxicology* 49: 59–67.
- II Vuokko A, Karvala K, Suojalehto H, Lindholm H, Selinheimo S, Heinonen-Guzejev M, Leppämäki S, Cederström S, Hublin C, Tuisku K, Sainio M. Clinical characteristics of disability in patients with indoor air related environmental intolerance. Submitted 15 October 2018.
- III Selinheimo S*, Vuokko A*, Sainio M, Karvala K, Suojalehto H, Järnefelt H, Paunio T (2016). Comparing cognitive behavioural psychotherapy and psychoeducation for non-specific symptoms associated with indoor air – an intervention (RCT) protocol. *BMJ Open* 6: e011003.
- IV Vuokko A, Karvala K, Lampi J, Keski-Nisula L, Pasanen M, Voutilainen R, Pekkanen J, Sainio M (2018). Environmental intolerance, symptoms and disability among fertile-aged women. *Inter J Environ Res Public Health* 15(2): 293.

* Contributed equally.

ABBREVIATIONS

AAQ-II	Acceptance and Action Questionnaire-II
ACT	Asthma Control Test
ANS	autonomic nervous system
ATS/ERS	American Thoracic Society/European Respiratory Society
AUDIT	Alcohol Use Disorders Identification Test
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BMI	Body Mass Index
BRI	building-related intolerance
CBT	cognitive-behavioral therapy
CI	Chemical Intolerance
CNS	central nervous system
DES	Dissociative Experience Scale
DSM	Diagnostic and Statistical Manual of Mental Disorders
EI	environmental intolerance
EOS	eosinophils
FeNO	fractional exhaled nitric oxide
FEV ₁	forced expiratory volume in one second
FIOH	Finnish Institute of Occupational Health
FSS	functional somatic syndrome
FVC	forced vital capacity
GAD-7	Generalized Anxiety Disorder 7-item Scale
HPA	hypothalamic-pituitary-adrenal
HRV	heart rate variability
HVPT	Hyperventilation Provocation Test
IAQ	indoor air quality
ICD	International Classification of Diseases
ICF	International Classification of Functioning, Disability and Health
IEI	idiopathic environmental intolerance
Ig	immunoglobulin
IIP	Intervention of Interpersonal Problems
INT	intervention
ISI	Insomnia Severity Index
IWS	Illness Worry Scale
KuBiCo	Kuopio Birth Cohort
LF/HF	low-frequency power/high-frequency power
MARDS	Montgomery-Åsberg Depression Rating Scale
MCS	multiple chemical sensitivity
NBRs	non-specific building-related symptoms
NRF	Need for Recovery
OASIS	Overall Anxiety Severity and Impairment Scale

OH(S)	occupational health (service)
PD	provocative dose
PEF	peak expiratory flow
PHQ-9	Patient Health Questionnaire
PPA	Personal Projects Analysis
PSWQ	Penn State Worry Questionnaire
QEESI	Quick Environmental Exposure and Sensitivity Inventory
QOL	quality of life
RAND-MCS	Quality of Life Survey mental component summary
RAND-PCS	Quality of Life Survey physical component summary
RCT	randomized controlled trial
RMSSD	root mean square of successive differences
RTW-RQ	Return-to-Work Readiness questionnaire
RTW-SE	Return-to-Work Self-efficacy
SAQ	Strategy and Attribution Questionnaire
SBS	sick building syndrome
SCID	Structured Clinical Interview for DSM-IV Disorders
SCL-90	Symptom Checklist-90
SD	standard deviation
SDS	Sheehan Disability Scale
SMBM	Shirom-Melamed Burnout Measure
SOC-13	Sense of Coherence
SOFAS	Social and Occupational Functioning Assessment Scale
SPT	skin prick test
SRRS	Social Readjustment Rating Scale
S5	Short Five
TAS-20	Toronto Alexithymia Scale
TAU	treatment as usual
TERM	the extended reattribution and management
Toba	Revised Paranormal Belief Scale
WAI	Work Ability Index
WAIS-IV	Wechsler Adult Intelligence Scale IV
WAS	Work Ability Score
WHO	World Health Organization
VOC	volatile organic compound
WMS-III	Wechsler Memory Scale-III
Y-BOCS	Yale-Brown Obsessive Compulsive Scale

ABSTRACT

Background and aims: Symptoms attributed to indoor air work environments may persist even without observed significant deficiencies in indoor air quality. This kind of symptomatology may lead to disability, which can cause severe restrictions in daily life and interfere with work participation. Disability due to indoor environments is poorly understood from the medical perspective, and effective treatments are lacking.

The main aim of this thesis was to characterize indoor air-related disability and develop interventions for symptom management. We evaluated whether clinical intervention including counseling has an impact on the quality of life (QOL) and work ability of patients with indoor air-related symptoms and work disability; and developed a randomized controlled trial (RCT) setting to evaluate the effect of cognitive-behavioral therapy (CBT) and psychoeducation on workers' QOL and work ability. Furthermore, we carried out thorough clinical characterization of the possible medical causes of disability among a group of patients. In addition, we explored the self-reported intolerance attributed to different environmental factors and its associations with disability on a population level, using a maternity clinic sample.

Material and methods: This thesis consists of four individual studies, which all comprised working-aged adults. The first RCT (Study I) recruited 55 participants from consecutive patients examined at the Finnish Institute of Occupational Health (FIOH) for a suspected occupational disease. The inclusion criteria for work disability were a self-assessed decreased work ability and indoor air-related sick leave days during the preceding year. The RCT setting evaluated the effect of the intervention (counseling by a physician and psychologist given counseling for symptom management) on self-assessed work ability, sick leave days, QOL, and illness worries, which were our outcome measures.

Clinical characterization (Study II) was conducted of 12 patients who were referred to FIOH for clinical evaluation due to responsiveness to workplace indoor air, and a disabling condition that interfered with work participation despite improvements to occupational facilities and adjustments to work. The clinical evaluation was based on structured somatic, psychological and psychiatric evaluations; allergy tests; and measurements of respiratory function and the autonomic nervous system. The questionnaires gathered data on self-assessed disability, insomnia, pain, anxiety, depression and burnout.

In Study III, FIOH created an RCT setting, and recruitment was carried out in collaboration with five large occupational health service (OHS) units. The RCT recruited patients who had sought medical advice from OHS due to recurrent medically unexplained multiorgan symptoms and disability attributed to the indoor work environment. After baseline clinical examinations, the participants were randomized into two psychosocial

treatment groups (psychoeducation or CBT) and a treatment-as-usual group. Questionnaires were completed at baseline and at follow-up at 3, 6, and 12 months. The primary outcome was health-related QOL, and the secondary outcomes included measures of factors that could impact on work ability and functioning in daily life.

The questionnaire survey (Study IV) was based on a sample of 680 pregnant women, who were recruited at maternity clinics in the Kuopio region, in Eastern Finland. The participants were asked about annoyance with 12 environmental factors, symptoms, behavioral changes, and the extent to which their intolerance had disturbed their work, household responsibilities or social life. The study concentrated on exploring intolerance attributed to chemicals, indoor molds and electromagnetic fields (EMFs).

Results: In the clinical studies (Study I, II), patients' symptoms manifested in multiple organ systems, with no medical explanation and in spite of workplace interventions and the absence of exposure-related causes of symptomatology. Most patients with asthma presented normal lung function tests but reported abundant respiratory symptoms. Co-occurrent somatic diseases and psychiatric disorders were frequently present. Often patients presented a variety of signs of distress (multiple pain, insomnia, burnout) and had environment-related health concerns. The patients were worried about a serious disease or loss of health due to indoor air (Study I). Almost all the patients reported reactions triggered mainly by indoor molds; the majority reported sensitivity to odorous chemicals and one fourth to electric devices (Study II). The need to avoid certain environments had led to restrictions in several life areas, such as work participation, socializing and leisure activities. Disability indicated a higher severity on self-assessment scales than in physician assessments.

Physician and psychologist counseling for symptom management showed no effect on self-assessed work ability and QOL after the six-month follow-up (Study I).

In Study IV, the participants (n=680) evaluated their intolerance in the time prior to their pregnancy. Of the study group, 33% reported symptoms related to chemicals, indoor molds or EMFs, and 15% had made behavioral changes to avoid the symptoms. In terms of disability, 8.4% experienced at least 'some' difficulties related to any of the three environmental factors, 2.2% 'very much' or 'extreme', and 0.9% 'extreme' difficulties. Of the latter 2.2% (n=15), all reported intolerance to indoor molds, and two thirds also to chemicals. Of these 15 participants, 12 reported having had to change apartments or jobs to avoid symptoms due to intolerance, and four reported having done both. As the severity of disability increased, the number of organ systems, behavioral changes, and the co-occurrence of intolerance to various environmental factors also grew.

Conclusions: Chronic indoor air-related symptomatology fulfills WHO's criteria for idiopathic environmental intolerance (IEI). The symptomatology includes comorbidity of somatic and psychiatric diseases that does not explain the disability. A similar phenomenon, symptomatology and comorbidity, is described in functional somatic syndromes (FSS).

Effective treatment interventions are required for indoor air-related disability prevention. The usefulness of treatment approaches that have shown to be efficient for FSS, such as different CBTs, should be evaluated in the treatment of IEI.

The estimate of the prevalence of intolerance to environmental factors, depends on the definition of intolerance. The manifestation of intolerance to various environmental factors forms an increasing severity continuum, ranging from annoyance to severe disability. As regards environmental intolerance with severe disability, indoor molds seem to be the most common environmental factor in Finland.

TIIVISTELMÄ

Tausta ja tavoitteet: Työpaikan sisäilmaan liittyvä oireilu saattaa pitkittyä silloinkin, kun merkittäviä puutteita sisäilman laadussa ei todeta. Tämänkaltainen oireilu voi rajoittaa merkittävästi elämänpiiriä ja työkykyä. Lääketieteellinen ymmärrys sisäilmaan liittyvästä toimintakykyä heikentävästä oireilusta ja sen hoitokeinoista on puutteellinen.

Väitöskirjatyön pääasiallisena tavoitteena oli tutkia sisäilmaan liittyvää pitkittyvää oireistoa, joka heikentää toimintakykyä, ja kehittää interventioita oireilun hallintaan. Tavoitteina oli 1) arvioida parantaako tietojen anto ja neuvonta elämänlaatua ja työkykyä potilailla, joilla oli sisäilmaan liittyen oireita ja työkyvyn heikentymistä; 2) luoda satunnaistettu kontrolloitu koeasetelma, jossa tutkitaan kognitiivisen käyttäytymisterapian (KKT) ja psykoedukaation vaikutusta elämänlaatuun ja työkykyyn. Kolmantena tavoitteena oli tutkia ryhmä potilaita huolellisin kliinisin tutkimusmenetelmin ja arvioida mitkä löydökset selittävät heikentynyttä toimintakykyä. Lisäksi tavoitteena oli tutkia väestötason herkkyyttä eri ympäristötekijöille ja sen vaikutusta toimintakykyyn, mikä toteutettiin äitiysneuvolakyselyssä.

Aineisto ja menetelmät: Väitöskirjatyö koostuu neljästä erillisestä osatyöstä, joissa osallistujat olivat työikäisiä. Ensimmäiseen interventiotutkimukseen (osatyö I) rekrytoitiin 55 ammattitautiepäilyn vuoksi Työterveyslaitoksella (TTL) tutkimukseen tullutta potilasta. Sisäänottokriteerinä oli heikentynyt itsearvioitu työkyky ja sairauspoissaoloja sisäilmaan liittyvien oireiden vuoksi viimeisen vuoden aikana. Satunnaistetussa kontrolloidussa tutkimusasetelmassa arvioitiin intervention (lääkärin toteuttama tietojen anto ja ohjaus sekä psykologin ohjaus oirehallintaan) vaikutusta itsearvioituun työkykyyn, sairauspoissaolopäiviin, elämänlaatuun ja sairaushuoliin.

Kliininen tutkimus (osatyö II) toteutettiin 12 potilaalla, jotka oli lähetetty TTL:lle arvioon työpaikan sisäilmaan liittyvän työkykyä heikentävän pitkittyneen oireiston vuoksi. Oireisto oli jatkunut huolimatta työpaikan korjaustoimista ja työjärjestelyistä. Kliinisessä tutkimuksessa käytettiin strukturoituja somaattisia, psykologisia ja psykiatrisia menetelmiä; allergiatutkimuksia; hengitystoiminnan ja autonomisen hermoston tutkimuksia. Arviossa käytettiin myös kyselyitä, joissa kartoitettiin mm. toimintakykyä, unettomuutta, kipua, ahdistuneisuutta, masennusta ja työuupumusta.

Kolmannessa osatyössä luotiin satunnaistettu kontrolloitu tutkimusasetelma, joka käynnistettiin yhteistyössä TTL:n ja viiden suuren työterveyshuoltoyksikön kanssa. Tutkimukseen rekrytoitiin potilaita, jotka olivat hakeutuneet työterveyshuoltoon työpaikan sisäilmaan liittyvien toistuvien ja usean elinjärjestelmän oireiden takia. Oireet olivat heikentäneet työkykyä eivätkä ne olleet selittyneet lääketieteellisillä syillä. Alkututkimusten

jälkeen valitut osallistujat satunnaistettiin kahteen psykososiaaliseen hoitoryhmään (psykoedukaatio tai KKT) ja tavanomaisen hoidon ryhmään. Seurantakyselyt toteutettiin lähtötilanteessa ja 3, 6 sekä 12 kuukauden kuluttua. Päävastemuuttujana oli terveyteen liittyvä elämänlaatu, ja lisäksi kartoitettiin lukuisia työ- ja toimintakykyyn vaikuttavia tekijöitä.

Neljäs osatyö oli Kuopion alueen äitiysneuvola-asiakkaille toteutettu kyselytutkimus. Tutkimukseen osallistui 680 raskaana olevaa naista, joilta kysyttiin herkkyyttä 12 ympäristötekijälle ja herkkyyden vaikutusta oireisiin, arkielämään, työ- ja toimintakykyyn. Erikseen tarkasteltiin niitä, jotka ilmoittivat sietokyvyn alenemista kemikaaleille, sisäilman homeille ja sähkömagneettisille kentille.

Tulokset: Kliinisisä tutkimuksissa (osatyöt I ja II) potilailla ilmeni oireita useasta elinjärjestelmästä ilman lääketieteellistä selittävää löydöstä ja oireet olivat jatkuneet huolimatta työpaikalla tehdyistä interventioista eikä ajankohtainen oireisto ollut selitettävissä sisäilmatekijöillä. Astmaa sairastavilla astma oli keuhkojen toimintakokeiden perusteella pääsääntöisesti hyvässä hallinnassa, vaikka heillä oli runsaasti astmaan sopivia oireita. Samanaikaisia muita somaattisia sairauksia ja psykiatrisia häiriöitä todettiin usein. Useilla potilailla oli monia oireita kuten laaja-alaista kipua, unettomuutta ja työuupumusta sekä huolta ympäristötekijöiden vaikutuksesta terveyteen. Osallistujilla todettiin huolestuneisuutta terveyden menettämisestä sisäilman takia (osatyö I). Oireiluherkkyys liittyi lähes kaikilla sisäilman homeisiin. Lisäksi valtaosa ilmoitti sietokyvyn heikentyneen hajusteille ja neljäsosa myös sähkömagneettisille kentille (osatyö II). Tarve välttää tiettyjä ympäristöjä oli johtanut rajoituksiin useilla elämänalueilla, kuten työssä, sosiaalisessa kanssakäymisessä ja vapaa-ajan aktiviteeteissa. Itsearvioitu toimintakyky oli arviointiasteikkojen perusteella huonompi kuin lääkärin arvioimana.

Lääkärin tietojen annolla ja ohjauksella sekä psykologin antamalla oirehallinnan ohjauksella ei todettu vaikutusta itsearvioituun työkykyyn eikä elämänlaatuun kuuden kuukauden seurannassa verrattuna kontrolliryhmään (osatyö I).

Osatyössä IV vastaajat (n=680) arvioivat herkkyytään ympäristötekijöille ennen raskautta. Vastaajista 33 % raportoi saavansa oireita kemikaaleista, sisäilman homeista tai sähkömagneettisista kentistä ja 15 % oli tehnyt muutoksia eri elämänalueilla välttääkseen oireita. Vastaajista 8,4 % koki vähintään jossain määrin toimintakyvyn alenemaa liittyen herkkyyteen kemikaaleille, sisäilman homeille tai sähkömagneettisille kentille, 2,2 % raportoi merkittävää ja 0,9 % erittäin merkittävää toimintakyvyn heikentymistä. Kaikki merkittävää toimintakyvyn heikentymistä raportoivista (15 vastaajaa) ilmoittivat sietokykynsä heikentyneen sisäilman homeille ja kolmasosa myös kemikaaleille. Näistä 15 vastaajasta 12 ilmoitti joutuneensa vaihtamaan asuntoa tai työpaikkaa oireiden välttämiseksi, neljä vastaajaa oli vaihtanut sekä asunnon että työpaikan. Mitä vaikeampi toimintakyvyn heikentyminen oli, sitä useammasta elinjärjestelmästä oireita ilmeni ja sitä

enemmän oli ollut tarve tehdä arkielämän muutoksia. Lisäksi mitä vaikeampi toimintakyvyn heikentyminen oli, sitä useammalle ympäristötekijälle ilmeni samanaikainen herkkyys.

Johtopäätökset: Pitkäaikainen sisäilmaan liittyvä oireisto täyttää WHO:n määrittelemän ympäristöherkkyyden (idiopathic environmental intolerance) kriteerit. Oireistoon liittyy samanaikaisia somaattisia sairauksia ja psykiatrisia häiriöitä, jotka eivät kuitenkaan selitä heikentyneitä toimintakykyä. Samanlainen oirekuva ja komorbiditeetti on kuvattu toiminnallisissa häiriöissä.

Sisäilmaan liittyvän pitkäaikaisen oireiston hoitoon tarvitaan tehokkaita hoitomuotoja. Sellaisten hoitomuotojen, joilla on todettu vaikutusta toiminnallisiin häiriöihin, kuten erilaiset käyttäytymisterapiat, hyödyllisyyttä pitää tutkia ympäristöherkkyyden hoidossa.

Arvio siitä, kuinka yleistä herkkyys ympäristötekijöille on, riippuu siitä, miten herkkyys on määritelty. Herkkyys eri ympäristötekijöille on jatkumo vähäisestä sietokyvyn alentumisesta oireistoon, joka rajoittaa merkittävästi toimintakykyä. Ympäristöherkkyys, johon liittyy merkittävää toimintakyvyn heikentymistä, näyttää Suomessa yhdistyvän sisäilman homeisiin.

1 INTRODUCTION

Since the 1970s, health complaints attributed to the indoor non-industrial work environment, at pollutant levels below toxic levels, have received increasing attention that have become a public health concern (Bluyssen et al. 2016; Redlich et al. 1997; WHO 1983). This ill health may lead to functional restrictions in daily life and severe restrictions to work participation. Office workers' case reports first raised this issue (WHO 1983), but later, other indoor environments such as hospitals, schools, public buildings and residences reported similar symptoms. Individuals typically describe symptoms as occurring while residing in a particular building and diminishing when away from it (Redlich et al. 1997).

The perception of deficiencies in indoor air quality (IAQ) has been associated with impaired well-being and reports of discomfort and symptoms, mainly mucous membrane and respiratory symptoms, which ought to improve when indoor facilities are repaired (Redlich et al. 1997; Wolkoff 2013). Good practices and guidelines exist for recognizing and improving IAQ (Salonen 2009; WHO 2009), as do laws and regulations for built environments which aim to ensure healthy living and indoor working conditions (In Finland, Decree on Housing Health 545/2015; Health Protection Act 763/1994). Research has not been able to explain indoor air pollutants' long-term adverse health effects on individuals (Caillaud et al. 2018; Hetherington and Battershill 2013; Redlich et al. 1997; Thörn 1999; WHO 2009; Wolkoff 2013). Clinicians and patients face problems when these symptoms persist despite improvements to IAQ. The dilemma has been whether the persistent environment-related symptoms are due to exposure or to increased reactivity and responsiveness among individuals (Kipen and Fiedler 2002; Levy 1997; Rief and Broadbent 2007; Watanabe et al. 2003a).

Numerous studies on human reactions to indoor air use symptom reporting. Symptoms attributed to indoor air environments can be unpleasant, disruptive, cause lost work time and reduced productivity, and may persist in some individuals despite remodeling of the building concerned or removal of the factors that provoke symptoms (Al-Ahmad et al. 2010; Edvardsson et al. 2008; Redlich et al. 1997; Sauni et al. 2015; Thörn 1999). The chronic symptoms and disability of individuals attributed to a certain indoor air pollutant, or merely of indoor air, can impair quality of life (QOL), and cause considerable lifestyle limitations with social, occupational and economic consequences (Al-Ahmad et al. 2010; Edvardsson et al. 2008, 2013; Karvala et al. 2013, 2014; Söderholm et al. 2016).

Previous studies on indoor air-related health problems have proposed a biopsychosocial approach to disability prevention (Karvala 2012; Thörn 1999), as well as interventions that generally aim to improve activity and participation among individuals with disabilities (WHO 2001). Since the

nature of indoor air-related disability has not been sufficiently medically characterized, methods for treatment and prevention are lacking. A lack of knowledge hampers the appropriate language for conceptualizing the indoor air-related disability phenomenon and impedes effective communication between patients and health care providers. In order to improve health care and gain a better understanding of the disability and its underlying mechanisms, a thorough medical and psychological characterization is needed, as well as controlled interventions for disability treatment.

2 REVIEW OF THE LITERATURE

2.1 INDOOR AIR-RELATED SYMPTOMS AND DISEASES

2.1.1 INDOOR AIR-RELATED SYMPTOMS

The health complaints attributed to indoor environments range from comfort complaints to multiple symptoms and functional restrictions to daily life. These complaints typically occur while residing in a particular building and diminish when away from it. For some, however, they may persist.

To describe the reactions/symptoms in indoor environments, in 1983 the World Health Organization (WHO) launched the term sick building syndrome (SBS) for the non-specific building-related combination of (general, mucosal membranes and skin) symptoms with an often unclear cause (WHO 1983, 1986). However, SBS has failed to develop into a well-defined condition; it, has remained complex and inadequate because of its vagueness and dualistic nature (Thörn 1999; Wolkoff 2013). SBS includes transient non-specific symptoms of a multifactorial origin (individual, psychosocial, and environmental risk factors) with a possible relation to indoor pollutants (Marmot et al. 2006; Norbäck 2009), but no known long-term adverse health effects (Redlich et al. 1997). The core symptoms of SBS are typically characterized as follows (Redlich et al. 1997; Thörn 1999; WHO 1983):

- Mucous-membrane irritation (eyes, nose, throat);
- Dry skin, rash and pruritus;
- Fatigue, headache and lack of concentration;
- High frequency of airway infections;
- Hoarseness, wheezing, shortness of breath and coughing;
- Nausea and dizziness and
- Enhanced or abnormal odor perception.

In addition, the term SBS is regarded as a group phenomenon rather than a syndrome among individuals (Norbäck 2009). SBS gives no indication of symptom severity and does not differentiate transient non-specific symptoms from more severe health problems.

Non-specificity of symptoms. Numerous questionnaire studies have shown that the perceived indoor air-related symptoms span a wide spectrum of organ systems, typically airways, the nervous system, mucosal membranes, and the skin, as well as general symptoms. In a Finnish study conducted at 122 workplaces (with suspected indoor-air problems) with total of 11 154 employees, the most common work-related symptoms that had occurred weekly during the past three months were an irritated, stuffy or runny nose (20%), eye symptoms (17%), fatigue (16%), skin symptoms (15%) or a hoarse,

dry throat (14%) (Reijula and Sundman-Digert 2004). Similar symptom spectrums have appeared in office environments (Bluyssen et al. 2016; Salonen et al. 2009a) and hospitals (Hellgren et al. 2011), as well as in buildings with no obvious IAQ deficiencies (Andersson and Stridh 1992; Purokivi et al. 2001) or following building repairs (Sauni et al. 2015). In addition, studies have reported similar symptoms with no symptom attributions to indoor spaces (Eriksson and Stenberg 2006; Norbäck and Edling 1991), and with different clinical conditions and no obvious medical reasons (Fink et al. 2007; Nimnuan et al. 2001).

Later, Norbäck (2009) divided human reactions to the indoor environment into three main categories: 1) complaint reactions due to poor subjective IAQ, 2) disease or building-related illness (e.g. legionellosis) that may be caused by factors in the indoor environment and 3) medical symptoms with an unclear cause, but with a possible relation to the indoor environment.

Prevalence of symptoms. The prevalence data on indoor air-related symptoms come from self-reports and typically from cross-sectional surveys on specified samples (e.g. workforce or employees working in a certain building). The population-based data are limited, and mainly based on symptoms compatible with SBS, which are illustrated in Table 1. In a prospective study, the 10-year incidence of new onset of any work-related SBS-symptom that occurred weekly was 9.4% in the municipality of Uppsala, Sweden (Zhang et al. 2012). The studies based on the definition of SBS do not properly describe the prevalence of indoor air-related symptoms because of their symptom attribution to work/home environments or because they do not question symptom attribution.

As regards office building studies (not included in Table 1), in a study of indoor workers from 28 companies (n=4029) in the Latium region of Italy, 27% reported at least one of the 12 work-related symptoms compatible with SBS, and 32% at least one of the 18 work-related symptoms, and two-thirds (65%) complained of at least one perceived indoor problem (Magnavita 2015). In a Japanese sample of office employees (n=3335), 25% reported suffering from at least one building-related symptom (out of 19 symptoms) weekly (Azuma et al. 2015a). A large European research project, OFFICAIR, was conducted in 167 office buildings in eight European countries (Portugal, Spain, Italy, Greece, France, Hungary, the Netherlands, Finland) with a total of 7441 office workers (Bluyssen et al. 2016). More than one-third of the workers reported complaints about the indoor environment, and half of them had suffered from at least one building-related symptom in the preceding month. The most prevalent symptoms were dry eyes (31%) and headache (29%) (Bluyssen et al. 2016).

Table 1. Prevalence studies on symptoms related to SBS in the adult general population.

Prevalence	Case definition	Method and sample	Reference
6–30%	Responding ‘yes’ to at least one (of 16) different symptoms in the preceding three months. No questions on attribution included	Random sampling. Postal survey in a three-county region (Gävleborg, Kopparberg, Uppsala) in Sweden (n=466)	Nordbäck and Edling (1991)
4.3%	Responding ‘yes’ to at least one weekly general, mucosal and skin symptom in the preceding three months. No questions on attribution included	Random sampling of Swedish adult population (n=2154)	Eriksson and Stenberg (2006)
21% (58% of 114 women)	Responding ‘yes’ to at least one (of 16) weekly symptom, related to home or work environment OR Responding ‘yes’ to weekly symptoms from at least three (of five) symptom groups (general, skin, nasal, throat, eye)	Random sampling. Postal survey in Uppsala region in Sweden (n=418)	Björnsson et al. (1998)
18% (21% of 260 women)	Responding ‘yes’ to at least one (of 16) work-related symptom OR	Random sampling. Postal survey in Sweden (n=532, occupationally active)	Runeson-Broberg and Norbäck (2013)
4.9% (5.0% of 260 women)	Responding ‘yes’ to at least one (of 16) home-related symptom		

SBS, sick building syndrome.

2.1.2 INDOOR AIR-RELATED DISEASES

Dampness and molds in buildings are associated with the development of asthma. The epidemiological evidence of this association is mainly based on studies among children, as there is no causative evidence of asthma development among adults (Caillaud et al. 2018; Mendell et al. 2011; WHO 2009). In addition, the scientific literature reveals no evidence of an association between indoor microbial exposure and the development of the following health outcomes: cancer, rheumatological and other immune

diseases, genotoxic and cardiogenic effects, or reproductive and development effects (Eduard 2009; IOM 2004; WHO 2009). Sporadic case reports of allergic alveolitis in damp non-industrial indoor environments have been published, often associated with the use of humidifiers (Mendell et al. 2011; WHO 2009). Building-related illness can include infectious diseases such as legionellosis, which has been associated with ventilation and air-conditioning systems (Norbäck 2009).

Volatile organic compounds (VOCs) and formaldehyde indoors are associated with suggestive evidence of an increased risk of asthma (Hulin et al. 2012; WHO 2010). There is also evidence that second-hand tobacco smoke has adverse environmental exposure effects on the respiratory and circulatory systems, and plays a carcinogen role (lung cancer) in adults (WHO 2007). Indoor radon gas of soil origin, as a human carcinogen, increases the risk of lung cancer (WHO 2010). Exposure to airborne particulate matter has shown to affect respiratory and cardiovascular morbidity, aggravate asthma, and cause mortality from cardiovascular and respiratory diseases and from lung cancer (WHO 2013).

2.1.3 FACTORS ASSOCIATED WITH INDOOR AIR-RELATED SYMPTOMS

Indoor air-related symptoms, or SBS have been considered multifactorial in origin (Redlich et al. 1997). Various building-related factors, as well as individual and psychosocial factors, interact or coexist in these symptoms. They vary from case to case and have time-variance in the same person (Azuma et al. 2015a; Azuma et al. 2017; Bluysen et al. 2016; Carrer and Wolkoff 2018; Lu et al. 2017; Magnavita 2015; Marmot et al. 2006; Norbäck et al. 1990; Norbäck 2009; Runeson-Broberg and Norbäck 2013; Thörn 1999; WHO 1983). The multifactorial nature and risk factors of indoor air-related symptoms are mainly based on associations with increased risks of reported symptoms compatible with SBS.

Figure 1 presents a simplified model of the worker and the non-industrial work environment, and the relations between environmental determinants and health outcomes. The phenomenon (human health and well-being) has both physiological and psychological mechanisms and manifestations (Jaakkola and Jaakkola 2010).

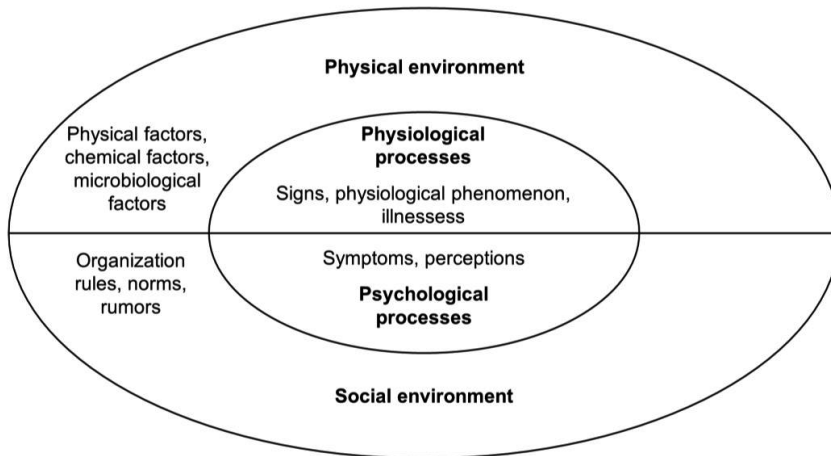


Figure 1 Office environment model: the worker (inner circle) with domains of physical and psychological phenomena and the non-industrial work environment (outer circle-inner circle) divided into physical and social environments (Jaakkola and Jaakkola 2010).

Building-related factors. In the non-industrial work environment, reports of health complaints have been associated with inadequate ventilation, high indoor temperatures, high or low relative humidity, type of ventilation (e.g. artificial, cooling system), molds in moisture-damaged buildings, cleaning activities, environmental tobacco smoke, several workers sharing a work area, visual display terminal work, lack of operable windows, carpet floor covering and an inappropriate visual, ergonomic or acoustic environment (Bluyssen et al. 2016; Mendell 1993; Norbäck 2009; Redlich et al. 1997; Salonen et al. 2013; Sundell et al. 2011; Wolkoff 2018). Similar health complaints and exposures have also been reported in home environments (Norbäck 2009; Wolkoff 2018). Proximity to outdoor pollution such as traffic has also been linked to impaired IAQ (de Kluizenaar et al. 2016; Norbäck 2009), as have indoor pollutants emitted by building materials or equipment (Nielsen et al. 2017; Norbäck 2009; Norbäck et al. 1990; Redlich et al. 1997; Salonen et al. 2009a; Wells et al. 2017; Wolkoff 2013). Indoor manmade vitreous fibers (also called man-made mineral fibers or synthetic vitreous fibers) have also been associated with impaired IAQ (Salonen et al. 2009b; Schneider 2008).

Inhaled chemicals. As regards inhaled chemicals, sensory irritation of the eyes and upper airways has been an essential endpoint for setting occupational exposure limits (Nielsen and Wolkoff 2017). The thresholds for sensory irritation (trigeminal stimulation) are typically several orders of magnitude higher than the corresponding odor thresholds (activation of *nervus olfactorius*). Odor perception per se is not associated with adverse health

effects (Wolkoff 2013). Findings regarding odor detection have not revealed altered odor thresholds in odor sensitive individuals (Hetherington and Battershill 2013) or different thresholds for sensory irritation among mild to moderate asthmatics (Wolkoff 2013). A review on the health effects of fragrances revealed that even when the measured maximum indoor concentrations of common airborne fragrances are close to or above their odor thresholds, they can still be far below the thresholds for sensory irritation (Wolkoff and Nielsen 2017). Human exposure studies shown no sensitization of the airways or toxic effects of fragrances; lung function effects have likely been due to olfactory-associated effects in airways (Wolkoff and Nielsen 2017).

Data on indoor pollutants emitted by building materials or equipment (e.g. ozone, phthalates, VOCs, formaldehyde) have shown no evidence of adverse health effects at non-industrial exposure levels (Mandin et al. 2017; Nielsen et al. 2017; Norbäck et al. 1990; Norbäck 2009; Redlich et al. 1997; Salonen et al. 2009a; Wells et al. 2017; Wolkoff 2013). Indoor pollutants of VOCs may be perceived at very low concentration levels, but their concentrations have been several orders of magnitude below their threshold limits for sensory irritation in non-industrial work environments (Mandin et al. 2017; Wolkoff 2013). Formaldehyde is a strong sensory irritant, but its concentrations in non-industrial work environments have also been revealed to be too low to cause sensory irritation (Salonen et al. 2009a; Wolkoff 2013).

Indoor molds. Dampness and molds in the indoor environment have been associated with respiratory symptoms (e.g. coughing, wheezing, dyspnea), upper respiratory symptoms and asthma development. However, evidence supporting a causal association with health effects in adults is insufficient (Caillaud et al. 2018; Mendell et al. 2011; WHO 2009). Eduard (2009) reviewed the toxicological and allergological evidence of the health effects of exposure to inhaled mold particles. According to the review, mold spore levels in common indoor environments have generally been lower than those in outdoor air, and a magnitude lower than those in workplaces in which fungi are used for production (e.g. food industry) or in highly contaminated environments. In damp buildings, the levels of airborne molds have shown to be mostly similar to or only moderately elevated in comparison to outdoor levels (Eduard 2009). The toxic mechanism of molds has not been associated with immunoglobulin (Ig)E-mediated allergy and its inflammatory mediators. It is considered non-allergic, as are other, different inflammatory mechanisms. However, the toxic mechanism of molds has not been verified (Eduard 2009).

There is very low-quality long-term evidence that repairing mold-damaged houses and offices decreases asthma-related symptoms and respiratory infections among adults to a greater than no intervention (Sauni et al. 2015). In a recent follow-up study of 1175 office employees, building-related respiratory and other severe non-respiratory symptoms did not improve, despite multiple remediation activities over a seven-year period (Park et al. 2018).

Individual factors. A number of studies have associated female gender with a higher prevalence of indoor air-related symptoms than male gender (e.g. Brasche et al. 2001; Mendell 1993; Runeson et al. 2006). A definite explanation for this over-presentation among women is lacking, but several suggestions exist, such as that females generally report psychosomatic symptoms more often (Stenberg and Wall 1995), females perceive psychological working conditions differently and possibly react differently to job stressors than men (Runeson et al. 2006), females tend to experience more health worries (Indregard et al. 2013), and females are more likely to identify odors than men (Dalton et al. 2002). Self-reported allergy, atopy and asthma have also been associated with a high manifestation of symptoms (Björnsson et al. 1998; Mendell 1993; Norbäck 2009; Runeson-Broberg and Norbäck 2013; Runeson et al. 2006). A review by Norbäck (2009) found no consistent association between age and SBS symptoms. From the psychological aspect, a low sense of coherence (Runeson et al. 2003), a tendency to somatize (Berglund and Gunnarsson 2000), neuroticism (Gomzi et al. 2007), anxiety and aggression (Runeson et al. 2006), and anxiety and depression (Björnsson et al. 1998) have shown to associate with increased reports of symptoms, as have personality traits and personal vulnerability (Runeson et al. 2004; Runeson and Norbäck 2005). Increased stress load, measured by a nonverbal projective drawing test, has also revealed an association with SBS symptoms (Runeson et al. 2007). An inquiry among indoor workers showed that personal factors (gender, smoking habit and atopy), anxiety and depression, and environmental discomfort and job strain were associated with both SBS and other work-related symptoms (Magnavita 2015). Findings have also suggested that those reporting symptoms in general may be more prone to reporting problems with the indoor environment (Brauer et al. 2006; Brauer and Mikkelsen 2010).

Psychosocial factors. There is explicit evidence that psychosocial factors are related to health, well-being, perceived comfort and symptoms in indoor non-industrial work environments (Bluyssen et al. 2016; Lahtinen et al. 1998, 2004; Marmot et al. 2006; Runeson-Broberg and Norbäck 2013). A wide range of psychosocial factors have shown to aggravate complaints attributed to indoor air, such as workload, work-related stress, work dissatisfaction, lack of control over one's work situation, lack of social support, poor interpersonal relationships, role ambiguity, and conflicting work demands (Lahtinen et al. 1998, 2004; Runeson-Broberg and Norbäck 2013; Runeson et al. 2006).

Cross-sectional data from a Whitehall II study of 4052 civil service office workers working in 44 buildings showed that the psychosocial work environment appeared to play a greater role in explaining differences in the prevalence of symptoms compatible with SBS than physical work environments (Marmot et al. 2006). In a Swedish cross-sectional study of a random sample of 1000 subjects aged 20–65 from the civil registration register, the most influential psychosocial factor in building-related symptoms

both at work and at home was poor social support, especially low supervisor support (Runeson-Broberg and Norbäck 2013).

In a recent Finnish longitudinal study focusing on the effect of 986 students' psychosocial problems, increased socioemotional difficulties were associated with a higher number of indoor air-related symptoms (Finell et al. 2018b). In addition, among school-age children, increased problems in teacher-student relations were related to perceived impaired IAQ (Finell et al. 2018b). In another Finnish study of a working population (n=4633), the risk of reporting experiences of injustice (e.g. information, attitudes, remuneration) was significantly higher among those who perceived the indoor environment as harmful than among those with no such problems (Finell and Seppälä 2018). The risk was higher among respondents who reported harm from mold than among those who reported harm from only ventilation (Finell and Seppälä 2018). It has been suggested that awareness of psychosocial effects is important for the prevention of unnecessary escalation of psychosocial problems at workplaces that have observed and suspected indoor air problems (Bluyssen et al. 2016; Finell and Seppälä 2018).

2.2 INDOOR AIR-RELATED DISABILITY

Non-specific symptoms attributed to indoor air environments can be very unpleasant and disruptive for some individuals, causing loss of work and reduced productivity and disability (Redlich et al. 1997). Data on indoor air-related disability are fragmented and scarce (the concept of disability is described in Section 2.5). Descriptions of disability are based on self-reports, and questionnaires have been used to evaluate the prevalence and nature of disability, and to objectify and quantify subjective feelings and sensations. Individuals' perceptions of symptoms are typically elicited to obtain data on the associations of common risk factors. Persistent symptomatology that causes impaired QOL and impacts several aspects of daily life is revealed by follow-up studies of clinically examined patients (Edvardsson et al. 2008, 2013; Karvala et al. 2013, 2014) and by qualitative approaches (Finell and Seppälä 2018; Söderholm et al. 2016). Among symptomatic individuals, multifaceted experiences of injustice are common (Finell et al. 2018a; Finell and Seppälä 2018; Söderholm et al. 2016). Previous findings have also shown adverse perceptions of other environmental factors, such as inhaled chemicals and electric devices (Edvardsson et al. 2008; Söderholm et al. 2016). Table 2 presents the outlines and main findings of the studies that describe indoor air-related disability.

Table 2. *Studies of patients with indoor air-related disability.*

Reference	Study design	Population	Outcomes/findings
Edvardsson et al. (2008)	Cross-sectional study with follow-up	Patients (n=189) with building-related symptoms were followed up using a postal questionnaire 1–13 years after being examined at an outpatient clinic of the University Hospital, Sweden. Criteria for inclusion: 1) a least one building-related typical SBS symptom, 2) signs of deficiencies in indoor air quality, and 3) possible association between exposure and symptoms not ruled out (Statistical analyses restricted to women, n=174)	In the follow-up, building-related symptoms mostly remained unchanged despite actions taken; persistent symptoms impaired work ability and affected social life. Risk factors for work disability were symptom duration of over one year and multiple symptoms present at the start. Symptoms were aggravated by various encounters in everyday life. The symptom profile showed similarity to patients with hypersensitivity to electricity and visual display terminal-related symptoms
Edvardsson et al. (2013)	Cross-sectional study with follow-up	Patients (n=189) as in the Edvardsson et al. study (2008)	The patients rated their self-images as more spontaneous, more positive, and less negative than the control group. Among women (n=174), one risk factor for work disability was a low score on negative self-image
Karvala et al. (2013)	Cross-sectional study with follow-up	Patients (n=1295) with asthma or other symptoms attributed to workplace dampness and mold were followed up 3–12 years after being examined at the FIOH occupational medicine clinic, Finland	In the follow-up, patients presented multiple symptoms, decreased QoL, limitations in everyday life, and work disability. Occupational asthma induced by indoor molds associated with various disability outcomes and persistent asthma symptoms
Karvala et al. (2014)	Cross-sectional study with follow-up	Patients (n=1098) as in the Karvala et al. study (2013), excluding those with diagnosed hypersensitivity pneumonitis and over 65 years of age	Occupational asthma and perceived poor social work environment associated with both impaired work ability and early withdrawal from work. Multiple indoor air-related long-term symptoms increased the risk of impaired work ability; multiple symptoms and disability were not explained by medical conditions only

Al-Ahmad et al. (2010)	Cross-sectional study with follow-up	Patients (n=32) investigated at outpatient clinics of Toronto Western Hospital (Canada) because of asthma or asthma-like symptoms attributed to documented mold exposure. Follow-up (time range 1–4 years) completed by 17 patients	In the follow-up, a subsample of patients presented frequent persisting asthma-like symptoms and non-specific symptoms not explained by asthma or current mold exposure. Non-specific symptoms attributed to molds resembled SBS, and were persistent despite removal from or remediation of mold exposure. Patient reports included complaints about new carpets and a chemical/metallic taste, and problems with concentration and short-term memory
Söderholm et al. (2016)	Qualitative	Patients (n=11) with diagnosed NBRBS at an outpatient clinic of the University Hospital, Sweden. Criteria for NBRBS: 1) at least one typical general, mucosal or skin symptom, 2) no alternative explanations for symptoms, and 3) records supporting exposure to an indoor environment that evokes such symptoms (e.g. documented building dampness)	Impact on patients' daily life included of i) attitudes of others, ii) consequences in daily activities, and social, financial and emotional aspects and iii) coping strategies (both problem- and emotionally- focused). Experiences of not being taken seriously by others (e.g. health care professionals) were common
Finell and Seppälä (2018)	Qualitative	Individuals (n=23) who suffered from suspected or observed indoor air problems at their workplace were recruited by public health organizations, magazines, and online (e.g. via news of Finnish broadcasting company), in Finland	Accounts revealed effects on a few areas of life outside the workplace; multidimensional experiences of injustice related to conflicts and moral exclusions: A major factor behind these experiences was the discrepancy between self-reported illness attributions and those validated by others
Finell et al. (2018a)	Qualitative	Individuals (n=20) as in the Finell and Seppälä study (2018)	Study group showed six different identity management strategies on two continua: i) between individual and collective level and ii) between dissolved and emphasized (sub)category boundaries

SBS, sick building symptoms; FIOH, Finnish Institute of Occupational Health; QOL, quality of life; NBRBS, non-specific building-related symptoms.

2.2.1 FOLLOW-UP STUDIES OF CLINICALLY EXAMINED PATIENTS

Two Swedish follow-up studies by Edvardsson et al. (2008, 2013) described the medical and social prognoses of patients who had initially been examined at an occupational and environmental clinic because of building-related symptoms (Table 2). Almost half of the patients had been exposed to environments with visible water damage, and the others to some other IAQ problems. At baseline investigations, the patients also reported health problems from dental fillings (4.0%), visual display terminal use (12.7%), and hypersensitivity to electricity (6.9%) (Edvardsson et al. 2008). At follow-up, nearly half of the patients claimed that their symptoms remained unchanged after seven years or more, despite actions taken at the workplace. The patients reported a wide range of symptoms, and the symptom profile had similarities to those of other patients with hypersensitivity to electricity or patients with visual display terminal-related skin symptoms (Edvardsson et al. 2008).

The follow-up also showed that the patients' symptoms had impacted their social life and ability to work (Edvardsson et al. 2008). The risk factors for work disability were symptom duration of over one year prior to first hospital visit, and the presence of wide-ranging symptoms at the time of the first visit. Symptoms were aggravated by various surroundings and factors, such as shopping, using public transportation, visiting a movie theater, using a printer, and/or reading newly printed newspaper (Edvardsson et al. 2008). The patients' self-images and cognitive coping abilities differed from those of the general population, for example, female patients with a low negative self-image were at an increased risk of being unable to work (Edvardsson et al. 2013). The authors emphasized the importance of early, comprehensive rehabilitation measures (Edvardsson et al. 2008), and how certain personality traits may be risk factors for encountering and experiencing stressful work situations and contribute to the risk of developing long-standing building-related non-specific symptoms under certain circumstances (Edvardsson et al. 2013).

Two Finnish studies followed patients initially examined in occupational medicine clinic for suspected occupational respiratory diseases related to mold exposure at the workplace (Table 2) (Karvala et al. 2013, 2014). The patients reported multiple symptoms, decreased QOL, long-standing limitations in everyday life and work disability of over 3–12 years. Those who had been diagnosed with occupational asthma induced by indoor molds reported more severe disability outcomes. Patients with occupational asthma were compared to patients in corresponding environments with work-exacerbation asthma or only symptoms (Karvala et al. 2013). Based on their use of asthma medication, the patients with occupational asthma also had more persistent asthma symptoms than other patients with asthma (Karvala et al. 2013). In addition, they had a strong risk for early withdrawal from work (Karvala et al. 2014). At follow-up, 40% of those diagnosed with occupational asthma were outside work life, in comparison to 23% of the work-exacerbated asthma subgroup and 15% of the upper respiratory symptom subgroup (n=176) at baseline. Twelve

percent of patients reported that they had changed occupations, and 13% had changed employers because of dampness-related symptoms. A wide range of indoor air-related long-term symptoms increased the risk of impaired self-assessed work ability. Those who evaluated their social work environment more negatively (social climate at workplace or co-operation with a supervisor) were at an increased risk of early withdrawal from work. When self-reported depression and somatization were taken into account, the risks remained significantly elevated. Long-term work disability outcomes were associated with mold exposure-related asthma, multiple symptoms and disability as a multifactorial origin not explained by medical conditions only (Karvala et al. 2014).

A Canadian study followed 32 patients who were initially examined in a tertiary clinic for asthma or asthma-like symptoms attributed to documented mold exposures, 82% of whom were mold-exposed at work (Table 2) (Al-Ahmad et al. 2010). The time from onset of exposure-attributed symptoms to the clinic assessment ranged from one to ten (mean 1.9) years. At the time of follow-up, none of them (n=17) had ongoing exposure to mold, and six (out of 17, 35%) had asthma. The majority of the 17 respondents reported a long-lasting non-specific symptom complex despite removal from/remediation of the mold exposure. Comparison of the mold-exposure patients to a group of individuals (n=233) with an SBS symptom cluster revealed a similar frequency of asthma-like symptoms and non-specific symptoms. The authors concluded that the subsample of mold-exposure patients had long-lasting symptoms that could not be explained by asthma or the current exposure (Al-Ahmad et al. 2010).

2.2.2 QUALITATIVE STUDIES

The patients of a qualitative study (n=11) reported that living with non-specific building-related symptoms (NBRS) affected several aspects of their daily lives (Table 2) (Söderholm et al. 2016). The data were based on descriptive, written reports and telephone interviews. The effects on daily activities were diverse due to the heterogeneity of the trigger factors. Patients had difficulties with transportation, shopping, reading books/newspapers, going to the gym, visiting certain buildings and socializing with friends in general. They also reported financial difficulties. NBRS had an impact on social relationships, as well as emotional consequences from surrounding attitudes. Patients typically felt they were not taken seriously by health care professionals or others. They encountered disbelief and prejudice in relation to their suffering which they supposed to be due to a lack of knowledge regarding NBRS. Patients' coping strategies included both problem-focused and emotionally focused strategies, such as struggling with their work ability, avoiding trigger factors, finding positive aspects, learning to accept and finding solutions, and making one's home a sanctuary (Söderholm et al. 2016).

In order to study experiences of injustice, a Finnish qualitative study analyzed the content of 23 essays written by individuals who suffered from indoor air problems (Table 2) (Finell and Seppälä 2018). All the participants attributed their symptoms to their previous or present workplace. They had also experienced being blamed and objectified because of their many sick-leave days and situations in which their work ability was evaluated due to indoor air-related health problems. Experiences of not being taken seriously or treated with respect, and instead being stigmatized, treated as a problematic object and left without help and care were common. A major factor behind experiences of injustice was the discrepancy between self-reported illness attributions and those validated by others (Finell and Seppälä 2018). Another study by Finell et al. (2018a) identified individuals' (n=20) managements strategies for living with indoor air-related health problems (Table 2). The study identified six strategies that individuals used to protect their threatened identities: the normal individual (e.g. symptoms as normal bodily reactions to an unhealth environment), the good citizen (e.g. a diligent employee), the ideal individual (e.g. an ideal, strong character who had survived difficult conditions), the real sufferer (e.g. underlining the roles of others), the awakened sufferer (e.g. spiritual maturation, heightened morality and social relationship due to their experiences of suffering) and the promoter of in-group rights (e.g. validating their own past or current suffering by referring to other suffers). The authors concluded that these coping strategies might interact effectively with individual suffering from contested illnesses (Finell et al. 2018a).

2.2.3 OTHER REPORTS OF DISABILITY

Other reports (not peer-reviewed) from Finland also reveal patients' experiences of indoor air-related disability. An interview study of individuals with indoor air-related ill health (n=30), using public recruitment via magazines and on line, showed multiple symptoms: Using avoidance of perceived triggers as a main coping strategy, economic consequences, the importance of social support, negative experiences related to health care providers, and positive experiences of employers making workplace adjustments (Mäki and Nokela 2014). Homepakolaiset ry, a patient association, has commissioned three secondary education dissertations (final projects). Pimiä-Suwal (2017) describes the experiences of individuals (n=18) who suffer from indoor air-related health problems related to remaining employed. They reported challenges in maintaining their work ability and employment due to a lack of appropriate aid and support. They also reported controversy over their ill health, the lack of a proper diagnosis and failure to fulfil the official definition of disability (Pimiä-Suwal 2017). Another report on the experiences of factors that impact the ability to function among individuals (n=6) with indoor air-related ill health showed impaired QOL and a wide range of limitations in everyday functioning (Vesikallio and Väisänen 2018).

Avoiding triggers and situations that evoke symptoms appeared to be the most essential coping strategy, for example, avoiding indoor molds and other exposures, and restricting one's living environment. In order to facilitate healing, individuals reported how they ensured that their basic needs were met – specific diets, medication and respiratory masks if needed. The interviews revealed experiences of loneliness, health care providers' underestimations and individuals' dissatisfaction with health care providers (Vesikallio and Väisänen 2018). A third report has gathered data on everyday life through theme interviews (n=3) and a questionnaire (n=101) (Lappalainen et al. 2018). The participants' ill health had impacts on everyday life; on personal, occupational and environmental aspects. The participants experienced a lack of support and help from social and health care providers (Lappalainen et al. 2018).

The Finnish Trade Union of Education carried out a questionnaire study (not peer-reviewed) of indoor air-related problems (OAJ 2014). The survey had 529 respondents whom included supervisors in day care, directors, principals and safety delegates. The principals reported that 11% of the schoolteachers (total n=9500) had been on sick leave due to indoor air problems in the preceding two years. For 0.2% (n=19), the length of work absence had been over 90 days, and their inability to participate in work had persisted despite adjustments and repairs made to workplace facilities and workplace relocation (OAJ 2014). The teachers with long-term sickness absence and persistent indoor air-related ill health possibly represent a proportion of the cases with severe functional impairments.

2.3 ENVIRONMENTAL INTOLERANCE

Similar features of disability are seen in symptoms attributed to other environmental factors such as inhaled chemicals. Here, the term environmental intolerance (EI) covers all conditions with recurring, non-specific symptoms in multiple organ systems attributed to environmental factors with no medical and exposure-related explanation (IPCS/WHO 1996; Lacour et al. 2005; MCS consensus conference 1999). Some individuals become intolerant/sensitive/reactive/responsive to very low levels of indoor pollutants which most people tolerate with no problems. SBS shares similar features and overlaps with EI (or multiple chemical sensitivity, MCS) (Bardana 1997; Das-Munshi et al. 2007; Frías 2015; IPCS/WHO 1996; Hetherington and Battershill 2013; Staudenmayer 2001; Van den Bergh et al. 2017a; Watanabe et al. 2003b; Wiesmüller et al. 2003). A subset of SBS also develops MCS, a more general sensitivity to many environmental factors with symptoms that persist despite improvements to the original environments (Redlich et al. 1997).

2.3.1 OVERVIEW AND DEFINITIONS

Several criteria have been proposed for sensitivities/intolerances to various environmental factors, formerly often called MCS (described in detail in Appendix 1). The origin of MCS dates to the work of Randolph in the 1950s and 1960s (Randolph 1956, 1962), who described MCS patients with multiple chemical and food sensitivities and how they attempted to avoid various chemical substances and foods (Randolph 1956, 1962). Later, the Cullen criteria (Cullen 1987), for example, outlined the diagnostic features of MCS. Due to a lack of underlying exposure-related mechanisms, the causal criterion between exposure and symptoms was later removed (IPCS/WHO 1996). A workshop organized by WHO and two other United Nations agencies (IPCS/WHO 1996) stated that disorders that share similar symptomatologies associated with diverse environmental factors including chemicals (e.g. VOCs) and biological (e.g. molds), physical (electromagnetic fields, EMFs) and psychological (e.g. stress) factors (tolerated by the majority of people), should be labeled under one same term, idiopathic (I)EI, and this should replace terms such as MCS. Clinical assessment rules out conditions that require specific treatments, and the evaluation should be based on a biopsychosocial understanding (IPCS/WHO 1996).

In 1999, an MCS consensus emphasized that symptoms associated with MCS must involve multiple organ systems (MCS consensus conference 1999). According to the consensus, the presentation of MCS includes individuals with minimal disability and mild occasional symptoms as well as those who are totally disabled by severe symptoms on a daily basis. It was recommended that any clinical diagnosis of MCS should be characterized using indices of life impact or disability, symptom severity, symptom frequency and sensory involvement (identification of which sensory pathways are altered) (MCS consensus conference 1999). To restrict MCS criteria to the more severe condition, Lacour et al. (2005) added the following: Central nervous system (CNS) symptoms (as the leading complaints) and at least one other symptom of another organ system, symptom duration of at least six months and significant lifestyle or functional impairments. Comorbidity should also be taken into account in the differential diagnostic procedure (Lacour et al. 2005).

Both the terms EI and IEI appear in the literature. IPCS/WHO (1996) has stated that IEI should only be used for clinically examined patients. In this thesis, the term IEI is restricted to clinically verified cases. EI is used as a general term to describe intolerance to environmental factors.

The unifying term IEI brings together EIs to different environmental factors that share similar symptomatologies. However, other terms continue to exist, such as MCS or chemical sensitivity/intolerance; SBS, building-related intolerance (BRI), NBRS, building-related disorders; electromagnetic (hyper)sensitivity, electro(hyper)sensitivity, hypersensitivity to EMFs; and infrasound hypersensitivity, wind turbine syndrome and vibroacoustic

syndrome (Baliatsas et al. 2012; Karvala et al. 2018b; Menzies and Bourbeau 1997; Van den Bergh et al. 2017a; WHO 2005; Wiesmüller et al. 2003).

The definitions of IEI are mainly based on intolerance to chemicals. In addition, in 2005, WHO, for example described the characteristics of patients with IEI attributed to EMFs (IEI-EMFs) (WHO 2005). Later, to improve the identification and management of patients by health care professionals, Baliatsas et al. (2012) reviewed the identifying criteria for individuals with IEI-EMFs (in detail in Appendix 1).

2.3.2 MECHANISMS OF ENVIRONMENTAL INTOLERANCE

A number of theories have been proposed for the cause of EI and the mechanism by which the diverse environmental exposures produce a wide range of symptoms: Toxicological, neurotoxic, immunological, psychological, psychiatric, sociological and behavioral (Bell 1982; Bell et al. 1992; Graveling et al. 1999; Hetherington and Battershill 2013; Korkina et al. 2009; Labarge and McCaffrey 2000; Miller 1992; Staudenmayer et al. 2003a, b; Winder 2002). Nonetheless, current scientific literature emphasizes that IEI is not organically based and cannot be explained by a toxicological response. Instead, findings support a biopsychosocial nature (Dantoft et al. 2015; Hetherington and Battershill 2013; Van den Bergh et al. 2017a). Although the majority of this evidence concerning IEI is based on chemicals, it can probably be generalized across different but similar conditions. In addition, no plausible physical explanations have been found for IEI attributed to EMFs and infrasound (from wind turbines) (Crichton and Petrie 2015; Hetherington and Battershill 2013; Rubin et al. 2005, 2011, 2014; Schmidt and Klokker 2014; Van den Bergh et al. 2017a).

The biopsychosocial explanation is based on the integrative and multidimensional approach, with the behavioral and social aspects of the physiological, emotional and cognitive processes (Kipen and Fiedler 2002; Van den Bergh et al. 2017a). This explanation proposes that the central mechanisms of central sensitization, for example, expectancy and nocebo mechanisms, are involved in the development of the symptoms that occur in response to environmental triggers with no exposure-related direct physiological causes, and that these responses become linked to specific environmental cues (Van den Bergh et al. 2017a) (see also Section 2.3.6). Central sensitization can be defined as an amplified response of the CNS to any select stress input (Yunus 2015). The role of central mechanisms in MCS and in IEI-EMFs is supported by provocation/experimental studies that have found reactions related to expectations and prior beliefs (Das-Munshi et al. 2006; Eltiti et al. 2018), as well as brain imaging during odor provocations in odor-sensitive individuals or increased capsaicin-induced secondary hyperalgesia (Hillert et al. 2007; Orriols et al. 2009; Tran et al. 2013a).

2.3.3 CLINICAL CHARACTERISTICS

IEI has no commonly accepted definition. The conditions are descriptive and do not include any diagnostic test or specified symptom set. Characterization relies on self-reported non-specific symptoms, which are attributed to certain environmental factors or environments. The conditions can incorporate mild annoyance (Dantoft et al. 2015), although the more severe expression has more clinical relevance (Lacour et al. 2005). IEI should be diagnosed only after a thorough examination of the patients (IPCS/WHO 1996; Lacour et al. 2005; MCS consensus conference 1999).

A Finnish review (Sainio and Karvala 2017) summarized the following distinctive features of the IEI condition (Bailer et al. 2008b; Dantoft et al. 2015; Dalton and Jaen 2010; Das-Munshi et al. 2007; Eis et al. 2008; Gupta and Horne 2001; Hausteiner et al. 2007; Hetherington and Battershill 2013; IPCS/WHO 1996; Labarge and McCaffrey 2000; Lacour et al. 2005; Skovbjerg et al. 2009a; Van den Bergh et al. 2017a; Watanabe et al. 2003a, b):

- Chronic condition and recurrent symptoms
- Non-specific symptoms that involve several organ systems, including CNS
- Symptoms in response to several different environmental pollutants at levels with no evidence of health hazards and tolerated by the majority of the general population
- The mechanisms of how the environmental factor causes the physical symptoms cannot be proved
- The relation to environmental exposures is based on the individual's description
- Symptoms are already initiated or induced when the harmful exposure is anticipated
- Odor sensitivity to cues of harmful exposure
- Recurrent symptoms may lead to significant restrictions in daily life
- Symptoms are alleviated by avoidance
- Difficult for patients to accept other than environment-related explanations for the symptoms
- Concern that environmental factors cause health hazards
- Spread of intolerance to other environmental factors, e.g., chemicals, electricity
- Lack of specific clinical or medical findings
- Comorbidity is common and can precede EI
- Female predominance

Data on IEI disability are mainly based on MCS patients and their self-reported impaired well-being in everyday functioning. Restraints in the functional areas (activity and participation) of everyday life can appear in work activities (e.g. sick leave, part-time work, unemployment), leisure activities and socializing (e.g. isolation); while traveling, living in homes, visiting public

places, wearing normal clothing and eating a normal diet; in wellbeing (e.g. decreased QOL) and health behavior (e.g. increased health service use) or as financial consequences (e.g. loss of incomes) (Baliatsas et al. 2014; Black et al. 1999, 2001; Dantoft et al. 2015; Gibson et al. 2011; Gibson and Vogel 2008; Katerndahl et al. 2012; Lavergne et al. 2010; Skovbjerg 2009; Watanabe et al. 2003a).

Previous findings support the claim that the overall pathway to adverse consequences and disability in IEI is associated with situation-bound avoidance due to perceived symptom triggers (Dantoft et al. 2015; IPCS/WHO 1996; Skovbjerg et al. 2009a, 2012b; Watanabe et al. 2003a). Attitudes in social surroundings and misunderstandings can also add to adverse illness behaviors and promote social and occupational restraints (Skovbjerg 2009; Watanabe et al. 2003a). Patients with IEI typically described encountering negative experiences of being misunderstood in health care and by other social sources when seeking support (Gibson et al. 2005, 2016; Skovbjerg 2009; Wiesmüller et al. 2003).

2.3.4 PREVALENCE OF ENVIRONMENTAL INTOLERANCE

Epidemiological surveys have been used to study the prevalence of EI and its manifestations in different populations. The findings endorse the heterogeneous nature of EI and the contribution of cultural and societal factors to its prevalence. There is no generally agreed EI definition for estimating prevalence. Case definitions of EI are based on self-reports, typically by a single-item question, and are associated with environmental factor(s). Prevalence data are mainly from studies of intolerance to various chemicals (e.g. perfumes, air fresheners, cleaning solvents, fresh paints, freshly printed papers, cigarette smoke, pesticides, new furnishings, vehicle exhaust and, for example, hairdressers or departments in stores) and intolerance to EMFs (e.g. electric devices), but are limited to indoor environments (e.g. certain buildings, BRI). A recent study by Karvala et al. (2018b) showed prevalence differences between Finland and Sweden in self-reported EI attributed to chemicals (15.2% vs. 12.2%), EI to EMFs (1.6% vs. 2.7%), and in BRI (7.1% vs. 4.8%), respectively.

Prevalence demographics have shown that EI can develop throughout the lifespan, but onsets usually occur in middle age, and female gender is a risk-factor (Dantoft et al. 2015; Watanabe et al. 2003a). In addition, as pregnancy, especially early pregnancy, increases the perception of odors and unpleasant qualities, this may increase reporting of EI (Cameron 2014; Nordin et al. 2004, 2005, 2007). The association between education or socio-economic class and EI is inconsistent (Dantoft et al. 2015; Kipen and Fiedler 2002; Watanabe et al. 2003a).

Different degrees of severity. EI spans different degrees of severity ranging from unpleasantness or annoyance to multiorgan symptoms leading to lifestyle changes and functional impairments and representing different

degrees of severity (Berg et al. 2008; Dantoft et al. 2015). Prevalence data on EI disability are still fragmented and severity is described non-uniformly with no precise severity measure for disability. The increasing severity of EI has been described by the grade of annoyance (Carlsson et al. 2005), the severity of symptoms (Caress and Steinemann 2004a), the strength of symptoms (Johansson et al. 2005), the frequency of symptoms (Meggs et al. 1996), the number of symptom groups (Björnsson et al. 1998), requiring CNS symptoms (Karvala et al. 2018a, b) and co-occurrence (Palmquist et al. 2014). The intolerance-related effects on lifestyle and behavior, and physician diagnosed EI have been used to define more severe conditions (Berg et al. 2008; Black et al. 2000b; Caress and Steinemann 2004a; Karvala et al. 2018a, b; Kreutzer et al. 1999). The different measures used in the literature for evaluating EI prevalence are illustrated in Figure 2.

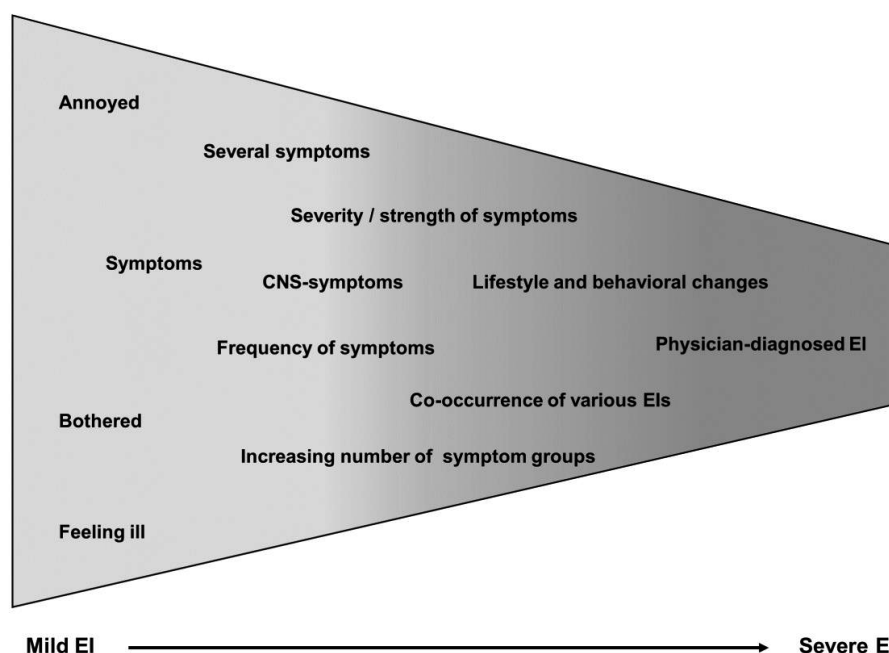


Figure 2 Different measures used for evaluating the prevalence of environmental intolerance (EI) in the literature. CNS, central nervous system.

EI attributed to chemicals. Few previous studies have shown the spectrum of increasing severity (annoyance, symptoms, behavioral consequences) of EI attributed to chemicals (Berg et al. 2008; Black et al. 2000a; Johansson et al. 2005). In one Danish population-based sample, 45% of the 4242 participants reported annoyance due to at least one of the eleven inhaled chemicals, 27% reported intolerance-related symptoms, 3.3% had

made one or more adjustments to their social lives or occupational conditions because of symptoms, and 0.5% reported having done both (Berg et al. 2008). In the same study, women reported more symptoms and adjustments to personal lifestyle than men, but gender had no effect on reporting adjustments to social life or occupational conditions (Berg et al. 2008). In a Swedish population-based sample, 33% of 1387 participants reported being bothered by strong odors, half of them had moderate or severe symptoms, and 19% reported intolerance-related affective and behavioral consequences (Johansson et al. 2005).

Annoyance. Prevalence has shown higher estimates when patients are asked questions about unpleasantness or annoyance, feeling ill or unwell, being sick, and being bothered by an environmental exposure (Figure 2). According to these questions, EI attributed to chemicals or odors varied from 4.1% to 52% in population-based (US, Australian, Swedish, Danish) samples of adults (Berg et al. 2008; Carlsson et al. 2005; Dantoft et al. 2017; Johansson et al. 2005; Meggs et al. 1996; NSW Department of Health 2003). More severe annoyance has been associated with more greatly impaired health and daily function (Carlsson et al. 2005). It has been suggested that annoyance is a mediating factor between exposure and health effects (Berglund et al. 1987; Dantoft et al. 2015) and that it is affected by prior positive and negative experiences with the exposure (Greenberg et al. 2013; Van Thriel et al. 2008). A Swedish study showed that annoyance and symptoms mediated perceived pollution and health risk perception in environments with non-toxic levels of odorous pollution (Claeson et al. 2013).

Increased sensitivity. EI has also been determined by asking if respondents consider themselves to be allergic or unusually sensitive to everyday exposures in comparison with other people. According to the responses, EI attributed to chemicals varied from 11% to 16% in population-based samples in the USA (Caress and Steinemann 2004a, b; Kreutzer et al. 1999).

Symptoms related to the environment. If symptoms were required, the prevalence of EI to chemicals fell to 12%–33 % in the (Danish, Swedish, Finnish) samples (Berg et al. 2008; Johansson et al. 2005; Karvala et al. 2018b; Palmquist et al. 2014). The number and nature of symptoms vary extensively, and are commonly categorized into different organ systems depending on their expression (Dantoft et al. 2015). CNS symptoms have been seen as a characteristic feature of a more severe condition (Lacour et al. 2005). For example, when the definition of EI required multiorgan symptoms including CNS symptoms, the prevalence of EI to chemicals fell from 12.2% to 8.0% in a Swedish sample, and from 15.2% to 10.0% in a Finnish population-based sample (Karvala et al. 2018b).

Adverse effects on lifestyle or behavior. When lifestyle or behavioral alterations were studied, the prevalence of EI to chemicals fell to 0.4%–20.7% in (Danish, Swedish and US) samples (Berg et al. 2008; Caress and Steinemann 2004a; Johansson et al. 2005; Kreutzer et al. 1999). Typical adjustments are made to behavior due to symptoms in personal lifestyle, social

life and in occupational conditions such as changing personal hygiene products; using a special diet or protective clothes; taking precautions at home or being careful with home furnishing; moving to a new home; avoiding social situations, public spaces, stores and transportation; leaving or changing employment or inability to work. Due to intolerance to chemicals, 1.5% of a US population-based sample reported losing their jobs and 0.8% reported moving houses (Caress and Steinemann 2004a), and 0.8% of the Danish adult population reported having left employment permanently (Berg et al. 2008).

Physician-diagnosed EI. Self-reported physician-diagnosed (or medically diagnosed) EI has been used to define the more severe EI phenomenon. According to this definition, EI to chemicals in (German, Swedish, Finnish, Japanese, Australian, Danish, Canadian and US) population-based samples have varied between 0.5% and 6.5% (Azuma et al. 2015b; Caress and Steinemann 2009, 2004a; Dantoft et al. 2017; Fitzgerald 2008; Hausteiner et al. 2005; Karvala et al. 2018b; Kreutzer et al. 1999; NSW Department of Health 2003; Palmquist et al. 2014; Park and Knudson 2007; Steinemann 2018b). In a recent US study, the prevalence rate was as high as 12.8% for self-reported physician-diagnosed EI to chemicals (Steinemann 2018a).

EI attributed to EMFs. The prevalence rates for EI attributed to EMFs have varied between 0.1% and 20.9% in (Swedish, Finnish, Swiss, US, Austrian, Dutch, German, Taiwanese and English) population-based samples on the basis of responses to various definition questions, such as being allergic or (hyper)sensitivity, experiencing annoyance, having health symptoms, having adverse health effects due to electric devices or EMFs, or physician-diagnosed hypersensitivity to EMFs (Baliatsas et al. 2015a; Blettner et al. 2008; Carlsson et al. 2005; Eltiti et al. 2007; Hillert et al. 2002; Karvala et al. 2018b; Levallois et al. 2002; Mohler et al. 2010; Palmquist et al. 2014; Schreier et al. 2006; Schröttner and Leitgeb 2008; Tseng et al. 2011; Van Dongen et al. 2014).

Building-related intolerance. Population-based prevalence studies of EI to certain buildings (e.g. BRI) are sparse (Table 3). A few population-based studies on BRI have separated the prevalence of any building-related symptoms from the more severe ones (Karvala et al. 2018a, b; Palmquist et al. 2014). More severe BRI was defined as reported BRI with CNS symptoms, and secondly, reported physician-diagnosed BRI (Table 3). The presumption was that the cases with a physician diagnosis represented a more severe condition, and perhaps more functional impairments, than self-reported BRI. Women generally reported BRI more often than men (Karvala et al. 2018b). BRI appeared to be a long-lasting condition, of 12 years on average (Karvala et al. 2018a). In addition, daily or weekly building-related symptoms had significantly more negative emotional and behavioral impact than monthly symptoms (Karvala et al. 2018a).

Table 3. Prevalence studies of building-related intolerance in adult general populations.

Prevalence	Case definition	Method and sample	Reference
4.8%	Responding 'yes' to: 'Are you getting symptoms from residing in certain buildings (non-specific building related symptoms) that you were not getting symptoms from before or that you believe most other people are not getting symptoms from?' (= BRI)	Random sampling. Postal survey in Västerbotten, Sweden (n=3406)	Palmquist et al. (2014)
7.2%	OR	Random sampling. Postal survey in Österbotten, Finland (n=1535)	Karvala et al. (2018b)
3.4%	Affirmative response to BRI (above) and reporting at least one CNS symptom and at least one non-CNS symptom	Swedish sample	
5.0%	OR	Finnish sample	
1.4%	Responding 'yes' to: 'Have you been diagnosed with a BRI by a physician?'	Swedish sample	
1.3%		Finnish sample	
5.6%	Affirmative response to BRI	Combined survey of both (above) Swedish and Finnish samples (n=4941)	Karvala et al. (2018a)
	OR		
2.5%	Affirmative response to BRI and reported weekly mucosal/airway, skin, and general symptoms		

CNS, central nervous system; BRI, building-related intolerance.

Co-occurrence of different EIs. It is characteristic that among individuals with EI (to chemicals), the number of symptom-evoking exposure substances increases over time, and a higher number of triggering substances are seen in more severe cases (Winder 2002). In a sample of 2072 Californians, reporting being chemically sensitive was a strong predictor of reporting being sensitive to EMFs, and the prediction was strongest if chemical sensitivity had been diagnosed by a physician (Levallois et al. 2002). In the study, 8.4% of those who reported chemical sensitivity reported sensitivity to EMFs, whereas among those not sensitive to chemicals, 1.8% reported sensitivity to EMFs (Levallois et al. 2002). A Swedish study showed co-prevalence of EI attributed to chemicals and EI to any electrical factor among 4.8% (Carlsson et al. 2005). Later, another Swedish study showed co-prevalence of EI attributed to chemicals, certain buildings, EMFs, and everyday sounds (Palmquist et al. 2014). In the same study, 12.1% of

respondents reported only one type of EI (chemicals, certain buildings or EMFs), 3.1% reported two of the different varieties, and 0.4% all three. The prevalence estimates for the co-occurrence of physician-diagnosed EI were 3.4% (only one type of EI), 0.7% (two types of EI), and 0.06% (all three) (Palmquist et al. 2014). An overlap between building-related non-specific symptoms and various EI has also been shown in clinical settings (Edvardsson et al. 2008; Söderholm et al. 2016). The overlap between different types of EI suggest that various EIs represent the same phenomenon.

2.3.5 COMORBIDITY

The comorbidity of somatic diseases and psychiatric disorders is prevalent in EI. This has typically been shown using cross-sectional designs and self-reports, but longitudinal data are scarce. Most comorbidity data are from both epidemiological and clinical studies of MCS.

In epidemiological surveys, a typical somatic MCS comorbidity is that of asthma and allergic rhinitis. In MCS, the co-prevalence of asthma has varied from 10% to 42%, depending on the sample (Baldwin and Bell 1998; Bell et al. 1993, 1996a; Caress and Steinemann 2004a), and that of allergic rhinitis from 8% to 44% (Baldwin and Bell 1998; Bell et al. 1993, 1996a). Clinical studies have also shown co-occurrence of asthma and rhinitis with MCS (Katerndahl et al. 2012). In a population-based combined Swedish and Finnish sample, the co-prevalence of asthma was 28% among individuals with BRI (Karvala et al. 2018a). In general, asthma is a common chronic disease, and has a prevalence of 9.4% in the Finnish adult population (Pallasaho et al. 2011). A Swedish population-based study expressed multimorbidity in asthma/allergy with intolerance to chemicals and BRI as a higher risk than comorbidity with either one of the two intolerances (Lind et al. 2017).

A number of studies have investigated the comorbidity of psychiatric disorders in MCS. In comparison, in general populations, a review of 174 surveys across 63 countries providing pooled prevalence data showed that on average one in five (18%) adults had experienced a common mental disorder in the past 12 months, and 29% had experienced one at some point in their lifetime (Steel et al. 2014). The period prevalence of mood disorder was 5.4% with a pooled lifetime prevalence of 9.6%. For anxiety disorders, the pooled period prevalence was 6.7% with a lifetime prevalence of 12.9% (Steel et al. 2014). In a general population sample of Finnish adults (n=6005), depressive and anxiety disorders were found among 6.5% and 4.1%, respectively (Pirkola et al. 2000).

As regards comorbidity in IEI, a review by Bornschein et al. (2001) showed how eight investigations found well-defined psychiatric disorders in 36%–100% of IEI/MCS patients. Of these psychiatric disorders, somatoform disorders were the most prevalent, ranging from 17% to 72% among patients with IEI/MCS (Bailer et al. 2008b; Black et al. 2001; Bornschein et al. 2002; Caccappolo-van Vliet et al. 2002; Eis et al. 2008; Hausteiner et al. 2003, 2006;

Witthöft et al. 2008), and 2%–4% in two population-based samples of self-reported MCS cases (Bell et al. 1996a; Jason et al. 2000). In addition, the co-prevalence of current and lifetime anxiety disorders were 10% and 3%–13%, respectively, in two population-based samples (Bell et al. 1996a; Jason et al. 2000). In patients with IEI/MCS, a comorbid current anxiety disorder was seen in 15%–71%, and a lifetime anxiety disorder in 7%–56% (Bailer et al. 2008b; Black et al. 2000b, 2001; Bornschein et al. 2002; Caccappolo-van Vliet et al. 2002; Hausteiner et al. 2003, 2006; Saito et al. 2005; Witthöft et al. 2008). Similarly, the co-prevalence of current and lifetime depression disorders were 22% and 7%–49%, respectively, in two population-based samples (Bell et al. 1996a; Jason et al. 2000). Among patients with IEI/MCS, a comorbidity of current depression was found in 10%–40%, and lifetime depression in 7%–83% (Bailer et al. 2008b; Black et al. 2000b; Caccappolo-van Vliet et al. 2002; Eis et al. 2008; Hausteiner et al. 2003, 2006; Witthöft et al. 2008). Some questionnaire-based studies have also reported associations between SBS and depression or anxiety (Björnsson et al. 1998; Kinman and Griffin 2008; Marnavita 2015).

2.3.6 SIMILARITIES WITH FUNCTIONAL SOMATIC SYNDROMES

The phenomenon of EI and functional somatic syndromes (FSS) are similar and overlap substantially (Bailer et al. 2005; Barsky and Borus 1999; Lacour et al. 2005; Kipen and Fiedler 2002; Wiesmüller et al. 2003). These conditions cover a complex of prolonged physical symptoms for which adequate examination does not reveal explanatory causes in terms of a somatic or psychiatric disease or exposure (Barsky and Borus 1999; Kipen and Fiedler 2002; Rief et al. 2017; Wiesmüller et al. 2003). Both conditions hold an increased burden of disability and diminished QOL (Harris et al. 2009; Jackson et al. 2006; Kjellqvist et al. 2016), female preponderance, comorbid conditions (e.g. anxiety, depression) (Henningsen et al. 2003, 2007), great use of health services and work withdrawal due to inability to work (Aamland et al. 2012; Frías 2015; Rief and Broadbent 2007). Similar predisposing factors together with maintaining factors (e.g. cognitive and emotional processes with external or a monocausal attributional traits, illness worry, rumination, illness behavior and emotional distress) have been associated with the onset and maintenance of adverse reactions (Figure 3) (Brown 2004; Deary et al. 2007; Henningsen et al. 2007, 2018; Rief and Broadbent 2007; Witthöft et al. 2006). Central mechanisms (central sensitization) have suggested that the development and maintenance of adverse reactions play an essential role, due to dysfunctional cognitions that may increasingly enhance reactions to actual or anticipated stimuli (Bell et al. 1996b; Henningsen et al. 2007, 2018; Kipen and Fiedler 2002; Rief and Broadbent 2007; Van den Bergh et al. 2017a; Yunus 2007).

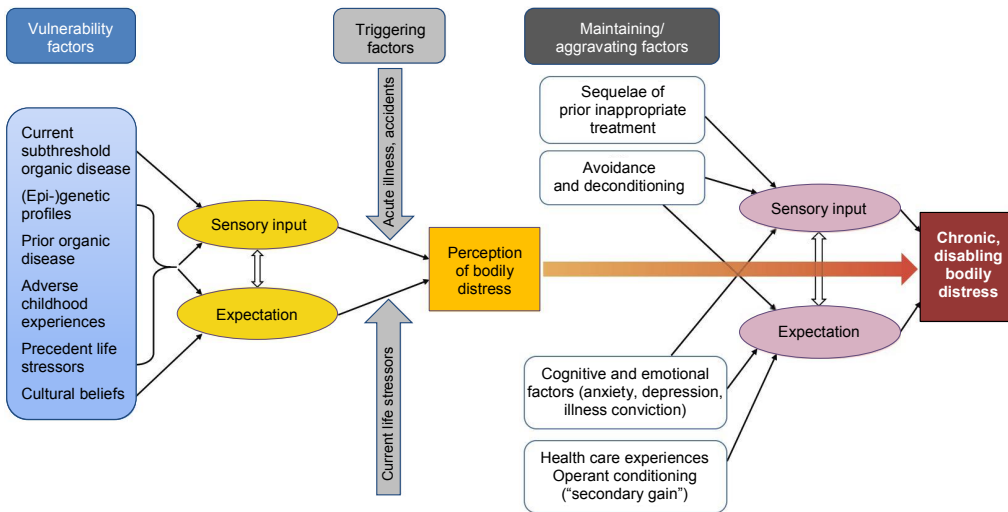


Figure 3 Schematic model of bodily distress etiology by Henningsen et al. (2018). Note: The distinction of vulnerability/triggering and aggravating/maintaining factors is to some extent artificial, as most factors influence both sides. (Figure reproduced with permission from S. Karger AG, Basel.)

Symptoms with no clear underlying medical disease are common in all areas of medicine (Henningsen et al. 2007, 2018; Nimnuan et al. 2001). The prevalence of FSS (or functional somatic symptoms) has widely varied between 10% and 50% in patients in general practice and special health care, depending on the case definition and study sample (de Waal et al. 2004; Fink et al. 1999; Nimnuan et al. 2001; Reid et al. 2001; Toft et al. 2005).

Terminology. Chronic disabling bodily distress (or FSS) (Figure 3) has a variety of names for which adequate examination does not provide sufficient explanation in terms of a defined medical disease, such as a bodily distress disorder or syndrome, functional (somatic) syndrome or disorder, functional somatic symptoms, somatization, medically unexplained (physical) symptoms or persistent physical symptoms (Fink and Schröder 2010; Henningsen et al. 2018; Wessely et al. 1999). The proposition of unifying the terminology aims to abolish patient-blaming and the stigmatization of mind-body dualism (e.g. somatization, medically unexplained symptoms) (Barsky and Borus 1999; Creed et al. 2010; Fink and Rosendal 2008; Nimnuan et al. 2001; Yunus 2015). The diagnostic approach to FSS varies across and within medical specialties (Henningsen et al. 2007). The name of the syndromes typically depends on the medical specialty and signifies the main symptoms or the implied cause, for example, a typical facial pain, chronic benign pain syndrome, chronic pelvic pain or premenstrual syndrome, fibromyalgia, hyperventilation syndrome, irritable bowel syndrome, somatoform disorders, and IEI (or MCS, BRI, hypersensitivity to EMFs) (Fink and Rosendal 2008; Henningsen et al. 2007; Nimnuan et al. 2001; Wessely et al. 1999). Many of these terms are classified in the different medical sections of the *International Classification of Diseases*

10th Revision (ICD-10). In addition, the term ‘somatic symptom disorder’, in the upcoming 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM)*, will cover some of the above (Henningsen 2018). Somatic symptom disorder is a plausible candidate for an overarching term (Hubley et al. 2016). Each of the various above-mentioned syndromes is described as a unique diagnostic entity with its own characteristics. Clinical presentations can vary considerably, in terms of, for example, symptom severity, duration and comorbidity (Kroenke et al. 2007). However, they seem to overlap to a large extent and reflect the same phenomenon (Aaron and Buchwald 2001; Barsky and Borus 1999; Bornschein et al. 2001; Fink et al. 2004, 2007; Fink and Schröder 2010; Kipen and Fiedler 2002; Nimnuan et al. 2001; Wessely et al. 1999).

2.3.7 MANAGEMENT OF ENVIRONMENTAL INTOLERANCE

EI has been considered a chronic, potentially disabling condition that is stable over time, with resistant cognitions concerning environmental stimuli. Evidence-based effective treatments are currently unavailable. The current knowledge regarding EI mechanisms supports the idea that biopsychosocial aspects are involved in the onset and maintenance of adverse health effects. Within the biological spectrum, evidence points towards abnormal responses in the CNS, i.e. central sensitization, and shared mechanisms with FSS (Yunus 2007). This supports the use of similar strategies as those in the managements of FSS, such as cognitive-behavioral therapy (CBT) (e.g. Henningsen et al. 2018; Van Dessel et al. 2014).

Numerous treatments have been used for MCS (or IEI), but data on interventions are mainly based on case reports and/or uncontrolled set-ups (NICNAS and OCSEH 2010). Many management regimes are based on toxicological/exposure hypotheses and thus focus on (short-term or long-term) avoiding the agents that trigger symptoms (NICNAS and OCSEH 2010). This aspect has included treatments aiming to raise the immunity against exposure, for example, special dietary or nutritional supplements, detoxification and desensitization techniques, holistic or body therapies, prescription medicines, and behavioral therapies (Dantoft et al. 2015; Das-Munshi et al. 2007; NICNAS and OCSEH 2010; Somerville 2001; Watanabe et al. 2003b). In terms of explanations for CNS sensitization, some randomized controlled trial (RCT) studies of mindfulness-based techniques have shown positive effects on the perception of illness, coping strategies and improved sleep quality, but these have had no overall impact on daily life or reactions following exposures (Hauge et al. 2015; Sampalli et al. 2009; Skovbjerg et al. 2012a). RCT studies of transcranial magnetic stimulation have shown positive effects on symptom severity, but have had no effects on impairments in MCS (Tran et al. 2014, 2017). Case reports have shown limited benefits from antidepressant pharmacological treatments and/or desensitization therapy (e.g. Stenn and Binkley 1998).

Published reports on treatment models for patients are mainly based on FSS. For example, the Nova Scotia Environmental Medicine Clinic in Canada has designed a model of integrated care, a multidisciplinary approach for multiple chronic conditions, to address the specific needs of patients with reduced functioning (Sampalli et al. 2012, 2016). The treatment model in the Research Clinic for Functional Disorders and Psychosomatics in Aarhus, Denmark, has developed an education program for the assessment and treatment of FSS, the Extended Reattribution and Management (TERM) model (Fink et al. 2002; Fink and Rosendal 2015). The TERM intervention is largely based on CBT and includes various steps in diagnostic assessments and planning of management courses with patients, as well as treatments and interview techniques (Fink et al. 2002; Fink and Rosendal 2015). In recent years, several national guidelines on FSS management have been published (e.g. in the Netherlands, Denmark and Germany) containing the principles of different management options that use a stepped-care approach based on the stages of FSS severity (mild, moderate, severe) (olde Hartman et al. 2017). The guidelines also emphasize the doctor-patient relationship and communication, as well as the importance of providing a targeted, tangible explanation in the patient's language of the cause of their symptoms (Henningsen 2018; olde Hartman et al. 2017).

Environmental control and avoiding exposures that trigger symptoms is a typical coping outcome among affected individuals with IEI. It is natural that individuals who interpret sensation as a sign of illness and a disabling condition seek medical advice from health care providers, which can also in itself be a source of maintaining stability of perception in adverse conditions (Barsky et al. 2005; Dantoft et al. 2015; Rief and Broadbent 2007; Skovbjerg et al. 2009b; Watanabe et al. 2003a). Possible opposing views among health care professionals regarding the underlying mechanisms of ill health and a lack of validation may set a barrier to complying with the CNS sensitivity approaches of management strategies, and lead to, for example, avoidance. A Danish study described general practitioners' experiences (n=691) of patients with self-reported MCS (Skovbjerg et al. 2009b). It showed that many (46%) practitioners find it difficult to meet patients' expectations (Skovbjerg et al. 2009b); this is typically reported in the health care of patients with medically unexplained symptoms (Dowrick et al. 2004; Frostholm et al. 2005). The Danish study showed a pragmatic approach to dealing with patients in health care (Skovbjerg et al. 2009b). In terms of MCS etiology, 28% of the practitioners provided a somatic/biological explanation, and 7% primarily a psychological explanation. Regarding clinical advice, 75% recommended that the patients avoid chemical exposures that provoke symptoms and 12% advised avoiding all exposure to chemicals, whereas 2.8% did not advise avoiding common airborne chemicals. The general practitioners who did not advise avoidance perceived the patients' conditions as more likely to be psychological (Skovbjerg et al. 2009b). This pragmatic approach to recommending avoidance to patients may be the only tool in health care for

providing advice regarding the management of health consequences related to environments (Dantoft et al. 2015). The lack of evidence-based treatment options calls for well-conducted randomized trials that evaluate the effect of possible therapeutic options.

2.4 MANAGEMENT OF INDOOR AIR-RELATED DISABILITY

Laws and regulations on the built environment in Finland regulate building constructions, improvements and renovations that aim to assure healthy living and working conditions (Decree on Housing Health 545/2015; Health Protection Act 763/1994). The Occupational Safety and Health Act (738/2002) aims to improve the healthiness and safety of work and the work environment in order to ensure and maintain the health, work ability and functional capacity of employees, to prevent work-related illnesses and accidents and to eliminate work environment hazards to the health of employees.

Various guidelines for recognizing and solving IAQ problems exist (e.g. WHO 2009). In the assessment and management of IAQ problems, the role of the occupational health service (OHS) is to collaborate in risk assessments, workers' health evaluations and surveillance in cases of clinical examinations and health promotion, or when other risk factors need to be taken into account (Carrer and Wolkoff 2018; Magnavita 2015). In Finland, guides are available for health care providers and workplaces which aim to prevent disability and impaired well-being and health problems among employees related to indoor work environments (Haahtela et al. 1993; Haahtela and Reijula 1997; Majvik 1998; Lahtinen et al. 2006; Salonen et al. 2014; Patient exposed to moisture damage: Current Care Guidelines Abstract 2016; Latvala et al. 2017).

For symptomatic individuals, the strategies of management actions have focused on making adjustments to improve environmental facilities, avoiding environments that trigger symptoms, and improving conventional treatments of underlying diseases. The concept of occupational disease varies in different countries as it is based on national legislation. In Finland, asthma induced by indoor air molds was classed an occupational disease in non-industrial work environments in the 1990s (Karvala et al. 2010). Since then, patients with asthma or asthma-like symptoms attributed to water-damaged work environments have been clinically examined. However, diagnostic tools do not differentiate between work-exacerbated asthma and occupational asthma (Karvala 2012). Study findings have shown that asthma as an occupational disease induced by indoor molds, has not succeeded in preventing disability (Karvala 2012).

To avoid the exposure perceived as harmful is a natural effort to alleviate symptoms. According to a questionnaire study, over 60% of BRI respondents reported actively trying to avoid buildings that evoked symptoms (Karvala et

al. 2018a). In the context of IEI, being forced to avoid certain environmental pollutants due to symptoms may increase the development of disability (Dantoft et al. 2015; Watanabe et al. 2003a). Similarly, findings regarding chronic pain have supported the hypothesis that the fear of pain experience relates to avoidance behaviors leading to disability (Hartvigsen et al. 2018; Samwel et al. 2007; Wideman et al. 2013). In addition, in cases of chronic pain and anxiety disorders, higher degrees of cognitive and behavioral avoidance have predicted worse long-term outcomes (Beesdo-Baum et al. 2012; Leeuw et al. 2007). For iatrogenic avoidance from support advice to avoidance, see Section 2.3.7.

Adjustments to occupational facilities and conventional treatments of underlying disease have been insufficient to cure some individuals' indoor air-related disability. Previous studies support a biopsychosocial approach to disability prevention (Karvala 2012; Thörn 1999). In this context, however, effective and practical guidelines to target aid and support for these individuals with indoor air-related disability are lacking. Part of the challenge in indoor air-related disability may be that the disability has not been sufficiently characterized, and that appropriate language to conceptualize indoor air-related ill health manifestations and mechanisms for patients and health care providers to effectively communicate is needed.

2.5 THE CONCEPTS OF FUNCTIONING AND DISABILITY

WHO's International Classification of Functioning, Disability, and Health (ICF) is a framework for classifying health and health-related domains and disability (WHO 2001). In the ICF context, functioning and disability are complex, interactive and dynamic states, consisting of interaction between an individual's health and their personal features and the context in which the individual lives (Figure 4). The ICF context incorporates the biopsychosocial approach, in which both medical and social models are integrated. In ICF, the term **functioning** refers to body functions and structures (physiological and psychological), activities (level of capacity) and participation (level of performance). **Disability** (problems in functioning) is the negative outcome of impairments to body functions and structures, limitations to activities, and restrictions to participation (WHO 2001). Disability can be described as *an imbalance between the individual and the environment* (Gould et al. 2008), or something that restricts or limits (Martimo 2010). According to ICF, disability may occur in one or more of the three domains (bodily function, activities, participation), and does not require total dysfunction in any domain (WHO 2001). ICF views functioning and disability as outcomes of interactions between health conditions (diseases, disorders, injuries) and contextual (environmental and personal) factors (WHO 2001). The classic definition of **health** by WHO involves a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity (WHO 1948).

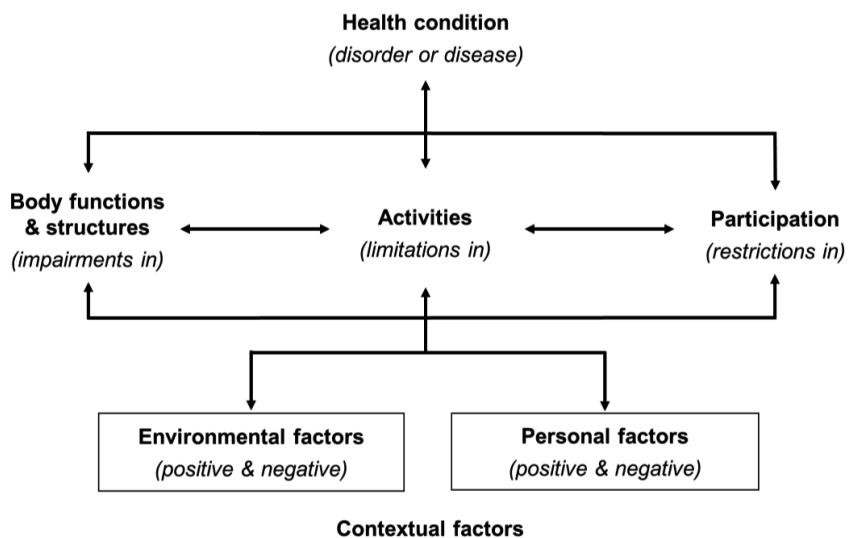


Figure 4 Interactions between the components of International Classification of Functioning, Disability, and Health (ICF) (WHO 2001).

In the ICF classification, environmental factors can include, for example, support and relationships, health professionals, social attitudes, architectural characteristics, legal and social structures, and climate and air quality (WHO 2001). The ICF scheme has been criticized due to, for example, the dominant position of the medical approach, a possible overlap between mental functions and personal factors, and a lack of relevant items in the classification of the working environment (Heerkens et al. 2018). In addition, although personal factors play an essential part in functioning and disability, they are not currently classified in the ICF due to large social and cultural variance (Heerkens et al. 2018; WHO 2001). Personal factors can be, for example, age, gender, personality factors, attitudes, basic skills and behavior patterns, life situation and socioeconomic/sociocultural factors, and other factors that impact on the perception functioning of disability (Grotkamp et al. 2012; WHO 2001).

Work disability is a major public health and economic concern. The term refers to individuals who have discontinued their participation in occupational activities (WHO 2001). Work (or occupational) disability is also defined as time off work, reduced productivity, or working with functional limitations as a result of either traumatic or non-traumatic clinical conditions (Schultz et al. 2007). The concept of **work ability** includes several models and can be described in terms of *the balance between human resources and work demands*, and includes such aspects such as the workplace and environments outside work (Gould et al. 2008). The term work ability is typically used in the context of promoting and maintaining work capacity and performance. The

definitions of work disability and work ability also depend on each independent evaluator's perspective (Gould et al. 2008). For example, the emphasis in many welfare benefits is on disease-related dysfunctions.

Bearing the above ICF biopsychosocial concept in mind, impaired functioning and disability can be affected by disease or illness, psychological and social reasons, including aspects of knowledge, and other barriers due to environmental and/or individual factors. Therefore, it is relevant to distinguish between disease and illness. **Disease** can be defined as an objective (demonstrable by) biological event involving the disruption of specific function and/or structure of body organs and systems due to pathological abnormalities (Eisenberg 1977). In contrast, **illness** (absence of above pathology) is a subjective experience or self-attribution that a disease is present, which creates physical discomfort, behavioral limitations and psychosocial distress; or a subjective experience of negative changes in well-being (Eisenberg 1977; Spurgeon 2002; Yunus 2008). Disease can either make an individual feel ill, or have no impact on well-being. On the other hand, an individual may feel ill despite a lack of objective evidence of underlying disease (Coggon 2005). Biology and psychology are intertwined, thus patients with an illness can also suffer from a disease, or the other way around. Often the two go hand in hand (Coggon 2005; Yunus 2008).

The concept of ICF provides a framework to address not only physical and psychological impairments (problems in body functions and structures), but also subsequent limitations to activities and restrictions to participation, resulting in a health state that impacts an individual's ability to participate in life activities. Within the ICF model, the environmental and personal factors unique to an individual serve as possibilities to either support or hinder recovery (Figure 4). The ICF framework integrates the understanding of multi-modal interventions for disability reduction, targeting interventions to improve activities and participation among patients with disabilities. In addition, it has been proposed that the ICF context is a suitable framework for measuring and evaluating functioning and disability, on both individual and population levels (Wasiak et al. 2007; WHO 2001).

2.5.1 ASSESSMENT OF FUNCTIONING AND DISABILITY

The assessment of functioning and disability provides essential data on health and well-being for adequate interventions and for allocating preventive and management actions, on both individual and population levels. On an individual level, the data are essential for promoting and monitoring patients' health and well-being in everyday life, for example, as well as for targeting preventive actions. In addition to determining disability, it is important to clarify the remaining functional capacity, resources, strengths and coping mechanisms of the examined individual and the possibilities to support functioning (Tuisku et al. 2012). The data on functioning and disability are a crucial basis for all effective decision-making among health care providers.

Assessment tools. Assessment instruments and concepts provide a structure for collecting and evaluating data on functioning and disability. Therefore, various guides and recommendations exist for courses of action targeted at harmonizing and developing assessment strategies and for choosing the correct instruments for different contexts and goals. Assessment methods can sometimes require a wide-ranging scope, and different instruments for data collection. The data may have to be gathered from an array of simultaneous and non-simultaneous measures and observations, such as the individual's own reports (reflecting subjective needs and experiences), health care providers' (objective) measures and observations, network collaboration and individuals' performance in practical situations such as trial work periods. Information across time also provides information on the course of functioning and disability. Comparing the data on functioning and disability, identifying possible disparities (e.g. between subjective and objective evaluations, or different functions) and determining the root causes of discrepancies are necessary for deciding on and taking the actions required for improvement (Vuokko and Tuisku 2017).

Self-assessment tools provide an interactive evaluation and possibilities for follow-up, discussing one's personal resources and limitations and for promoting work ability (Vuokko and Tuisku 2017). There are a range of different kinds of instruments. Typically, these instruments are allocated according to the specific purpose of use. Many focus on screening for diseases and/or symptom expression, such as screening scales of depression and anxiety symptoms. These screening instruments can indirectly (e.g. through severity of symptoms) provide information on disability. An item of functioning and disability can also be included in the instrument. For example, the depression scale of the Patient Health Questionnaire (PHQ-9) includes a single item that measures the severity of disability at work, home or in social duties (Kroenke et al. 2001).

Another example of a functional self-assessment tool is the Sheehan Disability Scale (SDS), which elicits functional impairments and takes into account the three sub-domains of work, social life and home (Sheehan et al. 1996). SDS is widely used in psychiatry, but also with other chronic illnesses such as FSS and IEI (Rief et al. 2017; Tran et al. 2013b). Some generic instruments also include different kinds of interviews and questionnaires for gathering information. For example, the generic assessment instrument based on the conceptual framework of ICF, WHO's Disability Assessment Schedule version 2.0, has been launched for scoring disability associated with all physical and mental disorders, in both clinical and general population settings (Üstün et al. 2010). This instrument includes different methods for data collection and explores disability in the following domains: cognition, mobility, self-care, coping, life activities, and participation (Üstün et al. 2010).

Although the work ability (or disability) aspect can be included in the above tools, some specific work-related questions and aspects aim to detect deterioration in work ability as early as possible in order to prevent work

disability. The subjective perception of work ability is a prognostic factor that predicts return to work and the course of work ability (Blank et al. 2008; Cornelius et al. 2011; Gould et al. 2008). Perceived work ability reflects many different dimensions of individual and environmental factors, as well as biopsychosocial approaches (Gould et al. 2008). The Work Ability Index (WAI) questionnaire combines several dimensions of work ability (current work ability, demands of the job, physician-diagnosed diseases, work impairments due to diseases, sick leave during the past year, own prognosis of work ability, mental resources) (Tuomi et al. 1998). The WAI contains two independent questions that predict the course of work ability: the individual's own evaluation of current work ability (work ability score, WAS) and their own prognosis of work ability in two years' time (Tuomi et al. 1998).

Absenteeism at work is also a prognostic factor and refers to a possible imbalance between an employee's resources and their work demands. Work absence (or sickness absence) can be measured by, for example, asking the individual how much time and/or how many sporadic periods they have missed from work because of ill health (Martimo 2010). The dimensions of self-efficacy, readiness for return to work, and sense of coherence and job strain have been associated with work disability and return-to-work outcomes (Jackson et al. 2014; Lagerveld et al. 2010; Loisel et al. 2005; Rashid et al. 2018; Volker et al. 2015). For example, in chronic musculoskeletal disorders, higher self-efficacy levels are associated with greater physical functioning, participation in physical activity, health status, work status, satisfaction with performance, efficacy beliefs, and lower levels of pain intensity, disability, disease activity, depressive symptoms, presence of tender points, fatigue and presenteeism (productivity loss at work) (Martinez-Calderon et al. 2017).

Individuals' QOL has been used to describe the function and well-being of populations with medical conditions and to evaluate the effectiveness of treatment interventions (Heinonen et al. 2004). The term health-related QOL is often used. The roots of this term for health research lie in WHO's definition of 'health' in 1948 (described above): the 'well-being' in this definition is probably the main factor in the conceptualization of QOL (Post 2014). Therefore, many QOL scales include at least the physical, emotional and social dimensions of health (Post 2014). To measure QOL, both specific instruments (e.g. group of patients, particular function, or disease) and generic instruments (can be used for comparing the health status of patients with different conditions) are used (Karvala 2012). Among the commonly used validated generic instruments for health-related QOL are, for example, the Quality of Life Survey (RAND)-Inventory (Hays et al. 1993), and the 15D scale instrument (Sintonen 1994, 2001).

Illness perceptions (or experiences), include a range of individual, contextual and cultural factors, which influence outcomes such as emotional and cognitive response, recovery and disability, and coping strategies (Arat et al. 2018). Open-ended questions and different questionnaires are useful for gathering information on illness perceptions (e.g. concerns, consequences,

personal control, beliefs in ability or effect of treatment), but drawings can also be used to uncover how patients feel about their illness and identify idiosyncratic beliefs or misconceptions about the illness when determining future management methods (Petrie and Weinman 2012).

Objective assessment tools can quantify individuals' functioning and disability, their relation to health and diagnoses and monitor diseases. An example of a tool that is based on health care providers' clinical interviews is the Social and Occupational Functioning Assessment Scale (SOFAS), which is used to quantify the severity of disability in social and occupational functioning (Goldman et al. 1992). Structured clinical interviews, as a basis for psychiatric diagnostics, contain aspects of suffering and disability (e.g. cognitive impairments, limitations to activities, restrictions to participation). Physiological measurements are an example of objective investigations of body functions and structures, such as flow-volume spirometry for measuring respiratory function. In some situations, assessment may require a comprehensive approach with objective observations from the functional environment and they may be best realized multi-professionally, through collaboration in a network (Tuisku et al. 2012).

2.5.2 WORK DISABILITY PREVENTION

Work disability intervention approaches have typically been reviewed in terms of primary, secondary and tertiary prevention. *Primary prevention* aims to prevent the onset of disability, *secondary prevention* aims to prevent progression from an acute condition to chronic disability habituation, and *tertiary prevention* aims to prevent the development of further disability in someone whose condition has evolved into a chronic state of disability (Gatchel 2004; Sullivan et al. 2005). Similarly, secondary work disability prevention refers to interventions that aim to enable the return to work as quickly as possible. Tertiary prevention attempts to avoid the consequences arising from workers developing progressive disability (Gatchel 2004; Sullivan et al. 2005).

The major exploration of work disability prevention targets musculoskeletal disorders, namely low-back pain, perhaps because this is the most common reason for long-term absence and work disability in working populations worldwide (Hartvigsen et al. 2018; Loisel et al. 2005). The scientific knowledge regarding musculoskeletal disorders offers perspectives for the prevention of work disability, and most likely includes sections that can be generalized across similar conditions.

Research on musculoskeletal disorders has shown substantial evidence of the various determinants of work disability prevention (Figure 5). These determinants can be linked not only to the patients' personal characteristics (physical and psychosocial), but also to those of many stakeholders, such as the workplace, health care providers, compensation system, and local culture and society (Loisel et al. 2001, 2005). Therefore, the prevention of work

disability can involve a number of cooperation challenges in the multi-player decision-making system. In addition, most barriers to and facilitators of recovery and work ability have related more to psychosocial, workplace and management issues than to the emerging disease or disorder. The main point has thus been not only to improve medical care in order to achieve better prevention.

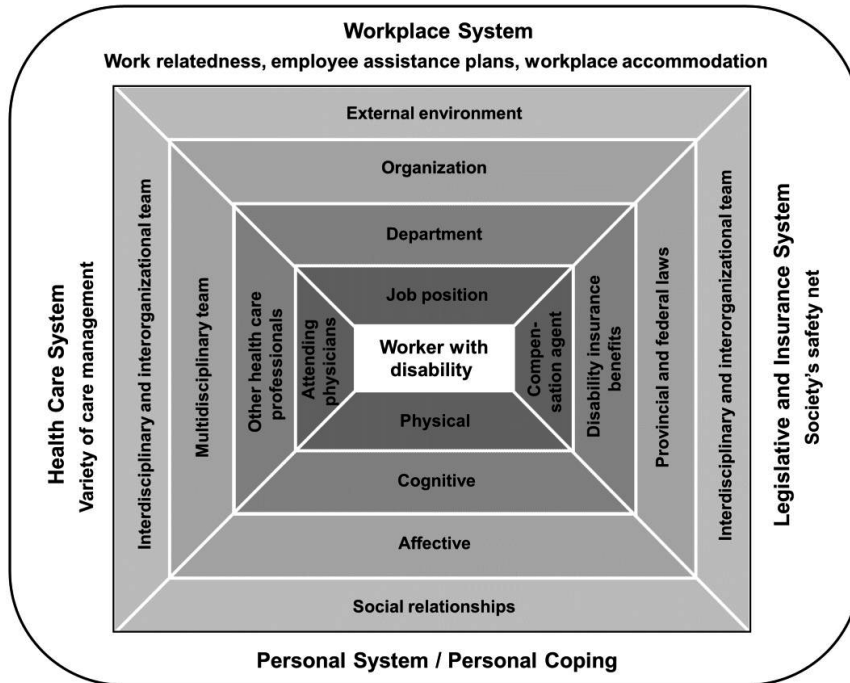


Figure 5 Work disability prevention arena (figure adapted and modified from Loisel et al. 2001).

Biopsychosocial models have outlined possible psychosocial risk factors and behavioral, cognitive and emotional mechanisms to explain why some individuals experience more disability than others. In this context, findings have emphasized the importance of shifting the goals of intervention strategies in cases of chronic pain, and to aim to change beliefs and behaviors, typically focusing on risk factors such as pain catastrophizing, beliefs and expectancies (Hartvigsen et al. 2018; Sullivan et al. 2005). Individuals' perceptions and expectations of personal and environmental issues may influence the decision to return to work. Psychological distress and fear, as intermediate factors, have explained some of the pathways to disability (Lee et al. 2015). The biopsychosocial framework of disability management and prevention encourages a collaborative approach involving early diagnostic triage and knowledge of evidence-based treatment and occupational interventions, the

identification of potential psychosocial and environmental barriers and impediments, and employee education and reassurance of health condition and self-care. It also supports activity with self-limiting barriers (Foster et al. 2018; Loisel et al. 2005). Based on the principles of the biopsychosocial model, the individual is the active participant, and others serve only to facilitate the rehabilitation process (Schultz et al. 2000).

The biopsychosocial approach has been modified in many different ways and applied as a framework to understand and treat the complexities of many health problems involving disability in preference to a purely biomedical (disease-based) approach (Henningsen et al. 2007, 2018; Rief and Broadbent 2007; Schultz et al. 2007; Sullivan et al. 2005). In general, the biopsychosocial approach demands a conceptual shift from the linear way of thinking of the biomedical basis to an open system perspective (Martimo 2010), in which human health can be seen as a continuum rather than a dichotomy between the presence or absence of disease (Spurgeon 2002).

Indoor air-related ill health lacks effective management and practical guidelines for work disability prevention (see Section 2.4). Despite the lack of intervention studies based on the biopsychosocial approach aiming to prevent work disability in indoor air-related ill health, similar approaches to those for other analogous disabling conditions can most likely be used to aid and support these individuals. Evidence of the role of CNS mechanisms in the development and maintenance of adverse health effects and disability is increasing in terms of many similar conditions (see Section 2.3.7). Cognitive behavioral approaches are typically used in the management of psychosocial risk factors for work disability, and intervene with individuals' interpretation, evaluation and beliefs regarding illness and repertoire for coping with symptoms and disability (Sullivan et al. 2005). The term cognitive-behavioral does not refer to a specific intervention, but to a wide variety of intervention strategies that might include self-instruction (e.g., motivational self-talk), relaxation or biofeedback techniques, developing coping strategies (e.g., distraction, imagery), increasing assertiveness, interpersonal communication strategies, minimizing negative or self-defeating thoughts, changing maladaptive beliefs about symptoms and goal setting (Sullivan et al. 2005). In the active behavioral component, which is an essential part of CBT, one focus has been on changing and increasing the awareness of one's own body sensations, behaviors/strategies and cognitions. In RCT interventions involving patients with FSS and CBT, including patient education, activity regulation strategies, and illness attribution replacement from monocausal or catastrophizing to more adaptive strategies, has shown to be effective. This also applies to patients suffering from disability in general (Allen et al. 2006; Deary et al. 2007; Escobar et al. 2007; Henningsen et al. 2018; Kleinstäuber et al. 2011; Speckens et al. 1995).

3 AIMS OF THE STUDY

The data on the clinical description of and practices for indoor air-related disability and its prevalence are limited. The main aim of this thesis was to characterize indoor air-related disability and to develop interventions.

This thesis consists of four studies. The aim of each study is followed by a rationale that includes the study background.

- 1. To evaluate whether clinical intervention including counseling aimed at symptom management, has an impact on the QOL and work ability of patients with indoor air-related symptoms and work disability. In addition, to clinically evaluate and characterize these patients (Study I).**

Because the biopsychosocial model has shown to be an effective framework in work disability prevention, we designed an intervention with a multifactorial approach, aiming to improve health and coping, and to reduce environment-associated disability.

- 2. To clinically evaluate the medical etiology of symptoms and disability related to indoor air, and to assess whether the condition fulfills the criteria of IEI (Study II).**

The medical characterization of indoor air-related disability is unclear. We studied whether the condition is a form of IEI. The characteristics and the mechanisms of the condition are the basis for the development of effective interventions.

- 3. To study if the effectiveness of CBT and psychoeducation can be evaluated in the management of persistent indoor air-related non-specific symptoms (Study III).**

To develop effective interventions, we designed an RCT study with three interventions based on the biopsychosocial model. Our ultimate aim was to develop an intervention suitable for OHS patients with indoor air-related disability.

4. To assess the prevalence of self-reported EI with different manifestations, including behavioral changes and disability (Study IV).

The prevalence data on EI are sparse due to the phenomenon's heterogenous nature and definitions. We studied how severe EI, defined in several ways, manifests in a Finnish maternity clinic population. Knowledge of prevalence is needed to understand the extent of the problem and the required actions.

4 MATERIALS AND METHODS

4.1 STUDY POPULATIONS AND DESIGN (STUDIES I–IV)

In all the individual studies, the participants were working-age adults. The clinical study (Studies I–III), participants were active in working life and recruited from among patients of the Finnish Institute of Occupational Health’s (FIOH) occupational medicine clinic (Studies I, II) or from among patients of OHS units (Study III). All the patients had symptoms related to indoor air factors in non-industrial workplaces, which had led to work disability that interfered with work participation (e.g. inability to work). The participants of the survey (Study IV) were pregnant women recruited from the ongoing Kuopio Birth Cohort (KuBiCo) in Eastern Finland. Table 4 summarizes the design and population of the individual studies.

Table 4. Description of included studies.

Study	Study design	Population
I	RCT and clinical (descriptive) characterization	Workers (n=55) examined at FIOH clinic due to suspicion of an occupational disease, with symptoms and work disability related to indoor air
II	Clinical (descriptive) characterization	Workers (n=12) referred to FIOH clinic for clinical evaluation because of responsiveness to factors in workplace indoor air, and a disabling condition that interferes with work participation despite adjustments to occupational facilities
III	RCT (protocol)	Workers (n=60) seeking medical advice from OHSs with recurrent medically unexplained multiorgan symptoms, including respiratory symptoms and disability attributed to indoor work environment
IV	Prevalence survey (cross-sectional questionnaire study)	Pregnant women (n=680) from maternity clinic cohort in region of Kuopio University Hospital

RCT, randomized controlled trial; FIOH, Finnish Institute of Occupational Health; OHS, occupational health service.

Study I. The clinical characterization of 55 patients was conducted in an RCT setting. They were recruited between November 2010 and June 2012 from among consecutive patients (n=194) examined at FIOH's occupational medicine clinic. The patients had been referred from all over Finland by their OH physician or pulmonologist due to a suspected occupational respiratory disease, mainly asthma. At study intake, all the patients had respiratory symptoms attributed to factors in non-industrial workplace indoor air. Patients eligible for this study (assessed by a screening questionnaire) fulfilled the following inclusion criteria for the disability: i) self-assessed current WAS of ≤ 7 (scale 0–10; 0 represents total work disability, 10 indicates lifetime best work ability) (Tuomi et al. 1998) and ii) indoor air-related sick leave of ≥ 14 days during the preceding year. A research physician informed the eligible patients of the study. The patients were excluded if they did not meet the inclusion criteria, were not active in working life (retired or unemployed) (n=115) or if they refused (n=24). The main reasons for refusing to participate in the study were mainly travel or timetable problems.

The total number included in the random group assignment was 55. Randomization was performed so that the physician allocated every other participant into an intervention (INT) group (n=28) or treatment as usual (TAU) group (n=27), with an allocation ratio of 1:1. The group assignment was not blinded. After randomization, three patients dropped out of the INT group and two out of the TAU group. Thus, the total number of patients who received INT or TAU was 50. At the six-month follow-up, a total of six patients did not return the postal paper-and-pencil questionnaire. Therefore, the six-month follow-up analysis was of 44 patients (INT: n=21; TAU: n=23). Participant flow throughout the study, including the reasons for dropout, is shown in Figure 1 of Article I.

All participants (n=55) took part in routine clinical examinations at FIOH and during the study they received possible concurrent health care in, for example, their own OHS units. The contents of the INT sessions and outcome measures are described in Section 4.4. The study protocol was registered to Single-center RCT (ISRCTN33165676).

Study II. Study II was based on the clinical characterization of the 12 patients referred by their OH physician to FIOH's occupational medicine clinic for clinical evaluation. All the patients had increased responsiveness to non-industrial workplace indoor air. Disability manifested as functional restrictions and had interfered with work participation (e.g. inability to work), despite improvements to occupational facilities and work adjustments. The referring physician had been unable to find a solution to manage the patient's ill health and disability. The referring physician had also eliminated the obvious medical reasons for the symptoms. All the recruited patients agreed to participate in the study. They were recruited between June 2015 and November 2015, and the clinical examinations were finalized in March 2016. At study intake, the disabling condition suggested features of EI. Figure 6 illustrates the study design.

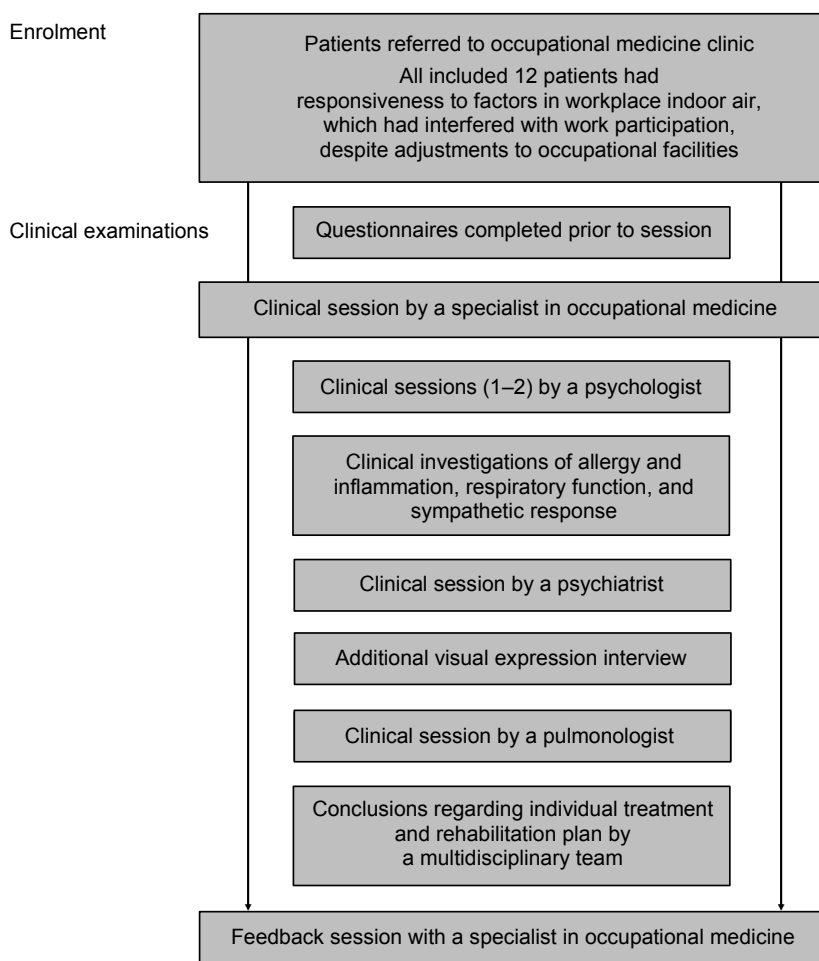


Figure 6 Description of study design and clinical examinations in Study II.

During the clinical examinations, of the 12 patients, two withdrew from part of the study (one because of symptoms while at the clinic facilities, the other because of timetable scheduling problems and feeling dissatisfied with the study). Thus, the number of participants in the examination of the sympathetic response was ten, and the psychiatrist clinically evaluated eleven patients.

Study III. The RCT was carried out by FIOH in collaboration with five large OHS units. The protocol of the study aimed to compare the effectiveness of two psychosocial treatments and TAU for persistent indoor air-related symptoms with work disability, among OHS unit patients. The feasibility of the study design was conferred and customized with proposals from two participating OHS units. Prior to study enrollment, one OHS unit also tested

the inclusion/exclusion criteria. The five OHS units (including three public and two private enterprises in the district of Helsinki and Uusimaa, Finland) joined the study consecutively: two units in January 2014, one in June 2014, one in August 2014 and one in March 2015. As this study, Study III, was ongoing, without follow-up results, this thesis only describes its protocol.

The participants were recruited from (OHS) practices and an OH physician, assisted by an OH nurse, assessed their eligibility. Participants aged 25 to 58 were recruited from among attendees of medical consultations at OHSs for indoor air-related symptoms and disability. The inclusion criteria were modified from WHO's IEI criteria (IPCS/WHO 1996) and that of Lacour et al. (2005). The main inclusion criterion was the presence of indoor air-related recurrent symptoms in ≥ 2 organ systems (including respiratory symptoms and symptoms in at least one of the following other symptom groups: dermal, musculoskeletal, neurological, cardiac, gastrointestinal, or general symptoms) and disability, with no obvious medical or exposure-related explanation or factors that could affect the outcome of the intervention. The duration from the onset of the disabling symptom was limited to a maximum of three years.

Before enrolling the participants, the recruiters from the OHS units participated in a 1–1.5-hour training session given by the researchers. The recruiters received a recruitment manual that included a description of the study proceedings, inclusion/exclusion criteria, patient information, informed consent, a questionnaire on indoor air pollutants and arrangements at the workplace, and prepaid envelopes for returning the enrolment documents, as well as a non-identifiable form to collect the reasons for refusal if inclusion criteria were met but the patient refused to participate. In order to aid and maintain the recruitment process during enrolment, information letters were available for the OHS units to inform workers and employers of the study collaboration. The researchers were also frequently in contact with the recruiters.

The patients who were enrolled at FIOH prefilled a questionnaire and underwent a respiratory evaluation to distinguish asthma symptoms from functional respiratory symptoms. The examinations included a two-week diurnal measurement of peak expiratory flow (PEF) and bronchial hyperresponsiveness. A respiratory physician evaluated the respiratory findings and the participants received an individual report. Participants with uncontrolled asthma, or any other revealed exclusion criteria, were excluded before the random assignment.

Randomization into the two INT and TAU groups was preprogrammed by the two researchers, using a numerical list of the tree arms. The allocation was grouped to contain participants from different OHS units, workplaces and of different genders with an allocation ratio of 1:1:1. After the clinical examinations, the researchers allocated the eligible participants into an individual CBT condition, psychoeducation or control (TAU) condition, which was next in order of listing after stratification. During the study, all the

participants received appropriate medical advice and treatment (determined as TAU) based on individual needs from their OHSs. The original study plan included four arms. The arm of applied relaxation group therapy that required group formation was excluded from the protocol due to recruitment process difficulties in ensuring completion of the study. Thus, based on the power calculations (for more detail, see Article III, page 6: Sample size), the initial target of 80 participants decreased to a total of 60.

The participants answered web-based questionnaires through a secure internet connection prior to their examinations at FIOH, at baseline and at follow-up at 3, 6 and 12 months. The confidentiality of the participants is protected by an encryption key for personal details in the data. Participants were also asked to consent to the use of their medical records for evaluating TAU during the study. Figure 2 of Article III shows the participant flow, data collection and intervention program timeline. The contents of the intervention programs and the outcome measures are described in Section 4.4. The study protocol is registered in the ClinicalTrials.gov registry (NCT02069002).

Study IV. The basis of the survey was that of the ongoing KuBiCo Study. The participants comprised pregnant women from the maternity clinics that serve all women who give birth at Kuopio University Hospital, which is the main maternity hospital in Eastern Finland, with about 2000–2500 deliveries annually. In Finland, in practice all pregnant women regardless of their socioeconomic status attend municipal maternity clinics that provide guidance in all matters related to pregnancy. Study recruitment was carried out via a web-based platform, which was used by more than two thirds of pregnant women in the region. At any stage of their pregnancy, these women are able to access the KuBiCo prospective data collection by signing their electronic informed consent.

An electronic questionnaire (described in Section 4.3) on EI and its different manifestations was offered in the first trimester to all Finnish-speaking pregnant women who participated in the KuBiCo during between July 2012 and February 2014. Altogether 680 women participated in this EI study. An exact participation rate cannot be given. Based on 2500 annual deliveries and taking in account the fact that the questionnaire was available to two thirds of the maternity clinic clients, approximately 27% of which were recruited for this study.

4.2 CLINICAL CHARACTERIZATION (STUDIES I–III)

4.2.1 INDOOR AIR POLLUTANTS AT WORKPLACE (STUDIES I–II)

Study I. The assessment of past and present exposure was based on objective measurements and investigations of the patient’s work environments, performed by the workplace. Detailed reports of working conditions and data on workplace investigations were collected by requesting them from the patients’ employers. The reports included technical inspections and quality measurements of the indoor air around the patients’ work environments. Physicians from FIOH also clinically interviewed the patients on their working conditions and exposures (and on indoor air pollutants in the home environment). For each patient, the indoor air microbial exposure level was classified into three categories (low, intermediate, high) based on the available data on microbiological measurement (Karvala et al. 2010).

Study II. Data on deficiencies in indoor air quality and pollutants at the workplace (and at home), including adjustments made to work environments, were based on self-reports through questionnaires, structured clinical interviews, and data from the referring OHS physician.

4.2.2 QUESTIONNAIRE INSTRUMENTS (STUDIES I–III)

Table 5 summarizes the self-report questionnaires and domains used in Studies I–III. The questionnaires were filled in at baseline and at six-month follow-up (Study I), during the clinical evaluation (Study II), or at baseline and at 3-, 6-, and 12-month follow-ups (Study III). The questionnaires were in paper-and-pencil form (Studies I and II), or participants replied to web-based questionnaires via a secure internet connection (Study III).

Table 5. Questionnaires in Studies I–III.

Items	Reference	Study		
		I	II	III
Work ability, occupational and psychosocial functioning				
Current work ability, Work Ability Score (WAS)	(Tuomi et al. 1998)	x	x	x
Own prognosis of work ability two years from now	(Tuomi et al. 1998)	.	x	x
Sheehan Disability Scale (SDS)	(Sheehan et al. 1996)	.	x	.
Return-to-Work Readiness questionnaire (RTW-RQ) ^a	(Tuisku et al. 2015)	.	x	.
Return-to-Work Self Efficacy (RTW-SE) ^a	(Tuisku et al. 2015; Lagerveld et al. 2010)	.	x	.
Job strain ^b	(Karasek et al. 1998; Theorell 1990)	.	x	x
Sense of Coherence (SOC-13)	(Antonovsky 1987)	.	x	x
Need for Recovery (NRF)	(Sluiter 1999)	.	.	x
Quality of life				
Quality of Life Survey (RAND-36)-Inventory	(Aalto et al. 1999; Hays et al. 1993)	x	.	.
15D instrument	(Sintonen 1994, 2001)	.	.	x
Respiratory functioning				
Asthma Control Test (ACT) ^c	(Nathan et al. 2004)	x	x	x
Nijmegen	(Van Dixhoorn and Duivenvoorden 1985)	.	x	.
Cognitive and emotional symptoms, and personality				
Generalized Anxiety Disorder 7-item Scale (GAD-7)	(Spitzer et al. 2006)	.	x	x
Beck Anxiety Inventory (BAI)	(Beck et al. 1988)	.	x	.
Overall Anxiety Severity and Impairment Scale (OASIS)	(Campbell-Sills et al. 2009)	.	x	.
Patient Health Questionnaire (PHQ-9)	(Kroenke et al. 2001; Kaila et al. 2012)	.	x	.
Beck Depression Inventory (BDI)	(Beck et al. 1961, 1979)	.	x	x
Insomnia Severity Index (ISI)	(Morin 1993; Morin et al. 2011)	.	x	x
Shirom-Melamed Burnout Measure (SMBM) ^b	(Shirom and Melamed 2006)	.	x	.
Illness Worry Scale (IWS)	(Robbins and Kirmayer 1996; Laakso et al. 2005)	x	.	x
Acceptance and Action Questionnaire-II (AAQ-II)	(Bond et al. 2011; Hayes et al. 2004)	.	x	x
Penn State Worry Questionnaire (PSWQ)	(Meyer et al. 1990)	.	x	x

Symptom Checklist-90 (SCL-90) somatization scale	(Derogatis et al. 1973; Holi 2003)	.	x	x
Toronto Alexithymia Scale (TAS-20)	(Bagby et al. 1994; Taylor et al. 1988)	.	x	.
Dissociative Experience Scale (DES)	(Bernstein and Putnam 1986)	.	x	.
Strategy and Attribution Questionnaire (SAQ)	(Nurmi et al. 1995)	.	x	x
Revised Paranormal Belief Scale (Toba)	(Tobacyk 2004)	.	x	.
Short Five (S5) personality inventory	(Lönnqvist et al. 2008)	.	x	.
Intervention of Interpersonal Problems (IIP)	(Horowitz et al. 2000)	.	.	x
Social Readjustment Rating Scale (SRRS)	(Holmes and Rahe 1967)	.	x	x
Assessment of treatment alliance and satisfaction				
Working Alliance Inventory	(Horvath and Greenberg 1989)	.	.	x
Treatment satisfaction	(Seligman 1995)	.	.	x
Indoor air-related symptoms				
Work environment-related symptoms	(Andersson 1998; Reijula and Sundman-Digert 2004)	x	x	x
Symptom disturbance		x	.	.
Environmental intolerances and concerns				
Quick Environmental Exposure and Sensitivity Inventory (QEESI)	(Miller and Prihoda 1999)	.	x	x
Intolerance to indoor air molds		.	x	x
Intolerance to electromagnetic fields		.	x	x
Environmental-related health concerns		.	x	x
Other characteristics				
Prolonged multi-site pain		.	x	.
Alcohol Use Disorders Identification Test (AUDIT)	(Saunders et al. 1993)	.	x	x

. = Not applicable.

^aThose who were not working.

^bThose who were working.

^cThose who had asthma. The Finnish version of the ACT. The ACT is a trademark of Quality Metric Incorporated 2002 GlaxoSmithKline.

Work ability and occupational and psychosocial functioning. As an indicator of work ability, in WAS, individuals assessed their current work ability on a scale of 0 (total work disability) to 10 (work ability at its best). They also gave their own prognosis of their work ability two years from now using the options 'fairly sure', 'not sure', or 'hardly'. These two items were taken from

the validated WAI which measures self-assessed work ability (Tuomi et al. 1998).

The SDS, self-reported functional measures, rated functional impairments in three sub-domains (work, social life, home), each on a scale of 0 to 10 (higher scores indicating higher disability): 0 (no disability or impairment at all), 1–3 (mild), 4–6 (moderate), 7–9 (marked), 10 (extreme disability) (Sheehan et al. 1996). The SDS Total was the mean of the three subscales.

Quality of life (QOL). Health-related QOL was measured using the 36-item Quality of Life Survey Inventory (RAND-36) and its physical (RAND-PCS) and mental component summary (RAND-MCS) scores (0–100) (Hays et al. 1993), Finnish version (Aalto et al. 1999).

Another QOL measure, the 15-dimensional standardized 15D scale instrument, is composed of physical, mental and social well-being (Sintonen 1994, 2001). In the 15D scale, each dimension has five grades of severity from 1 (highest/best level) to 5 (lowest/worst level). The 15D is presented as a single sum score measure from 1 (full health) to 0 (dead), as well as a profile of each dimension.

Respiratory functioning. For the asthma patients, the Asthma Control Test (ACT) defined the current self-assessed asthma control (Nathan et al. 2004). ACT assesses the elements of asthma control over the previous four weeks, including asthma symptoms, everyday functioning, use of rescue medications, and night time awakenings. The ACT scale ranges from 0 to 25: ‘controlled’ (≥ 20 points), ‘not well-controlled’ (16–19 points), and ‘uncontrolled’ (≤ 15 points).

Anxiety. For self-rated anxiety symptoms and the identification of clinical anxiety, three screening instruments were utilized: the Generalized Anxiety Disorder 7-item Scale (GAD-7) (Spitzer et al. 2006), the Beck Anxiety Inventory (BAI) (Beck et al. 1988), and the Overall Anxiety Severity and Impairment Scale (OASIS) (Campbell-Sills et al. 2009). A total sum score of a GAD-7 range between 0 and 21, and values of ≥ 10 indicates moderate or severe anxiety. The BAI included 21 items with a sum score of 0–63, and values of ≥ 16 show moderate or severe anxiety. In the five-item OASIS (sum score 0–20), values of ≥ 8 show high relevance of clinical anxiety.

Depression. For symptoms of depression, the two widely used tools PHQ-9 (Kroenke et al. 2001), in Finnish (Kaila et al. 2012) and the Beck Depression Inventory (BDI) (Beck et al. 1961, 1979) were used. PHQ-9 has a sum score of 0–27 and values of 10–14 indicate moderate depression, and in the 21-item BDI (sum score 0–63), values of 14–19 indicate mild depression symptoms.

Insomnia. The Insomnia Severity Index (ISI) was used to assess the severity of insomnia-related symptoms with seven questions (sum score 0–28) (Morin et al. 2011). The responses were scored as subthreshold insomnia (score 8–14), moderate severity (score 15–21), and severe insomnia (score 15–21).

Burnout. In order to evaluate burnout symptoms, the Shirom-Melamed Burnout Measure (SMBM) recognized work-related burnout in facets of physical, cognitive, and emotional functioning (Shirom and Melamed 2006). The SMBM includes 14 items, each on a scale of 1 to 7: 1 (never or almost never), 2 (very infrequently), 3 (quite infrequently), 4 (sometimes), 5 (quite frequently), 6 (very frequently), 7 (always or almost always). The SMBM total (1–7) was the mean of the 14 items and was divided into mild, moderate, or severe burnout.

Illness worries. The assessment of illness attributions and worry about being ill was performed using a nine-item Illness Worry Scale (IWS) (Laakso et al. 2005; Robbins and Kirmayer 1996). The response options for each item are ‘yes’ or ‘no’, and the IWS sum score (0–9) was calculated on the basis of the ‘yes’ answers.

Somatization. Of the Symptom Checklist-90 (SCL-90) symptom inventory subscales, the 12-item somatization subscale reflects physical illness, focusing on cardiovascular, gastrointestinal, respiratory and other systems with autonomic mediation (Derogatis et al. 1973; Holi 2003). The mean (score 0–4) of the 12 items was calculated, each item on a five-point scale from 0 (not at all) to 4 (extremely).

Indoor air-related symptoms. The current work environment-related symptoms were elicited using two items from FIOH’s Indoor Air Questionnaire (Reijula and Sundman-Digert 2004), which is based on the Örebro questionnaire (Andersson 1998). The questions were: 1) ‘*Have you had any of the following symptoms or discomforts during the last three months?*’ with response options ‘yes, every week’, ‘yes, sometimes’, or ‘never’ for each symptom; and 2) ‘*If you answered ‘yes’, do you think that the symptoms are explained by your work environment*’ (‘yes’, ‘no’ or ‘I don’t know’). Only weekly or more frequently occurring symptoms and those caused by the work environment were taken into consideration. In Study I, the included symptoms were divided into five categories representing different organ systems: 1) respiratory and eye symptoms (‘dyspnea’, ‘cough’, ‘cough disturbing sleep’, ‘wheezing of breath’, ‘hoarse or dry throat’, ‘irritated, stuffy and runny nose’, ‘irritation of the eyes’), 2) dermal symptoms (‘dry or flushed facial skin’, ‘dry, itching or red hands skin’), 3) neurological symptoms (‘headache’, ‘heavy head’, ‘difficulties in concentrating’), 4) general symptoms (‘fatigue’, ‘fever or chills’), and 5) musculoskeletal symptoms (‘arthralgia or rigidity’, ‘muscular and joint pain’).

The symptom disturbance index (scale 0–30) was based on self-named (up to three) indoor air-related current symptoms, with a self-rated severity of how much each symptom bothered the patient on a scale of 0 (not at all) to 10 (very much).

Environmental intolerances. Of the chemical intolerance screening instruments, the Quick Environmental Exposure and Sensitivity Inventory (QEESI), the Chemical Intolerance (CI) and the Life Impact scales were used (Miller and Prihoda 1999). Each scale contains 10 items from 0 to 10 and

produces a sum score from 0 to 100. In the CI scale, the response options for each item were ‘no problem at all’ (0), ‘moderate symptoms’ (5) and ‘disabling symptoms’ (10). A sum score of ≥ 40 indicated a high probability of intolerance to chemicals and a score of ≤ 20 low probability. Life Impact elicits the adverse effects of sensitivities on various life areas, including impact on diet, work ability or school attendance, choice of home furnishing, choice of clothing, ability to travel or drive, choice of personal care products, ability to be around others and enjoy social activities, choice of hobbies or recreation, relationships with spouse or family, and ability to perform household chores. The response options for each item were ‘not at all’ (0), ‘moderately’ (5) or ‘severely’ (10). In Life Impact, values of ≥ 24 indicate a high score.

In addition, we measured self-rated intolerance to indoor air molds in moisture-damaged buildings and intolerance to EMFs, each on a scale of 0 (no problem at all) to 10 (disabling symptoms).

Environmental-related health concerns. Health concerns regarding environmental exposures and indoor air exposures at the workplace were elicited on a scale of 0 (no concern at all) to 10 (extreme concern).

Medical diseases. The participants were asked to report their physician-diagnosed chronic diseases. Medication was also systematically elicited.

Prolonged multi-site pain. Chronic multi-site pain was defined using three questions: 1) ‘Have you recently experienced aches or pains?’ (‘yes’ or ‘no’); 2) ‘If yes, where on the body have the pains been?’ with options ‘yes’ or ‘no’ for each 16 areas of the body (‘head’, ‘neck’, ‘upper back’, ‘shoulder’, ‘brachium’, ‘forearm’, ‘arm’, ‘wrist’, ‘hand’, ‘lower back’, ‘hip’, ‘thigh’, ‘knee’, ‘leg’, ‘ankle’, ‘foot’); and 3) ‘Have the pains continued over three months?’ (‘yes’ or ‘no’). Only pain over three months and in at least three different areas of the body was taken into consideration.

Sick leave/work absence and physician visits. Studies I–III elicited the number of sick leave days, the reasons for work absence, and Studies II–III the number of physician visits and their reasons during the time period under study.

Workplace interventions. Measures and adjustments made at the workplace to solve the indoor problem were elicited, e.g. building repairs, other improvements, or relocation of the worker.

Other background variables. The basic characteristics of variables were elicited, including education, professional status, workplace, marital status, and smoking and alcohol consumption habits. The level of education was classified as basic (only comprehensive school, high school or vocational school), mid-level (college or other upper secondary education), and high-level (university degree).

4.2.3 CLINICAL MEASUREMENTS (STUDIES I–III)

In Studies I–III, the clinical examinations were carried out at the FIOH clinic. Table 6 summarizes the examination methods used in each individual study.

Table 6. Clinical measurements in Studies I–III.

Investigations	Study		
	I	II	III
Allergy and inflammation			
SPTs to common environmental allergens and molds	x	x	.
Serum total IgE	x	x	.
Blood eosinophils (EOS)	x	x	.
Respiratory function			
Flow-volume spirometry	x	x	x
Non-specific bronchial hyperresponsiveness	x	x	x
PEF monitoring for two weeks	.	x	x
Fractional exhaled nitric oxide (FeNO)	.	x	.
Sympathetic response			
Cardiovascular tests	.	x	.
Hyperventilation Provocation Test (HVPT)	.	x	.
Long-term recording of HRV in beat-to-beat intervals	.	x	.
Salivary cortisol	.	x	.

SPTs, skin prick tests; IgE, immunoglobulin E; PEF, peak expiratory flow; HRV, heart rate variability.
 . = Not applicable.

Allergy and inflammation. To assess sensitization, skin prick tests (SPTs) were carried out using a panel of common environmental allergens and different commercially available mold allergens. The panel of mold allergens included *Aspergillus fumigatus*, *Penicillium expansum* (ALK, Copenhagen, Denmark), *Aspergillus mix (fumigatus, nidulans, niger)*, *Cladosporium (herbarum, cladosporioides)*, *Alternaria alternata*, and *Penicillium mix (digitatum, expansum, notatum)* (Stallergenes SA, Antony, France). Sensitization to common environmental allergens was tested using SPTs with a panel of birch, alder, timothy, meadow fescue, mugwort, cat, dog, horse, cow (only in Study I), dust mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*), and molds (*Alternaria alternata*, *Cladosporium herbarum*) (ALK, Copenhagen, Denmark). SPTs included a histamine hydrochloride (10 mg/ml) as a positive control and a diluent control. A wheal diameter of ≥ 3 mm with at least half of the histamine reaction and with no

reaction of (≥ 2 mm, dermographism) negative control, was considered positive. An individual was considered atopic when at least one positive SPT to common allergens was positive.

Serum total IgE was measured using the Phadia UniCAP system (Phadia Uppsala, Sweden). Total IgE with values of <110 kU/L were regarded as normal. The number of blood eosinophils (EOS) was also calculated.

Respiratory function. Lung function was measured using flow-volume spirometry with a bronchodilation test (Studies I, II) or without a bronchodilation test but with a bronchial hyperresponsiveness test (Study III). Spirometry was performed using a standard spirometer (Spirostar USB Medikro, Kuopio, Finland), in accordance with the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (Miller et al. 2005) and the predictive values for the Finnish population (Viljanen 1982). The cut-off values for decreased spirometric parameters were for the forced vital capacity (FVC) and the forced expiratory volume in one second (FEV₁) below 80% of predicted, and for the ratio of FEV₁ and FVC below 75% of predicted. An increase of at least 12% (and >200 mL) in FEV₁ or FVC bronchodilator response was regarded as a significant bronchodilator effect (GINA 2014, 2018).

Non-specific bronchial hyperresponsiveness to histamine was tested according to the method of Sovijärvi et al. (1993). The provocative dose (PD) of inhaled histamine aerosol causing a 15% fall in FEV₁ values (PD₁₅) was measured. Hyperresponsiveness was classified as severe (PD₁₅ ≤ 0.10 mg), moderate (PD₁₅ 0.11–0.40 mg), mild (PD₁₅ 0.41–1.60 mg) or none (PD₁₅ >1.60 mg).

In two-week diurnal PEF monitoring, an average daily variability of $>10\%$ was considered excessive diurnal variability (GINA 2014, 2018). In addition, at least three positive bronchodilator responses ($\geq 15\%$ and 60 L) was considered a significant bronchodilator effect (Asthma: Current Care Guidelines Abstract 2012; Quanjer et al. 1997).

Fractional exhaled nitric oxide (FeNO) was examined using an online chemiluminescence analyzer (NIOX, Aerocrine AB, Solna, Sweden) in accordance with the ATS/ERS recommendations (ATS/ERS 2005). FeNO was classified as low (<25 ppb), mildly increased (25–50 ppb) or highly increased (>50 ppb) (Dweik et al. 2011).

Sympathetic response. Assessment of the autonomic nervous system (ANS) function was included in the evaluation of physiological stress and recovery processes in both laboratory and real-life settings. In laboratory testing, the hyperventilation provocation test (HVPT) (Vansteenkiste et al. 1991) and cardiovascular tests assessed the individual reactivity of ANS and excluded organic disturbances in autonomic regulation. HVPT was used to evaluate a possible hyperventilation syndrome. The cardiac reactivity tests included controlled and uncontrolled breathing, slow deep breathing, the active orthostatic test and the sustained hand grip test (Laitinen et al. 2004; Piha and Seppänen 1991). Continuous electrocardiogram and peripheral blood

pressure were analyzed using special software for ANS metrics (WinCPRS, Absolute Aliens, Turku, Finland). The main indicator of sympathovagal balance in the short-term provocation tests was the ratio of low-frequency power to high-frequency power (LF/HF ratio) in heart rate variability (HRV) at rest. A ratio of >2.8 was considered to indicate increased sympathetic dominance (Nunan et al. 2010).

In real life settings, stress and recovery balance was determined from recordings of R–R intervals and analyses of HRV over three days (Föhr et al. 2015), performed by a Firstbeat Bodyguard measurement device (Firstbeat Technologies Ltd, Jyväskylä, Finland). The analyses used the recovery percentage during a sleep period (from self-reported bedtime to awakening time). A recovery time of under 60% during sleep was used as an indicator of delayed recovery. This was based on findings that the mean of recovery time during sleep of the Finnish population ($n=20\ 000$, including 51 000 measurement days), using HRV analysis, is 60% (Firstbeat Technologies Ltd 2014).

As an indicator of the hypothalamic-pituitary-adrenal (HPA) axis, salivary cortisol samples were taken three times a day over a two-day period: Immediately after awakening, 30 minutes after awakening, and in the evening. Salivary cortisol was analyzed using chemiluminescence immunoassay analytics (LIA, IBL Hamburg, Germany). The non-anxious population has reported a range of 3.3–6.1 nmol/L in salivary evening cortisol levels using competitive electrochemiluminescence immunoassay analytics (Vreeburg et al. 2010). The study reported the evening analysis, and levels of >6.1 nmol/L were considered as deviating from the non-distressed population.

4.2.4 MEDICAL ASSESSMENTS (STUDIES I–II)

The clinical evaluation (Studies I, II) was based on structured clinical interviews and questionnaires, clinical examinations, previous medical records, and data on IAQ deficiencies in work environments.

Study I. The assessment included clinical evaluations by a specialist in occupational medicine and a pulmonologist, who focused on environment-related asthma and working conditions and work-related exposures. In addition to somatic status, other health conditions were also determined. During the INT sessions, the psychologist recorded concerns and fears regarding the participants' present health condition.

Study II. The evaluation included systematic multidisciplinary evaluations by a specialist in occupational medicine, a pulmonologist, a psychiatrist and a psychologist. As the participants completed questionnaires prior to the clinical sessions, self-assessments could be utilized in the clinical evaluations.

Somatic evaluation used a structured interview material and timeline sheet eliciting patients' health conditions and diseases, symptom profiles and courses of illness, occupational and social functioning, deficiencies in IAQ and

prior adjustments at work and in the participants' social lives. The onset time of symptoms extending to the disabling level and involving multiple organ systems was determined. Symptoms were grouped into six groups: respiratory or mucosal, dermal, CNS, musculoskeletal, cardiac and gastrointestinal symptoms. The respiratory evaluation aimed to recognize respiratory diseases and assess asthma control among asthma patients.

The purpose of the psychiatric evaluation was to assess the presence of possible psychiatric disorders, and functioning in daily life and well-being, using structured interview methods and self-assessed measures. Structured Clinical Interview for DSM-IV Disorders (SCID I–II) (First et al. 1997) was used for symptom assessment and diagnostic interviews. Yale-Brown's Obsessive Compulsive Scale (Y-BOCS) was used as a severity rating scale for obsessive-compulsive symptom dimensions (Moritz et al. 2002), and the Montgomery-Åsberg's Depression Rating Scale (MARDS) as a screening and diagnostic tools for depression (Montgomery and Asberg 1979). The psychiatrist specified the psychiatric ICD-10 diagnoses after clinical findings in the psychological assessments.

The psychological assessment aimed to clarify the potential predisposing and perpetuating factors, including the evaluation of cognitive, social and personality functioning. The evaluation focused on the individuals' resources and coping strategies using structured and validated questionnaires (as described in Table 5) and interviews: The Wechsler Adult Intelligence Scale IV (WAIS-IV) (Wechsler 2014) and the Wechsler Memory Scale-III (WMS-III) (Wechsler 1997). The evaluation included an additional semi-structured visual expression interview aiming to specify patients' perceptions of conditions in terms of their own bodies and the environment (Tuisku and Haravuori 2016).

Based on the physician interview, the SOFAS of the DSM-IV was used to rate the severity of disability in social and occupational functioning (Goldman et al. 1992). SOFAS has a scale of 1 to 100, with higher scores indicating an increasing level of functioning. In the study, SOFAS was presented by tertiles: 51–70 (moderate or some difficulty), 71–80 (slight impairment), 81–100 (good or superior functioning).

4.2.5 CRITERIA OF IDIOPATHIC ENVIRONMENTAL INTOLERANCE

The criteria that Study II used for IEI were based on 1) WHO's consensus criteria (IPCS/WHO 1996), which cover the acquired condition with multiple recurrent symptoms attributed to various environmental factors that are well tolerated by most people and which cannot be explained by any somatic or psychiatric disorder; and 2) the stricter criteria of Lacour et al. (2005), which require symptom duration of ≥ 6 months with significant life-style or functional impairments and symptoms to be present in the CNS with at least one symptom in another organ system.

4.3 MATERNITY CLINIC SURVEY (STUDY IV)

The questionnaire was designed to assess the increasing severity of intolerance attributed to certain environmental factors and associated symptoms, behavior changes and disability (Table 7). The respondents were asked to apply their evaluations to the time prior to their pregnancy.

The participants were asked to rate their annoyance with 12 different environmental factors on a scale of 0 (not at all) to 3 (very much). Those who considered themselves 'not at all' sensitive (n=50), were excluded from further questions on symptoms, behavioral changes and disability. As neurological and cognitive symptoms were regarded as CNS symptoms, the symptoms were divided into seven organ systems (Table 7).

Definitions of EI. Determining the different EI definitions (A–F) helped identify the different degrees of EI, which represent increasing severity and the strictness of the criteria (Table 8). The definitions only took ratings of 'rather much' or 'very much' annoyance (= intolerance) into account. Definition E was based on the EI criteria by Lacour et al. (2005).

EI attributed to chemicals, indoor molds and EMFs. EI attributed to chemicals was determined if the respondent reported intolerance to ≥ 2 (out of the six) chemical items in Table 7. EI attributed to indoor molds was defined by reported intolerance to 'indoor molds in moisture-damaged buildings' and EI attributed to EMFs was defined by intolerance to EMFs.

Table 7. Questions used in Study IV to assess environmental intolerance

Items, questions and response options ^a
<p>Annoyance <i>'Are you feeling ill or annoyed by the following types of environmental exposures or situations?'</i></p> <ul style="list-style-type: none"> - <i>Chemicals</i>^b: 1) vehicle exhaust; 2) paint or paint thinner; 3) perfumes, air fresheners or other fragrances; 4) new furnishings such as new carpeting, flooring, shower curtain, or the interior of a new car; 5) fresh ink on newspapers; and 6) tobacco smoke - <i>Indoor molds</i>: indoor molds in moisture-damaged buildings - <i>EMFs</i>: electromagnetic fields - <i>Other environmental factors</i>: beauty salons or hair salons^c, detergent departments in shops^c, moldy odors, and dust
<p>Sensitivity <i>'Are you exceptionally/unusually sensitive to the environmental exposures or situations above?'</i></p>
<p>Symptoms^b <i>'Have you ever had the following symptoms from the environmental exposures or situations listed above?'</i></p> <ul style="list-style-type: none"> - Neurological symptoms (e.g. headache, numbness, tingling) - Cognitive symptoms (e.g. memory deterioration, impaired concentration) - Pulmonary symptoms (e.g. dyspnea, coughing, wheezing) - Dermal symptoms (e.g. erythema, rash) - Muscles or joint pain - Gastrointestinal symptoms (e.g. flatulence, stomach ache) - Cardiac symptoms (e.g. palpitations) - General symptoms (e.g. fever, night sweats, fatigue, weight loss, increase in weight)
<p>Behavioral changes^b <i>'Have you made any behavioral changes to avoid the symptoms above?'</i></p> <ul style="list-style-type: none"> - Behavior or lifestyle change to minimize exposure - Changed interior decorations or furnishings at home - Moved to another apartment - Changed workplace, resigned from workplace or occupation - Taken vitamins, nutritional supplements, or changed diet - Eliminated the cause using antifungal agents or chemicals - Used protective equipment (e.g. respirator, gauntlet, clothing)
<p>Disability^d <i>'If you recognize the problems mentioned above, how difficult have these problems made it for you to do your work, take care of things at home or get along with other people?'</i></p>

^a Response options for each item: annoyance on a scale from 0 (not at all) to 3 (very much); sensitivity on a scale of 1 (not at all) to 4 (very much); symptoms 'yes' or 'no'; behavioral changes 'yes' or 'no'; and disability on a scale of 'not difficult at all', 'somewhat difficult', 'very difficult', and 'extremely difficult'.

^b Items are based on Black et al. (2000a).

^c Items are based on Kreutzer et al. (1999).

^d The single item is from the Patient Health Questionnaire (Kroenke et al. 2001).

Table 8. *Definitions of environmental intolerance (EI) used in Study IV.*

Definitions of EI ^a	
A	Feeling ill or annoyed (annoyance) by different environmental factors
B	Annoyance with symptoms
C	Annoyance with symptoms from multiple organ systems including the CNS (at least one CNS symptom and one non-CNS symptom)
D	Annoyance with multiple organ symptoms including CNS symptoms (= definition C) and behavioral changes (at least one behavioral change)
E^b	Annoyance with multiple organ symptoms including CNS symptoms, behavioral changes (= definition D) and disability
F^c	Annoyance with multiple organ symptoms including CNS symptoms, behavioral changes (= definition D) and severe disability.

CNS, central nervous system.

^a EI definitions (A–F) overlap: individuals fulfilling the criteria of definition F are also included in definitions A–E, individuals with EI definition E are also included in definitions A–D, etc.

^b In definition E, disability included responses of ‘somewhat difficult’, ‘very difficult’ and ‘extremely difficult’ in the disability question in Table 7.

^c In definition F, disability responses ‘very difficult’ and ‘extremely difficult’ were combined to represent severe disability.

4.4 INTERVENTIONS AND OUTCOMES (STUDIES I, III)

Intervention in Study I. The aim of the intervention (RCT) was to reduce excess concerns and worries related to the indoor work environment, and to help the patient find ways in which to cope with symptoms. The INT participants received counseling by a specialist in occupational medicine and two sessions of counseling by a psychologist. Both the INT and TAU groups received ‘treatment as usual’. The physician counseling was one to two weeks after the first visit to FIOH, followed by the psychologist sessions, beginning on average two weeks later. The time between the two psychological sessions varied from three to nine weeks. In addition, all asthma patients received structured asthma education from a nurse. All sessions were conducted at FIOH. Table 9 summarizes the contents of the counseling sessions.

Table 9. Contents of counseling by physician and psychologist.

Session I (counseling by physician, 45–60 minutes)
General information about health risks associated with indoor environment
<ul style="list-style-type: none">- Overview of main indoor exposures and their health effects- Indoor dampness and mold as risk factors to respiratory health, other health effects not known- Spectrum of symptoms- Multifactorial background of symptoms (indoor exposures, individual, psychosocial factors)- Nature of symptoms (transient; sometimes persistent; may be disabling though not dangerous)
General information about symptom management
<ul style="list-style-type: none">- Indoor air quality problems should be identified and solved- Asthma and other co-existing diseases should be recognized and treated- Maintaining normal activity levels is helpful (helps prevent long sickness absences from work)- Avoidance behavior may lead to symptom exacerbation- Physical exercise and smoking cessation have positive effects
Listening to and reflecting on the patient's experiences
Session II (counseling by psychologist, 120 minutes)
Interview and discussion concerning illness and how it limits everyday life
<ul style="list-style-type: none">- Identifying personal coping resources at work and during leisure time- Importance of health-related cognitions: The main purpose was to demonstrate the effect of thoughts on symptoms and behavior and to encourage patients to identify and challenge health-related dysfunctional beliefs and develop alternative, less restrictive ways of thinking
Personal Projects Analysis (PPA): Identifying goals at work and in one's personal life to support well-being
<ul style="list-style-type: none">- Structured worksheets for PPA
Appraising e.g. commitment to well-being goals
<ul style="list-style-type: none">- Identifying strategies of adaptation to illnesses and developing alternative behaviors- Naming health-supporting activities for the period before the next session and helping patients use them- All patients received worksheets to test their thoughts in symptom-provoking situations during the second session
Session III (counseling by psychologist, 120 minutes)
Evaluation of realization of health-supporting activities named in Session 2
<ul style="list-style-type: none">- Discussion on stress warning signs for which patient may need support and identification of personal resources for managing stress- Review of symptoms, how they limit everyday life and resources for coping at work and during leisure time- Continuation of discussion on challenging health-related concerns and developing alternative ways of thinking about health- Setting further personal goals and activities that support well-being

Study I outcomes. The primary outcome measures in the six-month follow-up were self-assessed current work ability and the total number of sick leave days and periods in the preceding six months. The secondary outcomes were QOL through the RAND-36 inventory tool, and illness worries through measurement of IWS. In addition, the symptom disturbance index and self-assessed asthma control among patients with asthma was assessed using the ACT tool. The questionnaires of the outcomes are described in Section 4.2.2.

Intervention in Study III. The main aim of the RCT including two different psychosocial interventions is to improve the QOL and work ability of workers with non-specific indoor-related symptomatology. The intervention programs (psychoeducation and CBT) have been developed at FIOH on the basis of knowledge of the previous RCT Study I and other previously studied intervention protocols for multiple similar ill health conditions (e.g. Allen et al. 2006; Escobar et al. 2007; Speckens et al. 1995; Woolfolk et al. 2007).

Tables 10 and 11 show the contents of the two intervention arms. The individual psychoeducation session was held by a specialist in occupational medicine and a psychologist. The CBT consisted of 11 sessions and the arm was delivered by three psychologists who are licensed psychotherapists. Before treatment, the psychotherapists attended training sessions to ensure the integrity of the treatment and they were supervised during the study. The intervention programs were manualized. Depending on the participants' approval, all the sessions were recorded for post hoc reliability to ensure intervention integrity.

Study III outcomes. The primary outcome measure in the follow-up was health-related QOL, measured using the 15D instrument. Other information was also collected from the patients via questionnaires (i.e. cognitive, emotional and social functioning and psychiatric symptoms) as secondary outcomes (see Section 4.2.2).

Table 10. *Content of psychoeducation session.*

Session (counseling by physician and psychologist, 90 minutes)
Information and discussion on 1) main indoor exposures, 2) symptoms and health risks associated with the indoor environment, and 3) factors that affect individual health behavior and symptom management:
- Factors related to indoor air-associated symptoms: environment, risk communication and management of problems, reflection on individual situation
- Explanation of indoor air-associated symptoms and diseases based on current scientific knowledge
- Physiological consequences of acute and chronic stress
- Stress management: reduction of physiological arousal through adaptive activities and deceleration of vicious circle of emotion-behavior-symptom-cognitions

Table 11. Summary of contents of cognitive-behavioral therapy (CBT).

Sessions	Contents
1	Treatment overview and description of treatment as intervention focusing on behavioral training and monitoring. Situation analysis, patient symptoms and establishment of rapport. Setting of personal goals for intervention and filling in first part of symptom-emotion-cognition-monitoring form
2–3	Discussion on how stress affects patients’ health and physiological consequences of stress. Coping strategies for stress and stress-reduction activities. Working with illness worries and symptom-perception interaction
4–5	Personal strengths and vicious circle of symptom behavior. Patient’s dysfunctional health and indoor air-related beliefs e.g. catastrophizing and cognitive restructuring
6–7	Evaluation of goals, discussion of obstacles to completing them. Validation of frustration and support of meaningful activities. Patient stress-reducing techniques and work-related activities
8–9	Health-related information and discussion on how to react to contradictory information about health-related issues. Increased awareness of emotions and how they affect symptom perception
10	Identifying warning signs that may affect recurrence of symptoms and working with patients to plan future actions if symptoms recur
11	Follow-up and booster session three months after intervention

4.5 STATISTICAL ANALYSES

In Study I, the data set consisted of both continuous and categorical variables. For categorical variables, Fisher’s exact test examined whether the backgrounds of the two groups differed. Before handling the continuous variables, the normality of the variables was evaluated. Student’s t-test for normality distributed variables and Mann-Whitney’s test for non-normality distributed variables were applied. When comparing the baseline results to the follow-up results, the statistical tests were used for repeated measurements. The level of significance was set at $p < 0.05$. All analyses were carried out using SAS 9.4 (SAS Institute In., Cary, NC, USA).

Study II used SPSS Version 25.0 (IBM Corporation, Chicago, Illinois, USA) software for descriptive statistical analyses [frequency, mean, median, range, and standard deviations (SD)].

The plan in Study III is to analyze and report the statistics (frequencies, means, median, and SD) of the baseline and follow-up data. Categorical outcomes are analyzed using the χ^2 test or Fisher’s exact test. When appropriate, the t-test and Mann-Whitney U test will be used to compare the

baseline and follow-up outcomes of the groups. Analysis of variance or covariance will be used for multiple comparisons of the groups, as well as for examining changes in the groups. Statistical analyses will be conducted using the latest version of IBM-SPSS for Windows (SPSS Illinois, Chicago, Illinois, USA) software.

In Study IV, Kruskal-Wallis test was used to compare the grade of disability with the number of organ systems, the number of behavioral changes, and the co-occurrence of the three EI, to compare the three types of EI with the number of organ systems, and to compare the increasing severity of EI (definition A–F) with the co-occurrence of the three EIs. The χ^2 test was used for the categorical variables. A p-value of <0.05 was considered statistically significant. If an individual fulfilled the stricter criteria for EI, they were also included in the lower severity EI definitions. For example, an individual fulfilling definition F (high intolerance) criteria also fulfilled EI definitions A–E. An individual was only included in the analyses once. Co-occurrence of EI attributed to chemicals, indoor molds, and EMFs were shown by Venn diagrams. Proportions expressed as percentages of the sample calculated the prevalence values for these three EIs (with or without co-occurrence). Statistical analyses were performed using IBM-SPSS Version 24.0 for Windows (SPSS Illinois, Chicago, Illinois, USA) software.

4.6 ETHICS

All the participants signed an informed consent document. Studies I, II and III were approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa, Finland (Study I: approval number 61/13/03/00/2010, dated 27.4.2010; Study II: approval number 81/13/03/00/15, dated 5.5.2015; and Study III: approval number 107/13/03/00/13, dated 17.12.2013 and its change in May 2015). Permission to conduct Study II was also granted by the Helsinki University Hospital and the FIOH ethical working group. Study IV was approved by the Ethics Committee of the Hospital District of Central Finland, Jyväskylä (approval number 18U/2011, dated 15.11.2011).

5 RESULTS

5.1 CLINICAL CHARACTERISTICS OF PATIENTS WITH INDOOR AIR-RELATED DISABILITY (STUDIES I–II)

Table 12 shows the basic characteristics of the patients in Studies I and II. The mean age of the patients in Study I was 46.5 (range 23.6–60.6 years) and in Study II, 49.8 (range 38.9–58.5). In both studies, most of the patients were female, highly educated and non-smokers. In Study I, the patients' workplaces were schools and kindergartens (36%), offices (33%), hospitals (29%) or similar. In Study II, the workplaces were schools and kindergartens (67%), offices (17%), a hospital (8%) and a fire station (8%, n=1).

In Study I, the mean of self-reported absence from work due to indoor air-related symptoms was 90.8 days (median 60.0 days, SD 82.2) during the preceding year. In Study II, the mean absence from work was 88.6 days (median 15.5 days, SD 134.6).

In Study I, Body Mass Index (BMI) was significantly higher ($p < 0.05$) in the INT group than in the TAU group (INT vs. TAU; mean 30.1 kg/m², SD 5.2 vs. mean 25.1 kg/m², SD 4.2). The INT and TAU groups did not differ significantly in terms of any other clinical variable (gender, age, family status, education, workplace, self-assessed work ability, sick leave days, smoking habits, symptom duration, presence of asthma and time from the onset of asthma, indicators of atopy, results of spirometry and bronchial hyperresponsiveness, and self-assessed asthma control) at baseline or during follow-up.

Table 12. Basic characteristics of patients in Studies I and II.

	Study I	Study II
	(at baseline)	
	All patients (n=55)	All patients (n=12)
Female, n (%)	52 (94.5)	11 (91.7)
Age, years, mean (SD)	46.5 (8.6)	49.8 (6.0)
Married or cohabitating, n (%)	36 (65.5)	12 (100)
Education		
High-level, n (%)	19 (34.5)	6 (50.0)
Mid-level, n (%)	27 (49.1)	3 (25.0)
Basic, n (%)	9 (16.4)	3 (25.0)
Non-smoker, n (%)	51 (92.7)	11 (91.7)
Body mass index, kg/m ² , mean (range)	27.9 (18.8–45.5)	26.9 (21.3–36.3)
Duration of indoor air-related symptoms, years (range)	4.6 (0.6–23.0)	10.5 (2.0–25.0)
Work absence days during preceding 12 months		
Due to indoor air-related symptoms, days, mean (range)	90.8 (15–365)	88.6 (0–365)
Due to any reason, days, mean (range)	.	92.4 (2–365)
Physician visits during preceding 12 months		
For indoor air-related symptoms, number, mean (range)	.	13.0 (0–36)
For any reason, number, mean (range)	.	14.8 (2–40)

. = Not applicable.

5.1.1 SYMPTOMS AND COURSE OF DISABILITY (STUDIES I-II)

In Study I, the mean duration of indoor air-related symptoms was 4.6 (median 2.5, range 0.6–23.0) years, and in Study II it was 10.5 (median 8.5, range 2.0–25.0) years (Table 12). In Study II, the mean duration from onset to the time when symptoms extended to a disabling level was 7.8 (range 0.5–23.0) years, and from this extension point to the current evaluation time 2.7 (range 1.0–7.0) years.

Patients attributed their symptoms to workplace indoor environments in non-industrial workplaces. In Study I, 81% of patients (n=39/48, n=7 missing because of incomplete questionnaire responses) reported work-related symptoms in multiple organ systems occurring at least weekly. Further, the majority (65%, n=31/48) reported these symptoms in at least three organ systems (out of five systems). According to these weekly symptoms, the mean number of organ systems was 2.8 (SD 1.4). Of the patients who had asthma, 13% (n=5/39, n=6 missing data) reported only work-related respiratory and eye symptoms (unpublished data). Most of the patients (72%, out of 55) reported laryngeal symptoms, such as hoarseness. Figure 2 in Article I shows the distribution of the symptoms in different organ systems. In Study II, all 12 patients reported indoor air-related symptoms in at least three organ systems (mean 4.5, range 3–6), and all had neurological and respiratory symptoms.

5.1.2 INDOOR AIR POLLUTANTS AND WORKPLACE MEASURES (STUDIES I-II)

In Study I, deficiencies in the IAQ of patients' non-industrial work environments consisted of deficiencies in ventilation, dustiness, dampness or material emissions. Exposure to building moisture and mold at work was verified (among 55%) and classified as low among 7% (n=4) of the patients and as intermediate or high among 47% (n=26). There was no correlation between microbial exposure level and continuation of symptoms or number of organ systems with symptoms. For most of the patients (96%), previous measures had been taken to solve the indoor air problem at the workplace, e.g. building repairs, other environmental improvements or relocation of the worker. Despite workplace interventions, symptoms remained unchanged among 54% of the patients, and diminished among 29%. Among 13% the symptoms had disappeared. No environmental improvements had been made at work in the case of two (4%) patients.

In Study II, most patients (n=10/12) described varied deficiencies in the IAQ of their previous work environments, mainly moisture and molds. The workplace facilities had been repaired or the worker had been relocated, and no significant exposure or deficiency in IAQ had been detected or suspected in their current work environments. For all the 12 patients, one or more of the following occupational adjustments had been made because of indoor air-related symptoms: relocation (n=11), work schedule arrangement (n=1), sabbatical leave (n=4), part-time work (n=2), and/or working as a freelance in several jobs (n=1). Responsiveness to the triggers in the work environment had continued among all patients, despite the interventions.

5.1.3 DISABILITY SCALES (STUDIES I-II)

In Study I, the mean of self-assessed current WAS was 5.4 (SD 1.8, range 0–7). It should however, be noted, that study intake required values of ≤ 7 .

In Study II, the mean of the self-assessed current WAS was 5.2 (2.4, range 0–8). Further, the majority were not sure (n=8) or hardly sure (n=2) of their work ability in two years' time. In Study II, the self-assessment disability scales indicated a higher disability severity than that of the SOFAS interview tool used in the physician's interview. The mean of the SOFAS score was 78.3 (SD 10.5, range 59–92), indicating a slight impairment, and the scores by tertiles were moderate or some difficulty (n=3), slight impairment (n=3), and good or superior functioning (n=6). On the inverse SDS, the mean scores were: SDS Work 6.1 (SD 2.7, range 1–10), SDS Social life 6.7 (1.9, 4–10), SDS Home 4.3 (2.3, 0.5–9), and SDS Total 5.7 (1.8, 3.7–9.7). All patients scored ≥ 5 on at least one of the three SDS subdomains, indicating significant functional impairment.

5.1.4 SELF-REPORTED ENVIRONMENTAL INTOLERANCES, HEALTH CONCERNS AND AVOIDANCE BEHAVIOR (STUDIES I-II)

Environmental intolerances and avoidance behavior. In Study II, the self-reported QEESI's CI scores indicated a high probability of intolerance to chemicals among 67% (n=8) of the patients, and low probability among 33% (n=4). On QEESI's Life Impact scale, ten patients showed a high score, representing adverse avoidance behaviors due to intolerance in various life areas. The mean of the CI score was 50.1 (range 4–91) and that of Life Impact was 55.5 (range 1–94). On the additional scale (0–10) of severity of intolerance to indoor air molds, 75% (n=9) patients scored 10, indicating disabling symptoms, and three patients responded with values of 1, 2, or 6 (scale 0–10) to the additional question analogues regarding EMFs of the QEESI.

During the clinical interviews in Study II, patients reported restraints to activities imposed by their indoor air-related avoidance behaviors, including work participation (n=12), visiting various places (n=12), socializing (n=10), leisure activities (n=6) and moving or living in conventional homes (n=3).

Environment-related health concerns. In the INT group (n=25) of Study I, during the psychologist's counseling sessions, 60% (n=15) of the participants showed prevalent concerns about a serious disease or loss of health. Sixteen percent (n=4) of the participants were even afraid of dying. Among 52% (n=13), concerns were associated with indoor air problems. Among one fifth (n=5), symptoms had led to avoidance behavior and restricted personal life. Concerns about a serious disease not related to indoor air were identified among four (16%) patients. One third (n=8) reported concerns about poor asthma prognosis.

In Study II, all the patients reported considerable environment-related concerns about loss of health. On the health concerns scale (0–10), the mean value of environmental exposures was 8.8 (range 3–10), and for indoor air exposure at the workplace, 9.4 (range 7–10).

5.1.5 SELF-REPORTED SIGNS OF DISTRESS (STUDIES I-II)

In Study I, based on the psychologist's interviews, 36% (9 out of 25) of the patients expressed current mental symptoms (depressive mood, feelings of anxiety, or sleeping problems), and one had previously suffered mental symptoms.

The patients of Study II had somatic, characterized cognitive and emotional symptoms and health-related QOL using self-rated measures, the results of which are summarized in Table 13. Half of the patients (n=6) reported insomnia-related symptoms using the ISI instrument, and two of these had moderate or severe insomnia. In addition, two thirds (n=8) of the patients reported prolonged multi-site pain.

Table 13. Self-rated symptoms of anxiety, depression, insomnia, burnout, somatization and health-related quality of life in Study II.

	All (n=12)
Anxiety	
GAD-7, mean (range)	4.8 (0–13)
Moderate anxiety (score 10–14), n	3
BAI, mean (range) ^a	7.0 (0–16)
Moderate anxiety (score 16–25), n	1
OASIS, mean (range) ^b	3.1 (0–10)
Identification of clinical anxiety (score ≥8), n	1
Depression	
PHQ-9, mean (range)	5.0 (0–12)
Moderate depression (score 10–14), n	2
BDI, mean (range) ^b	7.2 (1–17)
Mild depression (score 14–19), n	2
Insomnia	
ISI, mean (range)	9.3 (0–27)
Subthreshold insomnia (score 8–14), n	4
Moderate severity insomnia (score 15–21), n	1
Severe insomnia (score 22–28), n	1
Burnout	
SMBM total, mean (range) ^c	2.9 (1.4–4.6)
Mild or moderate burnout (score 2.3–3.7), n	5
Severe burnout (score ≥3.8), n	2
Somatization	
SCL-90 somatization, mean (range) ^a	1.2 (0.4–2.3)
Quality of life	
15D-score, mean (range)	0.84 (0.75–0.93)

GAD-7, Generalized Anxiety Disorder; BAI, Beck Anxiety Inventory; OASIS, Overall Anxiety Severity and Impairment Scale; PHQ-9, Patient Health Questionnaire; BDI, Beck Depression Inventory; ISI, Insomnia Severity Index; SMBM, Shirom-Melamed Burnout Measure; SCL-90, Symptom Checklist-90.

^a n=10.

^b n=11.

^c n=9, three patients who were on sick leave were excluded.

5.1.6 PHYSIOLOGICAL FUNCTION AS AN INDICATOR OF STRESS AND POOR RECOVERY (STUDY II)

In the analysis of the ANS and HPA axis functioning (n=10) examinations, the time domain parameters of HRV showed no indications of significant clinical cardiovascular disorders. One patient's resting blood pressure was above normal. Three patients' LF/HF ratio at rest in a supine position was elevated (>2.8), and two of these also showed the highest values while standing. None of the patients showed pathognomonic responses in the HVPT test indicating hyperventilation syndrome.

In a real-life setting, six (out of 10) patients showed insufficient recovery during sleep (recovery index <60%) in the long-term monitoring of HRV. In the salivary cortisol response, the cortisol levels in the evening salivary cortisol samples of three patients were elevated (>6.1 nmol/L). In total, three patients had both insufficient recovery in HRV during sleep and an elevated cortisol level. Further, six patients had either an elevated LF/HF ratio, insufficient recovery during sleep, or elevated evening cortisol levels. Table 14 shows the results of the examinations of the physiological function of stress and recovery.

Table 14. *Results of the examinations of sympathetic response used in Study II, mean (range).*

	N=10
Laboratory testing at rest	
Heart rate, bpm	66 (59–69)
RMSSD of adjacent RR-intervals, ms	34 (16–88)
Baroreceptor sensitivity, ms/mmHg	10 (6–17)
Systolic brachial blood pressure, mmHg	129 (100–154)
Diastolic brachial blood pressure, mmHg	80 (70–90)
Active orthostatic test in laboratory	
Power of low frequency band to high frequency band in the spectral analysis of heart rate variability (LF/HF ratio)	
Supine position	4.3 (0.7–21.0)
Standing	8.7 (1.0–23.0)
Home monitoring	
Heart rate variability in beat-to-beat R–R interval recording	
Percentage of recovery during sleep (recovery index) ^a	56.1 (22.0–89.7)
Salivary cortisol	
Evening sample, nmol/L ^b	6.2 (1.8–15.9)

RMSSD, root means square of successive differences.

^a Average of mean of three values over three days.

^b Average of mean of two different evening samples.

5.1.7 CO-OCCURRENT SOMATIC AND PSYCHIATRIC DISEASE (STUDIES I-II)

In Study I, based on medical history and clinical examinations, 93% (n=51/55) of the patients had one or more current diseases or symptomatologies, which are summarized in Table 15. Twenty-two (40%) patients had a symptomatology or disease other than asthma. Based on the clinical assessment, the disease possibly contributed to disability in only one patient with subacute thyroiditis. The respiratory symptoms of asthma patients (n=45) were not fully explained by their asthma condition. Other diseases had been treated under sufficient control.

Table 15. *Current diseases and symptomatologies of 55 patients in Study I.*

Diseases or symptomatologies^a	N=55
Asthma	45
Allergic rhinitis or conjunctivitis	8
Arterial hypertension	9
Atopic eczema	1
Chronic obstructive pulmonary disease	1
Depression	1
Diabetes mellitus type 2	1
Fibromyalgia	2
Hypothyreosis	6
Insomnia non-organic	1
Metabolic syndrome	1
Migraine	2
Obstructive sleep apnea	1
Seronegative oligoarthritis	1
Seropositive rheumatoid arthritis	1
Panic disorder	1
Paroxysmal trigeminal neuralgia	1
Scleroderma	1
Sjögren's syndrome	1
Subacute thyroiditis	1
Anxiety symptoms	1
Low mood	1
Low back pain	1
Non-specific musculoskeletal symptoms	5

^a An individual may have one or more diseases or symptomatologies.

In Study I, 17% (n=8/45) of the asthma patients showed low lung function in spirometry according to FVC% or FEV1% (<80% of the predicted values) or a positive FEV1% bronchodilator response (≥12%). Three patients with

asthma had mildly raised FeNO (≥ 25 ppb). According to the ACT instrument, 78% of the asthma patients' asthma was 'not well-controlled' or 'uncontrolled'. Table 16 summarizes the results of the examinations of allergy, inflammation and respiratory function, as well as the self-reported asthma control examined by the ACT instrument in Study I and II.

Table 16. Results of examinations of allergy, inflammation, and respiratory tract, and self-reported asthma control in Studies I and II.

	Study I		Study II	
	All patients (n=55)	Asthma patients (n=45)	All patients (n=12)	Asthma patients (n=6)
Indicators of atopy				
Positive skin prick test ^a				
Common environmental allergens, n (%)	27 (49.1)	22 (48.9)	5 (41.6)	2 (33.3)
Molds, n (%)	2 (3.6)	2 (4.4)	none	none
Total serum IgE ≥ 110 kU/L, n (%)	11 (20.0)	8 (17.7)	none	none
Blood EOS, $\times 10^9$ /L, mean (SD)	0.14 (0.23)	0.15 (0.25)	0.15 (0.03)	0.13 (0.04)
Spirometry ^b				
FVC% predicted, mean (SD)	96.2 (13.4)	96.5 (14.4)	101.7 (13.5)	102.6 (15.8)
FEV ₁ % predicted, mean (SD)	91.3 (16.6)	91.3 (17.8)	99.7 (14.1)	100.0 (17.3)
FEV ₁ /FVC, mean (SD)	77.9 (7.1)	77.9 (7.1)	79.7 (4.3)	79.0 (4.8)
FEV ₁ % bronchodilator response				
$\geq 12\%$, n (%)	3 (5.5)	3 (6.7)	none	none
Bronchial hyperresponsiveness ^c				
Severe, n (%)	1 (2.1)	1 (2.6)	none	none
Moderate, n (%)	2 (4.3)	2 (5.3)	1 (10.0)	1 (20.0)
Mild, n (%)	8 (17.0)	6 (15.8)	2 (20.0)	1 (20.0)
None, n (%)	36 (76.6)	29 (76.3)	7 (70.0)	3 (60.0)
FeNO, ppb, mean (SD) ^b	11.9 (6.5)	12.2 (6.9)	14.6 (7.5)	14.0 (7.9)
Average daily diurnal PEF variability over				
two weeks, percentage, mean (SD) ^d	.	.	5.9 (3.4)	5.0 (2.6)
ACT				
Controlled (≥ 20 points), n (%)	.	10 (22.2)	.	4 (66.6)
Not well-controlled (16–19 points), n (%)	.	9 (20.0)	.	1 (16.7)
Uncontrolled (≤ 15 points), n (%)	.	26 (57.8)	.	1 (16.7)

IgE, immunoglobulin E; EOS, eosinophils; FVC, forced vital capacity; FEV₁, forced expiratory volume in one second; FeNO, fractional exhaled nitric oxide; PEF, peak expiratory flow; ACT, Asthma Control Test (score 0–25).

. = Not applicable.

^a At least one positive skin prick test.

^b n=54 in Study I.

^c n=47 in Study I; n=10 in Study II.

^d n=11 in Study II.

In Study II, 83% (n=10/12) of the patients had one or more current somatic diseases based on clinical evaluation and medical history: Asthma (n=6), benign arrhythmia (n=1), fibromyalgia (n=1), hypothyreosis (controlled by medication) (n=2), irritable bowel syndrome (n=2), anal fissure (n=1), migraine (n=2) and/or musculoskeletal disorder (n=4). We detected no low lung function in spirometry in any of those who had asthma (n=6) according to FVC% or FEV1% (<80% of the predicted values) or in positive FEV1% bronchodilator response ($\geq 12\%$), and no excessive variability in daily diurnal PEF (>10% average daily variability) or in positive bronchodilator responses ($\geq 15\%$ and 60 L) (Table 16). The FeNO of two patients was mildly raised (≥ 25 ppb), and one of these had asthma. According to the ACT, asthma was more often controlled (67%) than ‘not well-controlled’ or ‘uncontrolled’ (33%). The medical assessment revealed no need for additional somatic investigations.

According to the ICD-10 diagnostic criteria in Study II, 73% (n=8/11) of the patients met the criteria for one or more psychiatric disorders, which are summarized in Table 17. Of these, five patients had one diagnosis and three patients had two or more. Based on their medical histories, two patients had previous psychiatric diagnoses (major depressive disorder, anxiety/phobic anxiety disorder, social phobia). Six patients fulfilled the diagnostic criteria for an anxiety disorder, two of whom also had a depressive disorder. One patient with anxiety and depressive disorders also had a personality disorder. Another two patients met the diagnostic criteria for a somatoform disorder.

Table 17. *Psychiatric disorders based on clinical evaluation.*

Psychiatric disorders^a	N=11
Anxiety disorders	
Social phobia	1
Specified phobic anxiety disorder	1
Other specified anxiety disorder ^b	4
Reaction to severe stress and adjustment disorder	1
Depressive disorders	
Moderate depressive disorder	1
Recurrent depressive disorder, current episode mild	1
Somatoform disorders	
Undifferentiated somatoform disorder	1
Somatoform autonomic dysfunction	1
Personality disorders	
Obsessive-compulsive personality disorder	1

^a An individual may have one or more psychiatric disorders.

^b Including features of panic and generalized anxiety disorders, autonomic dysfunction, anxiety and mental distress, and fluctuating anxiety with concerns of disease and avoidance behavior.

5.1.8 INDOOR AIR-RELATED DISABILITY (STUDIES I-II)

Patients' disability manifested as a condition with persistent and non-specific symptoms that patients attributed to pollutants in indoor air environments. In Study I, based on clinical evaluation, the patients' disabilities were not adequately explained by any disease, and symptomatology had not diminished despite previous arrangements at workplace facilities. In Study II, according to the clinical evaluation, all 12 patients fulfilled the IEI criteria in terms of responsiveness to indoor molds (n=11). Nine of them also reacted to odorous chemicals, three to electric devices and one individual was responsive to only odorous chemicals. Symptom responsiveness appeared in different buildings, and/or were provoked by a wide range of odorous. Seven patients (out of 12) reported symptoms when in the vicinity of people who had been in a moisture-damaged building.

5.2 PREVALENCE OF ENVIRONMENTAL INTOLERANCE TO CHEMICALS, INDOOR MOLDS AND ELECTRIC DEVICES IN MATERNITY CLINIC SAMPLE (STUDY IV)

The mean age of the 680 respondents in Study IV was 29.9 years (SD 4.8), ranging from 16 to 45. Of these, 90.9% (n=618) reported being non-smokers, and 94.9% (n=645) reported being at least somewhat annoyed by at least one of the inquired 12 environmental factors (Table 7, Section 4.3). The distribution of the degree of severity of annoyance attributed to the various environmental factors are shown in Table 2 of original Article IV.

5.2.1 ENVIRONMENTAL INTOLERANCE

Continuum from annoyance to disability. Of the respondents, 45.6% reported annoyance with chemicals, indoor molds, or EMFs (EI definition A, see definitions in Table 8, Section 4.3). Further, 33.2% reported symptoms related to at least one of these three EIs (Definition B), and 17.5% reported symptoms that contained CNS symptoms (Definition C), including behavioral changes (15.0%) (Definition D). In terms of disability, 8.4% experienced at least 'some' difficulties related to any of the three EIs (Definition E), 2.2% 'very' many or 'extreme' (Definition F) and 0.9% 'extreme'. Table 18 shows the distribution of prevalence of EIs among the various environmental factors and their combinations according to the increasingly strict criteria for the EI definitions (A–F) used in Study IV.

Table 18. Prevalence of environmental intolerances (EIs) according to EI definitions A–F^a used in Study IV. The percentage is calculated from the total n=680, n (%).

Definitions of EI	EI attributed to				
	Any of the 12 environmental factors	Any of the three items: chemicals, molds, or EMFs	Chemicals	Indoor molds	EMFs
A	457 (67.2)	310 (45.6)	198 (29.1)	222 (32.6)	20 (2.9)
B	302 (44.4)	226 (33.2)	155 (22.8)	166 (24.4)	16 (2.4)
C	145 (21.3)	119 (17.5)	80 (11.8)	93 (13.7)	9 (1.3)
D	122 (17.9)	102 (15.0)	67 (9.9)	83 (12.2)	9 (1.3)
E	68 (10.0)	57 (8.4)	39 (5.7)	52 (7.6)	5 (0.7)
F	15 (2.2)	15 (2.2)	10 (1.5)	15 (2.2)	2 (0.3)

EMFs, Electromagnetic fields.

^a An individual may have EI to one or more factors and may be included in various definitions A–F.

Symptoms. Of those (n=226) who reported intolerance to one or more symptoms (EI definition B) attributed to any of the three (chemicals, molds, EMFs) items, 38.9% reported symptoms in at least three (out of 1–7) different organ systems. The symptoms occurred mostly in the CNS, pulmonary tract, and dermal systems. Figure 1 of Article IV presents the proportion of self-reported symptoms in different organ systems in cases of EIs to chemicals, molds, EMFs and their combinations, as well as the mean numbers of organ systems.

Behavioral changes. The (n=102) participants who had any of the three EIs according to EI definition D reported having made the following behavioral changes to avoid symptoms: behavioral or lifestyle changes to minimize exposure (n=65), changed interior decorations or furnishings at home (n=29), moved to another apartment (n=24), changed workplace, resigned from workplace or occupation (n=19), taken vitamins, supplements, or changed diet (n=47), eliminated the cause using antifungal agents or chemicals (n=16) and used protective equipment (n=55). Nine respondents (1.3%) reported both a move to another apartment and a change of workplace.

Disability. All the participants (n=15) with ‘severe disability’ attributed their intolerance to indoor molds, and two thirds also to chemicals (Table 18; Table 4 of Article IV). Of these 15 participants, 12 reported having had to change apartment or job to avoid symptoms due to intolerance, four reported having done both. Among the 15 participants, the mean number of organ systems presenting symptoms was 4.4 (SD 2.0, range 2–7).

All the six respondents who reported *very severe* (‘extremely difficult’) disability (as shown in Table 4 of Article IV) had CNS and pulmonary tract

symptoms, and five had dermal system symptoms. The mean number of organ systems involved was 4.8 (SD 2.1; range 2–7).

Co-occurrence of EIs. Of the respondents who reported EI definition A to chemicals (n=198), indoor molds (n=222) or EMFs (n=20), 59%, 53%, and 75%, respectively, reported at least one other type of EI. Furthermore, co-occurrence of at least one other EI with definition E to chemicals, indoor molds or EMFs was reported by 87%, 65%, and 100%, respectively. Co-occurrence of the three types of EIs according to EI definitions A and E are shown with Venn diagrams in Figure 2 of Article IV.

5.2.2 FACTORS ASSOCIATED WITH INCREASING SEVERITY OF DISABILITY

As the number of difficulties increased, the number of organ systems, behavioral changes and overlaps of the three EIs also grew.

Among the respondents with EI definition B (n=226), an association was found between increasing severity of disability and pulmonary tract symptoms ($p=0.011$), and nearly significantly for CNS symptoms ($p=0.054$). In addition, the more severe disability was also associated with a higher number of organ systems presenting symptoms ($p<0.001$), and with a higher number of behavioral changes ($p<0.001$). The aforementioned association was also seen in the EI definition C group (n=119, $p=0.001$).

The association between the severity of disability and the co-occurrence (only one, two different types of EI, or all three EIs) of the three EIs (n=102, $p=0.037$; Table 4 of Article IV) was statistically significant. In addition, the increasing severity of the continuum of EI (definitions from A to F) was associated with the increasing overlaps of the three EIs (n=310, $p<0.001$).

5.3 EFFECTIVENESS OF COUNSELING FOR QUALITY OF LIFE AND WORK ABILITY AMONG PATIENTS WITH INDOOR AIR-RELATED DISABILITY (STUDY I)

After the six-month follow-up, the psychoeducation and counseling intervention provided no significant positive benefits in the following outcome measures (INT: n=21; TAU: n=23): self-assessed work ability (measured by WAS), illness worries (by IWS), health-related QOL domains (by RAND-PCS and RAND-MCS), Symptom disturbance index, and self-assessed asthma control (of those who had asthma, measured using the ACT instrument), as is presented in detail in Table 4 of Article I. Sick leave days and periods were not reported because of missing data in the six-month follow-up questionnaire.

5.4 TWO PSYCHOSOCIAL INTERVENTIONS TO MANAGE PATIENTS WITH INDOOR AIR-RELATED DISABILITY (STUDY III)

Participant recruitment began in February 2014 and ended in February 2017. After the end point, the last intervention sessions were conducted in spring 2017 and the following follow-up questionnaires until June 2018. Reporting of the results begins in 2018, and the results from the study follow-up are expected in 2019.

During the RCT, finding eligible individuals at the OHS units, was challenging, despite support for maintaining recruitment. Because of the slow enrolment process, an attempt was made to expand the number of recruits during the study intake and the recruitment period was extended from the end of 2016 to the beginning of 2017. In addition, in May 2015, the Applied Relaxation Group Therapy arm was removed from study interventions to ensure completion of the study.

6 DISCUSSION

6.1 MAIN FINDINGS

6.1.1 DISABILITY WITH PERSISTENT AND NON-SPECIFIC SYMPTOMS

In the clinical studies (Studies I, II), the patients' indoor air-related symptoms appeared to be long lasting and to involve several organ systems. Study II showed gradual exacerbation on the symptom spectrum as well as functional impairments. Previous clinical studies of similar clinical samples have shown that non-specific indoor air-related symptoms can persist over time (Al-Ahmad et al. 2010; Karvala et al. 2014; Khalili et al. 2005). In addition, long-lasting symptoms in multiple organ systems have been related to poor prognosis (Edvardsson et al. 2008). This seems to also occur among patients with mold-attributed asthma or asthma-like symptoms (Al-Ahmad et al. 2010; Karvala et al. 2014). In a study of an occupational clinic sample, the duration of more than one year and five or more symptoms were significant work disability risks (Edvardsson et al. 2008). In general, numerous somatic symptoms associate with lower physical and mental health and predict worse health status (Tomenson et al. 2013) and high rates of work disability (Rask et al. 2015).

Our clinical studies (Study I, II) found no medical or exposure-related explanation for the persistent symptomatology. In a previous follow-up study also, persistent symptoms and disability were not fully explained by asthma or current exposure (Al-Ahmad et al. 2010). Our findings regarding persistent and recurrent indoor air-related non-specific symptoms with multiorgan progression, not explained by exposure or disease, are in accordance with the phenomenon of IEI and FSS.

The patients' respiratory symptoms were not fully explained by asthma. Among those with asthma (Study I, II), lung function tests were normal in most cases, but the patients reported abundant respiratory and multiorgan symptoms. According to the ACT questionnaire (Study I) most (78%) of the asthma patients reported 'not well-controlled' or 'uncontrolled' asthma, as well as multiple respiratory symptoms, limitations to activity, usage of short-acting bronchodilation medication and poor self-assessed asthma control. The ACT score seemed to be lower than that in other studies of asthma patients (Romberg et al. 2014). The findings suggest that ACT based on self-assessed symptoms may exaggerate the non-control of asthma due to overlapping functional symptoms. Functional symptoms can be difficult to distinguish from asthma symptoms (Lehrer et al. 2002).

The functional nature is supported by the fact that the majority (69%) of the asthma patients (Study I) reported symptoms in three or more organ

systems, including typical functional symptoms such as hoarseness (Hoy et al. 2010). In Study II, all the patients had persistent multi-organ symptoms including CNS and respiratory symptoms, and disability was due to the recurrence of symptoms leading to avoidance. An increasing number of physical symptoms is a strong indicator of a non-organic nature and is a predictor of disability (Henningsen et al. 2007, 2018). Symptoms in multiple organs including CNS, as in SBS (Thörn 1999; Redlich et al. 1997; WHO 1983), are characteristic of IEI and FSS, as is disability that is not explained by medical conditions (Fink and Schröder 2010; Lacour et al. 2005; Rief et al. 2017).

6.1.2 DISABILITY WITH INCREASED REACTIVITY TO INDOOR POLLUTANTS

Clinically (Study I, II), the patients attributed their work disability to indoor work environments. Different environmental factors were recognized at the patients' workplaces as potential causes of impaired IAQ. However, they do not explain the persistent recurrent symptoms/responsiveness and avoidance. Similar indoor air pollutant levels are not regarded as an explanation for long-term adverse health effects in non-industrial workplaces (Hetherington and Battershill 2013; Redlich et al. 1997; WHO 2009; Wolkoff 2013). The patients' disability, symptoms and responsiveness to work and other indoor environments had continued despite interventions at their workplaces.

The disability manifested in all the patients in Study II as a chronic state of responsiveness to the indoor work environment, which the patients attributed to indoor pollutants, mainly molds. However, in the patients' current work environments, there was no evidence of or suspicion of harmful indoor exposures. Previous studies have shown that symptoms may persist despite building remediation (Al-Ahmad et al. 2010; Edvardsson et al. 2008; Sauni et al. 2015), even in cases in which the remediation is considered substantial or technically successful (Haverinen-Shaughnessy et al. 2008; Iossifova et al. 2011), or when remediation activities are repeated over many years (Park et al. 2018). In addition, as the symptoms were triggered by indoor air in one building, but then spread to other surroundings, it is unlikely that all these surroundings contain harmful indoor exposures. As an example of increased responsiveness, the majority of the patients in Study II reported symptoms in the vicinity of people who had been in a moisture-damaged building or near a moldy odor. These findings of persistent reactivity are in accordance with features of IEI (IPCS/WHO 1996; Lacour et al. 2005; MCS consensus conference 1999) in which individuals react to low levels of various everyday environmental exposures that are tolerated by most other people.

Furthermore, Study II showed that responsiveness had spread to other triggers, which is typical of IEI (Dantoft et al. 2015; Van den Bergh et al. 2017a). In addition to indoor molds, symptom triggers included odorous chemicals, and for some patients also electric devices. Previous provocation

studies have revealed no exposure-related evidence of physiological reactions caused by electric devices (Rubin et al. 2005, 2011). Our modified QEESI instrument, with its additional questions on indoor air molds and EMFs, supported the information gained from clinical history. A similar overlap has previously been seen in a few clinical samples (Edvardsson et al. 2008; Söderholm et al. 2016), and in a population-based questionnaire study (Palmquist et al. 2014). A survey of maternity clinic samples (Study IV) also showed that the greater the co-occurrence of EIs (chemicals, indoor molds, electric devices), the more severe was EI.

Overall, the findings support the hypothesis that the increased reactivity to perceived indoor air pollutants in non-industrial work environments share features with EI and FSS. They strengthen the previous understanding that the different forms of EI share similarities and represent the same phenomenon (Dantoft et al. 2015; IPCS/WHO 1996; Van den Bergh et al. 2017a).

6.1.3 ASSESSMENT OF INDOOR AIR-RELATED DISABILITY

The assessment of functioning and disability showed difficulties in many functional areas in daily life: not only at work, but also at home, and in the patients' social lives. As a sign of work disability, adjustments had been made at the workplaces of the patients in our clinical studies (Study I, II), but they also had high work absence rates during the past year and/or high health care seeking/utilization (physician visits during past year). These two factors have been predictors of work disability (Reis et al. 2011; Roberts et al. 2018; Sado et al. 2014), and are also typical of IEI and FSS (Bailer et al. 2005; Frías 2015; Henningsen et al. 2018). In general, work disability associates with impaired QOL (Idler and Benyamini 1997; Post et al. 2006) and psychosocial risk factors such as inappropriate fears and beliefs, catastrophizing, little hope of healing, loss of self-efficacy and lack of social support (Sullivan et al. 2005).

Health-related QOL describes the physical, mental and social dimensions of functioning and well-being. In Study II, patients reported lower health-related QOL when they measured it by the 15D score (0.84) than previous findings in the general population (0.94) or individuals with asthma (0.86), but similar levels to those individuals with any depressive disorder (0.84) or anxiety disorder (0.83) (Aromaa and Koskinen 2004; Koskinen et al. 2012; Saarni et al. 2006, 2007).

Clinical examinations (Study I, II) did not find that impairments in body functions or structures explained the disability. However, the clinical interviews and self-assessment tools (Study II) revealed that the patients' disabilities limited their activities and restricted their participation in everyday life because of individual avoidance behavior due to symptom triggers in certain surroundings. In IEI, disability is based on self-reported symptoms and limitations to everyday functioning, i.e. no laboratory test or other objective means is available to evaluate disability evaluation. In addition,

significant functional and lifestyle impairments are required by the extended MCS criteria (Lacour et al. 2005) that are applicable to IEI.

The subjective SDS assessment tool (Study II) showed limitations to activities and participation restrictions to the varying domains of work, social life and functioning at home. Self-assessments (SDS and WAS) of disability in psychosocial (levels of activity and participation) environments showed higher severity of disability than the physician assessment using the SOFAS interview tool. A recent follow-up study of psychiatric patients at a tertiary outpatient clinic did not find this disparity between the subjective (SDS) and objective (SOFAS) measures (Laukkala et al. 2018). Instead, the measures were inter-correlated, and both SOFAS and the SDS Work scores were associated with a return to work (Laukkala et al. 2018). In Study II, the disparity between subjective and objective measures may reflect the nature of the condition and is characteristic of IEI and FSS (Lacour et al. 2005; Watanabe et al. 2003a; Wessely et al. 1999).

In Study II, patients' functioning problems, enforced by their avoidance behaviors, applied to work participation, visiting various places, socializing, leisure activities and moving to or living in conventional homes. Avoidance behaviors were also seen in Study I. In addition, ten (out of 12) patients (Study II) reported adverse avoidance behaviors due to chemical intolerance in various life areas according to QEESI's Life Impact scale. Skovbjerg (2009) concluded in her thesis that the most prominent coping strategy among individuals with MCS was avoidance of exposure to common environmental odors, and that in the persisting states, avoidance led to increased disability levels which impacted many aspects of everyday life. In a previous questionnaire study, over 60% of BRI respondents reported avoiding buildings that evoked symptoms (Karvala et al. 2018a).

Avoidance behavior is also a well-established feature of FSS, for example, in chronic pain and in chronic fatigue syndrome (Hartvigsen et al. 2018; Nater et al. 2006; Samwel et al. 2007). The fear-avoidance model of chronic pain hypothesizes that the fear of pain experience leads (through cognitive, affective and behavioral processes) to avoidance behavior such as limitations to activities and disability (Wideman et al. 2013). There is a positive association between fear-avoidance and pain intensity (Kroska 2016). In addition, the avoidance model has expanded to include the influence of maladaptive learning process and disability beliefs in pain perception and behavior (Hartvigsen et al. 2018). Increasing evidence shows that CNS pain-modulating mechanisms and pain cognitions play a major role in the development of disability (Hartvigsen et al. 2018; Rainville et al. 2001; Ursin and Eriksen 2001). It has been proposed that in IEI too, central sensitivity is involved in the development of a chronic disabling condition (Van den Bergh et al. 2017a).

In previous epidemiological studies, symptoms and behavioral changes have described disability due to EI (Berg et al. 2008). In the maternity clinic survey (Study IV) the severity of EI disability was illustrated using the tenth

additional item of the PHQ-9. This item is originally a single severity measure in the depression scale and measures functioning (activity and participation) in daily life. The use of this item enabled us to identify individuals with functioning difficulties. Previously, in a primary care sample, this item correlated strongly with impairment in the domains of health-related QOL (Kroenke et al. 2001).

Earlier, a high number of symptoms has been associated with functional impairments among individuals with IEI-EMFs (Baliatsas et al. 2014), which reflects the severity of the condition. Study IV further showed, based on the single item of PHQ-9, that as the grade of disability increased, the number of organ systems, behavioral changes and overlaps between EI and different environmental factors also grew. In Study IV, 1.3% of the respondents reported moving to another apartment and changing workplaces due to various forms of EI. In a previous Danish population-based study, due to chemical intolerance, 3.3% of study participants had made adjustments to their social lives or occupational conditions, and 0.5% to both (Berg et al. 2008). In a population cohort from the US, 1.5% reported losing their jobs and 0.8% moving house because of their hypersensitivity to chemicals (Caress and Steinemann 2004a).

Within the ICF framework (WHO 2001), indoor air-related disability was successfully defined as limitations to activities and restrictions to participation in several areas in daily life. The disability was associated with individual avoidance behaviors due to symptom triggers in certain surroundings. It was not explained by medical disease and/or disruption of body functions/structures. Instead, disability and its dysfunctions were characterized by various instruments that assessed symptoms and functioning, including reports of symptoms and responsiveness (e.g. long-term, gradual exacerbation, multiorgan, impaired QOL, discrepancy in objective evaluation, fears and worries, avoidance, co-occurrences, spreading), and in terms of workplace interventions, work ability, work absence and utilization of health care.

6.1.4 SIGNS OF PHYSICAL AND EMOTIONAL DISTRESS

The findings show that indoor air-related disability had various signs of distress. In Study II, the patients reported numerous signs of distress (physical, emotional, cognitive). Self-reports revealed prevalent insomnia-related symptoms and multi-site pain. These are also typical features in FSS (Eliassen et al. 2018; Mariman et al. 2013) and MCS patients (Blanco et al. 2016; Weiss et al. 2017), and are associated with work disability (Saltychev and Laimi 2018; Sivertsen et al. 2009). Our patients also reported work-related burnout in facets of physical, cognitive and emotional functioning. Job strain/burnout has been found to be a predictor of work disability (Salvagioni et al. 2017), and co-occurs with distress disorders such as impaired sleep, pain and anxiety (Ekstedt et al. 2006; Salvagioni et al. 2017). In the psychological

interviews of Study I, one third of the INT group described symptoms typical of depressive mood, sleeping problems, or anxiety. A previous population-based follow-up study has shown that individuals who later began to attribute annoyance to environmental factors reported even at baseline, more health complaints, higher levels of stress, strain and lack of recovery, as well as more dissatisfaction with their work situation and lower personal social support than those who did not develop such environmental attribution (Eek et al. 2010).

Negative beliefs and great concerns regarding the effect of indoor air exposures on health were prevalent among the patients in the clinical studies (Study I, II). The counseling of the INT group (Study I) revealed prevalent concerns of a serious disease or a loss of health (60%), and in some, fears had led to avoidance and restricted personal life (20%). All the patients in Study II reported considerable health concerns related to indoor air environments. In previous findings, concerns regarding indoor air-related health hazards have been common (Bluyssen et al. 2016; Redlich et al. 1997). In general, health concerns attributed to environmental factors have been highly prevalent, and are typically encountered in IEI (Baliatsas et al. 2015b; Van den Bergh et al. 2017a). Health concerns have positively associated with perception and the amplification of the physical symptoms of IEI and these health worries may contribute to the development of IEI (Bailer et al. 2008a; Van den Bergh et al. 2017a). When an individual perceives certain environmental factors as health hazards, stress reactions can manifest as multiple organ symptoms (Van den Bergh et al. 2017a). The role of health anxiety and illness worries in FSS is also well established (Henningesen et al. 2018). Elevated concerns may predict the development of health complaints and lead to higher symptom reports (Rief and Broadbent 2007; Watt and Stewart 2000). Negative illness perceptions have also been associated with lower physical and mental health (Frostholm et al. 2007), as well as physical symptoms accompanied by health anxiety and considerable concerns (Tomenson et al. 2013). A pronounced high health threat can be subjectively valid even if its connection to the perceived source is tenuous (Bailer et al. 2008a; Brown 2004; Rief and Broadbent 2007).

Our results support the hypothesis that individuals' expectations of the symptoms and adverse effects of certain surroundings can induce and maintain health complaints (Van den Bergh et al. 2017a). It has been suggested that central mechanisms (central sensitization) play an essential role in the development and maintenance of adverse reactions. Dysfunctional cognitions may increasingly enhance the reactions to actual or anticipated stimuli (Bell et al. 1996b; Henningesen et al. 2007, 2018; Kipen and Fiedler 2002; Rief and Broadbent 2007; Van den Bergh et al. 2017a; Yunus 2007) (see Figure 3, Section 2.3.6). Further, increasing evidence proposes that expectancy and nocebo mechanisms are critically involved in the development of symptoms and in linking them to specific environmental cues (Martens et al. 2018; Van den Bergh et al. 2017a). The persisting illness attribution to environmental factors is associated with intensity of symptoms (Van Dongen et al. 2014). The

perception of a threat stimuli can lead to CNS activation including both early autonomic reactivity and later prefrontal responses to consciously attended fear and avoidant coping (Hofmann et al. 2012). Awareness of symptoms together with concerns can feed further into a vicious circle of adverse consequences, and the condition becomes worse, with subsequent chronification (McEwen 2007; Rief and Broadbent 2007; Van den Bergh et al. 2017b).

The physiological stress and arousal indicators in Study II showed insufficient recovery in the HRV recordings and raised evening cortisol levels in six (out of 10) patients, but there no specific profile emerged in the findings. Physiological arousal (Brosschot et al. 2006) due to stress and persevering illness cognition can be mediated and modulated by various complex mechanisms, such as the regulation of the ANS, HPA axis, and immune system (e.g. proinflammatory cytokines) (Yunus 2015). According to previous findings, physiological measurements do not necessarily correspond with symptoms and their severity (Van den Bergh et al. 2017b). In addition, the literature has shown similar inconsistent findings concerning HPA axis activity among individuals with clinical burnout (Grossi et al. 2015). ANS recordings have typically been used as arousal indicators in provocation studies. For example, a Swedish study of 18 individuals with MCS found that those with MCS expressed higher pulse rate and lower pulse rate variability as ANS responses during chemical exposure than healthy controls, as well as greater perceived odor intensities, more unpleasantness from the exposure, and increasing symptoms (Andersson et al. 2016).

Overall, the cognitive and emotional processes of dysfunctional illness perceptions and illness worries are associated with high symptom reports in IEI (Bailer et al. 2008b; Staudenmayer 2001; van Dongen et al. 2014), FSS (Bailer et al. 2008b; Frosthalm et al. 2007; Rief and Broadbent 2007) as well as in chronic diseases such as asthma (Horne and Weinman 2002; Lehrer et al. 2002). A plausible explanation is that mechanisms regulated by CNS, central sensitization, can act either with or without verified disease (Yunus 2015). For example, psychological mechanisms, i.e. cognitive and emotional processes, have shown to mediate asthma exacerbation (e.g. Van Lieshout and MacQueen 2008), and are involved in the reporting of respiratory symptoms (Selinheimo et al. 2018), which may result in an overestimation of the severity of asthma (Selinheimo et al. 2018; Van Lieshout and MacQueen 2008). The differentiation of symptoms and their different mechanisms is essential for effective management strategies (Hubley et al. 2016; Yunus 2015).

Recognition of the underlying signs of distress enables the use of various stress-reducing interventions in the management of disability.

6.1.5 CO-OCCURRENCE OF SOMATIC AND PSYCHIATRIC DISEASES

The clinical studies (Study I, II) revealed no medical diagnoses that fully explained the disability, although they did find a high co-occurrence of medical (somatic and psychiatric) diseases and other symptomatologies. In Study I, decreased work ability was associated with workplace indoor air-related asthma and the symptomatologies shared features with IEI and FSS. The overrepresentation of asthma in Study I can be explained by the study population consisting of FIOH's patients with a suspected occupational disease. However, asthma was also prevalent in Study II among patients with indoor air-related disability. A previous epidemiological survey has shown a high co-prevalence of asthma (28%) among individuals suffering BRI (Karvala et al. 2018b). MCS has also shown to overlap with asthma to a great extent (Caress and Steinemann 2009; Katerndahl et al. 2012; Kipen and Fiedler 2002; Lind et al. 2017). Asthma is associated with an increased risk of various work disability outcomes, such as job change, sickness absence, long-term work disability, and in combination with depression, an increased risk of work disability (Hakola et al. 2011; Kauppi et al. 2010; Thaon et al. 2008; Torén et al. 2009). Moreover, an acute onset or worsening of asthma symptoms has been associated with a variety of trigger factors, such as allergens, viral infections, emotional factors or irritants (GINA 2018; Vernon et al. 2012).

Previous findings have suggested that excess asthma trigger perceptions are not explained by asthma and sensory irritation alone (Jaén and Dalton 2014; Janssens et al. 2015; Janssens and Ritz 2013; Karvala et al. 2018c). It might be difficult for individuals to separate odor perception from sensory irritation, which may result in excessive reporting of sensory irritation due to odor cues (Jaén and Dalton 2014). Sensory thresholds for sensory irritations are typically an order of magnitude higher than the corresponding odor threshold (Nielsen and Wolkoff 2017; Wolkoff and Nielsen 2017). The manipulation of the perceived risk of exposure to a benign non-irritant odor may alter both the quality ratings of the odor and the symptom reports, as well as modulate the inflammatory airway response (Jaén and Dalton 2014).

Depression and anxiety associate with asthma, its severity and respiratory symptom perceptions (Bogaerts et al. 2005; Brady et al. 2017; Brunner et al. 2014; Eisner et al. 2005; Katon et al. 2007). The reverse is also true: Among asthma patients, concerns about experienced symptoms triggered by the environment may initiate cognitive and emotional processes (Chen and Miller 2007; Jaén and Dalton 2014). It can be hypothesized that, among asthma patients, increased responsivity to low-dose levels of indoor pollutants and enhanced illness behavior may have an impact on the development, maintenance and worsening of IEI.

In Study II, the majority of the patients met the ICD-10 criteria for one or more psychiatric disorder, mainly an anxiety disorder. However, the psychiatric symptoms (anxiety and depression) reported in the self-report questionnaires were quite modest in spite of the comorbidity of psychiatric disorders, which may reflect the patients' resistance to psychological and

psychiatric labels (Watanabe et al. 2003a; Weiss et al. 2017). High psychiatric comorbidity is in line with results of previous studies of patients with MCS (Bornschein et al. 2001), and has also been seen in population-based studies (Bell et al. 1996a; Jason et al. 2000). In the context of indoor air-related disability, however, psychiatric comorbidity has formerly received little attention. Psychiatric disorders are also commonly encountered among patients with FSS (Blanco et al. 2016; Hamilton et al. 1996; Henningsen et al. 2003).

Comorbidity of physical and mental disorders associates with work disability (Catalina-Romero et al. 2012), and in Finland, since 2000 psychiatric disorders have been a leading cause of disability pensions. The clinical studies (Study I, II), could not identify somatic diseases or psychiatric disorders as the major cause of disability, but psychiatric causes may certainly have contributed to it.

Comorbidity must be recognized, because treating all identified diseases may reduce disability.

6.1.6 ENVIRONMENTAL INTOLERANCE – PREVALENCE AND THE SEVERITY GRADIENT

The findings of Study IV confirm that the prevalence of EI depends on its definition. Almost all the respondents reported being at least somewhat annoyed by an environmental factor. Prevalence rates differed when EI included different ratings of annoyance, symptoms, behavioral change, or disability. These dimensions represent different manifestations of EI, seen as a continuum of increasing severity, which in numerous previous studies has appeared as varying prevalence rates, depending on the definition used. Study IV succeeded in demonstrating the increasing severity continuum of EI in more details than previous studies (Berg et al. 2008; Björnsson et al. 1998; Caress and Steinemann 2004a; Carlsson et al. 2005; Johansson et al. 2005; Kreutzer et al. 1999; Palmquist et al. 2014). The findings reveal that EI with difficulties in daily life is surprisingly prevalent, and can be differentiated from annoyance, which is less disabling and could be encountered by half the study population. Figure 7 illustrates similar increasing severity of FSS (Fink and Rosendal 2015). In FSS, the stages of severity, as a basis for the stepped-care approach, corresponded with the different management options in clinical practice (Henningsen et al. 2018; olde Hartman et al. 2017).

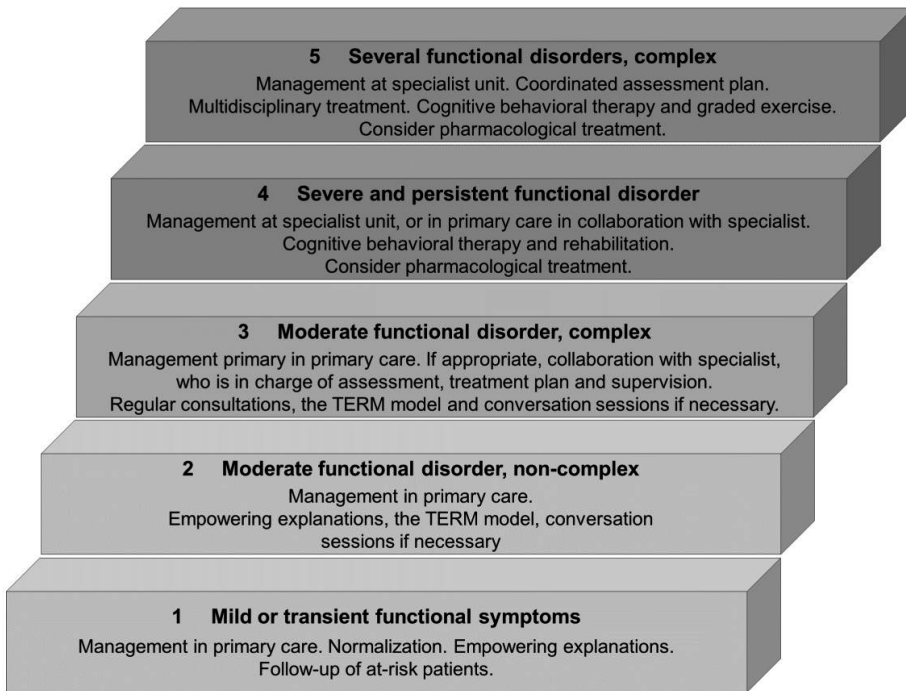


Figure 7 Increasing severity of functional somatic syndromes (FSS) and its' stepped care (based on Fink and Rosendal 2015). TERM, the extended reattribution and management.

Cultural and societal factors can affect symptom perception and reporting, and may contribute to the development of EI. Risk perception can be influenced by various aspects, such as heightened concerns about particularly dreaded consequences or lack of scientific information; mistrust, attitudes and beliefs about medicine; political or legal agendas and media and pressure group activity (MacGregor and Fleming 1996). For example, individuals in experimental studies who were given media warnings about the adverse effects of supposedly hazardous substances experienced more health-related concerns and symptoms attributed to the neutral exposure than those in the control group (Verrender et al. 2018; Winters et al. 2003; Withöft and Rubin 2013).

Few previous surveys have determined the dominating environmental factors in severe EI cases. Palmquist et al. (2014) found that physician-diagnosed EI attributed to chemicals was more common than EI attributed to certain buildings or to EMFs in a Swedish population-based sample. In Study IV, all respondents with 'severe' disability (2.2%) or 'very severe' disability (0.9%) attributed their EI to indoor molds, and two thirds to both molds and chemicals. The preponderance of EI attributed to indoor molds seen in clinical Study II and in epidemiological Study IV may reflect the general concern in Finland that indoor molds are an environmental health hazard. This was also

seen in a previous study of the working population in Finland, in which 11.4% perceived their workplaces' indoor environment as harmful due to molds (Finell and Seppälä 2018). The differences between the environmental factors to which EI is attributed in different countries may reflect the risk perceptions of the population, when the difference is not attributable to other risk-factor profiles (Karvala et al. 2018b).

6.1.7 BUILDING-RELATED INTOLERANCE

Chronic indoor air-related symptomatology fulfills the WHO's criteria for IEI (IPCS/WHO 1996). Previous findings concerning individuals with indoor air-related non-specific symptoms attributed to indoor molds have recognized similarities with IEI (Al-Ahmad et al. 2010; Khalili et al. 2005). Disability, as IEI, can be encountered among individuals with indoor air-related ill health. Our findings further revealed indoor air-related disability as a phenomenon with persistent and recurrent non-specific symptoms in several organ systems attributed to indoor air factors (e.g. indoor molds), leading to avoidance and restrictions to several daily life functions. In addition, the disability shows various signs of distress and comorbid diseases with no medical or exposure-related explanations. Our study findings add to the understanding of this phenomenon (Figure 8) (Norbäck 2009; Redlich et al. 1997; WHO 1983, 2009). These findings strengthen the hypothesis that indoor air-related disability with an increasing severity gradient shares features with EI and FSS, and that BRI and other EIs seem to represent the same phenomenon (Dantoft et al. 2015; Das-Munshi et al. 2007; Rief et al. 2017; Van den Bergh et al. 2017a; Watanabe et al. 2003a). Lacour et al. (2005) have previously summarized the overlap between EI and FSS, and these shared common mechanisms have been suggested as maintaining EI and FSS, i.e., sustained stress and arousal due to central sensitization (Yunus 2015).

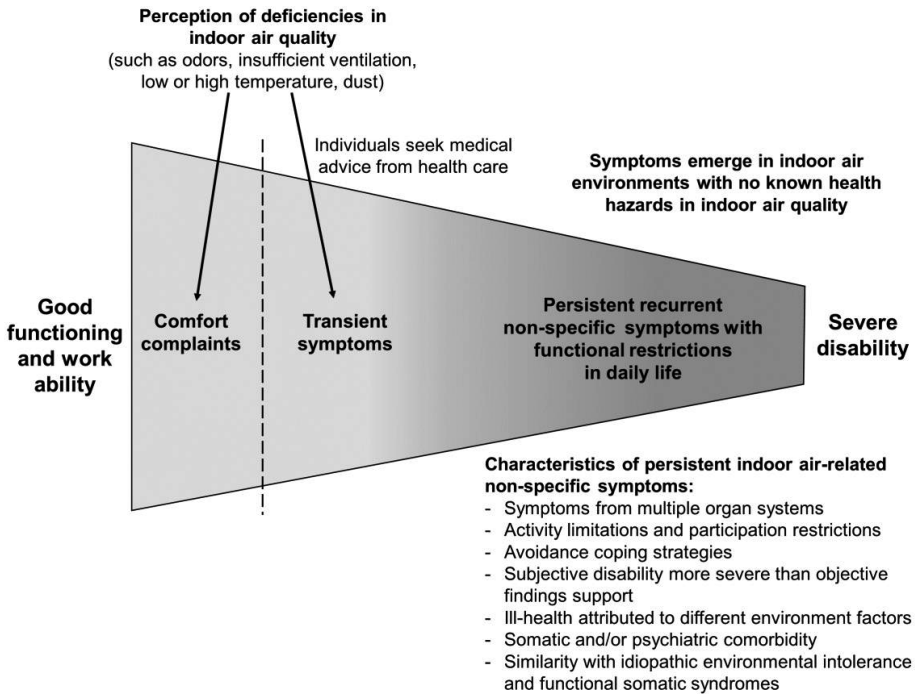


Figure 8 Manifestation of indoor air-related disability with typical characteristics.

6.1.8 MANAGEMENT OF INDOOR AIR-RELATED DISABILITY

So far, EI has been considered a chronic, stable condition, resistant to therapy (Bailer et al. 2008b; Black et al. 2001; Dantoft et al. 2015; Das-Munshi et al. 2007; Eek et al. 2010; Lacour et al. 2005). There is a lack of research on the course of EI and controlled interventions aiming to reduce reactivity to the environment. In a prospective study of the one year stability of somatic symptoms and IEL, the strongest predictor of IEL was somatic attributions, followed by prominent cognitions of environmental threats and a tendency to focus on unpleasant bodily sensations and consider them as pathological (Bailer et al. 2007). In addition, a five-year follow-up study in a general population sample showed that anxiety (negative affect) associated with the development and persistence of symptoms and life impact attributed to common airborne chemicals (Skovbjerg et al. 2015). Recent data on the natural course of EI have shown that EI is reversible (Palmquist 2017). In a longitudinal population-based study over a six-year period, one fifth of the individuals with self-reported EI attributed it to chemicals, certain buildings, EMFs or everyday sounds recovered, especially those with less affective and behavioral changes (Palmquist 2017). Furthermore, increasing evidence of central mechanisms in chronic responsiveness, as an active inferential process that is highly dependent on prior experiences, expectations and contextual cues, provides a compelling explanation for EI (Van den Bergh et al. 2017a),

which enables treatment strategies for prevention and recovery to be targeted, even in severe IEI.

Various biopsychosocial factors have shown to influence building residents' reports of symptoms. Previous clinical experiences of patients with indoor air-related ill health have revealed long-lasting, disproportionate amounts of functional restrictions in everyday life and sustained symptoms over follow-ups. This shows a need for a biopsychosocial approach in management (Al-Ahmad et al. 2010; Edvardsson et al. 2008; Karvala et al. 2013, 2014). Effective, practical means of support and treatment for these individuals are lacking.

The first RCT setting (Study I) aimed to decrease excess concerns, symptoms and disability through counseling and psychoeducation of patients with indoor air-related symptoms and work disability. Over the six-month follow-up, however, the limited counseling did not improve the patients' symptom management skills or work ability. There may be several reasons for the ineffectiveness of the intervention. A plausible explanation would be the long-lasting symptom history related to disability, which requires more intensive intervention. Characterization revealed numerous persistent, ongoing indoor air-related non-specific symptoms and disability among patients, and the features of IEI and FSS. Counseling that provides knowledge regarding mechanisms does not necessarily affect patients' interpretations of the causes of the symptoms. In a previous study of individuals with IEI-EMFs, accurate feedback after a placebo-controlled provocation study was insufficient to change their attributions to mobile phone signals or reduce symptoms over six-month follow-up (Nieto-Hernandez et al. 2008). In another previous study of patients with chronic health conditions, health promotion counseling provided by a physician seemed to improve health-related QOL, although this was not apparent in those with anxiety or depression (Al Sayah et al. 2014). The counseling techniques used in Study I for management of symptoms may not have taken into account all the emotional and cognitive features of IEI and FSS, although they aimed to minimize the perceived harmfulness of indoor air-related factors.

Although Study I found no intervention effect, it showed that this type of approach can be carried out, and that for features of IEI and FSS, the chosen framework may be helpful and suitable for health care. Therefore, the next RCT (Study III) was designed to target patients with a shorter symptom duration and aimed toward early detection of disability in OHS units. Taking into account previous findings regarding the features of IEI and FSS, inclusion was designed on the basis of IEI criteria and focused on indoor exposures. The intervention programs were developed on the basis of the evidence of effects in similar conditions. Thus, in the biopsychosocial approach, similar management strategies were applied as those for FSS (Henningesen et al. 2018; Van Dessel et al. 2014), despite a lack of evidence-based treatments for IEI. For FSS, CBT has shown positive effects; for example, reduction of somatic symptoms (Van Dessel et al. 2014). Therefore, CBT was the natural choice for

an intervention arm, as well as better counseling than that in Study I. Both arms in the RCT design (Study III) have focused on reducing stress and improving health behavior (e.g. mechanisms of physiological arousal and emotion-behavior-symptom cognitions) rather than on cognitive distortions. The unexpectedly slow recruitment processes in Study III may indicate the cultural, societal and general attitudes towards biopsychosocial approaches in the management of indoor air-related disability. In general, although precise data are lacking, the availability of psychosocial treatments (e.g. CBT) are probably inadequate in the Finnish healthcare system. Nevertheless, in many health problems, the functional nature is recognized and the care guidelines highlight psychosocial treatment options, such as in the case of different pains (e.g. Pain: Current Care Guidelines Abstract 2017) and insomnia (Insomnia: Current Care Guidelines Abstract 2017).

In the management of indoor air-related disability, individuals' social surroundings and responses (such as the environmental factors included in the ICF concept) can either support or hinder the well-being, health and work ability of individuals. This input may iatrogenically harm and maintain illness behaviors (Dantoft et al. 2015; Kirmayer and Taillefer 1997; Rief and Broadbent 2007; Watanabe et al. 2003a). For example, when interpretations of symptoms/physical sensations as a sign of illness lead individuals to seek medical advice, this in itself can lead to the individuals maintaining a sick role and to repeated tests and medicalization. In this model of a vicious circle in doctor-patient contact, the patient's physician can initiate further investigations even if there is no organic basis for the symptoms (Henningesen et al. 2007).

Disability from indoor air-related ill health can be identified and should be treated effectively. The findings of Study II showed that environmental control and avoiding factors perceived as harmful was a typical coping response among the patients. In IEL, the pathway toward disability is associated with avoidance due to perceived symptom triggers (Dantoft et al. 2015; Skovbjerg et al. 2009a, 2012b; Watanabe et al. 2003a). It is clear that when there is, for example, significant moisture and mold damage in buildings, avoidance before repairs may be reasonable; but needless avoidance should not be supported. Management to reduce fear response and adverse avoidance strategies requires that the patient feels in control of the exposure situation. This requires trust in health care providers' explanations for symptom mechanisms and that no health hazard exists in the indoor environment.

As regards indoor air-related ill health, recognition of features similar to IEL and FSS reduces the continuous search for medical and environmental explanations. Effective treatments for disability prevention are seriously needed. In the future, the course of interventions should be directed towards centrally mediated and threat-response mechanisms activated by environmental triggers. In addition, the stepped care FSS model, i.e. the more severe or complex the symptoms and limitations, the more intense and multifaceted is the treatment needed for patient recovery (Figure 7) (Fink and

Rosendal 2015; Henningsen et al. 2007, 2018; olde Hartman et al. 2017), could be utilized in the treatment strategy of BRI and other EIs.

6.2 METHOLOGICAL CONSIDERATIONS

The strength of this combination of studies is that the study participants were from different levels of health care, such as an occupational medicine clinic, OHS units, and maternity (preventative) clinics. In addition, the studies represent clinical characteristics, RCT settings and a questionnaire-based survey.

The primary strength of clinical characterization (Study I, II) was that the patients with work-associated symptoms and disability had been thoroughly and systematically medically examined. In addition, nearly all the patients had been examined earlier in their OHS units and by other physicians. In Study I, the clinical examinations focused exclusively on biomedical aspects, as is stipulated by the Finnish Act on Occupational Diseases, revealing the relationship between exposure and the disease/symptoms. However, all work-related and non-work-related symptoms and diseases were characterized during the differential diagnostics. It is thus highly unlikely that any underlying medical diseases resulting in disability would have remained unrevealed, despite the absence of a thorough evaluation of psychiatric disorders and psychological features. However, psychological counseling repeatedly revealed the emotional and cognitive symptoms and concerns of the subjective health condition. The consecutive patients with a suspected occupational disease made the study group (Study I) uniform, although very specific to an occupational medicine clinic. Although the eligible patients represented only a proportion of occupational medicine clinic material (41%; 79/194), the results may be generalized to patient populations suffering from indoor air-related non-specific symptoms with disability. The 24 patients who refused to participate were not assumed to differ from the study patients on the basis of their reasons for non-participation.

Study II focused on patients with indoor air-related disability. The clinical characterization (Study II) included a thorough, multi-professional clinical evaluation and the use of a large amount of various, validated and widely used instruments. The assessment of the individuals' functioning and disability was based on the ICF framework. The wide-ranging scope enables us to characterize the indoor air-related disability despite the small number of patients. The biopsychosocial approach (ICF) was suitable for evaluating a condition that is not necessarily explained by disease or physical body functions/structures, but which causes a substantial number of functional restrictions in daily life. A limitation was the small number of patients, which restricted generalization of the results.

In addition, selection bias may exist (Studies I–III) if the individuals who attended were better able to consider their condition from a biopsychosocial

viewpoint. Moreover, self-assessments in retrospective questions might have been affected by recall problems, such as time from the onset of symptoms. Therefore, in the clinical studies (Study I, II), data from medical records and clinical interviews were also gathered.

The goal in both the RCT settings (Study I, III) was to develop effective interventions for individuals with indoor air-related non-specific symptoms and disability. The focus was on reducing symptoms and disability related to indoor environments. The limited counseling in the first RCT setting (Study I) was conducted at an occupational medicine clinic during the normal differential diagnostic process. To our knowledge, this was the first RCT setting with a biopsychosocial approach in the context of indoor air-related (work) disability prevention. In Study III, the CBT program has been developed on the basis of previous intervention protocols from similar conditions, like FSS. The strength of its RCT design (Study III) is that the individuals are recruited from OHS, which is part of Finland's overall primary health care, and enables the evaluation of the usefulness of the psychosocial intervention in OHS and general practice settings. Based on the previous clinical (Study I) findings regarding the features of IEI and FSS, we included IEI criteria that focused on indoor exposures. We also target the early detection of indoor air-related disability. The well-defined inclusion and exclusion criteria diminish the heterogeneity among the participants verified by the recruiting physicians and help avoid obvious confounding factors. The individuals had also been clinically investigated by the recruiting physicians, and the additional clinical examination at FIOH was to ensure that there was no medical condition behind the patient's symptomatology and disability. The detailed data of the individuals' health conditions have generally been gathered via a questionnaire, and the longitudinal follow-up design increases the strength of the evaluation's effectiveness. The purpose of the high number of assessment methods as outcome measures is to enable observation of various aspects of health and well-being in everyday life. The potential bias of missing data is taken into account by using a web-based questionnaire in which respondents are forced to respond.

In both RCTs (Study I, III), potential contextual processes may have had an effect on the recruiting process, as well as on the outcomes of the intervention. The possible changes in OHS systems and/or at work, and other factors may affect motivation to participate and continue in the study. For example, pressure from social surroundings may affect individuals' attitudes toward the chosen framework for support and treatment. During the recruitment and waiting period, individuals were contacted, clinically examined and randomized, which may have had a placebo effect on a patient's condition in both RCTs. This in turn may have weakened intervention effects. Moreover, the CBT arm with eleven sessions (Study III), including homework and practicing, required longer commitment to treatment than limited psychoeducation (Study I, III). This might have increased the drop-out rate in the CBT group.

The strength of the maternity clinic survey (Study IV) was its representative sample of fertile-aged women, but its weakness was its low participation rate. The study focused on all fertile aged women who attended a birth clinic of the Kuopio central hospital region. The study succeeded in recruiting 27% of the pregnant women of the maternity clinic clients. The focus was on females because they typically report EI more often than men, and the sample represented an age group in which EI is prevalent (Dantoft et al. 2015; Watanabe et al. 2003a). Although the results represent EI among fertile aged women, the low participation rate calls for caution in the generalization of the results.

The questionnaire (Study IV) contained typical characteristics of EI in terms of different degrees of severity based on the MCS literature. The literature had no generally agreed on EI definition to clarify its prevalence, nor a precise severity measure of disability. Thus, we defined EI in several ways, which enabled us to study its severity gradient and the spectrum of different EIs and their associations with symptoms, behavioral changes, co-occurrence and disability due to different environmental factors. In the outcomes, the female gender (Berg et al. 2008; Carlsson et al. 2005), pregnancy (Cameron 2014), and the large spectrum of questioned environmental factors may explain at least the high prevalence of reported annoyance. The prevalence rates may also exaggerate whether individuals with environment-related annoyance are more likely to participate in a study investigating environmental issues. In addition, heightened perception of unpleasant qualities and odors is especially encountered in early pregnancy (Cameron 2014; Nordin et al. 2004, 2007), which may have increased the reporting of EI. To avoid excess reporting, the respondents were asked to evaluate the time prior to their pregnancy, not limited to a certain period of time. These may be sources of information bias. If early pregnancy increases the reporting of annoyance, it is unlikely that this would increase the number of respondents reporting severe difficulties due to EI. The study did not focus on concomitant diseases, thus we were unable to study their associations. Regardless of concomitant somatic or psychiatric diseases, the important factor is whether individuals attribute their symptoms, behavioral changes and disability to the environment.

7 CONCLUSIONS

This thesis aimed to characterize the disability related to non-industrial work indoor environments and to develop interventions for individuals with indoor air-related disability. The results suggest that:

- indoor air-related disability may be explained by EI (environmental intolerance) and shares features with FSS (functional somatic syndromes).
- in disability, comorbidity of medical (somatic and psychiatric) diseases is common and should be taken into account in disability prevention.
- indoor air-related disability encounters various signs of distress (physical, emotional and cognitive), which should be taken into account in disability prevention.
- indoor air-related work disability emerges in several life areas, not only at work, but also in social areas, and in functioning at home.
- indoor air-related disability is based on self-reports and is typically more severe than objective findings suppose.
- the prevalence of EI depends on its definition. EI with disability is surprisingly prevalent, and should be differentiated from annoyance, which is less disabling and prevalent in the population. As the severity of disability increases, the number of organ systems, behavioral changes and the co-occurrence of various EIs also grow.
- in Finland, in EI with severe disability, indoor molds seem to be the most common environmental factor to which individuals attribute symptoms.
- recognition of EI is possible and enables better targeting of disability management and rehabilitation instead of continuously searching for medical and environmental explanations.
- counseling including limited psychoeducation and symptom management among patients with indoor air-related disability seems to be insufficient. Effective treatments for disability prevention are desperately required, and need to be further developed. Similar treatment approaches that have been promising for FSS may already be in use, especially different psychosocial interventions, which should be further evaluated.

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APPENDICES

Appendix 1

Definitions of environmental intolerance (EI).

Appendix 1. *Definitions of environmental intolerance (EI).*

Reference	Term	Environmental factors included	Definition
Randolph (1956, 1962)	MCS	Chemicals	MCS affects multiple organ systems due to an inability to adapt to chemicals and result responsiveness to extremely low concentrations after sensitization. Symptoms occur when exposed to chemicals or during withdrawal from exposure after an adaptive response has occurred.
Thomson et al. (1985) ^a	Environmental hypersensitivity	Chemicals (e.g. natural gas fumes, tobacco smoke, formaldehyde), foods (e.g. milk, wheat, eggs), natural inhalants (e.g. pollens, dusts, molds)	<p>Working definition of environmental hypersensitivity:</p> <ul style="list-style-type: none"> - Chronic (of at least 3 months' duration), - usually includes symptoms of CNS and at least one other system, - affected individuals are frequently intolerant of some foods and react adversely to some chemicals and environmental agents, either singly or in combination, at levels generally tolerated by the majority, - varying degrees of morbidity (from mild discomfort to total disability), - upon physical examination, individuals are normally free from any abnormal objective findings, - improvement is associated with avoidance of suspected agents and symptoms recur with re-exposure.
Cullen (1987)	MCS	Chemicals	<p>Acquired disorder in relation to some documentable environmental exposure(s):</p> <ul style="list-style-type: none"> - Symptoms: involve more than one organ system, - recur and abate in response to predictable stimuli, - elicited by exposures to chemicals of diverse classes, - are in response to demonstrable exposures at doses far below those established as causing adverse human effects, - have no correlating single widely acceptable test of organ system function.

Ashford and Miller (1992)	MCS	Chemicals	<p>Definition for diagnostic purposes, based on challenge testing:</p> <ul style="list-style-type: none"> - MCS can be discovered by removing patient from the suspected offending agent and by rechallenge, after an appropriate interval, under strictly controlled environmental conditions. - Causality is inferred by the disappearance of symptoms when away from the offending environment and the recurrence of symptoms in response to a specific challenge.
National Research Council (1992)	MCS	Chemicals	<p>Sensitivity to chemicals with symptoms or signs of chemical exposure:</p> <ul style="list-style-type: none"> - Occur at levels tolerated by the population at large, distinct from well-recognized hypersensitivity phenomena (such as IgE-mediated immediate hypersensitivity reactions, contact dermatitis, and hypersensitivity pneumonitis), - may be expressed as symptoms and signs in one or more organ systems, - vary according to exposures. - It is not necessary to identify a chemical exposure associated with the onset of the condition. - Pre-existent or concurrent conditions, e.g. asthma, arthritis, somatization disorder or depression, should not exclude patients from consideration.
Nethercott et al. (1993)	MCS	Chemicals	<p>Following case definition for MCS:</p> <ul style="list-style-type: none"> - Condition is chronic, symptoms recur reproducibly with exposure. - Occurs in response to low levels of exposure, and to multiple unrelated chemicals which improve or disappear when incitants are removed.
IPCS/WHO (1996)	IEI	Chemicals (e.g. VOCs), biological (e.g. molds), physical (EMFs), and psychological (e.g. stress)	<p>IEI covers a number of disorders that share similar symptomatology as described in MCS:</p> <ul style="list-style-type: none"> - Acquired disorder with multiple recurrent symptoms, - associated with diverse environmental factors tolerated by the majority of people, and - not explained by any known medical or psychiatric/psychologic disorder.

MCS consensus conference (1999)	MCS	Chemicals	<p>Following criteria must be met in MCS:</p> <ul style="list-style-type: none"> - Condition is chronic, with symptoms that reproducibly recur, in multiple organ systems, - occurs in response to low levels of exposure, and to multiple unrelated chemicals, symptoms improve or disappear when incitants are removed. - Other disorders may also occur, such as asthma, allergy, migraine, chronic fatigue syndrome, and fibromyalgia.
Lacour et al. (2005)	MCS	Chemicals	<p>Definition expanded to also include:</p> <ul style="list-style-type: none"> - Duration of at least 6 months, caused significant lifestyle or functional impairments, - CNS symptoms association with self-reported MCS, - symptoms must be present in CNS and at least one symptom in another organ system.
Elberling et al. (2014)	MCS	Scents and chemicals (e.g. fragranced products, freshly printed papers or magazines, tobacco smoke and new furniture)	<p>Criteria of MCS in Danish diagnostic classification:</p> <ul style="list-style-type: none"> - Symptoms are attributed to common scents and chemicals, - CNS symptoms such as headache, dizziness, concentration difficulties and exhaustion are mandatory. In addition, symptoms in other organ systems are often reported (e.g. of the mucosal/respiratory tract, musculoskeletal system and gastro-intestinal tract). - Symptoms improve or disappear when exposures are removed. - Condition is chronic (of at least 6 months duration). - Symptoms are associated with significant lifestyle or functional impairments (e.g. loss of job or social network).

Baliatsas et al. (2012)	IEI-EMFs	Any EMF source (e.g. mobile phones, video display terminal/units)	Criteria of IEI-EMFs: <ul style="list-style-type: none"> - Self-reported sensitivity to EMFs, - attribution of non-specific physical symptoms to any EMF source, - absence of medical or psychiatric/psychological disorder that could account for symptoms, - symptoms should occur soon (up to 24 hours) after the individual perceives an exposure source or exposed area.
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MCS, multiple chemical sensitivity; CNS, central nervous system; IgE, immunoglobulin E; IPCS, international programme on chemical safety; IEI, idiopathic environmental intolerance; VOCs, volatile organic compounds; EMFs, Electromagnetic fields.

^a Based on the Ontario Ministry of Health Committee (1985) definition.

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