

Doctoral Programme in Psychology, Learning and Communication, Department of Psychology and Logopedics and Department of Psychiatry, Faculty of Medicine, University of Helsinki, Finland

# **COMPONENTS OF SUBJECTIVE HEALTH COMPLAINTS**

**EVIDENCE FROM PROSPECTIVE COHORT STUDY AND  
RANDOMIZED CONTROLLED TRIAL**

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# ABSTRACT

Several biological and behavioural risk factors for respiratory health have been established. However, individuals may perceive and interpret somatic symptoms and sensations differently. Psychiatric disorders, psychological dispositions, situational factors and prior experiences can influence the significance that individuals attach to bodily sensations and their regulation. Thus, as subjectively perceived respiratory complaints may not always align with objective clinical measurements, these factors may be linked with worse respiratory outcomes in populations of patients, samples of healthy individuals and moreover with persistent physical symptom (PPS) reports. In some cases, PPS appear despite good care and are associated with environmental factors such as indoor air, regardless of indoor environment quality. PPS challenge the health care system as they do not respond to standard medical treatment and cannot be explained by conventional medical models.

This thesis examines the association between psychological dispositional characteristics and subjectively and objectively assessed respiratory outcomes, and the discrepancy between subjective and objective health measures in cross-sectional (Study I) and follow-up designs (Study II) at the population level. The aim was to investigate the effects of these factors on health-related quality of life (HRQoL) among cases with PPS associated with the indoor environment (Study III) and the effectiveness of psychosocial treatment for these complaints (Study IV).

This thesis used two complementary datasets. First, we examined how sense of coherence, alexithymia and health anxiety were associated with respiratory health complaints without objectively assessed problems in lung function or incidence of respiratory diseases in a population-based data Health 2000 survey and its 11-year follow-up study Health 2011 (Studies I–II). Health 2000 is a nationally representative survey of over 30-year-old Finnish adults conducted by the Finnish Institute for Health and Welfare. Its data include comprehensive clinical health examinations, interviews covering respiratory symptoms and common psychiatric disorders, and validated questionnaires on psychological dispositions. The data of this study included the participants with complete information on lung function and respiratory symptoms (N=4544). The follow-up analyses in the Health 2011 sample were restricted to participants who were still working aged (<65 years) during the follow-up assessment in 2011 and had been included in the baseline study (N=2310).

The second part of the thesis examined a randomized controlled trial (RCT) that compared treatment as usual (TAU) enhanced with cognitive behavioural therapy (CBT) or psychoeducation for non-specific symptoms associated with the indoor environment (Studies III–IV). The RCT included data from the

participants recruited from occupational health service units. The inclusion criteria for participants were i) recurrent and persistent multiorgan symptoms and disability that they attributed to workplace indoor air, ii) symptoms not adequately explained by medical or indoor environment exposure-related reasons and iii) onset of symptoms with disability for a maximum of three years before the study. Candidates also had to be occupationally active. After baseline clinical examinations, the participants were randomized into TAU or TAU enhanced with psychoeducation or CBT. The primary outcome was HRQoL, and the secondary outcomes included measures of symptom severity and dispositional factors, which were followed up for 12 months after randomization.

The findings of this study show that over a quarter of the Finnish population report respiratory health complaints without objective signs of impaired lung function. Sense of coherence, alexithymia and high illness worry associated significantly with perceived complaints. Individuals reporting respiratory health complaints without any objective signs of respiratory pathology reported 1.25 (95% CI 1.15–1.35,  $p < 0.0001$ ) times more health care visits than those with normal lung function and no respiratory symptoms. The difference between these groups attenuated by almost 43% following adjustment for psychological factors. Further, high illness worry and alexithymic characteristics predicted the incidence of respiratory health complaints and respiratory diseases during the eleven-year follow-up. Individuals with PPS associated with the indoor environment had significantly poorer HRQoL than comparisons derived from the general population or subgroups of those with asthma, anxiety and depressive disorder, or a chronic condition that caused work disability. Of the dispositional factors, high neuroticism showed a significantly negative, and high sense of coherence a significantly positive correlation with good HRQoL. The analyses revealed no robust effect of psychosocial interventions on HRQoL but in some cases, they prevented the deterioration of HRQoL because of PPS associated with the indoor environment.

The findings from population-based Studies I and II including both objective and subjective health outcomes agree with previous studies conducted among populations of patients and in selected samples of healthy individuals and suggest that dispositional factors play a prominent part in respiratory outcomes at the population level. Our findings from Study III underline the need for improved treatment among patients with PPS associated with the indoor environment and further, that dispositional factors should be acknowledged in the treatment process. However, the results from Study IV suggest that improving the effectiveness of treatment for these health complaints requires information on the therapeutical change mechanisms related to the condition and a special focus on the acceptance of treatments. It is also important to promote further research of socio-cultural factors to explain the disease initiation and treatment process and to understand the emergence of the health complaints associated with environmental factors.

# TIIVISTELMÄ

Merkittävä osa väestöstä kokee päivittäin fyysisiä oireita, johon vaikuttavat monet yksilölliset sekä ulkoiset tekijät. Esimerkiksi hengitysterveyteen on havaittu vaikuttavan ympäristö- ja biologisten tekijöiden ohella psyykkiset tekijät: mielialahäiriöt lisäävät riskiä sairastua yleisiin kroonisiin hengityssairauksiin vaikuttaen myös hengitysoireiden voimakkuuden kokemiseen. Onkin havaittu, että psykiatriset sairaudet selittävät hengitysoireiden raportointia yhtä paljon kuin keuhkojen sairaustila. Lisäksi oireiden tunnistamista selvittämissä kokeellisissa tutkimuksissa on havaittu, että koehenkilöiden yksilölliset, käyttäytymisen säätelyyn vaikuttavat psykologiset tekijät selittävät eroja oireiden tunnistamisessa sekä niihin reagoinnissa. Siten sekä psykiatriset sairaudet että pitkäaikaiset psykologiset reagoitumallit vaikuttavat hengitysterveyteen. Toistaiseksi ei kuitenkaan ole väestötason tietoa koettujen oireiden suhteesta objektiivisiin keuhkojen toimintakokeisiin tai siitä, ovatko psykologiset tekijät itsenäisesti yhteydessä muutoksiin hengitysterveydessä. Myös sisäilmastoon liittyvissä pitkäaikaisissa ja hankalissa oireissa on tunnistettavissa objektiivisten hengitysoireiden lisäksi piirteitä, joiden ilmenemiseen edellä kuvatut tekijät voivat vaikuttaa. Näitä oireita voi ilmetä ilman osoitettavissa olevia sisäympäristön rakenteellisia vikoja tai ne voivat ilmetä useissa eri ympäristöissä. Toistaiseksi näille oireille ei ole vakiintuneita hoito- tai kuntoutusmuotoja eivätkä ne reagoi ympäristötekijöiden korjaukseen.

Tämän väitöskirjatyön tavoitteena oli selvittää väestötasolla, ovatko psykologiset käyttäytymisen säätelyyn vaikuttavat tekijät yhteydessä hengitysoireisiin tai -sairauksiin, jotka eivät ole yhteydessä lääketieteellisiin löydöksiin (Osajulkaisut I-II). Lisäksi tämän väitöskirjan tavoitteena oli selvittää, ovatko nämä tekijät yhteydessä sisäilmaan liittyvään pitkäaikaisesti ja hankalasti oireilevan potilaan elämänlaatuun ja millainen näiden henkilöiden elämänlaatu on verrattuna väestön tai yleisissä kliinisissä sairausryhmissä havaittuun elämänlaatuun. Tutkimme myös, onko terveyskäyttäytymistä tukeva psykososiaalinen hoito vaikuttavaa tavanomaiseen hoitoon nähden elämänlaadun tukemisessa.

Väitöskirjatyö koostuu neljästä osatyöstä, jotka pohjautuvat kahteen toisiaan täydentävään tutkimusaineistoon: a) yli 30-vuotiasta suomalaisväestöä edustava Terveys 2000 ja sen vuonna 2011 kerätty seuranta-aineisto (Terveys 2011) sekä b) satunnaistettu, kontrolloitu seurantatutkimus Toiminnalliset oireet ja työkyvyn tuki sisäilmaongelmissa - Toimintamalli työterveyshuoltoon (TOSI-hanke). Terveys 2000-aineistoon perustuvan tutkimuksen kohteena ovat ne keuhkojen kliinisiin toimintakokeeseen osallistuneet henkilöt, joilla ei ole diagnosoituja hengitys- tai muita keuhkojen toimintaan vaikuttavia sairauksia tai vaikeita mielenterveyshäiriöitä (N=4544) sekä heistä edelleen vuonna 2011 työiässä (<65 vuotta) olevien

seuranta-aineisto (N=2310). Selitettävänä muuttujina olivat koetut hengitysoireet ja terveystalveluiden käyttö sekä seurannassa hengitysoireilu, sairastuvuus hengityssairauteen sekä keuhkojen toiminta kliinisesti arvioituna. Selittävinä muuttujina olivat terveystalveluiden käyttöön vaikuttavat psykologiset tekijät: tutkittavien elämäntalveluiden hallintatunne, aleksityymiset piirteet sekä terveystalveluiden käyttöön. TOSI-hankkeeseen rekrytoitiin työssä käyviä aikuisia, joilla oli ollut työympäristön sisäilma-ongelmiin liittyvien pitkittyneiden hengitys- ja muiden epä-spesifien oireiden takia vaikeuksia selviytyä työssään. Kliinisten alkututkimusten jälkeen heidät (N=52) satunnaistettiin tutkimusryhmiin a) tavanomainen hoito tai tavanomainen hoito tuettuna b) psykoedukaatiolla tai c) 10 kerran kognitiivis-behavioraalisella psykoterapialla. Henkilöiden terveyteen liittyvää elämäntalvelua sekä psyykkisen ja fyysisen oireilun muutosta sekä pitkäaikaisia reagoitaitapumuksia seurattiin vuoden ajan tutkimuksen alusta.

Tulosten mukaan jopa neljännes suomalaisista kokee hengitysoireita, joiden taustalta ei ole osoitettavissa keuhkojen toimintaongelmia tai hengityssairautta. Psykologiset tekijät ennustivat koettuja oireita ja ne olivat yhteydessä terveystalveluiden kohonneeseen käyttöön henkilöillä, joilla ei ole keuhkojen toimintaongelmia. Tästä lähes 43% selittyi psykologisilla tekijöillä (Osajulkaisu I). Lisäksi tekijät olivat yhteydessä astman sekä COPD:n ilmaantuvuuteen ja hengenahdistukseen 11 vuoden seurannassa (Osajulkaisu II). Satunnaistetun, kontrolloidun tutkimuksen perusteella henkilöt, joiden kokemana oireilu sisäilmaan liittyen ei ole yhteydessä tehtyihin kliinisiin löydöksiin, elämäntalvelu on merkittävästi huonompi kuin väestössä keskimäärin sekä verrattuna väestötasolla merkittäviin kliinisiin sairausryhmiin (Osajulkaisu III). Psykososiaalisilla interventioilla ei todettu vaikutusta tutkittavien elämäntalveluun vaikka hoito saattaa ehkäistä tilan vaikeutumista (Osajulkaisu IV).

Terveystalveluiden käyttöön vaikuttavat tekijät vaikuttavat väestötasolla oireista seuraavaan terveydenhuollon sekä inhimilliseen kuormaan. Ne ennustavat sairastumista hengityssairauteen sekä ovat yhteydessä lisääntyneeseen terveystalveluiden käyttöön samaan aikaan ilmenevistä psykiatrisista sairauksista huolimatta. Terveystalveluiden käyttöä säätelevät tekijät ovat myös yhteydessä sisäilma-tekijöistä pitkäaikaisia ja hankalia oireita saavien henkilöiden huonoon elämäntalveluun. Lisätutkimusta tarvitaan yksilöllisistä hoitovasteeseen vaikuttavista tekijöistä. Lisäksi tutkimuksessa tulisi huomioida kulttuuriset tekijät, jotka voivat vaikuttaa sisäilma-tekijöihin yhdistyvien oireiden ilmaantuvuuteen, niille annettuihin selitysmalleihin sekä hoitovaihtoehtojen kehittämiseen.

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# LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

- I Selinheimo, S., Vasankari, T., Jokela, M., Kanervisto, M., Pirkola, S., Suvisaari, J., & Paunio, T. (2019). The association of psychological factors and healthcare use with the discrepancy between subjective and objective respiratory-health complaints in the general population. *Psychological medicine*, 49(1), 121-131.
- II Selinheimo, S., Jokela, M., Vasankari, T., Kanervisto, M., Pirkola, S., Suvisaari, J., & Paunio, T. (2021). Poor respiratory health outcomes associated with high illness worry and alexithymia: Eleven-year prospective cohort study among working-age population (*Submitted manuscript 2021*).
- III Selinheimo, S., Vuokko, A., Hublin, C., Järnefelt, H., Karvala, K., Sainio, M., Suojalehto, H. & Paunio, T. (2019). Health-related quality among life of employees with persistent nonspecific indoor-air-associated health complaints. *Journal of Psychosomatic Research*, 122, 112-120.
- IV Selinheimo, S., Vuokko, A., Hublin, C., Järnefelt, H., Karvala, K., Sainio, M., Suojalehto, H. & Paunio, T. (2020). Psychosocial treatments for employees with non-specific and persistent physical symptoms associated with indoor air: A randomised controlled trial with a one-year follow-up. *Journal of Psychosomatic Research*, 109962.

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# ABBREVIATIONS

|          |  |
|----------|--|
| COPD     | Chronic obstructive pulmonary disease                  |
| EBM      | Evidence-based medicine                                |
| FEV1     | Forced expiratory volume in one second                 |
| FIOH     | Finnish Institute of Occupational Health               |
| FSS      | Functional somatic symptoms                            |
| FVC      | Forced vital capacity                                  |
| GAD-7    | General Anxiety Disorder-7                             |
| HRQoL    | Health-related quality of life                         |
| IE       | Indoor environment                                     |
| ISI      | Insomnia Severity Index                                |
| ITT      | An intent-to-treat                                     |
| LLN      | Lower Limit of Normal                                  |
| MBCT     | Mindfulness-based cognitive therapy                    |
| MBSR     | Mindfulness-based stress reduction                     |
| MCS      | Multiple Chemical Sensitivity                          |
| MUS      | Medically unexplained symptoms                         |
| NA       | Negative affectivity                                   |
| NRF      | Need for Recovery scale                                |
| OHS      | Occupational Health Service                            |
| PE       | Psychoeducation  |
| PHQ-9    | Patient health questionnaire -9                        |
| PPS      | Persistent physical symptoms                           |
| QEESI    | Quick Environmental Exposure and Sensitivity Inventory |
| QEESI CI | QEESI Chemical Intolerance scale                       |
| QEESI LI | QEESI Life Impact scale                                |
| QoL      | Quality of Life  |
| RCT      | Randomized controlled trial                            |
| SD       | Standard deviation                                     |
| SOC      | Sense of Coherence                                     |
| SRS      | Self-reported symptoms                                 |
| TAS-20   | Toronto Alexithymia Scale-20                           |
| TAU      | Treatment as usual                                     |
| WHO      | World Health Organisation                              |

# 1 INTRODUCTION

A high number of physical health complaints, such as respiratory symptoms, pain or gastrointestinal symptoms, are prevalent in the general population. It is estimated that over 90% of the population experiences some distressing somatic symptoms weekly, and that of these, over 40% are associated with self-perceived disability (Eliassen et al., 2016; Hiller, Rief, & Brähler, 2006). The estimations of somatic complaints with unclear aetiology vary widely from 3% to 30% in the general population (Kirmayer, Groleau, Looer, & Dao, 2004; Loenggaard, Bjorner, Fink, Burr, & Rugulies, 2015; Rief, Hessel, & Braehler, 2001) and at the primary health care level, it is estimated that up to 50% to two-thirds of presented symptoms have unclear aetiology (Haller, Cramer, Lauche, & Dobos, 2015; Kirmayer et al., 2004; Loenggaard et al., 2015; Steinbrecher, Koerber, Frieser, & Hiller, 2011). Self-perceived respiratory symptoms with unclear aetiology vary in approximately 5% to 40% of the cases (Nimnuan, Hotopf, & Wessely, 2001; Reid, Wessely, Crayford, & Hotopf, 2001; Rief et al., 2001).

A high number of somatic complaints with complex or unclear backgrounds have been associated with several poor health outcomes. Together with general poor health status, these frequent somatic complaints predict high health care costs (Aamland, Malterud, & Werner, 2012; Fink, Ørnbøl, & Christensen, 2010; Kroenke, Spitzer, & Williams, 2002; Rask et al., 2015), increased work disability, and early withdrawal from the labour market, independently of other comorbid diseases (Aamland et al., 2012; Loenggaard et al., 2015). This underlines the need to deepen the understanding of the predictive and prognostic factors of these complaints.

Mental health status, i.e., psychiatric disorders have shown to play a prominent role in physical, including respiratory, health complaints. Mood and anxiety disorders have been linked to an increased risk of incidence of adult-onset asthma (Brunner, Schreiner, Sood, & Jacobs Jr, 2014) and poor health outcomes, including poor perceived asthma control and the severity of respiratory symptoms (Eisner, Katz, Lactao, & Iribarren, 2005; Katon, Lin, & Kroenke, 2007). These disorders have shown to associate with symptom counts so that symptoms were at least as strongly associated with common mental disorders as with the objective physiological functioning of the body (Katon et al., 2007). Individuals with symptoms of anxiety or depression have shown to report more respiratory symptoms, for example, wheezing or breathlessness, than comparisons without these symptoms (Janson, Björnsson, Hetta, & Boman, 1994). Thus, consistent evidence has linked mental and respiratory health to the burden of health.

Emerging evidence suggests that the relation between respiratory health and mental disorders is modified by self-regulatory processes and factors that influence regulation (Janssens, Verleden, De Peuter, Van Diest, & Van den

Bergh, 2009). In experimental studies, contextual factors have shown to influence respiratory symptom perception in both healthy populations and populations with respiratory diseases, showing that the accuracy of symptom perception is greatly influenced by the priming effect and becomes weaker in distressing conditions (Bogaerts et al., 2005; S. Cohen, Doyle, & Skoner, 1999; Cohen, Doyle, Turner, Alper, & Skoner, 2003; Janssens, Verleden, De Peuter, Petersen, & Van den Bergh, 2011; Van Lieshout & MacQueen, 2008). These results have been explained by individual differences in health regulation, i.e. by long-term dispositional factors that modify the interpretation and evaluation of physiological signals.

Thus, long-term psychological dispositions have shown to associate with differences in respiratory symptom perception and interpretation independently of comorbid mental disorders. They may potentiate respiratory symptomatology through direct mechanisms such as nonadherence to medical treatment, but also have an indirect effect on health regulatory processes. These may result in a vicious circle of disordered symptom perception, leading to challenging discrepancy between the opinion of the symptomatic individual and medical regimens regarding the severity of health complaints. Recent literature claims that the evaluation of recurring respiratory symptoms should thus also include health regulation factors to increase the understanding of discrepancies between symptom manifestation and the biomedical markers of health and disease. The role of regulatory factors in symptom perception is well established by experimental studies and studies based on clinical patient populations. However, information on the magnitude of the health regulation factors of the health outcomes in the general population level remains modest. To wit, although health regulation has shown to predict poor outcomes in selected populations, it is unclear whether it has any substantial effects on population level outcomes.

A clinical case example of symptoms with discrepancies between biomedical or environmental factors and health complaints are persistent physical symptoms (PPS) related to the indoor environment (IE). Health complaints related to IE are common in non-industrial work environments across Europe (Bluyssen et al., 2016; Koponen, Borodulin, Lundqvist, Sääksjärvi, & Koskinen, 2018; Magnavita, 2015). According to Norbäck (2009), they can be classified into three main categories, suggesting heterogeneity between the health outcomes and their explanations: 1) complaints due to poor subjective IE quality, 2) disease or building-related illness that may be caused by built IE factors 3) persistent and recurrent physical symptoms with an unclear cause, but with a possible relation to IE (Norbäck, 2009). For some individuals, the latter may lead to severe disability in both their occupational and private lives, with no adequate medical explanation, despite improvements in IE resulting from building repairs or occupational adjustments (Edvardsson et al., 2008; Iossifova, Cox-Ganser, Park, White, & Kreiss, 2011; Redlich, Sparer, & Cullen, 1997; Sauni et al., 2015; Vuokko et al., 2015).

The factors that explain such prolonged health conditions underline their multifactorial background (Marmot et al.; 2006, Norbäck, 2009), suggesting that improving the individual's health regulation could also improve the management of prolonged symptoms and quality of life (QoL) among symptomatic individuals. However, studies focusing on treatments to improve the functioning of individuals with PPS related to IE are scarce. The management strategies of IE-associated persistent health complaints have so far focused on repairs to the built environment (Lappalainen et al., 2017; Salonen et al., 2014; Sauni et al., 2015) and psychosocial factors increasing the perceived burden of IE-related symptoms at workplaces (Lahtinen, Huuhtanen, Kähkönen, & Reijula, 2002; Lahtinen et al., 2004; Lahtinen, Sundman-Digert, & Reijula, 2004). Thus, the mechanisms of perceived health complaints and health outcomes following symptom perception are classified into one broad category, suggesting that IE-related symptoms depend on the built environment and ignore the evidence showing that individuals differ in their perceptual styles and symptom management faculties.

To improve the understanding of this challenging condition, further information is needed on the factors associated with treatment responsiveness and outcomes.

## **2 REVIEW OF THE LITERATURE**

### **2.1 PERCEIVED HEALTH**

Frequent physical symptoms are highly prevalent among the general population. Symptom counts associate with self-perceived health, which is a well-known predictor of morbidity and exit from paid employment to disability pension or unemployment (Idler & Benyamini, 1997; Jylhä, 2009; van Rijn, Robroek, Brouwer, & Burdorf, 2014). A recent multifactorial model based on data from over 65 000 public sector employees predicting work disability suggested that of several factors, self-perceived health is the strongest predictor of work disability (Airaksinen et al., 2017). Thus, the factors that are associated with and predict self-perceived health are especially important for understanding the mechanisms of health outcomes and planning health care measures for symptomatic individuals.

### **2.2 HEALTH COMPLAINTS IN THE GENERAL POPULATION**

Cross-sectional estimates have shown that physical health complaints are highly prevalent in the general population. In a recent Danish population-based study, almost 95% of the population reported having experienced somewhat distressing physical symptoms in the preceding two weeks and nearly 40% of the population reported having experienced considerably distressing physical symptoms (one or more) during the same period. The proportion who reported somewhat distressing symptoms in at least three organs' systems in the preceding two weeks was over 75% of the population (Eliassen et al., 2016; Eliassen et al., 2017). Symptom reports have shown to be somewhat consistent across timelines (Eriksen, Svendsrod, Ursin, & Ursin, 1998) and other population-based surveys have shown similar results (Hiller et al., 2006). Frequent symptom counts associate with poor self-perceived health, poor QoL and limitations due to physical health, although the magnitude of the effect of symptoms from different organ systems on self-perceived health vary (Creed et al., 2012; Eliassen et al., 2016). Further, studies on the prevalence of PPS in general populations and their association with the use of health care services and medication have shown that frequent symptom reports associate not only with reduced QoL but also with increased health care visits by symptomatic individuals (Elnegaard et al., 2015; Petrie, Faasse, Crichton, & Grey, 2014; Zonneveld, Sprangers, Kooiman, van't Spijker, & Busschbach, 2013). The results remain robust even after adjustment for both psychiatric and chronic somatic comorbidity, suggesting that individuals with

PPS are at an increased risk of receiving health-related benefits and early withdrawal from working life (Rask et al., 2015).

Typically, physical symptoms lead to high health care utilization when they are associated with daily disability or the individual is excessively worried about serious illness related to their symptoms (Fink, Ørnbøl, & Christensen, 2010; Frosthalm et al., 2005; Rief et al., 2001). However, studies conducted among primary health care patients show that one to two thirds of the physical symptoms presented at health care appointments cannot be explained by conventional medical models, i.e., they remain undiagnosed (Kroenke et al., 1994; Steinbrecher et al., 2011).

Estimations of self-perceived health complaints with no objectively measurable bodily correlates and known disease or environmental factors that explain the symptoms vary widely in general populations and populations of primary and secondary care patients. In population-based samples, estimations of self-perceived health complaints have shown to vary between 3% and 30% (Kirmayer et al., 2004; Loenggaard et al., 2015; Rief et al., 2001) and in primary care consultations, estimations have even risen to 50% of health care visits (Haller et al., 2015; Kirmayer et al., 2004; Loenggaard et al., 2015; van der Sluijs et al., 2015). Comparisons between different medical specialties have shown that the prevalence of physical health complaints with unclear backgrounds also vary across specialties, estimations ranging from nearly 40% of the symptoms reported in the dental sector to over 60% of the symptoms reported in gynaecology (Nimnuan, Hotopf, et al., 2001). Generally, the prevalence estimates for single organ symptoms with no objectively measurable correlates show a smaller prevalence in population level surveys, and the prevalence increases drastically in different medical specialties in tertiary care. For example, respiratory symptomatology with an unclear background varies from approximately 5% at the population level to up to 40% of the cases in chest medicine (Nimnuan, Hotopf, et al., 2001; Reid et al., 2001; Rief et al., 2001).

Recurrent and persistent symptoms without sufficient explanatory peripheral organ pathology associate with symptom-related disability, increased health care utilization and the number of sick leaves among symptomatic individuals (Kroenke et al., 2002). The association between the high number of sick leaves and persistent physical symptoms (PPS) was replicated in a review that examined the factors associated with sick leaves among primary care patients with PPS (Aamland et al., 2012). The findings from general population-based studies reinforced the previous suggestions that individuals with PPS have a significantly lower QoL than healthy controls (Joustra, Janssens, Bültmann, & Rosmalen, 2015). Their participation in working life was comparable to the participation of participants with some conventional medical disease. However, both groups showed significantly reduced occupational activity assessed by high number of sick leaves and early retirement due to health-related reasons in comparison to healthy individuals (Joustra et al., 2015). Loenggaard et al. expanded on these results. They showed

that at the population level, frequent physical symptoms, independently of physical diseases, predicted long-term sickness absence and low labour market participation (Loengaard et al., 2015). Several studies have further replicated the findings that in comparison to patients with well-defined chronic diseases, primary health care patients with frequent PPS not attributable to any conventionally defined diseases more often have full or partial disability pension, poorer physical and mental health, and more physical and psychiatric comorbidity (Rask et al., 2015). These findings have led to estimations of overall health care costs related to PPS. For example, Rask et al. (2017) showed that the costs were significantly higher among this group of patients than among primary health care patients with other complaints (Rask, Ørnbøl, Rosendal, & Fink, 2017; Reid, Wessely, Crayford, & Hotopf, 2002). Further, health care costs have shown to even double compared to those of patients with conventionally diagnosed diseases independent of somatic or psychiatric comorbidity (Barsky, Orav, & Bates, 2005). In severe cases, social security costs may be fourfold (Rask et al., 2015). Thus, the association between both direct health care costs and indirect costs related to the loss of labour market and the social security system and recurrent and PPS are well documented. It is noteworthy that the societal cost related to these symptoms are even comparable with those of common mental health problems such as depression (Konnopka et al., 2013; Konnopka et al., 2012), which is one of the leading causes of disability worldwide (James et al., 2018) and a leading cause of premature disability pension in, for example, Finland (Nyman, 2020).

The terminology related to recurrent and persistent symptoms with no objectively measurable bodily correlates, conventional disease or environmental factors explaining the symptoms has varied over time and disciplines and deserves further consideration. The terms 'medically unexplained symptoms' (MUS), 'functional somatic symptoms' (FSS) or PPS are widely used to describe symptoms exhibited at the population or primary care level, whereas medical specialties have characterized specialty-specific categories for these symptoms (Grover & Kate, 2013; Nimnuan, Rabe-Hesketh, Wessely, & Hotopf, 2001). MUS is widely criticized because of its vague definition of what symptoms are not, rather than what they are, and the uncertainty that this kind of definition might cause individuals experiencing symptoms (Creed et al., 2010; Sharpe & Carson, 2001). Some studies show that the most recent term 'PPS' has become most acceptance among individuals who experience health complaints with discrepant subjective and objective measurements (Marks & Hunter, 2015; Picariello, Ali, Moss-Morris, & Chalder, 2015). These findings suggest that MUS is outdated among health care professionals and individuals who are experts through experience. As the debate on the terminology and the acceptance of conditions is ongoing, terms that support a shared understanding between health care professionals and symptomatic individuals are urgently needed. However, this thesis aimed to study individual faculties for managing health rather than diagnostic concepts



of PPS. Thus, the expression 'subjective health complaint' was chosen due to the lack of consensus concerning the definition of symptoms and to highlight the individual faculties that influence health regulation and provide a common ground for conventional and more complex health states and their management.

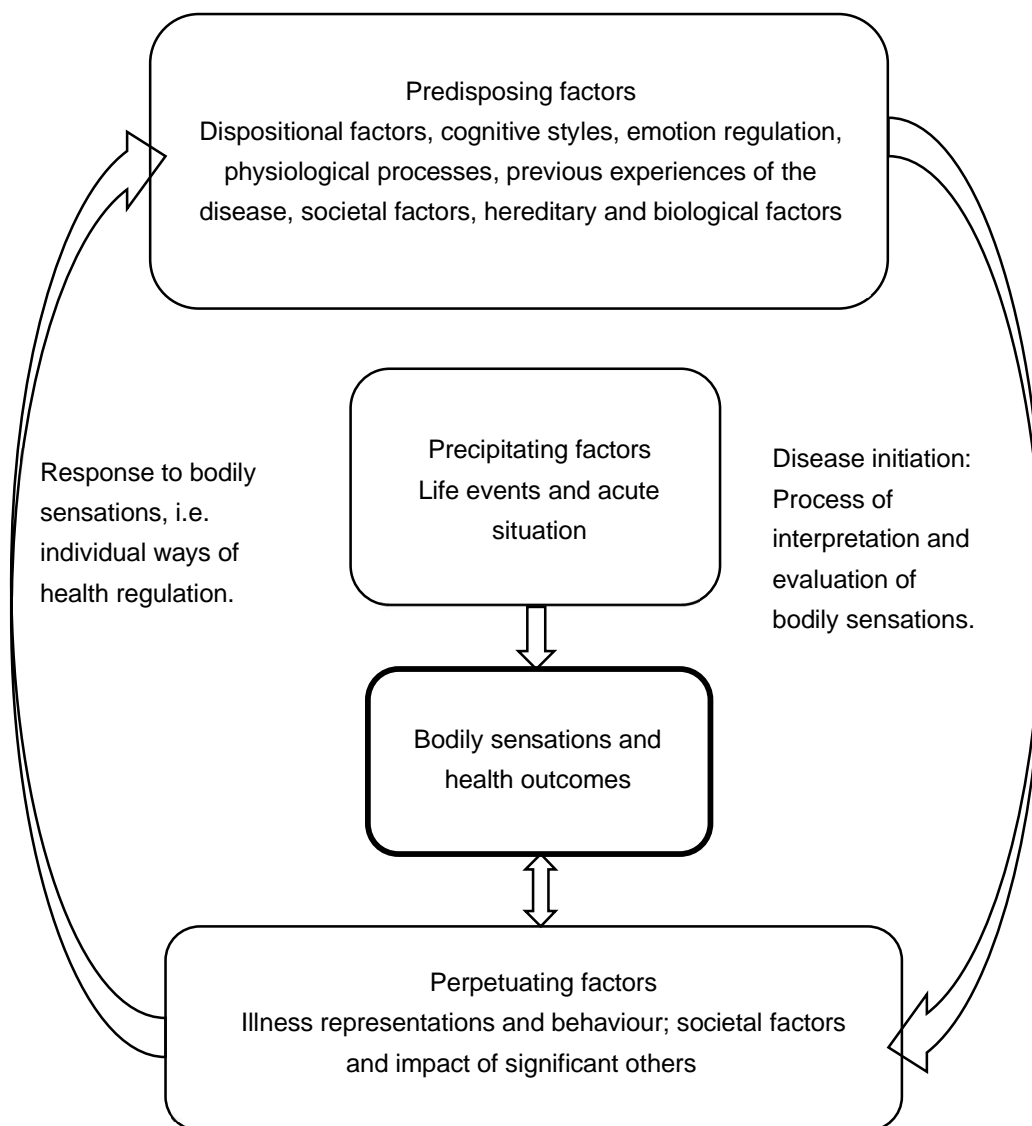
To continue, subjective health complaints might be a sign of an underlying pathology related to a well-known disease that is untreated or represent bodily reactions to perceived daily distress or bodily symptoms related to psychiatric diseases such as depression or anxiety. In some cases, health complaints have a multifactorial background, in which the severity of symptoms is influenced by several biological, psychosocial and environmental factors (see also Ezra, Hammerman, & Shahar, 2019 for further theoretical discussion). According to the highly variable prevalence estimates of general population-based studies or clinical samples of patients, the individual burden and high societal costs related to persistent health complaints highlight a need for a more comprehensive understanding of these complaints, in which psychosocial factors are suggested to play a prominent part (Lehrer, Feldman, Giardino, Song, & Schmaling, 2002; Rief & Broadbent, 2007). Thus, more information is needed on the factors that influence subjective health complaints and the regulation of health at the population level.

### **2.2.1 SELF-REGULATION OF HEALTH**

Several theoretical models and approaches aim to explain the health outcomes and mechanisms of the self-regulation of health (e.g. the medical model, the health belief model, and the common-sense model of illness). Whereas the medical model suggests that health outcome consequences come directly from biomedical dysfunction that can be detected and treated according to standard medical procedures, the latter have included the role of psychological and social factors in the shaping of health outcomes. These models make assumptions regarding self-regulatory factors and their interactions that influence an individual's health behaviour so that health outcomes are formed by the way in which people interpret, evaluate, perceive and respond to bodily sensations (Figure 1).

The self-regulation of health and illness is seen as a complex construct of interplay between a range of physical, social, cultural and psychological factors so that none of these alone can explain the health outcomes. Studies conducted among selected populations of patients have shown that to enhance the understanding of the prognosis of the disease, it is essential to identify the determinants that affect an individual's faculties for coping with and adapting to chronic diseases (Disler, Gallagher, & Davidson, 2012; Stewart & Yuen, 2011). Health regulation problems also modify ways of seeking help from health care or alternative options: failure to perceive bodily sensations or misinterpret symptoms manifesting as problems in the self-management of health and the over-utilization of health services (Frosthalm et al., 2005; Rhee

et al., 2011; Serrano et al., 2006). A review of resiliency, i.e. the ability to cope and adjust to everyday challenges, among physically ill patients concluded that supporting factors such as a patient's sense of self-efficacy concerning the disease, self-esteem, self-empowerment or acceptance of illness increases their abilities to master the situation. These abilities in turn positively influence the outcomes of illness (Stewart & Yuen, 2011). Although not surprising, supporting resiliency in such a way was directly associated with factors directly salient to good treatment of diseases, such as enhanced self-care and adherence to treatment (Stewart & Yuen, 2011).



**Figure 1** Biopsychosocial factors that influence health outcomes and their interactions.

### **2.2.2 MODERATORS AND MEDIATORS OF HEALTH REGULATION**

Individuals differ in their attributional styles, i.e. cognitive schemas to interpret and explain bodily and emotional sensations. These schemas influence how one assesses the body for possible signs of illness and responds to these signs (Barsky, Peekna, & Borus, 2001; Kaptein, Klok, Moss-Morris, & Brand, 2010; Petrie & Weinman, 2012; Robbins & Kirmayer, 1991). Illness attributions constitute an individual's subjective beliefs and emotional responses to their illness and form an ongoing learning process from prior experiences to the current situation. In more detail, illness attributions consist of explanations for the cause of illness (causal beliefs), expectations regarding the consequences of the illness, how illness should be cured or treated (control beliefs), duration of the illness (timeline beliefs) and overall understanding of the illness and its meaning to the individual (Hagger & Orbell, 2003; Leventhal, Meyer, & Nerenz, 1980). These health-related attributions are affected by several internal and external factors such as the perceived threat related to the symptoms or the concrete availability of medication for the symptoms when they occur. These factors influence how an individual manages and copes with occurring signs of an illness or with health threats, guiding the behaviour aimed to manage the illness, i.e. they influence health regulation. Thus, health attributions also influence how accurately both healthy people and patients with physical diseases or psychiatric disorders perceive their symptomatology. They also predict outcomes of illness as well as treatment-related behaviour such as adherence to treatment (Petrie & Weinman, 2012).

Several studies suggest that illness attributions are modified by psychological dispositions, i.e. pervasive and long-term styles for cognitive, emotion and behaviour regulation, which influence how one perceives external and internal stimuli (Cohen et al., 2003; Hynninen, Breivte, Wiborg, Pallesen, & Nordhus, 2005; Lehrer et al., 2002; Nici et al., 2006). For example, the pervasive tendency to experience negative emotions (negative affectivity) has proved to be influential in terms of distorting the symptom perception processes related to respiratory diseases (Bogaerts et al., 2015; Lehrer et al., 2002) as well as respiratory-symptom perception in healthy individuals. In an experimental study conducted by Van den Bergh et al., contextual cues, i.e. framing, had a priming effect on respiratory symptom perception during the breathing trial (Van den Bergh et al., 2004). Healthy participants with a high tendency to experience negative emotions were significantly less accurate in symptom perception after negative framing than participants with low negative affectivity. However, during the positive information frame, there were no significant differences between the interoceptive accuracy of the participants with high or low negative affectivity (Van den Bergh et al., 2004; Bogaerts et al., 2005; Bogaerts et al., 2010; Cohen et al., 2003; Janssens, Verleden et al., 2011b; Put et al., 2004).

Similar results have been found among healthy individuals and patients with asthma, suggesting that individual dispositions moderate symptom reporting patterns, depending on contextual cues, and lead to higher variability in symptom reporting in different affective contexts. Accumulating evidence has led to comprehensive models that explain the interaction between individual self-regulation and the context of symptom perception related to specifically respiratory diseases (Janssens et al., 2009; Marlow, Faull, Finnegan, & Pattinson, 2019) and overall symptom perception (Petersen, van den Berg, Janssens, & Van den Bergh, 2011; Van den Bergh, Witthöft, Petersen, & Brown, 2017). These models suggest that symptom perception is developed and modified through the continuous learning between top-down processes in which, depending on the specific condition, the perception of bodily sensations may be prone to prior expectations. It is suggested that psychological dispositions act as vulnerability factors that predispose individuals to distorted symptom perception, but that these do not necessarily play a sufficient role in developing distorted symptom perception (Bogaerts et al., 2015). However, the interplay between psychological dispositions and expectations can lead to maladaptive chains in which they mutually reinforce distortion, resulting in heightened or more intense symptom reports and behaviour following the sensations than the objective bodily measurements suggest.

Together with the dispositional characteristics that influence health-regulation, psychiatric disorders have shown to influence somatic symptom perception. Depression has shown to not only increase the severity of perceived asthma symptoms (Eisner et al., 2005) but also to be a risk factor for incident asthma (Brunner et al., 2014). Individuals with symptoms of anxiety and depression report more asthma-like symptoms (e.g. dyspnoea) than those without anxiety or depression symptoms, independently of asthma diagnosis (Janson et al., 1994). Depressive and anxiety disorders have also shown to predict dyspnoea, but not vice versa (Neuman et al., 2006; Leander et al., 2014). Further, a comprehensive review examining the cross-sectional and longitudinal associations between depression and anxiety disorders with physical outcomes revealed that respiratory health complaints are at least as strongly associated with common psychiatric disorders as they are with objective clinical tests of lung function (Katon et al., 2007). Thus, psychological distress is highly comorbid with reported physical complaints. In cases with no comorbid organic diseases, physical health complaints have most frequently shown to occur with concurrent symptoms of depression or anxiety (Haug, Mykletun, & Dahl, 2004). In cases of physical symptoms related to specific disease with concurrent health complaints that have no clear background, the risk of mood disorders increases significantly (van der Sluijs et al., 2015). These findings indicate that there is no difference in the association between psychological distress and the symptoms from different organ systems (Haug et al., 2004; Mostafaei et al., 2019), although recent findings regarding somatic symptom profiles propose that symptom profiles

could be distinguished by number or type of physical symptom (Eliassen et al., 2017).

To continue, although dispositional factors influence health regulation, and state characteristics have an effect on symptom perception, attributions related to illness and health have also shown to modify help-seeking behaviour related to health complaints (Frosthalm, Petrie, Ornbol, & Fink 2014). Excessive and sometimes uncontrollable worries and preoccupation with the belief that one is physically unwell and exaggerated rumination about health indicates attentional bias in the self-monitoring of illness-related cues from bodily sensations (Owens, Asmundson, Hadjistavropoulos, & Owens, 2004), and are even suggested to decrease the interoceptive accuracy of bodily sensations (Krautwurst, Gerlach, Gomille, Hiller, & Witthöft, 2014). These worries are often conceptualized as health anxiety, a multidimensional construct of affective, behavioural, perceptual and cognitive components that influence how one highlights the threads related to physical symptoms and simultaneously ignores their multifactorial background (Rief & Broadbent, 2007). It is common that the tendency for health-related worries increases reassurance-seeking from, for example, health care and the internet (Barsky, Ettner, Horsky, & Bates, 2001; Bleichhardt & Hiller, 2007; Frosthalm et al., 2005; McMullan, Berle, Arnáez, & Starcevic, 2019; Sunderland, Newby, & Andrews, 2013) and that individuals with health anxiety are at risk of experiencing counterproductive outcomes from online searches (McMullan et al., 2019). In contrast, individuals who report frequent physical health complaints in primary or secondary care generally express more severe health-related worries than individuals with no frequent health complaints (Clarke, Piterman, Byrne, & Austin, 2008; Robbins & Kirmayer, 1996), a phenomena that is also seen across different medical specialties (Tyrer et al., 2011). A variety of physical health complaints linked to health-related worries appear to associate with poorer health outcomes and high health care utilization in a way that cannot be solely attributed to concurrent psychiatric disorders or physical diseases (Barsky, Ettner, et al., 2001; Creed & Barsky, 2004). These findings suggest that the characteristics of health anxiety are a long-term risk factor for moderating health regulation.

Similarly, with health anxiety, challenges in identifying and naming bodily sensations related to emotional arousal and an externally oriented thinking style are suggested to alter the overall cognitive processing of bodily sensations. Also known as alexithymia, these characteristics are considered to lead to unfavourable health outcomes and increased symptom reports, although systematic, prospective studies are still lacking (Kojima, 2012). However, the construct of alexithymia is especially interesting from a respiratory health point of view, as some pilot results suggest that it is associated with poorer asthma control (Baiardini, Sicuro, Balbi, Canonica, & Braido, 2015; Chugg, Barton, Antic, & Crockett, 2009; Vazquez et al., 2010). As patients' symptom reports play an important role in the diagnostic process, the factors influencing symptom perception should be taken into account to

avoid iatrogenic harms related to medical examinations and the treatment process.

Thus, the involvement of long-term dispositional characteristics and psychiatric disorders in distorted respiratory symptom perception and in respiratory disease control is established in studies based on experimental designs and patient populations. Self-regulation of health, i.e. the actions taken to manage and cope with the health complaints, thus results from the interaction of dispositional factors and the context in which the bodily sensations are evoked. From a practical point of view this may develop into situations in which vicious learning circles based on previous experiences of symptoms strengthen the distorted symptom perception. This might be especially true in cases in which the contextual cues are perceived as threatening or uncontrollable (Hofmann, 2008; Janssens, De Peuter, et al., 2011; Janssens, Verleden, et al., 2011; Janssens et al., 2009).

To conclude, health behaviour is influenced by several intrinsic and extrinsic factors. However, information on the causality and magnitude of these factors and the health outcomes among the general, healthy population is scarce. Thus, the burden of the moderators and mediators of health behaviour is still unclear, especially in the general population.

### **2.2.3 CONTEXTUAL CUES AS COVARIATES OF HEALTH REGULATION**

Environmental factors are an example of how context can influence individuals' perceptions of health and health-related actions by affecting the ways in which individuals interpret physical sensations (off note: writing about contextual cues influencing health-regulation during the Covid-19 outbreak feels somewhat trivial...). Originally Petrie et al. formulated the term 'modern health worries' to conceptualize the perceived risk to personal health associated with modern environmental factors such as radiation or toxic interventions (e.g. 5G radiation, poor building ventilation or toxic chemicals in household products) (Petrie et al., 2005; Petrie et al., 2001). Modern health worries are associated with multiple recurrent health complaints attributed to various environmental factors that are well tolerated by most people, cannot be explained by any medical disorder (IPCS/WHO, 1996), and cause severe disability related to daily functioning (Lacour, Zunder, Schmidtke, Vaith, & Scheidt, 2005). Such health complaints related specifically to IE are a common topic in the Finnish media and challenge the health care system, as there are no current care guidelines or consensus on the treatment of these burdensome health complaints.

## 2.3 INDOOR ENVIRONMENT-ASSOCIATED HEALTH COMPLAINTS

Various IE-associated health complaints are common in non-industrial work environments across European countries (Bluyssen et al., 2016; Magnavita, 2015; WHO, 1983). For example, a survey conducted in eight European countries showed that approximately one-third of office workers report some kind of health complaints (e.g. dry eyes, dry, irritated throat, headache) associated with IE. The most irritating environmental conditions are excessively dry air or changing temperatures, and noise in the work environment (Bluyssen et al., 2016; Magnavita, 2015). In the comprehensive FinHealth 2017 Survey conducted among a nationally representative sample of Finnish people, one-fifth of working-age women and one-tenth of working-age men reported health complaints associated with workplace IE. Approximately every tenth woman and every twentieth man reported that these complaints had led to visits to health care (Koponen et al., 2018). In some cases, these complaints may lead to diminished productivity at work (Seppänen et al., 2006): a branch of IE research focuses solely on productivity losses due to IE-related factors (Antikainen et al., 2008).

Typically, health complaints associated with IE are building related, meaning that an individual reports no complaints when they are away from the building in question. Health complaints reported in different studies share similarities: the most frequent health complaints related to indoor air include respiratory symptoms such as coughing, breathlessness, or a sore throat. General complaints such as lightheadedness, fatigue, dizziness, memory and gastrointestinal problems are also reported (Norbäck, 2009; Reijula & Sundman-Digert, 2004), so symptom profiles related to IE are not specific to certain organ groups.

The continuum of the IE-associated health complaints ranges from frequently reported discomfort complaints, as described above, to rare multiple and persistent physical symptoms. These associate with wide-ranging disability in everyday life and restrictions on both occupational and social life among symptomatic individuals (Edvardsson et al., 2008; Karvala, Nordman, Luukkonen, & Uitti, 2014; Karvala, Uitti, Luukkonen, & Nordman, 2013). Typical of the IE-related PPS is that they persist despite building repairs or occur in environments about which other people have not complained, i.e. expand from building-related complaints to general IE or other environmental factor-associated complaints (Al-Ahmad et al., 2010; Haverinen-Shaughnessy, Hyvärinen, Putus, & Nevalainen, 2008; Iossifova et al., 2011; Park, Cho, White, & Cox-Ganser, 2018; Sauni et al., 2015). Although IE-associated health complaints are frequently reported and recognized as a central factor in environmental health issues (Koponen et al., 2018) there are, however, no data on the prevalence of the most severe cases of IE-related PPS in the population.

Research approaches to factors that explain the health conditions associated with IE include built IE-related, psychosocial approaches such as psychosocial climate at the workplace and individual-related factors. The health effects of physical, biological and chemical factors in IE have been extensively studied, but so far, the role of the mechanisms of most of these factors in adverse health effects has remained ambiguous (Nordin, 2020). The associations between certain environmental factors such as volatile organic compounds, passive smoking, radon gas of soil origin and severe respiratory and cardiovascular health outcomes (WHO, 2010; WHO, 2007) are well-documented. Further, the findings from epidemiological research based mainly on studies of children suggest associations between moisture damage and mould in IEs with an increased risk of asthma (Asthma: Current Care Guidelines 2012) and upper respiratory symptoms for adults. However, evidence of causality between IE factors and health complaints has not been established (Mendell, Mirer, Cheung, Tong, & Douwes, 2011; Sauni et al., 2015; WHO, 2009).

Together with building-related factors, health complaints associated with IE have shown to be prone to psychosocial burden at workplaces. Lahtinen & al. showed already in 2002 that vague problem-managing processes and psychosocial conflicts are common when attempting to solve indoor air problems (Lahtinen et al., 2002). They suggested that factors related to psychosocial work climate play a significant role in indoor air problems, as exhibited in various symptoms reports (Lahtinen et al., 2002; Lahtinen et al., 2004b), meaning that the interaction between indoor air and health complaints is moderated by psychosocial factors. Further, in their recently published study, Finell and Nätti showed that together with poor perceived IE, psychosocial stressors increase the risk of long-term sickness absence (Finell & Nätti, 2019). They suggested that adaptive coping with or adapting to everyday stressors is limited in workplaces with psychosocial problems and that this influences the persistence of IE-associated health complaints. Although their study design does not enable us to draw conclusions regarding the cause-relation between either IE or psychosocial factors and persistent health complaints exhibited in workplaces, the results underline the importance of the multifactorial assessment of IE-related health complaints.

### **2.3.1 PERSISTENT HEALTH COMPLAINTS ASSOCIATED WITH THE INDOOR ENVIRONMENT**

At the severe end of the continuum, IE-associated persistent health complaints may lead to disability without adequate medical explanation and despite improvements in IE quality in the form of building repairs or occupational adjustments (e.g. remote work, change of office). Participants with persistent complaints may attribute their symptoms to poor IE, even in an environment that has contaminant levels far below those toxicologically established as causing harmful health effects (Das-Munshi, Rubin, & Wessely, 2007; Lacour



et al., 2005; Van den Bergh, Brown, Petersen, & Witthöft, 2017). It has also been shown in clinical settings that the severity of the symptoms and disability related to the condition is not always adequately explained by medical causes (Vuokko et al., 2019; Vuokko et al., 2015). Among the severe cases, attributions to other environmental triggers, such as electromagnetic fields or multiple chemical sensitivities, have been reported as overlapping with IE-associated health complaints (Palmquist, Claeson, Neely, Stenberg, & Nordin, 2014).

### **2.3.2 FACTORS ASSOCIATED WITH PERSISTENT HEALTH COMPLAINTS ASSOCIATED WITH THE INDOOR ENVIRONMENT**

Both comorbid health conditions and some specific stable dispositions and state characteristics have been linked to IE-related health outcomes. Consistent findings show personality characteristics, i.e. long-term cognitive-affective-behavioural reaction patterns to intrinsic and extrinsic cues, are associated with IE-related adverse health effects. Runeson et al. showed in their cohort study of the Swedish working-age population that a pervasive tendency to experience negative feelings such as anxiety is associated with increased symptom levels in buildings with suspected indoor air problems (Runeson & Norbäck, 2005). Gomzi et al. replicated these findings by showing that neuroticism is associated with increased indoor air-related symptom reports (Gomzi et al., 2007), indicating that it facilitates the attribution of health complaints to a wide array of environmental factors (Österberg, Persson, Karlson, Eek, & Ørbæk, 2007). Some evidence also shows that stable dispositions may serve as protective factors against IE-related health complaints. The role of sense of coherence (SOC) as a contributor for better perceived health in general is well established in various health conditions (Eriksson & Lindström, 2006). Runeson et al. showed that low SOC was related to a higher prevalence of various health complaints in their study of a longitudinal follow-up cohort of Swedish employees working in buildings with suspected indoor air problems (Runeson, Norbäck, & Stattin, 2003). Their results suggest that individual faculties maintain and promote health and thus also contribute to IE-associated health complaints.

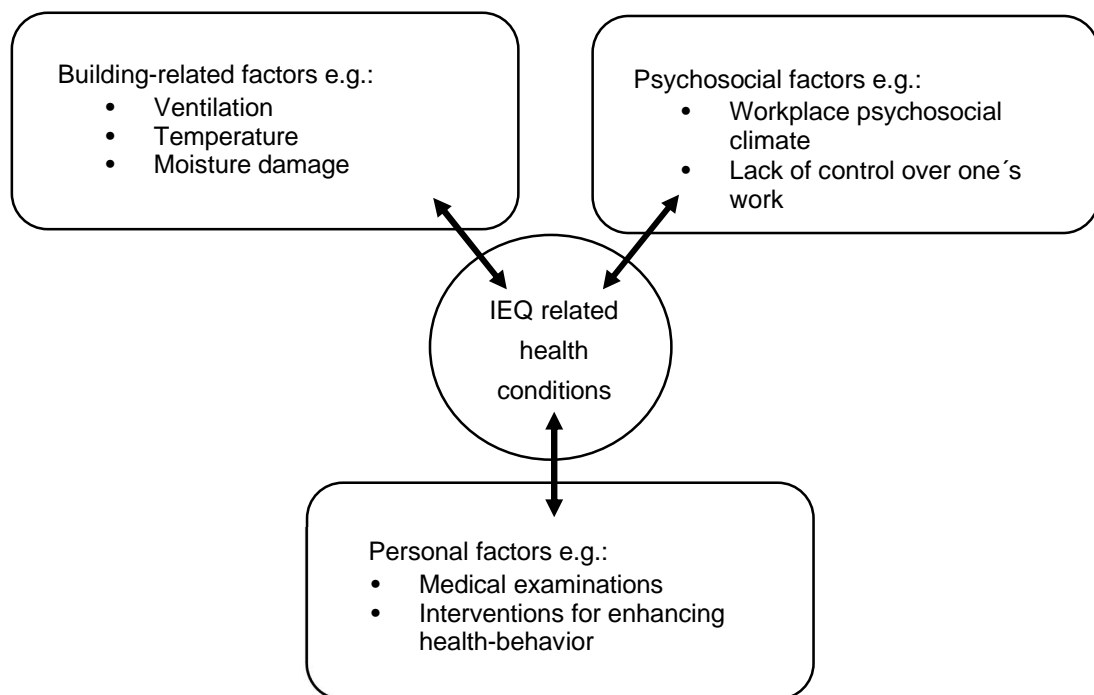
A number of studies have reported associations of individual factors (gender, smoking habit, age) and further, the comorbidity of somatic diseases such as asthma and psychiatric disorders, with cases of IE-associated health complaints (Magnavita, 2015; Norbäck, 2009; Runeson-Broberg & Norbäck, 2013; Runeson, Wahlstedt, Wieslander, & Norbäck, 2006). In clinical studies based on highly select populations of patients, comorbidities are generally highly prevalent. Vuokko et al., for example, showed in their intervention study on enhancing health behaviour among patients with non-specific building-related symptomatology, that up to 58% of the study participants had several comorbidities (Vuokko et al., 2015; Vuokko et al., 2019). However, no prospective studies have assessed the causality of these comorbidities and it

remains unclear whether they serve as risk factors for IE-related health complaints, are caused by IE-related factors, or are related to some other underlying mechanism of poor health outcomes.

## **2.4 MANAGEMENT OF HEALTH CONDITIONS ASSOCIATED WITH THE INDOOR ENVIRONMENT**

As IE-associated health conditions are influenced by environmental, psychosocial and individual factors, it is not plausible to suggest that a single mechanism explains health outcomes (Marmot et al., 2006; Norbäck, 2009). Thus, the management of health complaints associated with IE requires a multifactorial strategy that includes actions based on the evaluation of environmental, psychosocial and individual factors (Figure 2.).

The World Health Organization (WHO) has developed guidelines to help public health authorities and policy-makers improve IEs and make them healthier (WHO, 2009). In Finland, evidence-based guidelines and criteria for solving IE problems at workplaces (Lappalainen et al., 2016; Salonen et al., 2014) summarize a comprehensive system for assessing and managing suspected indoor air problems at workplaces, taking into account Finnish legislation and guidelines (Decree on Housing Health 545/2015; Health Protection Act 763/1994; The Occupational Safety and Health Act 738/2002; Tähtinen et al., 2018). In addition, evidence-based guidelines for extensive multidisciplinary collaboration and participative action at workplaces for managing problem-solving and conflicts related to indoor air problems have been proposed (Lahtinen et al., 2010; Lahtinen et al., 2002; Lahtinen et al., 2004a; Lahtinen et al., 2004b). These are based on the theoretical assumption that indoor air problems caused by built environmental factors influence organizational processes. Difficulties in the processes, such as workplace communication and stagnation in problem-solving situations have an indirect effect on the negative perceptions of IE. This means that psychosocial factors may mediate the adverse health effects related to IE by decreasing the ability to cope with symptoms and increasing the negative effects on the work community's functioning (Finell & Seppälä, 2018; Lahtinen et al., 2004). Thus, suspected indoor air problems are defined as a phenomenon that also influences social interactions, and the management of indoor air problems includes expertise in social and human aspects as well as in built-environment assessment and remediation.



**Figure 2** Multifactorial approach to managing health conditions associated with indoor environment quality (IEQ)

To continue, recent current care guideline for patients exposed to moisture damage in buildings (Patient exposed to moisture damage: Current Care Guidelines 2016) were developed to enhance the medical examinations and treatment of patients. However, the Guidelines summarize that on the basis of current scientific knowledge, no clinical health examinations exist that can be used to assess the association between potential moisture damage and the perceived health complaints of the patient, and that further, no specific biomedical or psychosocial treatments exist for prolonged health complaints associated with moisture damage (Patient exposed to moisture damage: Current Care Guidelines 2016). Current care guidelines for asthma in turn recognize moisture and mould damage in buildings as risk factors for poor asthma outcomes (Asthma: Current Care Guidelines 2012). The clinical management of the patient is, however, based on general asthma guidelines, so that moisture and mould damage repairs in buildings are suggested to improve asthma outcomes (Asthma: Current Care Guidelines 2012).

Finally, evidence-based recommendations for occupational health service (OHS) measures in cases of suspected indoor air problems at workplaces (Latvala et al., 2017) have been developed to support the process management of IE-associated problems at workplaces. This comprehensive guideline combines the tasks of the different parties (multidisciplinary OHS, employee,

employer, health and safety management at workplaces, and the owner of the building) involved in the indoor air problem-solving process. The recommendations also include general principles for enhancing patient-professional interaction, which is especially invaluable in cases in which the symptoms persist despite building remediation or other occupational adjustments.

To summarize, thus far, the clinical health examinations and good treatment of the patient have focused on specific diseases or the procedures of solving indoor air problems in the built environment. The principles of enhancing general medical practices and communication with the patient are combined with recommendations. One could summarize that the key to the care is the remediation of the buildings and occupational adjustments in line with the treatment of chronic diseases, if such exist. Challenges arise when distressing and disabling health complaints persist even after several occupational adjustments, including adequate repairs, and the disability associated with the health complaints is more severe than objective medical health examinations suggest.

## **2.5 CLINICAL MANAGEMENT OF PERSISTENT PHYSICAL SYMPTOMS ASSOCIATED WITH THE INDOOR ENVIRONMENT**

Remediation of the built IE and interventions to enhance the workplace psychosocial climate, i.e. work team functioning and communication at workplaces, are essential in any case of suspected IE problem. However, the information and guidelines for managing with IE-related PPS cases, i.e. discrepancy between subjective health and daily functioning and the environmental and medical factors, are lacking. The burden of these symptoms challenges the health care system, as they are not covered by standard care guidelines. Studies conducted in similar populations of patients with PPS show that medical examinations and treatment actions may result in patients having repeated unpleasant experiences when seeking help from health care (Creed et al., 2010; Escobar et al., 2010). The patient may face a high degree of uncertainty and disappointment if the burden of their condition cannot be operationalized or treated in a standard clinical manner (Dirkzwager & Verhaak, 2007). They may also limit the information they share with health professionals for fear that exhibiting a variety of physical but also psychological symptoms leads to precluding medical explanations for the condition (Peters et al., 2009). In contrast, health care professionals also find it difficult to meet patients' expectations in cases in which discrepancy exists (Skovbjerg, Johansen, Rasmussen, Thorsen, & Elberling, 2009), in some cases leading to professionals' attempts to explain the origin of the symptoms by not taking the patient's views into account (olde Hartman et al., 2013). This is especially unfortunate, as it has been shown that physicians' validation of the

health complaints exhibited in health care is less frequent in PPS cases than in cases of more conventional diseases (Epstein et al., 2006), even though validation is a key element of patient-centred care. One could claim that these perceptions arise from being unfamiliar with the condition, as shown in, for example, a study conducted among primary care-level physicians treating persistent health complaints related to environmental factors (Gibson & Lindberg, 2011). This underlines the fact that the clinical management of PPS is influenced by the bidirectional interaction between the professional and the patient.

Cumulative evidence of patients' and professionals' poor experiences have thus shown that clinical management of cases in which there is discrepancy between objective and perceived health complaints cannot fully rely on a biomedical model of the symptoms. Several studies have noted the importance of psychosocial treatments in parallel with relevant biomedical actions to enhance the treatment of PPS (Henningsen, Zipfel, & Herzog, 2007; Henningsen, Zipfel, Sattel, & Creed, 2018). They have concluded that the effectiveness of the treatments of PPS relies on patient-activating methods that support individual faculties in managing their health. National guidelines also exist for primary care management and on stepped care management of persistent health complaints (e.g. in the Netherlands, Denmark and Germany), containing treatment options according to the severity of the condition (mild, moderate, severe) (olde Hartman et al., 2017; Rosendal, Christensen, Agersnap, Fink, & Vinther, 2013; Schaefert et al., 2012; van der Feltz-Cornelis, Hoedeman, Keuter, & Swinkels, 2012). The severity of the condition is defined according to not only biomedical factors but also the psychosocial markers of the patient's health regulation and daily functioning. Generally, the multidisciplinary approach to the treatment increases in accordance with the severity of the condition. These guidelines further emphasize that in addition to biomedical factors, it is crucial to understand the patients' self-regulation of the illness to support the recovery process and management of the persistent condition from the mild to the severe end of the illness continuum.

Studies on psychosocial interventions aiming to support coping with PPS related to IE are scarce. A study conducted by Vuokko et al. examined the effectiveness of three-session psychoeducation (PE) and the promotion of health behaviour for work ability and QoL (Vuokko et al., 2015) among specialist clinic patients with a suspected occupational disease. Of the study participants, 60% showed prevalent worries about a serious disease or loss of health, and among 52% of the participants, the health worries were associated with IE. Thirty-six percent of the participants expressed current psychological distress in terms of depressive mood, anxiety or insomnia symptoms. The psychosocial counselling did not show statistically significant effects on work ability, but physical health, measured by the Quality of Life (RAND-36) inventory (Hayes, 1993), improved significantly in the treatment group (Vuokko et al., 2015).

Some intervention studies have been conducted in a population of patients with persistent health complaints associated with similar toxicological or chemical environmental factors to IE. Hauge et al. studied the effectiveness of eight weekly mindfulness-based cognitive therapy (MBCT) sessions on multiple chemical sensitivities (MCS) (Hauge et al., 2015). Mindfulness-based treatments are a form of 'third wave' cognitive therapies that have shown promising effects of improving the ability to cope with the disease and reducing psychological distress, thereby improving wellbeing (Hayes et al., 2017). Hauge et al. combined the mindfulness-based stress reduction techniques (originally developed by Kabat-Zinn et al., 2009) with cognitive therapy. They found that MBCT did not appear to change the overall illness status, but it positively affected participants' sense of personal control over their condition (Hauge et al., 2015). This is one of the key components of resiliency, which has shown to improve health outcomes (Stewart & Yuen, 2011). Skovbjerg et al. found similar modest results in their pilot randomized controlled trial (RCT) of MBCT on MCS. There were no significant differences between the effect measures of the treatment as usual (TAU) and the intervention group, but those in the intervention group generally reported benefiting in terms of improved coping strategies and sleep quality (Skovbjerg, Hauge, Rasmussen, Winkel, & Elberling, 2012). Sampalli, Berlasso, Fox, and Petter (2009) in turn showed significant improvement after a body-mind-awareness programme based on 10 weekly mindfulness-based stress reduction sessions among a group of participants including patients with MCS. Significant improvements, reduced global severity of the condition in the post-intervention assessment and the improvement in seven out of nine outcome subscales, including somatization, remained until three-month follow-up in the intervention group (Sampalli et al., 2009). The results of these studies suggest that the physical symptoms do not respond to the treatment so easily, but the patient might benefit from the psychosocial treatment as it enhances the regulation of the complaints.

The common factors in these abovementioned trials include working with mechanisms that are suggested to maintain PPS (Figure 1.) (Rief & Broadbent, 2007). Psychoeducation is a structured and didactic working method for sharing information of illness with the patient. It is aimed to increase the patient's awareness about the behaviours that influence symptoms and for supporting the motivational aspects of illness adaptation. Whereas psychoeducation mainly focuses on the cognitive aspects of the illness, 'third way' cognitive therapies prioritize behavioural and experiential methods of working on the self-perpetuating cycle of predisposing, perpetuating and precipitating factors of PPS (Figure 1.) (Rief & Broadbent, 2007). Mindfulness exercises study how thoughts influence feelings, i.e. bodily sensations, and vice versa and how this interaction prolongs the physiological activation that maintains symptoms. Body-orientated methods such as relaxation or breathing exercises are used to enhance the individual's insight into this interaction and to regulate bodily sensations. Further aim of the 'third way'

cognitive therapies is to defuse centred relationship between thoughts, feelings, and bodily sensations.

The aim of these methods is to support adaptive attributional styles and patient's abilities to manage symptoms, i.e. support health regulation. Although the information on the effectiveness of such treatment options among patients with PPS related to indoor air is scarce, various meta-analytical studies support such approaches among patients with various PPS. In their meta-analysis of short-term psychotherapy for PPS, Kleinstauber et al. (2011) found small but robust effect sizes in treatment and non-treatment groups. They suggest that, as therapeutic strategies aim to improve coping with symptoms rather than curing them, somatic symptoms as primary outcome might not reveal the effectiveness that could be reached. Further, their results show that disorder specific treatments are more effective than treatments for multiple PPS profiles. In their meta-analysis of the effectiveness of CBT for PPS, Liu et al. (2019) further show a modest but consistent effect on the alleviation of PPS using CBT. The results were sustained until 3 to 12 months follow-up (Liu, Gill, Teodorczuk, Li & Sun, 2019). Thus, although there are caveats, the results of multiple meta-analyses of studies on the treatment of PPS suggest that increasing patient's abilities to deal with PPS leads to stable outcomes.

To conclude, the evidence of the effectiveness of psychosocial treatments on symptoms associated with environmental factors is limited and somewhat mixed, and the studied treatment modalities are also limited. However, when compared to the standard treatment for chronic diseases, such as asthma, the results provide evidence that psychosocial symptom management programmes that aim to support the resiliency of physically ill people (Stewart et al., 2011) or, for example, improve asthma-specific QoL and reduce the severity of asthma, are potentially beneficial (Yorke, Fleming, & Shuldham, 2006; Yorke, Fleming, & Shuldham, 2007). In line with this, controlled studies conducted in patient populations with PPS show that management strategies that support patients' activity, resiliency and faculties for coping with illness are more effective than passive or organ-focused treatments (Henningesen et al., 2018). These kinds of treatment models aim to increase patient awareness of the psychobiological mechanisms of symptom exacerbation, to support anticipatory coping and to normalize interpretations of bodily symptoms. The aim is to support patients' health regulation so that the treatment goal is to increase coping with the disabling condition rather than curing it from a biomedical perspective. This also means that these treatment models emphasize building appropriate expectations of improvement during the treatment, which serves as a shared working platform between the health care professional and the patient.

### 3 OBJECTIVES

The aim was to assess whether the psychological factors underlying health behaviour influence subjective health complaints and whether they predict the incidence of symptoms or diseases at the population level. A further aim was to assess the effectiveness of psychosocial interventions for health-related quality of life (HRQoL) in cases with discrepancy between medical and environmental explanations and disability caused by health complaints.

More specifically, the thesis intended to examine:

Study I: What is the prevalence of subjective respiratory health complaints with no objective medical explanations in the general population? How do the psychological factors, illness worry, SOC and alexithymic characteristics that affect health regulation associate with the burden of health in cases with discrepancy between subjective and objective factors?

Study II: Do illness worry, SOC and alexithymic characteristics predict the incidence of subjective and objective respiratory health outcomes in the general population?

Study III: How does the HRQoL among individuals with subjective health complaints associated with IE compare with population-based reference groups and the association of psychological factors with HRQoL?

Study IV: Do psychosocial interventions influence HRQoL among individuals with subjective health complaints associated with IE?



## 4 MATERIALS AND METHODS

The data for the present study were derived from two complementary datasets i) a population-based survey, Health 2000, and its follow-up study, Health 2011 (Aromaa, Koskinen, & (Eds.), 2004; Lundqvist & Mäki-Opas, 2016) and ii) an RCT comparing TAU enhanced with CBT or PE for HRQoL among individuals with non-specific symptoms associated with indoor air (Selinheimo *et al.*, 2016) and ii). In both datasets, the individuals were working-age adults, followed up for either eleven years (a population-based study) or one year (RCT). In both studies, information on the participants was collected through an extensive health examination and several questionnaires. Table 1 summarizes the design and population of the individual studies.

**Table 1** *Description of included studies.*

| Study | Study Design                                 | Population  |
|-------|--|---|
| 1     | Cross-sectional population-based study       | A nationally representative sample of Finnish adults, excluding individuals with a diagnosed respiratory disease or a severe psychiatric disorder (N=4544). The study examined the prevalence of subjective respiratory health complaints in the absence of objective findings regarding respiratory pathology, and the association of such prevalence with psychological factors and the use of health care. |
| 2     | Eleven-year follow-up population-based study | A follow-up study of the previous cross-sectional study following the incidence of respiratory diseases and respiratory health complaints among working-aged individuals.   |
| 3     | RCT (baseline)                               | Baseline results for RCT comparing TAU enhanced with CBT or PE for HRQoL among individuals with PPS including respiratory symptoms and disability associated with IE among occupationally active individuals (n=52).  |
| 4     | RCT (follow-up)                              | One-year follow-up study of the RCT examining the effectiveness of CBT and PE for HRQoL of individuals with PPS associated with IE (n=44 at one-year follow-up).  |

RCT=Randomized controlled trial; CBT= Cognitive behavioural psychotherapy; PE=Psychoeducation; PPS=Persistent physical symptoms; HRQoL=Health Related Quality of Life; IE=Indoor environment.

## 4.1 STUDY POPULATION AND DESIGN (STUDIES I–IV)

Studies I–II. The sample for the present study was from the population-based Health 2000 survey, carried out in 2000–2001 in Finland and its follow-up study 11 years later, Health 2011 (see Aromaa *et al.*, 2004 and Lundqvist & Mäki-Opas, 2016 for a detailed description of the sampling procedure). The surveys were conducted by the Finnish Institute for Health and Welfare, formerly known as the National Public Health Institute.

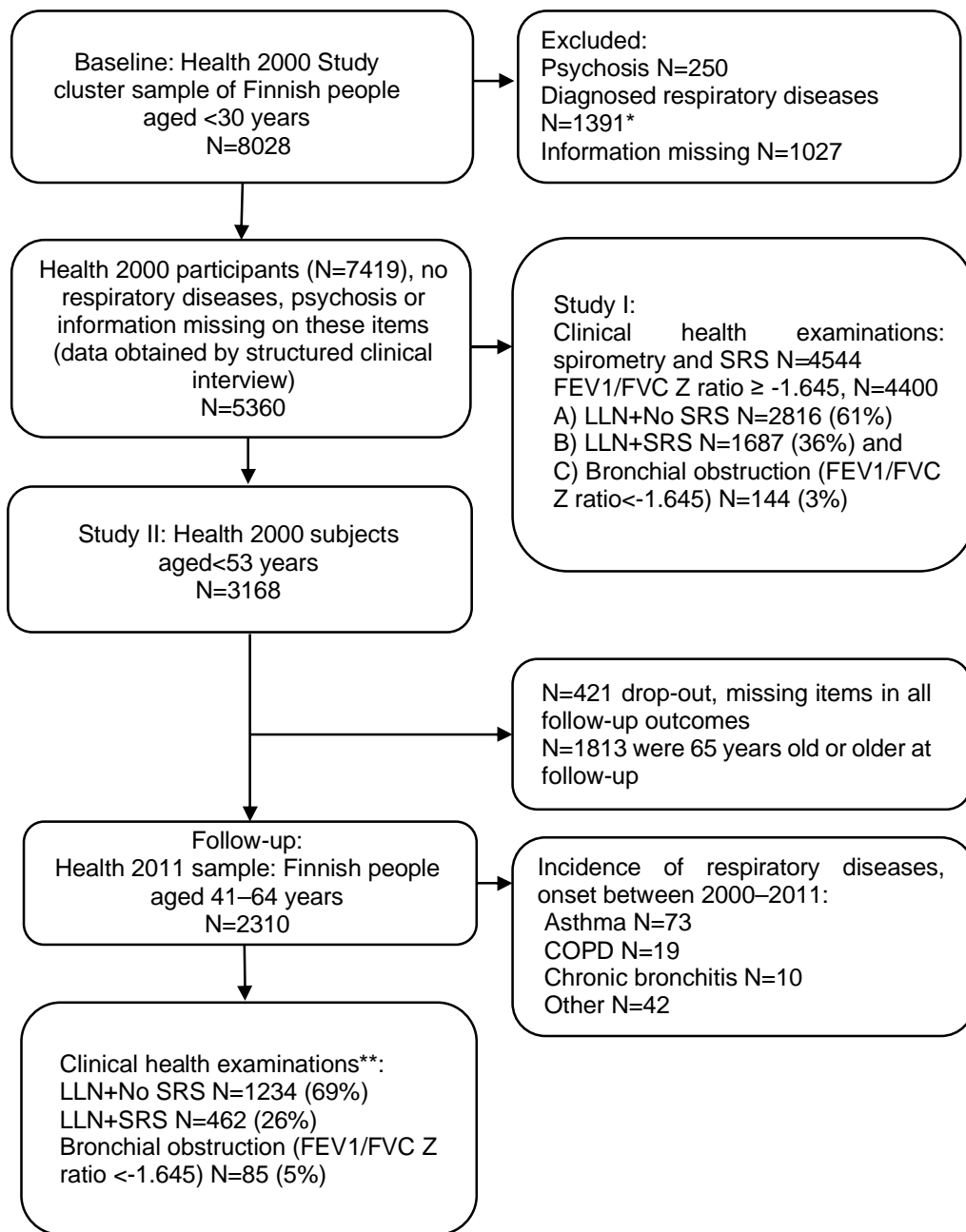
A nationally representative sample of 8028 participants over the age of 30 was invited to participate at baseline in 2000–2001. Of these, 6005 participated in a clinical health examination focusing on lung function, and in a structured interview covering respiratory symptomatology and common depressive, anxiety and alcohol-use disorders. In addition, clinical health examination information on the participants was collected through several questionnaires.

The sample analysed for Study I included participants with information on lung function assessed by a spirometry test and information on self-reported respiratory symptoms (N=4544). Participants were excluded from the study according to the following criteria:

- i. Having any psychotic disorder (described in Perala *et al.*, 2007). One participant who was diagnosed after the study sample was modified was excluded,
- ii. Self-reported respiratory disease diagnosed by a physician (asthma, COPD, chronic bronchitis, other respiratory diseases) and
- iii. Missing information on these items.

The mean age of the included participants n=4544 was 51 (SD=14.13), with a range of 30–94 years, and 54% were female. The majority of the participants were married or cohabiting (73%) and worked full time (58%). A total of 52% of the participants were overweight or obese and 22% were daily smokers. Eighteen per cent of the participants had been diagnosed with a mentally related (mood, anxiety or alcohol-related disorder) illness in the last 12 months, assessed by the Mental Health Composite International Diagnostic Interview (CIDI).

All members of the Health 2000 survey sample alive and living in Finland and willing to participate were invited to the Health 2011 survey. The sample analysed for Study II included all working-age participants (<65 years old) in 2011 who had no missing information on respiratory symptoms, diseases or lung function in 2011, and who were included in the study analysis in Study I (N=2310). Figure 2 outlines the participant flow through the baseline (Study I) and the follow-up study (Study II).



**Figure 3** Participant flowchart in Health 2000 and 2011 surveys. SRS=Self-reported respiratory symptoms; LLN =lower limit of normal. Study groups A) LLN + No SRS included participants with a spirometry FEV1/FVC Z ratio  $\geq -1.645$  who did not report respiratory symptoms; Group B) LLN + SRS included those with a spirometry FEV1/FVC Z ratio  $\geq -1.645$  who reported respiratory symptoms and Group C) Bronchial obstruction included those with spirometry FEV1/FVC Z ratio  $< -1.645$ . \* Diagnosed respiratory diseases included asthma, COPD, chronic bronchitis, and other respiratory diseases; \*\* Spirometry values were missing N=470 and information on self-reported symptoms was missing N=389.

Studies III–IV. The RCT study participants were recruited during 2014–2017 from five OHS units that represented both public and private sector enterprises in urban areas of southern Finland and the capital area. The feasibility of the recruitment process and the usability of the inclusion criteria were piloted and customized according to proposals from two participating OHS units before recruitment began. The recruiting OHS units also received a 1–1.5-hour training session by the researchers. The session included information on PPS associated with IE and on the study proceedings. In addition, all recruiting OHS specialists received a recruitment manual containing i) the study description, ii) inclusion/exclusion criteria, iii) an information letter and informed consent for the participant candidates, and iv) a questionnaire on indoor environmental pollutants and work arrangements conducted for the candidate. In addition, information on the reasons for participant refusal if inclusion criteria were met but the participant refused to participate were collected through structured forms.

Before enrolment in the study, a physician specialized in occupational health evaluated the participant candidates in line with the inclusion criteria. The cases were identified on the basis of the idiopathic environmental intolerance criteria compatible with those proposed by Lacour *et al.* in 2005 (Lacour *et al.*, 2005) as follows:

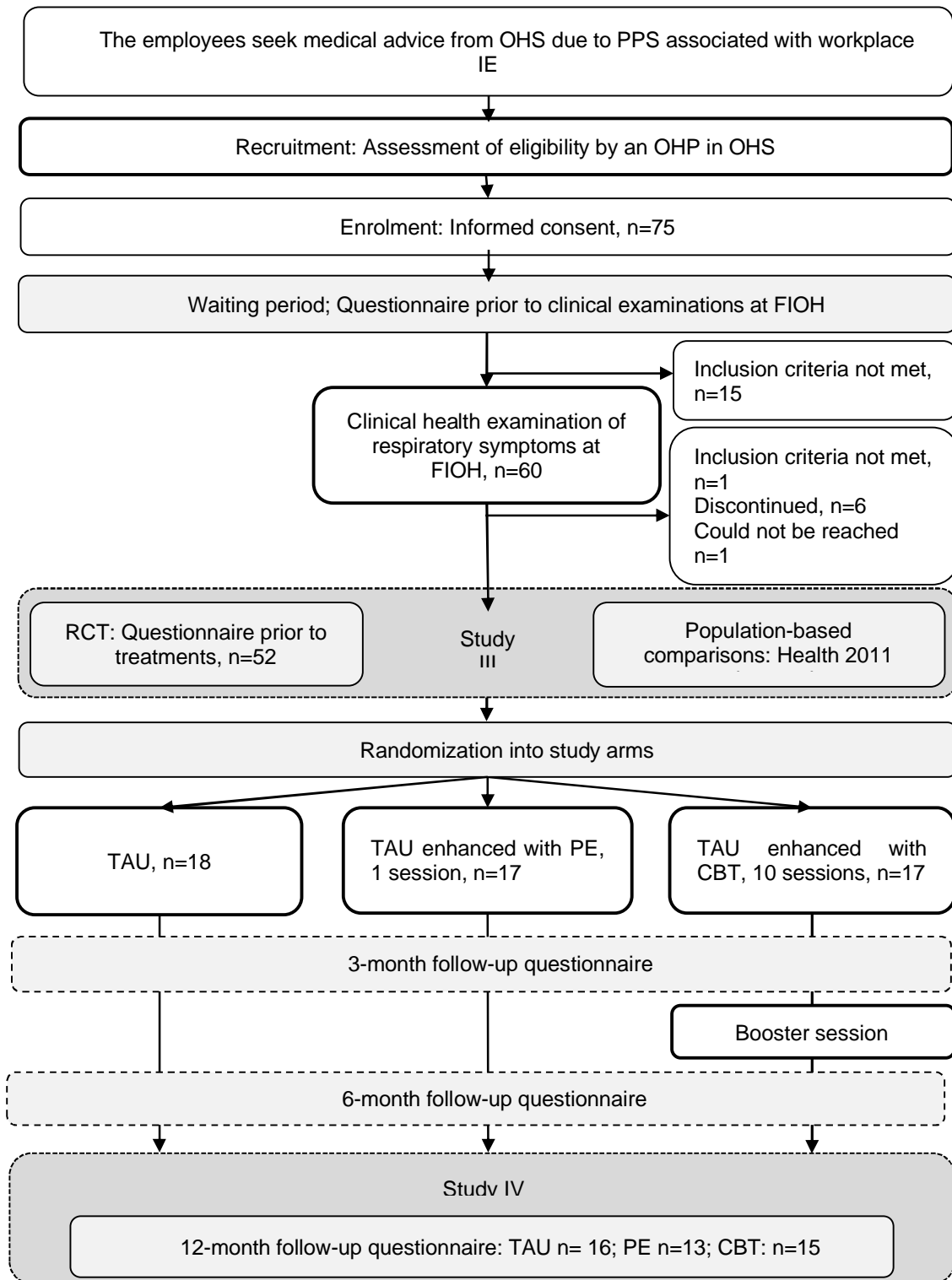
- i. Recurrent and PPS (respiratory symptoms and symptoms in at least one other organ system) and disability that the participants attributed to workplace indoor air
- ii. PPS not adequately explained by medical examinations or environment exposure-related reasons (i.e. symptoms continued after building repairs or despite the primary disease being under control).
- iii. PPS occurring in more than one indoor environment or despite workplace adjustments (e.g., work arrangements).
- iv. Onset of PPS with disability a maximum of three years before the study. Candidates had to be occupationally active.

After being recruited, all the participants filled in a questionnaire and attended a clinical examination of their respiratory symptoms at the Finnish Institute of Occupational Health (FIOH). The examinations included a two-week diurnal peak-expiratory-flow (PEF) measurement and a bronchial hyperresponsiveness test (Quanjer, Lebowitz, Gregg, Miller, & Pedersen, 1997; Sovijärvi, Malmberg, Reinikainen, Ryttilä, & Poppius, 1993). The results were evaluated by a physician specialized in pulmonology. In cases of undiagnosed or uncontrolled asthma as the cause of respiratory symptoms, or if other exclusion criteria were revealed, the participants were excluded. The original study protocol was published in 2016 (Selinheimo *et al.*, 2016). The study was also registered in the ClinicalTrials.gov registry (NCT02069002).

The eligible participants were allocated into TAU, or TAU enhanced with PE or cognitive-behavioural therapy (CBT) groups. Thus, all the participants

received TAU based on their individual needs from their OHS during the study. Allocation was based on pre-programmed randomization with an allocation ratio of 1:1:1. The final study sample consisted of n=52 participants who were  $44 \pm 8.9$  years old and 92% of whom were women. A total of 73.1% of them had a higher and 23.1% a lower education, 65.4% were married or cohabiting. Most of them (76.9%) had never smoked. Further, they had been in working life on average  $20.3 \pm 9.6$  years and during the last six months they had been on sick leave for  $21.3 \pm 34$  days. The participants reported on average  $5.2 \pm 5.2$  physician visits due to PPS related to IE during the last six months. Only 19.2% reported no comorbid diseases with PPS. Fifteen participants had asthma, which nevertheless did not explain the symptoms, based on an evaluation by a physician specialized in pulmonology.

Figure 4 shows the participant flow throughout the study.



**Figure 4** Participant flow throughout the randomized controlled trial and study populations in Studies III and IV. This study includes results from before the treatment questionnaires (Studies III and IV) and from 12-month follow-up (Study IV). CBT=Cognitive-Behavioural Therapy; FIOH=The Finnish Institute of Occupational Health; OHP=occupational health physician; OHS=occupational healthcare service; PE=Psychoeducation; PPS=Persistent physical symptoms; TAU=Treatment as usual.

## 4.2 OUTCOMES (STUDIES I-II)

Sense of Coherence (SOC). The Sense of Coherence scale was used to assess participants' SOC using a 12-item questionnaire derived from the Finnish SOC-13 scale (Antonovsky, 1987; Bernabe et al., 2009). Item 9 was not included in the final questionnaire of the Health 2000 survey. The scale has a seven-point Likert scale format with anchoring responses, 'very often=1' and '7=very seldom or never'. The sum-score ranges from 12 to 84 and a high score indicates a strong SOC. The Cronbach's alpha for the total scale was .85 and .87 in Studies I and II, respectively. The psychometric properties of the SOC scale have proven to be good, and the scale has been validated in both normal and clinical populations (Eriksson, Ek, & Johansson, 2000; Eriksson & Lindström, 2006).

Alexithymia, i.e. a lack of awareness of internal body sensations related to emotional arousal and externally orientated thinking style. Alexithymia was assessed using the Finnish version of the Toronto Alexithymia Scale-20 (TAS-20) (Bagby, Parker, & Taylor, 1994; Bagby, Taylor, & Parker, 1994; Hiirola et al., 2017; Joukamaa et al., 2001). The scale has a five-point Likert scale format with two anchoring phrases '1=strongly disagree' and '5=strongly agree'. A high sum score of responses to all 20 items indicates difficulties in identifying and describing feelings and a tendency towards an externally-orientated thinking style. A study based on the Health 2000 sample showed a Cronbach's alpha coefficient of 0.85 for TAS-20 (Mattila et al., 2008). The psychometric properties of the TAS-20 have proven to be good (Bagby, Parker, et al., 1994; Bagby, Taylor, et al., 1994; Hiirola et al., 2017; Joukamaa et al., 2001), and TAS-20 has also been validated in both general and patient populations (Baiardini et al., 2011; Feldman, Lehrer, & Hochron, 2002; Jyväsjärvi et al., 2001; Waller & Scheidt, 2006; Vazquez et al., 2010).

Health anxiety. The Whiteley Index is a frequently used instrument that assesses the continuum of health-related worries in the form of excessive health-related worries and beliefs and convictions about having a serious illness. We used a seven-item measure, Whiteley-7, rated on a five-point Likert scale ranging from 7 to 35 points, on which a high score indicates a tendency towards health anxiety (Fink et al., 1999; Pilowsky, 1967). In line with other measurements in our studies, the scale has proven to be reliable and to have high internal consistency (Speckens, Spinhoven, Sloekers, Bolk, & van Hemert, 1996). In Studies I and II, Cronbach's alpha coefficient was .77 and .73 for the scale, respectively.

Lung function and respiratory symptoms. Bronchial obstruction was diagnosed by spirometry, using a Vitalograph bellow spirometer (Vitalograph Ltd. Buckingham, UK) model. Studies I and II used the lower limit of normal (LLN) for the FEV1/FVC Z ratio (the proportion of vital capacity that people can expire: forced expiratory volume in one second (FEV1) / forced vital capacity (FVC) of six seconds duration) as airflow-obstruction criteria.

The LLN is defined as the value that identifies the lower fifth percentile of a population. It is calculated by subtracting 1.645 times the standard deviation from the mean, i.e. the expected value, with age-correction. A value below -1.645 predicts bronchial obstruction and values above -1.645 are considered normal (Quanjer *et al.*, 2012). Self-reported respiratory symptoms (SRS) were assessed in line with WHO-recommended sets of dichotomous questions (Fletcher, Elmes, Fairbairn, & Wood, 1959; Rose & Blackburn, 1968) on coughing, bringing up phlegm and being short of breath. If participants answered 'yes' to one or more items they were classified as having self-reported respiratory symptoms in Study I whereas follow-up included only self-perceived shortness of breath. The Spirometry LLN FEV1/FVC Z ratio measured in 2000 was used as a continuous explanatory variable in Studies I and II and as an outcome variable in 2011 in Study II.

To assess the discrepancy between self-reported symptoms and respiratory health in terms of normal lung function and no respiratory diseases at baseline and follow-up, participants were divided into three study groups based on their spirometry values and self-reported respiratory symptoms. The LLN + No SRS Group included those with a spirometry LLN FEV1/FVC Z ratio of  $\geq -1.645$  who did not report respiratory symptoms; the LLN + SRS Group included those with a FEV1/FVC Z ratio of  $\geq -1.645$  who reported respiratory symptoms; the Obstruction group included those with a spirometry FEV1/FVC Z ratio of below  $-1.645$  (bronchial obstruction) (Figure 3).

Background variables. Gender and age, marital status (single, married, cohabiting, divorced/separated and widowed), information related to socio-economic position including education (basic, secondary and higher education) and main activity (full-time employed, part-time employed, unemployed or laid off, retired, homemaker, student and other) were used as covariates. Other categorical covariates were smoking (daily, occasionally, previous 1–12 months or over, and never) and common psychiatric disorders classified into mood, anxiety or alcohol-related disorders according to the structured Mental Health Composite International Diagnostic Interview (CIDI). Body mass index (BMI), the maximum hand-grip strength of the dominating hand for measuring physical condition, and C-reactive protein (CRP) as a measure of acute inflammation were used as continuous covariates.

Health care use. The frequency of health care use was determined by self-reported number of physician visits during the previous 12 months.

## **4.3 OUTCOMES AND INTERVENTIONS (STUDIES III–IV)**

### **4.3.1 OUTCOMES**

Health-related quality of life. Studies III–IV used HRQoL as a primary outcome measure. HRQoL was measured using the 15D questionnaire



(Sintonen, 1994, Sintonen, 2001, 2013) to evaluate the influence of PPS on individuals' daily lives and functioning in comparison with population-based reference groups and to assess the effectiveness of the interventions during the follow-up. The 15D is a generic, 15-dimensional standardized measure composed of physical, mental and social wellbeing. The dimensions are mobility, vision, hearing, breathing, sleeping, eating, speech, elimination, usual activities, mental functioning, discomfort and symptoms, depression, distress, vitality, and sexual activity. Each dimension has five grades of severity (1=the best level and 5=the worst level of functioning). The 15D was used as a single sum score measure with values from 1 (full health) to 0 (dead) as a primary outcome, and a symptom profile also had to be presented. Cronbach's  $\alpha$  for 15D questionnaire varied from 0.74 to 0.86 across the measurement points during the study.

The secondary outcome measures used in Studies III–IV included a variety of symptoms and measurements of dispositional, psychological functioning. The clinical cut-off scores defined in population-based samples or clinical populations were used in psychiatric measurements to assess the severity of the symptoms. Study III also assessed the association between HRQoL and dispositional factors such as personality traits, SOC, tendency to worry, and psychological flexibility. Participants answered the questionnaires prior to the clinical health examinations at FIOH, prior to treatments (baseline), and at 3, 6- and 12-month follow-ups.

**Depression.** Symptoms of depression were assessed using the Finnish version of the Patient Health Questionnaire-9 (PHQ-9) (Kroenke, Spitzer, & Williams, 2001; Kaila *et al.*, 2012). The PHQ-9 consists of nine questions on depression-related symptoms during the preceding two weeks on a scale of 0 (*not at all*) to 3 (*nearly every day*). The PHQ-9 has a sum score of 0–27 and scores of  $\leq 5$  were considered the clinical cut-off for mild depression.

**Anxiety.** Self-rated anxiety was measured by the seven-item General Anxiety Disorder-7 (GAD-7) (Spitzer, Kroenke, Williams, & Löwe, 2006). GAD-7 includes seven questions on anxiety-related symptoms during the past two weeks on a scale of 0 (*not at all*) to 3 (*nearly every day*). A cut-off score of  $\geq 5$  was given to mild to severe anxiety.

**Insomnia.** The Insomnia Severity Index (ISI) [(Morin & Barlow, 1993; Morin, Belleville, Bélanger, & Ivers, 2011) in Finnish (Järnefelt & Hublin, 2012)] was used to assess the severity of insomnia-related symptoms. The questionnaire contains seven items on insomnia-related symptoms and cognitions in the preceding two weeks. The sum score ranges from 0 (*no problems at all*) to 28 (*severe problems*). Responses of  $> 7$  were scored as subthreshold to severe insomnia.

**Environmental intolerances.** Two scales from the Quick Environmental Exposure and Sensitivity Inventory (QEESI), Chemical Intolerance (CI) and Life Impact (LI) were used to assess multiple chemical intolerance related to environmental factors. A sum score from 0 to 100 was calculated to assess the severity of the chemical intolerance. In the CI scale

(cut-off  $\geq 40$ ), the response options for each item assessing whether certain exposures would cause a respondent to feel sick were on a scale from 0 (*no problem at all*), through 5 (*moderate symptoms*) to 10 (*disabling symptoms*). In the LI scale (cut-off  $\geq 24$ ) the response options for each item (e.g. 'How much have your sensitivities affected 1. Your diet') were on a scale from 0 (*not at all*), through 5 (*moderately*) to 10 (*severely*) (Miller & Prihoda, 1999).

Work-related fatigue. The Need for Recovery scale (NFR) was used to assesses the frequency of problems recovering from work (Sluiter, De Croon, Meijman, & Frings-Dresen, 2003; Sluiter, 1999; Van Veldhoven & Broersen, 2003). The NFR assesses the work-induced fatigue and quality of an employee's recovery time using 11 items. The participant responded to the items (e.g. 'I find it hard to relax at the end of a working day') on a scale from 1 (*never*) to 4 (*always*) and the summary score was calculated to assess the severity of work-induced fatigue.

Personality traits. The Extra Short Five (S5) questionnaire was used to assess the participants long-term reaction patterns. S5 measures dimensions of the five-factor model: neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness (Konstabel et al., 2017; Konstabel, Lönnqvist, Walkowitz, Konstabel, & Verkasalo, 2012). Each dimension was measured by six questions. The participant answered the questions on a scale from -3 (*does not apply*), through 0 (*unsure*) to 3 (*applies well*). The S5 has proven to be a reliable, valid instrument (Konstabel et al., 2017; Konstabel et al., 2012).

Sense of coherence. SOC was assessed on the Finnish SOC-13 scale (Antonovsky, 1987; Bernabe et al., 2009). The questionnaire has 13 items to which the participant responded on a scale from 1 (*very often*) to 7 (*never*). Five items were reversed before the summary score of all the questions were calculated and a higher sum score indicated a better SOC. The psychometric properties of SOC-13 have proven to be good, and the instrument has been validated in both general populations and several clinical populations (Eriksson & Lindström, 2005, 2006).

Tendency to worry. The Penn State Worry Questionnaire (Meyer, Miller, Metzger, & Borkovec, 1990) was used to measure worry as an independent construct of anxiety. The questionnaire assesses the tendency, intensity, and uncontrollability of general worry with 16 items. The participant responded to the items (e.g. 'If I do not have enough time to do everything, I do not worry about it') on a scale from 1 (*not at all typical of me*) to 5 (*very typical of me*).

Psychological flexibility. Psychological flexibility was assessed using the Acceptance and Action Questionnaire-II (Bond et al., 2011; Mccurry et al., 2004) which includes seven items (e.g. 'I'm afraid of my feelings') to be rated on a scale from 1 (*Never true*) to 7 (*always true*). All the items were added up and a higher sum score indicated less flexibility.

Cronbach's alpha for the secondary outcome scales varied from 0.83 to 0.97. The questionnaires were assessed prior to the interventions and at 3-, 6- and 12-month follow-ups.

**Satisfaction with treatment.** Participants' experiences related to PE or CBT were assessed using a questionnaire based on a psychotherapy consumer report study at the 3- and 12 -month follow-up measurement points (Seligman, 1995). The questionnaire included questions on improvement and satisfaction with treatment (e.g. 'How much did treatment help with the specific problem that led you to therapy?') to which the participants answered on a seven-point Likert scale ranging from 1 (*made things a lot worse*), through 4 (*Indifferent*), to 7 (*made things a lot better*) (questions 1, 2, and 5). The participants were further asked to evaluate their current life situation prior to treatment [a five-point Likert scale ranging from 1 (*very poor*), through 3 (*so so*), to 5 (*very good*)]. They were also asked whether they would recommend the treatment to someone else with similar kinds of symptoms. The answer was dichotomized as 1 (*yes*) and 2 (*no*).

**Background variables.** Gender, age, marital status (unmarried, married, cohabiting, divorced, widowed), educational level (graduate, lower secondary, higher secondary and unknown), smoking (never, ex-smoker and smoker), alcohol consumption measured by the AUDIT alcohol consumption questionnaire (AUDIT-C) (Kriston, Hölzel, Weiser, Berner, & Härter, 2008) and BMI were used as background variables. Further, clinical characteristics included self-reported onset of PPS, diagnosed diseases, medication usage, frequency of health care use and asthma control, measured by the Finnish version of the asthma control test (The ACTTM is a trademark of Quality Metric Incorporated © 2002 GlaxoSmithKline). Lung function was assessed by spirometry, bronchial hyperresponsiveness and PEF monitoring for two weeks before randomization.

### **4.3.2 INTERVENTIONS**

Study IV used TAU enhanced with PE or CBT as interventions. Both interventions were structured and based on the participants' approval. The intervention sessions were also recorded for post-hoc reliability.

TAU covered OHS that offered general medical care and support of work ability by a specialist in occupational medicine and an occupational nurse. By the physician's referral, standard OHS also included the possibility of consulting an occupational health psychologist, physiotherapist, or other medical specialist. In addition to TAU, study participants received PE or CBT. The rationale of both of the interventions and the implementation is described further in the protocol paper of the study (Selinheimo *et al.* 2016).

PE included one 90-minute session delivered by a psychologist and physician specialized in occupational health. The session included 1) an overview of the main IE exposures, 2) factors related to IE-associated

symptoms and diseases based on current scientific knowledge, and 3) physiological consequences of prolonged stress reactions, management of physiological arousal of stress and decelerating the vicious circle of emotion-behaviour-symptom-cognitions.

CBT consisted of 10 individual semi-structured sessions and homework such as increasing meaningful activities between the sessions planned together with the psychologist, who was a licensed psychotherapist. The aim of CBT was to challenge the dysfunctional cognitions related to health and to support health behaviour, emotion regulation and coping strategies. The introduction session (90 min) was followed by nine 45-minute sessions at weekly intervals, with the last two sessions at two-week intervals. A booster session was conducted three months after treatment ended. Table 2 shows an overview of the sessions' contents.

**Table 2** *Table 2. Contents of cognitive behavioural therapy*

| Session                       | Description of session contents   |
|-------------------------------|---|
| 1.                            | Introduction of treatment as intervention focusing on behavioural training and monitoring. Case formulation of patient's situation and symptoms. Setting of personal goals for the intervention and starting the symptom-emotion-cognition-monitoring form. |
| 2.–3.                         | Discussion on how stress reactions influence patients' health and the short- and long-term physiological consequences of stress. Coping with stress. Working with health-related worries and symptom-perception interaction.                                |
| 4.–5.                         | Patient's strengths and vicious circle of illness behaviour. Patient's dysfunctional health-related attribution strategies, e.g. catastrophizing. Cognitive restructuring.  |
| 6.–7.                         | Assessment of goals and evaluating obstacles that hinder their achievement. Validation of frustration related to the treatment and support of meaningful coping strategies.   |
| 8.–9.                         | Discussion on how to react to contradictory information (e.g. in media or among health care professionals or patient organizations) on IE and health-related issues. Increasing awareness of emotions and how they may influence symptom perception.        |
| 10.                           | Identifying warning signs that may influence recurrence of PPS. Planning future actions to prevent relapse.   |
| Follow-up and booster session | Three months after the intervention, all the participants were seen again to support progress or troubleshoot challenges.   |

IE = Indoor environment; PPS = Persistent physical symptoms

## 4.4 STATISTICAL METHODS

In Studies I–II, categorical sociodemographic and clinical outcomes were analysed using Pearson's  $\chi^2$  test. In Study I, analyses of covariance were conducted to compare the study groups in terms of psychological factors (TAS, SOC and WI), controlled for gender and age. The standardized values, including the confidence intervals (CIs) of the standard error of the means were presented as results.

Binary logistic regression was used to estimate the influence of psychological factors on the reporting of respiratory health complaints (0=health complaints, 1=health complaints) in the cross-sectional analyses (Study I) and at follow-up (Study II). The analyses were adjusted for potentially clinically significant factors of the gender, age, spirometry LLN value, CIDI diagnosis, smoking, BMI, hand grip strength, and CRP in 2000 in both studies.

In Study I, separate binary logistic regression analyses were conducted to assess the interactions between the SOC, WI and TAS-20 factors and gender, age and LLN which were added to the models separately to estimate the possible interactions between the factors and the covariates (3 × 3 models). CIDI diagnosis and smoking status were controlled for in the analyses both together and separately (nine+nine models). Finally, Poisson regression was run to predict the number of physician visits during the previous 12 months as a dependent variable and gender, age, study group, psychological factors, and other markers as independent variables in separate models. CIDI diagnoses were separately adjusted in the models, but because the associations did not change, only the sum score was shown.

The attrition analyses in Studies I and II were conducted by comparing the demographic factors of the participants in 2000 who dropped out during the follow-up with those of the participants with data at both measurement points. In additional analyses conducted for this summary, the associations between the study groups in 2000 with respiratory symptoms, incidence of respiratory diseases and psychiatric disorders in 2011 were tested using the  $\chi^2$  test.

In Study II, a binary logistic regression analysis was conducted, but incidence of asthma and COPD were analysed separately during the follow-up as the dependent variable (0=no respiratory disease, 1=respiratory disease). In addition, linear regression was run to predict the lung function measured by a continuous spirometry LLN value in 2011 as a dependent variable. The analyses were adjusted for gender, age and respiratory symptoms and psychological factors in 2000 in separate models. The analyses were further adjusted for CIDI diagnosis, smoking, BMI, CRP and hand grip strength in 2000. The results are presented with ORs including 95% CIs and p values.

Study III analysed demographic outcomes using the  $\chi^2$  test. The outliers were checked on a scatter plot of the primary-outcome overall score, and one outlier was detected. The analyses were repeated both including and excluding the outlier because there was no reason to exclude it. The results were similar

in both cases and are thus reported for the analyses that included all the participants.

Analysis of covariance was used to compare the participants' HRQoL scores with the available population-based 15D reference values based on the Health 2011 survey. The reference values included data on participants with valid 15D scores who were comparable with the RCT study participants in terms of working status and age (29 to 56 years). The demographic and health-related variables available in both datasets were adjusted in the analyses. The distribution of the HRQoL dimension profiles were compared with those of the Mann Whitney U-tests.

Ninety-two percent of Study III participants were women. Thus, statistical analyses were conducted for both women only and both genders. Student's t-tests were used to assess the significance of any group differences in the mean HRQoL based on divisions according to the clinical cut-off scores in the psychiatric measurements (no complaints – complaints). Pearson's r was used to measure the correlations between continuous psychological measurements with no diagnosis-based or other well-defined cut-off scores. The analyses comparing personality traits and SOC were Bonferroni corrected. The results based on an effect size above small ( $r^2 > 0.2$ ) were presented. Further, multiple linear regression (enter method) was used to analyse the associations between the psychiatric and psychological measurements with HRQoL as a dependent variable. To avoid multicollinearity, tolerances above 0.5 and variance inflator factors under 2 were considered acceptable. The model with the significantly best adjusted R-square was chosen.

In Study IV the 15D was used both as a continuous variable and a minimally important difference score ( $\pm 0.03$  in 15D). Power calculations made during the planning stage of the study were based on the minimally important difference in the 15D scores (Sintonen, 2013). A priori power calculations suggested that a sample size of  $n > 17$  had 80% power ( $\alpha = 0.05$ , two tail) to reject the null hypothesis of no improvement in HRQoL following treatment.

Before the primary analyses, the intervention arm allocation was concealed by a researcher who was not involved in the data analysis. T-test and analysis of covariance were used for pairwise and multiple comparisons of the arms, and for examining changes in them. Post hoc tests were corrected using the Bonferroni correction. In the analysis, a natural logarithm transformation with a constant of 1 was used for the secondary variables with non-normally distributed residuals (PHQ, GAD, and chemical intolerance by the QEESI). The  $\chi^2$  test was used to analyse any categorical minimally important difference during the follow-up in the primary outcome and the number of participants above the clinical cut-off scores in the secondary outcomes between the groups. Analysis of the study completers were used in addition to an intent-to-treat (ITT) analysis to handle drop-out data. In the post-hoc analyses, two intervention groups (CBT and PE) were combined, and the analyses of covariance were repeated with no intervention – intervention as a grouping variable.

In all the studies, the level of significance was set at  $p < 0.05$ . The effect sizes between the study groups were computed as Hedges'  $g$  in Studies III–IV. The following suggestions were used to interpret the magnitude of the effect size:  $g = 0.20$  (small),  $g = 0.50$  (medium) and  $g = 0.80$  (large) (Cohen, 2013, Durlak, 2009). Table 3 summarizes the analytical methods and outcomes of the different studies.

**Table 3** *Table 3. Summary of statistical analyses in each study.*

|           | Design  | Statistical analysis   | Variables   |
|-----------|---|--|---|
| Study I   | Cross-sectional, population based   | Pearson's $\chi^2$ test<br>Analysis of covariance<br>Binary logistic regression<br>Poisson regression  | Dependent variable:<br>TAS, SOC and WI,<br>Self-reported respiratory symptoms,<br>Physician visits<br>Explanatory variables:<br>TAS, SOC and WI<br>Covariates   |
| Study II  | Follow-up, population based   | Pearson's $\chi^2$ -test<br>Analysis of covariance<br>Linear regression  | Dependent variables:<br>Self-reported respiratory symptoms,<br>Incidence of respiratory disease,<br>Spirometry LLN value<br>Explanatory variables:<br>TAS, SOC and WI<br>Covariates                                 |
| Study III | Cross-sectional, comparison of clinical data with population-based references | Pearson's $\chi^2$ -test<br>Mann Whitney U-tests<br>Student's t-test<br>Pearson's r<br>Analysis of covariance<br>Multiple linear regression (enter method) | Primary outcome: HRQoL<br>Secondary outcomes: Psychiatric symptoms (PHQ, ISI, GAD),<br>Chemical intolerance (QEESI CI and LI),<br>Psychological factors (PSWQ, NRF, AAQ-II, SCL-90 GSI, SOC and personality traits) |
| Study IV  | Follow-up, clinical data  | Pearson's $\chi^2$ test<br>Student's t-test<br>Analysis of covariance  | Primary outcome: HRQoL<br>Secondary outcomes:<br>Psychiatric symptoms (PHQ, ISI, GAD),<br>Chemical intolerance (QEESI CI and LI),<br>Treatment satisfaction   |

PHQ=Patient Health Questionnaire , ISI=Insomnia Severity Index, GAD=Generalized Anxiety Disorder, QEESI=Quick Environmental Exposure and Sensitivity Inventory, CI =Chemical Intolerance and LI=Life Impact; PSWQ=Penn State Worry Questionnaire, NRF=Need for Recovery, AAQ-II=Acceptance and Action Questionnaire–II, SCL-90 GSI=Symptom Check List - 90, Global Severity Index, SOC=Sense of Coherence



#### **4.4.1 STATISTICAL PROGRAMMES**

The statistical analyses were carried out using 22.0 (Study I) and 25.0 version (Studies II–IV) for IBM-SPSS for Windows (SPSS Illinois, Chicago, Illinois, USA) software.

### **4.5 ETHICS AND STUDY MONITORING**

The Health 2000 and 2011 surveys were approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa. The steering committee of the Health 2000 and 2011 surveys accepted the research plan for Studies I–II and granted usage of Health 2011 data in Study III before the studies were conducted.

The Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa, Finland, approved the RCT (number 107/13/03/00/13) and the amendments of the trial. The RCT study is registered at the ClinicalTrials.gov registry (NCT02069002) and the study protocol was published in the British Medical Journal Open in 2016 (Selinheimo *et al.*, 2016). The final follow-up results of the RCT were reported by following the Consolidated Standards of Reporting Trials (CONSORT) statement (Schulz *et al.*, 2010).

The RCT procedures were audited by the steering group. The protocol modifications were approved by the ethics committee of the Hospital District of Helsinki and Uusimaa and the ClinicalTrials.gov registry was informed accordingly.

## 5 RESULTS

### 5.1 PREVALENCE AND PSYCHOLOGICAL RISK FACTORS ASSOCIATED WITH SUBJECTIVE RESPIRATORY HEALTH COMPLAINTS (STUDY I)

The findings from Study I showed that 26% of the general population and even 36% of the population without respiratory diseases or severe psychiatric disorders perceived respiratory health complaints without objective signs of impaired lung function. SOC, alexithymia and high illness worry associated significantly with perceived health complaints.

High socioeconomic status in terms of being married, highly educated and in full-time work were more common among the participants without respiratory health complaints and with normal lung function than among those with respiratory health complaints and normal lung function. In contrast, diagnosed depression or anxiety disorder and overweight were more common among participants with respiratory health complaints but normal lung function than among those without these health complaints. The former also reported more physician visits (OR 1.25, 95% CI, 1.15-1.35) than the latter.

The analysis of the associations between SOC, TAS and WI and self-reported respiratory health complaints indicated statistically significant associations between these factors. Even after adjustment for all covariates, a high SOC was associated with a decrease in the odds of self-reported respiratory health complaints (OR 0.89, 95% CI 0.81-0.98). Further, high health anxiety (OR 1.29, 95% CI 1.19-1.41) and alexithymic characteristics (OR 1.11, 95% CI 1.01-1.22) were associated with an increase in self-reported respiratory health complaints.

Individuals with respiratory health complaints but no objective signs of respiratory pathology reported 1.25 (95% CI 1.15–1.35,  $p < 0.0001$ ) times more physician visits than those with no signs of objective or subjective respiratory health complaints. The difference between these groups diminished by 42.7% (from 1.25 to 1.10) following adjustment for SOC, alexithymia and illness worry. The direction of the difference between the groups remained the same when the covariates were added to the analysis. Health anxiety showed the strongest predictive power over physician visits (OR 1.35, 95% CI 1.32-1.38), even after adjustment for all covariates.

## 5.2 PSYCHOLOGICAL RISK FACTORS PREDICTING SUBJECTIVE RESPIRATORY HEALTH COMPLAINTS (STUDY II)

The follow-up in Study I showed significant differences between the drop-out participants and the study sample. The drop-out participants were more generally men (56%) than women, were younger, and had a lower education than the participants in the Study II sample. The participants in the study sample were more often married and non-smokers.

The participants' tendency to report respiratory health complaints without signs of respiratory pathology in 2000 and participants' bronchial obstruction associated with respiratory health complaints in 2011,  $\chi^2(2)=86.43$ ,  $p<.000$  and incidence of asthma  $\chi^2(2)=37.52$ ,  $p<.000$  during follow-up. The participants' tendency to report health complaints without signs of respiratory pathology in 2000 associated with alcohol use disorders  $\chi^2(2)=6.44$ ,  $p=.04$ , anxiety disorders  $\chi^2(2)=11.78$ ,  $p<.003$ , and mood disorders  $\chi^2(2)=16.79$ ,  $p<.000$  at 2011 (Table 4.). However, we did not establish converse associations between psychiatric disorders in 2000 and respiratory symptoms in 2011.

**Table 4** Association between study groups\* in 2000 and respiratory symptoms and diseases and psychiatric disorders in 2011

|                    |     | LLN + No SRS |       | LLN + SRS |       | Obstruction |        | $\chi^2$ -test, $p$ |
|--------------------|-----|--------------|-------|-----------|-------|-------------|--------|---------------------|
|                    |     | N            | N%    | N         | N%    | N           | N%     |                     |
| Short of breath    | No  | 1055         | 77.7% | 301       | 58.4% | 22          | 44.9%  | $p<.000$            |
|                    | Yes | 302          | 22.3% | 214       | 41.6% | 27          | 55.1%  |                     |
| Asthma             | No  | 1575         | 97.8% | 596       | 95.5% | 48          | 84.2%  | $p<.000$            |
|                    | Yes | 36           | 2.2%  | 28        | 4.5%  | 9           | 15.8%  |                     |
| COPD               | No  | 1606         | 99.7% | 615       | 98.7% | 51          | 89.5%  | $p<.000$            |
|                    | Yes | 5            | 0.3%  | 8         | 1.3%  | 6           | 10.5%  |                     |
| Chronic bronchitis | No  | 1604         | 99.6% | 620       | 99.5% | 57          | 100.0% | $p=.87$             |
|                    | Yes | 7            | 0.4%  | 3         | 0.5%  | 0           | 0.0%   |                     |
| Other              | No  | 1279         | 98.7% | 481       | 96.0% | 43          | 95.6%  | $p=.001$            |
|                    | Yes | 17           | 1.3%  | 20        | 4.0%  | 2           | 4.4%   |                     |
| CIDI: Alco         | No  | 1289         | 94.4% | 482       | 91.3% | 45          | 91.8%  | $p=.04$             |
|                    | Yes | 76           | 5.6%  | 46        | 8.7%  | 4           | 8.2%   |                     |
| CIDI: Anxiety      | No  | 1322         | 96.8% | 495       | 93.8% | 49          | 100.0% | $p=.003$            |
|                    | Yes | 43           | 3.2%  | 33        | 6.3%  | 0           | 0.0%   |                     |
| CIDI: Mood         | No  | 1286         | 94.2% | 469       | 88.8% | 44          | 89.8%  | $p<.000$            |
|                    | Yes | 79           | 5.8%  | 59        | 11.2% | 5           | 10.2%  |                     |

LLN + No SRS=group includes participants whose spirometry lower limits of normal (LLN) ratio FEV1/FVC Z ratio was normal ( $\geq -1.645$ ) and who did not report respiratory symptoms; LLN + SRS=group includes participants whose Z ratio was normal ( $\geq -1.645$ ) and who reported respiratory symptoms; Obstruction = participants with bronchial obstruction (FEV1/FVC Z ratio  $< -1.645$ ); CIDI: Alco, alcohol-related disorders by Mental Health Composite International Diagnostic Interview (CIDI); CIDI: Anxiety, anxiety disorders; CIDI: Mood, mood disorders; \* the analyses do not include the participants (N=39) who had missing information on SRS and/or spirometry in 2000.

Alexithymia predicted self-reported shortness of breath even after several adjustments at the follow-up measurement point (OR 1.30, 95% CI 1.12 - 1.52).

Other significant associations were not found between psychological factors in 2000 and perceived respiratory health complaints in 2011.

High illness worry predicted the incidence of asthma even after adjustment for the health-related variables in 2000 and 2011 (OR 1.49, 95% CI 1.10 - 2.01). Alexithymia increased the risk of 10-year incidence of COPD during the follow-up after several adjustments (OR 3.12, 95% CI 1.48 - 6.60). The analysis showed neither significant associations between the psychological factors at baseline and lung functioning measured by spirometry at eleven-year follow-up.

### **5.3 HRQOL AMONG EMPLOYEES WITH IE-RELATED PPS (STUDY III)**

Comparative analysis between individuals with PPS related to IE and population-based reference groups showed that individuals with PPS have significantly poorer HRQoL than comparisons derived from the general population. These individuals had poorer HRQoL than the general population (Hedges'  $g=2.33$ ) or clinical subgroups of patients: those with asthma (Hedges'  $g=1.46$ ), patients with anxiety or depressive disorders (Hedges'  $g=0.73$ ), or patients with a chronic condition associated with work disability (Hedges'  $g=1.11$ ).

Symptoms of depression, anxiety and insomnia were common among individuals with IE-related PPS and these were also associated with decreased HRQoL ( $p<.01$ ). Life impact related to chemical intolerance was associated with poor HRQoL ( $p=.02$ ) whereas a high level of chemical intolerance did not show a statistically significant association with HRQoL.

Need for recovery from work had a strong, negative correlation with poor HRQoL ( $r=-0.65$ ,  $p<.001$ ), explaining up to 42% of the variation between the factors.

Of the dispositional factors, high neuroticism had a significantly negative correlation with HRQoL ( $r=-.45$ ,  $p=.005$ , two-tailed;  $r^2=0.20$ ). In contrast, high SOC had a positive, significant correlation with good HRQoL ( $r=.49$ ,  $p=.005$ , two-tailed;  $r^2=0.24$ ). Poor psychological flexibility, measured by the Acceptance and Action Questionnaire-II ( $r=-.45$ ,  $p<.001$ , two-tailed;  $r^2=0.21$ ) and high tendency to worry, measured by the Penn State Worry Questionnaire ( $r=-.48$ ,  $p<.001$ , two-tailed;  $r^2=0.23$ ), also showed significant correlations with HRQoL ( $p<.001$ ).

#### **5.3.1 COMPARISON BETWEEN EMPLOYEES WITH IE-RELATED PPS AND POPULATION-BASED SAMPLE**

There was a substantial difference in the HRQoL of the RCT participants ( $M=.83$ ,  $SD=.09$ ) and those in the Health 2000 reference groups in Study I:

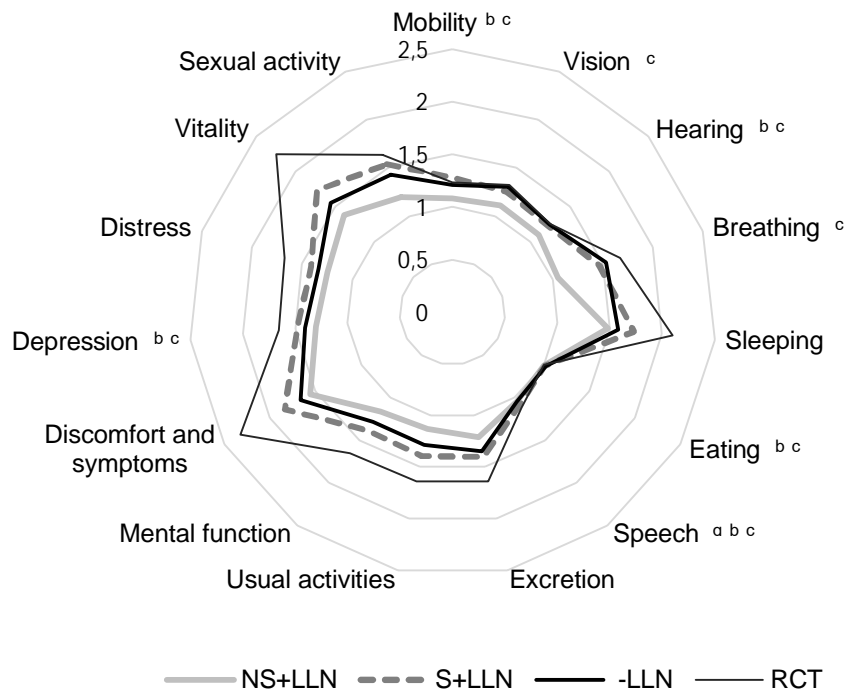
those without respiratory health complaints and with normal lung function, those with respiratory health complaints and with normal lung function, and those with bronchial obstruction (Table 5.).

Table 5 *Heath 2000 reference group means (standard deviations) and effect sizes compared with RCT study participants.*

| Group  | N    | M    | SD   | Hedges' g |
|--------|------|------|------|-----------|
| NS+LLN | 2625 | 0.95 | 0.06 | 1.98      |
| S+LLN  | 1552 | 0.89 | 0.10 | 0.60      |
| -LLN   | 123  | 0.91 | 0.08 | 0.96      |

M=Mean, SD=Standard Deviation; NS+LNN=Health 2000 participants with normal lung functioning and without respiratory symptoms; S+LNN=Health 2000 participants with normal lung functioning and respiratory symptoms; -LNN=Health 2000 participants with bronchial obstruction.

The distributions of the 15D-items between the RCT study participants and the Health 2000 groups in Study I differed significantly. Figure 5 shows the mean results of the 15D, item by item, for the RCT study participants and the Health 2000 groups.



**Figure 5** Dimensions of the 15D-based HRQoL among the RCT study participants and the Health 2000 reference groups. NS+LNN: Health 2000 participants with normal lung function and without respiratory symptoms; S+LNN: Health 2000 participants with normal lung function and respiratory symptoms; -LNN: Health 2000 participants with bronchial obstruction; RCT: the RCT study sample. a Distribution of the 15D-dimension among the Health 2000 NS+LNN and the RCT study participants is the same (Mann Whitney U). b Distribution of the 15D-dimension among the Health 2000 S+LNN and the RCT study participants is the same (Mann Whitney U). c Distribution of the 15D-dimension among the Health 2000 LNN and RCT study participants is the same (Mann Whitney U).

## 5.4 EFFECTIVENESS OF PSYCHOSOCIAL INTERVENTIONS ON IE-RELATED PPS (STUDY IV)

The findings from the fourth study showed no statistically significant differences between the HRQoL of the intervention groups and those receiving TAU. However, when the PE and CBT intervention groups were combined and the analysis was repeated, the results showed significant improvement in the combined intervention group [ $F(1,47)=5.06$ ,  $p=.03$ , Hedges  $g=0.41$ ]. Moreover, when study groups were compared according to the clinically important changes in HRQoL during the follow-up, the HRQoL of the majority of the participants in the intervention groups had improved (47% in CBT and 38% in PE) or remained stable (40% in CBT+TAU and 54% in PE+TAU). At the same time, HRQoL decreased more among the controls (31%) than among the treatment groups.

There were no statistically significant differences between the groups in terms of the level of depressive, anxiety of insomnia symptoms, nor the level

of chemical intolerance and the life impact of chemical intolerance at the 12-month follow-up assessment point.

Linear regression analyses were run to explore the associations between psychiatric symptoms and dimensional psychological factors at baseline with HRQoL at 12-month follow-up. As the intervention group experienced no significant effects on HRQoL, it was excluded from the models. Regarding psychiatric symptoms, the level of depression ( $F(4, 47)=9.2, p<.001, R^2=.44$ ), the level of anxiety ( $F(4, 47)=7.34, p<.001, R^2=.38$ ) and the level of insomnia ( $F(4, 47)=8.09, p<.001, R^2=.41$ ) significantly predicted HRQoL at 12-month follow-up (Table 6.). Regarding dispositional factors, psychological flexibility ( $F(1, 47)=6.90, p<.000, R^2=.37$ ) and SOC ( $F(1, 47)=7.04, p<.001, R^2=.38$ ) predicted HRQoL at 12-month follow-up (Table 6.). Work-related fatigue at baseline predicted ( $F(4, 47)=6.21, p<.001, R^2=.35$ ) HRQoL at 12-month follow-up. Chemical intolerance related to environmental factors and life impact related to chemical intolerance, and general tendency to worry, neuroticism and poor recovery from work did not predict HRQoL at 12-month follow-up (Table 6.).

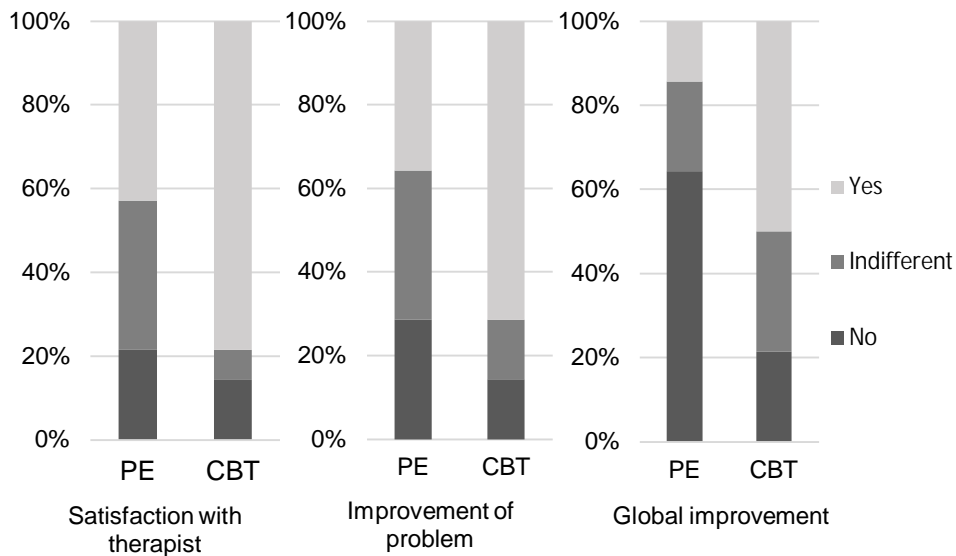
Table 6 Stepwise Linear Regression to Predict HRQoL at 12-month Follow-up.

| Model | Predictor variable | Adjusted R <sup>2</sup> |                | R <sup>2</sup> Change | F Change | Sig. F Change | Standardized Coefficients Beta |       |           |
|-------|--------------------|-------------------------|----------------|-----------------------|----------|---------------|--------------------------------|-------|-----------|
|       |                    | R <sup>2</sup>          | R <sup>2</sup> |                       |          |               | Beta                           | t     | Sig. Beta |
| 1.    | PHQ-9              | 0.44                    | 0.39           | 0.15                  | 12.44    | 0.001         | -0.44                          | -3.53 | 0.001     |
| 2.    | ISI                | 0.41                    | 0.36           | 0.12                  | 9.42     | 0.004         | -0.35                          | -3.07 | 0.004     |
| 3.    | GAD-7              | 0.38                    | 0.33           | 0.1                   | 7.29     | 0.01          | -0.36                          | -2.7  | 0.01      |
| 4.    | AAQ-II             | 0.37                    | 0.32           | 0.081                 | 6.04     | 0.018         | 0.32                           | 2.46  | 0.018     |
| 5.    | SOC-13             | 0.38                    | 0.32           | 0.09                  | 6.44     | 0.015         | 0.37                           | 2.54  | 0.015     |
| 6.    | NFR                | 0.35                    | 0.29           | 0.06                  | 4.07     | 0.049         | -0.27                          | -2.02 | 0.049     |

Analyses are adjusted for age, gender and HRQoL prior to treatments. Intent-to-treat data were combined for the interventions.

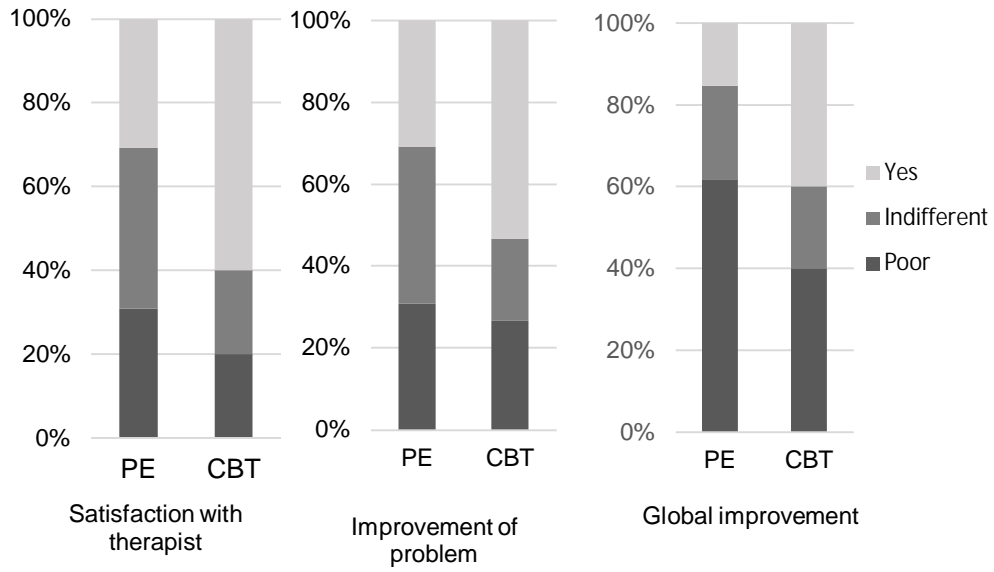
PHQ-9=Patient Health Questionnaire-9; ISI=Insomnia Severity Index; GAD-7=Generalized Anxiety Disorder-7; Acceptance and Action Questionnaire-II; SOC=Sense of Coherence; NFR=Need for Recovery

Among the CBT+TAU and PE+TAU participants, 71% and 43%, respectively reported that they would recommend this treatment for individuals with a similar kind of condition at the three-month follow-up assessment point. At the 12-month follow-up assessment point, 53% of the CBT+TAU, and 62% of the PE+TAU participants reported that they would recommend this treatment. Figures 6 and 7 show the descriptive statistics of satisfaction with the therapist work and improvement related to the treatment.



**Figure 6** Satisfaction with treatment and improvement related to treatment in psychoeducation (PE) (n=14) and cognitive behavioural therapy (CBT) (n=14) groups at 3-month follow-up.





**Figure 7** Satisfaction with treatment and improvement related to treatment in psychoeducation (PE) (n=13) and cognitive behavioral therapy (CBT) (n=15) groups at 12-month follow-up.

## **6 DISCUSSION**

The present study aimed to examine the discrepancy between self-perceived respiratory health complaints and objective signs of respiratory health status, and whether the psychological factors that influence health regulation associate with the discrepancy in the population-based data. Another aim was to study the psychological risk factors for the incidence of new respiratory health complaints at eleven-year follow-up. The final objective was to examine the HRQoL of the clinical population with IE-related PPS, i.e. compare the discrepancy between subjective and objective health complaints with population-based references and the effectiveness of psychosocial treatments on the HRQoL of these individuals.

### **6.1 COMPARISON OF CURRENT AND PREVIOUS FINDINGS**

#### **6.1.1 FACTORS ASSOCIATED WITH SYMPTOM BURDEN**

Study I found that 26% of the general population reported respiratory health complaints without objective signs of impaired lung function. When individuals with respiratory diseases or severe psychiatric illnesses were excluded, the prevalence estimate increased to 36% of the population. Respiratory health complaints without signs of impaired lung function were significantly related to psychological dispositions, poor SOC, alexithymic characteristics and high illness worry, suggesting that they influence health regulation and increase the burden related to health complaints. Our results further suggest that these psychological dispositions increase the medical burden related to health complaints at the population level, as 42.7% of the association between perceived health complaints and physician visits were explained by these factors.

The tendency towards self-reported respiratory health complaints without respiratory pathology in terms of respiratory diseases or problems in lung function was associated with an increased risk of mood, anxiety or alcohol use disorders after an eleven-year follow-up. These results are in line with those of Van den Sluijs et al. (2015), who showed that physical symptoms without adequate organ pathology or a pathophysiological basis increase the risk of three-year incidence of these psychiatric disorders (van der Sluijs et al., 2015). According to these results, one could claim that insecurity regarding self-perceived health complaints without a clear explanation might increase the burden related to the symptoms and thus result in psychiatric distress. However, the analyses did not show any opposing association between common psychiatric disorders at baseline and perceived respiratory health

complaints in 2011 or eleven-year incidence of any respiratory disease. The results thus contradict those of Brunner et al. which showed that depression is a risk of adult-onset asthma (Brunner et al., 2014). To conclude, in comparison with the results of Study I and other previous cross-sectional studies that have shown that mood and anxiety disorders are associated with the discrepancy between subjective and objective respiratory health (Eisner et al., 2005; Katon et al., 2007), and with persistent and recurrent physical symptoms with no clear medical explanation (Haug et al., 2004; Henningsen, Zimmermann, & Sattel, 2003; Steinbrecher et al., 2011), our results suggest that psychiatric disorders do not have predictive power over respiratory health complaints.

Several studies have shown that psychiatric disorders associate with physical symptoms without objective signs of somatic diseases (Barsky & Borus, 1999; Haug et al., 2004; Henningsen et al., 2003; Löwe et al., 2008) and with poor lung function (van Milligen, Lamers, Guus, Smit, & Penninx, 2011), and that they increase the burden of respiratory health complaints (Brunner et al., 2014; Eisner et al., 2005; Katon et al., 2007). Psychiatric diseases have also shown to explain more of the variance of disease-specific symptoms than the specific disease itself (Katon et al., 2007; Lehrer et al., 2002). The results of Study I support these previous results by showing that individuals with common psychiatric disorders are at risk of perceiving more respiratory health complaints than individuals without these disorders at the population level. It is also noteworthy that over 40% of the participants in Study III reported a psychiatric disorder diagnosed by a physician and as much as a fifth of the participants reported symptoms of depression above clinical cut-off scores. Because of the cross-sectional nature of Study I, we cannot assess whether psychiatric distress is a consequence of adjusting to IE-related PPS, a sign of other mental health processes, an underlying reason for prolonged physical health complaints, or all of these. Psychiatric disorders have, however, shown to have a more detrimental effect on HRQoL than other medical conditions among the working-age population (Saarni et al., 2007). In their general population-based survey, Rief et al. (2012) further showed that depressive symptoms constitute a risk factor for poor QoL related to environmental factors (Rief et al., 2012). Thus, although common psychiatric disorders did not have predictive power over the 11-year incidence of respiratory health complaints as noted above, they play an important role in patients' overall health status, and QoL and should be taken into account in the overall treatment of an individual.

Although high comorbidities were shown between self-reported respiratory health complaints and IE-related PPS and other diseases or disorders, our population-based data results also indicate that psychological dispositions associate with the perceived burden of the health complaints, independently of the comorbidities. Our results support previous findings by showing that perceived health complaints, independently of physical diseases or psychiatric disorders, have an influence on health care utilization (Aamland et al., 2012;

Barsky et al., 2005; Burton, 2003; Kolk, Hanewald, Schagen, & van Wijk, 2002; Tomenson et al., 2013) and further, that SOC, alexithymia and illness worry contribute even independently to an increased risk of health care use. Experimental studies have repeatedly shown that certain psychological dispositions increase the risk of distorted symptom perception and non-adaptive health behaviour (see e.g. Bogaerts et al., 2015), but our study demonstrates the magnitude of these dispositions at the population level.

High SOC correlated positively with good HRQoL among individuals with PPS associated with IE. However, in contrast to previous studies (Eriksson & Lindström, 2005; Gallagher, Donoghue, Chenoweth, & Stein-Parbury, 2008; Stewart & Yuen, 2011), our results showed only modest predictive power between SOC and respiratory symptom burden in Studies I and II. Antonovsky himself noted that the role of SOC in health outcomes is more prominent in chronic or very severe diseases (Antonovsky, 1987). Thus, our studies conducted among the general population might not reveal the predictive power of SOC. In their longitudinal study based on two samples, Kivimäki et al. further found that low SOC predicted adverse health effects more than a high SOC had a health protective role (Kivimäki, Feldt, Vahtera, & Nurmi, 2000). Thus, low SOC could be more relevant than high SOC in influencing health regulation. From this point of view, the association seen in our study between SOC and HRQoL in individuals with PPS could have more clinical importance in cases with low, rather than high SOC. More research is needed to define SOC as either a risk or protective factor in environmental-related health.

The alexithymic characteristics showed only modest associations with frequent physician visits in Study I, although they have repeatedly shown to associate with poor perceived health outcomes without objective medical explanations (Bailey & Henry, 2007; Deary, Scott, & Wilson, 1997; Mattila et al., 2008). However, during the follow-up period in Study II, the alexithymic characteristics showed strong predictive power over respiratory health complaints and incidence of COPD. The development of COPD is greatly influenced by unhealthy behaviours (e.g., smoking) and some evidence also suggests behavioural pathways between alexithymia and poor physical health (Kajanoja, Scheinin, Karlsson, Karlsson, & Karukivi, 2017; Kajanoja, Scheinin, Karukivi, Karlsson, & Karlsson, 2019; Lumley, Stettner, & Wehmer, 1996). For example, in their recently published study, Kajanoja et al. found that the alexithymic dimension of low levels of observation of one's own mental processes and pragmatic thinking style associated with increased levels of daily smoking (Kajanoja et al., 2019). Thus, behaviour modified by alexithymia could influence somatic outcomes in a long follow-up period. According to our results, alexithymia could be a covariate of physical health by modifying health behaviours and influence accurate health care-seeking. Thus, it could be used in further epidemiological studies as a risk factor for health outcomes.

We also found that high illness worry was associated with self-reported respiratory health complaints, regardless of the spirometry results and

without diagnosed respiratory diseases. Illness worry even predicted the 11-year incidence of asthma in Study II. Several studies have shown that illness worry has detrimental effects on health regulation both in the processes of symptom perception and adaptive coping with health complaints. Negative illness perceptions or concerns related to having an illness have been shown to predict poor health outcomes (Frostholm et al., 2007) and at this an end of the continuum, the most severe health anxiety increases the risk of frequent physical symptom counts, increases health care utilization (Fink et al., 2010, Frostholm et al., 2007) and has shown to increase poor recovery rates in cases of PPS (olde Hartman et al., 2009). The results of this study also suggests that illness worry as a dimensional and not a diagnostic concept of health anxiety also influences the risk of a new respiratory disease. The fact that our results remained significant after adjusting for several mentally and physically health-related factors implies that individuals' subjective respiratory health complaints reflect psychological vulnerability related to health regulation, and not only severity of physical condition from a biomedical perspective (Frostholm et al., 2005). From this point of view, the results of Study II strengthen the findings of Study I, suggesting that psychological dispositions increase the medical burden related to the health complaints at the population level, even over a considerably long period of time.

### **6.1.2 QUALITY OF LIFE: MORE THAN MERELY A SYMPTOM COUNT**

The results of Study III showed that employees with PPS related to workplace IE have substantially lower HRQoL than the general-population reference groups with globally burdensome diseases such as asthma, depressive or anxiety disorders, or a chronic condition affecting their work ability and functioning. Higher levels of psychological distress in terms of symptoms of depression or anxiety, insufficient recovery assessed by levels of symptoms of insomnia, and poor recovery from work were associated with HRQoL.

The additional, descriptive analyses conducted for this summary showed that the RCT participants had significantly lower HRQoL than the individuals in population-based Study I. Interestingly, large effect sizes were found in comparisons with healthy individuals (i.e., participants with normal lung function and without respiratory health complaints) and individuals with lung obstruction. However, in comparison with those with respiratory health complaints but no signs of impaired lung function, the effect size describing the difference between the study groups remained moderate. In line with the comparison with the globally burdensome diseases discussed above, this could indicate that health regulatory factors mediate the HRQoL outcomes of individuals with PPS related to IE over the severity of medical conditions such as lung obstruction per se. Thus, more attention should be given to the mechanisms that modify the subjective experiences that associate with poor HRQoL outcomes and the biomedical approach.

Parallel with our results, Runeson & Norbäck (2005) showed that a high and pervasive tendency to experience negative feelings decreased the HRQoL of employees with PPS related to workplace IE and, in contrast, that high SOC associated with better QoL outcomes (Runeson et al., 2003). These results could indicate that individual dispositions might modify the self-regulation of health in stressful situations and thus influence health outcomes related to IE, in line with the results of Study I. These results also support those showing that the tendency to experience negative feelings is linked to a reduced QoL and to a poorer perceived health status among individuals suffering from well-defined somatic diseases such as asthma (Huovinen, Kaprio, & Koskenvuo, 2001; Van De Ven & Engels, 2011). Thus, our results suggest that, independently of the aetiology of the health complaints, individual characteristics influence overall health status and should also be taken into account when planning treatments for these health complaints.

In our RCT, the effectiveness of TAU enhanced by PE or CBT was evaluated at one-year follow-up. The intent-to-treat analysis showed no statistical significance of the primary outcome but among those who completed the study, the primary outcome had a significant effect in the study groups. According to minimally important changes in HRQoL during the follow-up, the majority of the participants in the treatment groups improved, or their HRQoL remained stable, whereas HRQoL decreased to a greater extent among the controls. These results suggest that CBT for PPS, or PE, might not have a strong, robust effect on HRQoL when PPS are related to IE. However, in some cases it might prevent the deterioration of HRQoL when PPS is associated with indoor air, although the effect sizes in our study remained low, as in earlier intervention studies for treating PPS (Kleinstaub, Witthoft, & Hiller, 2011). One could suggest that physical symptoms do not change so easily that the treatment should focus on the determinants of HRQoL, barriers of daily functioning and maladaptive cognitions, and safety-seeking behaviour, i.e. self-regulation, but not the symptoms per se. In 2005, Christensen et al. examined the mechanisms of change in their study for the effectiveness of CBT for PPS (Christensen, Frostholm, Ørnbøl, & Schröder, 2015). In agreement with Leventhal's model of health behaviour (Hagger & Orbell, 2003; Leventhal et al., 1980), their results suggest that improvement in illness perceptions and perceived control over the condition mediate the treatment outcomes. In PPS related to environmental factors, strong somatic attributions, i.e. causal beliefs, have also shown to relate to poor prospective outcomes (Bailer, Witthöft, Bayerl, & Rist, 2007; Bailer, Witthöft, & Rist, 2008; Gupta & Horne, 2001). Poor outcomes in turn have shown to associate with maladaptive illness perceptions independently of medical comorbidity (Baliatsas, Van Kamp, Hooiveld, Yzermans, & Lebrecht, 2014). In our study, one could thus suggest that therapeutic work may not have anchored the individual reaction patterns to illness perceptions associated with IE. Thus, a stronger orientation towards PPS related to IE-relevant mechanisms and processes is needed to enhance the effectiveness of treatments (see e.g., Řiháček & Čevelíček, 2019 review of

effectiveness of psychotherapeutic techniques for PPS). To the best of our knowledge, no such studies have examined the treatment mechanisms for IE-related PPS, although some studies have recognized the role of various psychological predictive factors in IE-related health outcomes.

In addition to treatment mechanisms, current comorbid health conditions deserve further consideration. Among our sample, over 40% of the participants reported a physician-diagnosed mental disorder at baseline, and between 15% to 40% of the participants reported current anxiety, or depressive or insomnia symptoms that exceeded the clinical cut-off scores. As discussed above, Rief et al. have shown that this kind of psychological distress may increase vulnerability to poor QoL associated with environmental factors at the population level (Rief et al., 2012), and increase the risk of adverse health effects related to workplace IE (Magnavita, 2015). Further, some findings have shown that PPS with comorbid symptoms, including depression and anxiety, requires a longer treatment duration to alleviate physical symptoms and to increase physical functioning (Liu et al., 2019). Thus, our results also raise the question as to whether these comorbid states influenced the psychosocial treatment outcomes, especially as our interventions were designed for a short, intensive period. Further, it is presumable that psychological distress would have required more attention during the intervention than we had planned in our study protocol.

According to the participants' evaluations of treatment satisfaction and efficacy for their condition, they considered CBT feasible. As several studies have reported that psychosocial treatments are not easily accepted by individuals with PPS the participants in our study presumably accepted this biopsychosocial approach to their situation. Thus, a qualitative process evaluation of the interventions could deepen the understanding of the factors that might support the acceptance and adherence of the treatments and respond to participants' individual needs (Craig et al., 2008). Further qualitative analysis could also shed light on the mechanisms that are particular to IE-related health complaints and help form testable theories of treatment effectiveness.

## **6.2 METHODOLOGICAL CONSIDERATIONS**

The studies that comprise this thesis are based on two complementary study designs that combine data from epidemiological and RCT studies. The study design enabled us to assess the magnitude of psychological health-regulatory factors related to perceived health complaints at the population level, as data were available on several important covariates regarding subjective and objective health status and sociodemographic factors. These results are accompanied by naturalistic, clinical intervention data. This clinical data enabled us to bridge the epidemiological findings on clinical practice in cases that have discrepancy between subjective and objective health. The strengths

of our RCT include the naturalistic and multicentre OHS recruitment setting and a priori published study protocol (Selinheimo *et al.*, 2016).

Studies I and II combined several data sources from participant-reported outcomes with structured clinical interviews and clinical health examinations. This enabled us to assess the influence of lifestyle factors, such as obesity and smoking, and physical and mental health status on the respiratory health outcomes that have repeatedly shown to associate with reporting frequent physical symptoms (Creed & Barsky, 2004; Löwe *et al.*, 2008). However, the information on respiratory health complaints and respiratory diseases was based on retrospective self-reports. Thus, recall bias might also have influenced the validity of the reports. Long recall periods in particular may cause underestimation of self-reported health care utilization per year (Bhandari & Wagner, 2006; Short *et al.*, 2009) and cause bias in the self-reported incidence of respiratory diseases during follow-up. Thus, the Health 2000 data may slightly underestimate the true frequency of reported physician visits during the preceding 12 months.

Studies I and II focused on respiratory health and thus generalization of the self-regulatory mechanisms to other organ systems is not really possible. We could see that dispositional factors differed, even in their predictive power over the incidence of different respiratory diseases, suggesting various mechanisms between health regulation and respiratory outcomes. Studying the self-regulatory mechanisms of specific diseases is thus a subject of interest for further research. In addition, the fact that we focused on working-age participants in our follow-up studies diminished the feasibility of generalizing the results to younger or older people who nevertheless generally have more physical symptoms and physical diseases. Thus, our result could provide important information for focusing on preventive health care among the working-age population to decrease the burden of diseases on retired people. Attrition analyses showed some differences between the included and drop-out participants, which may have influenced the generalizability of the results. The drop-out participants were more likely younger, male, had lower education, and were smokers or had alcohol use disorders more frequently at baseline than the participants who were included in this follow-up study. Thus, they might have more general health-related problems than the included participants and thus the results might underestimate the incidence of new adverse respiratory health effects and should be interpreted with caution.

Our RCT followed well-defined participants with disabling PPS associated with IE at the primary care level. The treatments examined in our RCT study were chosen to be fluently implemented into primary care or OHS practices, but the acceptability of the contents was not assessed or piloted with the target group of the study before the trial began. The recruitment of the study participants proceeded slowly so that the original study protocol needed to be modified: the applied relaxation-based group intervention was removed from the intervention arms (Selinheimo *et al.*, 2016). Further, the study received frequent public attention and interest from active patient organizations,



suggesting that immunological–toxicological mechanisms are crucial for explaining IE-related PPS. This view contradicted our study hypothesis and is sustained by the common narrative across several interest groups related to IE issues. It was repeatedly seen in the Finnish public media during the long recruitment period (see also Nordin, 2020; and for further discussion Tuuminen, Haggqvist, & Uusitalo, 2016; Vuokko et al., 2016), and might have influenced the study recruitment, resulting in study protocol amendments. Although these experiences may limit the interpretation of our results to individuals who accept the biopsychosocial explanations for their condition, they also support further research focusing on the acceptability of the treatments among symptomatic individuals.

To continue, Study IV used a comparatively small analytic sample and had limited statistical power. This limited our possibilities to assess the effectiveness of treatment components such as stress-reducing techniques or completion of homework for outcome improvement. The information on the participants' health status and additional treatments during the follow-up was based on the participants' self-reports. These might affect the interpretation of the follow-up results. However, the comparative analysis conducted of the RCT study sample and population-based data in Study III and the additional analysis for this summary showed that IE-related PPS has a strong effect on HRQoL. Although the cross-sectional analyses diminish the interpretation of the results data, no earlier studies have been able to show the magnitude of loss of HRQoL related to PPS associated with IE. As earlier findings suggest that individuals' psychological dispositions are inherent in all health complaints and diseases in the context of employee discomfort and health complaints related to IE (Gomzi et al., 2007; Herr et al., 2017; Marmot et al., 2006; Nordin, 2020), and as they associate with the loss of HRQoL in our study, our results further emphasize the multifactorial mechanisms of IE-related health conditions.

Evidence-based medicine (EBM) and practice have been criticized for their shallow understanding of change mechanisms in psychotherapy. Although EBM focuses on treatments that lead to therapeutic change, it does not answer how or why the treatment leads to change (Kazdin, 2007). Further, EBM aims to increase treatment integrity from the health care perspective, but at the same time might diminish feasibility from the individual's perspective (Hoffmann, Montori, & Del Mar, 2014). Thus, the question is whether the intervention offered to our study participants reached the issues relevant to them. Focusing on group means in the RCT might have diminished our understanding of this phenomena with relatively scarce information on predisposing and underlying factors. Joint decision-making and practice-based evidence have been proposed for approaches to improving clinicians' self-management to increase effectiveness in daily practice and to achieve a better understanding of patients' values, preferences and circumstances that influence treatment compliance (Hoffmann et al., 2014; Margison et al., 2000). The aim is to increase treatment effectiveness by increasing clinicians'

metacognition, i.e. the ability to assess the reasoning of the methods used for individuals by developing assessment methods and testable theories for the process of change (Margison et al., 2000). From the client's point of view, these approaches aim to increase their participation in health care actions. As our results showed that almost half of the intervention participants improved during the follow-up period (n.s.). Thus more focus should be placed on the treatment mechanisms as described in recently published treatment model of symptoms associated with environmental factors (Van den Bergh, Bräscher & Witthöft, 2021) to increase the effectiveness of the treatment and thus support the development of EBM in the area of persistent health complaints

Further, the results from Study II showed preliminary evidence of the individual factors that predispose patients to adverse health outcomes during a relatively long follow-up period. Such personalized factors were not, however, taken into account when implementing the RCT. To support the participant's active role in receiving treatment, study implementation could include a discussion with the participant on the predisposing and perpetuating factors of PPS and their causes. The aim of such case formulation should be to improve participant's understanding of the functional relationships among the factors that contribute to the situation and to increase the participant's deliberation concerning the treatment contents and their correspondence to the situation. Sharing case formulation during the implementation phase could increase the participants active role in treatment as they are invited to take part in treatment implementation according to their individual situation.

Finally, the studies included in this thesis could be criticized for using an extensive number of patient-reported outcomes (Deshpande, Rajan, Sudeepthi, & Nazir, 2011). This critique mirrors the dilemma behind contested illnesses that have a discrepancy between the severity of the health complaints according to medical examinations and the patient's daily functioning. The patient's subjective experiences, i.e., health complaints or symptoms, however, are important in themselves, as they constitute the basis of compliance with the treatments, regardless of the diagnostic information they carry (Barsky, Peekna, et al., 2001; Petrie & Weinman, 2012). As patient-activating methods have been shown to be more effective than passive and organ-focused ones in treating PPS (Henningsen et al., 2018), should patient-reported outcomes be evaluated to increase communication and patient adherence to treatment, which has shown to support patient satisfaction, increase adherence, and improve outcomes (Detmar, Muller, Schornagel, Wever, & Aaronson, 2002; Greene & Hibbard, 2012; Greenhalgh, 2009).

### **6.3 IMPLICATIONS FOR FUTURE RESEARCH**

There is an ongoing debate among medical regimens, patient associations and public media on the theoretical explanations for IE-related adverse and/or persistent health effects (Bluyssen, Janssen, van den Brink, & de Kluizenaar,

2011; Marmot et al., 2006; Norbäck, 2009). The biomedical perspective assumes a direct link between chemical and biological compounds and physical symptoms, whereas the psychobiological perspective proposes a multifactorial background for the illness. This variety of hypotheses is also reflected in research and practice and is visible in the diverse views of health care professionals (Hausteiner, Bornschein, Zilker, Henningsen, & Förstl, 2007; Hetherington & Battershill, 2013; Katerndahl, Bell, Palmer, & Miller, 2012; Nordin, 2020; Tuuminen et al., 2016; WHO, 2009; Vuokko et al., 2016), which could be seen as a challenge for further understanding the mechanisms of IE-related health complaints.

Although the biomedical model could be seen as prominent in trying to explain IE-related symptoms, there is also some preliminary evidence of societal and contextual factors associated with IE-related health complaints: parental symptoms and health worry related to IE have shown to increase the risk of children's IE-related symptoms at school, reported by both parent and child (Nissilä et al., 2019; Selinheimo, Lampi & Pekkanen, 2020, accepted 24.3.2021). Results from these cross-sectional studies suggest that parental IE-related health complaints may in some schools partially explain the association between IE quality problems and symptom reporting. The associations shown are much stronger than are typically seen between built IE factors and health complaints (Mendell et al., 2011; WHO, 2009). These results raise the question of whether social context shapes the interpretation of bodily distress and explanations attached to them, which in some cases leads to impaired functioning.

Further, although various IE-related health complaints are common across Europe (Bluyssen et al., 2016; Magnavita, 2015) information on the prevalence of PPS and severe disability related to IE factors across different countries is scarce. The environmental factor-associated symptom prevalence differs between countries (Haanes et al., 2020; Karvala, Sainio, Palmquist, Nyback, & Nordin, 2018), which suggests disparities in the health attributions related to these factors (Karvala et al., 2018). In Finland, news on IE-related adverse health effects is frequent in the media and several active patient organizations support the immunotoxic mechanisms of IE-related health effects. One could thus argue that the leading societal narrative explaining the IE-related health effects consists of the toxicological effects of environmental factors and further, that the societal models support the dualism between the explanatory models of the health complaints.

These kinds of cultural explanatory models of health and illness have shown to influence illness representations so that explanatory models of PPS are shaped by the socio-cultural context (Kirmayer & Sartorius, 2007). In parallel with the individual's illness attributions, cultural models of illness also consist of explanations for the mechanisms and consequences of illness and further assumptions of treatment modalities. These explanations take form in the disease initiation and treatment process and shape adherence to treatment (Consedine & Soto, 2014). In other words, culturally based explanations for

health complaints influence the meaning attached to them and reflect the likelihood of presentation to health care (Baumann, 2003; Kirmayer & Sartorius, 2007; Ryder et al., 2008; Simon, Gater, Kisely, & Piccinelli, 1996). This should encourage further research of IE-related health effects that includes cultural considerations and methods for assessing the societal impact on the health effects, as to date, no comprehensive studies exist that examine the societal factors explaining IE-related PPS. Studies have suggested risk factors for PPS based on sociodemographic factors, such as gender or education. These are, however, inconclusive and rather crude attempts to explain the mechanisms for PPS. Thus, further research should begin by theoretically and methodologically detangling cultural effects from sociodemographic factors to improve the understanding of IE-related PPS (Consedine & Soto, 2014).

Together with cultural explanations for IE-related health complaints, the challenge is that individuals with PPS do not easily accept psychosocial treatments for their condition, as indicated by the slow recruitment process in our RCT (see also e.g. Dirkzwager & Verhaak, 2007; Rosendal, Carlsen, & Rask, 2016). Possible explanations for this could be the stigma attached to psychosocial treatments, reflecting a somewhat narrow conception that psychosocial treatments are issued only for mental health issues rather than 'an actual disease'. Moreover, a possible fear that the condition is not taken seriously in health care might influence the presentation of health complaints (Nettleton, 2006; Peters et al., 2009). This might further influence the acceptance of treatments offered for complaints and suggest a great need for health care to help patients make sense of the multifactorial nature of their health complaints. Future studies, as well as clinical work among individuals with PPS related to IE, should address the obstacles to treatment acceptability by, for instance, piloting intervention information together with patients and addressing the individual's views on the treatment according to a joint decision-making approach (Hoffmann et al., 2014), which is suggested to improve treatment agreement especially in cases of long-term, chronic illnesses (Joosten et al., 2008). Studies of common mechanisms for effective psychosocial treatments for PPS have further shown that joint action might increase a shared understanding of the intervention aims and validate the symptom-related experiences of the patients, aiming to prepare them for treatment (Řiháček & Čevelíček, 2019). Thus, although the effects in our study remained low, the adherence rate and satisfaction with treatment reported by the RCT study participants supports the need for further research on treatment acceptance to increase the effectiveness of treatments.

## **6.4 CLINICAL IMPLICATIONS**

According to our results, individual dispositions that influence the self-regulation of health may independently explain a large proportion of the

tendency to suffer from physical complaints. Recognizing the high prevalence of respiratory health complaints among the general population may help normalize the health burden experience of symptomatic individuals. In cases of IE-related PPS, one would need to tailor the treatment by taking into account the dispositional factors that influence individual health behaviour as an integral part of individual symptom management, as recommended for the management of respiratory diseases (Nici et al., 2006; Yorke et al., 2007). However, explaining to a patient that some of their dispositions may modify their health outcomes and QoL might be challenging for clinicians. Thus, although further research is required to understand the treatment strategies for individuals that differ in their ways of interpreting and perceiving physical sensations, health professionals' education should focus in detail on how to build a clinical working alliance with the patient.

The multifactorial background of the symptom experience should be considered an essential aspect in the diagnosis and treatment of prolonged health complaints. An enhanced understanding of seeking help for health complaints from health care may guide health care professionals in identifying patients who are at risk of frequent health care visits and thus support targeting health care measures based on patients' individual needs. Some data suggest that digital treatment tailored according to respiratory symptom profiles might support self-care, so that the understanding of the illness improves and, in some cases, even weakens the intentions to consult a medical doctor because of symptoms (Yardley et al., 2010). For public health development, eHealth interventions that aim to change health-related behaviour might be especially persuasive, as they could be offered to a large number of individuals with various health complaints in a standardized manner. Further, a large body of evidence on the effectiveness of digital health interventions for several globally burdensome and more conventional diseases encourages their development for PPS. In the development of these interventions, a person-based approach is recommended to enhance their feasibility (Yardley, Morrison, Bradbury, & Muller, 2015) in line with the practice-based evidence discussed above. The core of the person-based approach is understanding the psychosocial context of the symptomatic individual to make the intervention more relevant to the individual's situation. From the viewpoint of our study results, this could mean that a symptom profile-personalized intervention should consider the individual dispositions that influence health regulation, and that these psychosocial factors should be the specific focus of attention in treatment targeting.

Further research is required to confirm the clinical standards and cut-offs for the diagnostic evaluation of psychological dispositions in the respiratory symptom burden. Further integration of clinical interventions and research on self-regulation of health would benefit from the joint development of systematic assessment methods for evaluating the predisposing and perpetuating factors of PPS. This might enhance our understanding of change mechanisms in this complex PPS condition.

Recognizing and understanding the role of dispositional factors such as SOC, alexithymia and high illness worry in symptom perception and regulation could facilitate clinical practices among PPS patients. Although common psychiatric disorders have not shown predictive power over respiratory health complaints, they are associated with poor HRQoL among these patients. It might be a challenge for health care professionals to handle both PPS and common psychiatric disorders, as the patient might feel stigmatized or that they are not taken seriously when pointing out these comorbidities. However, from a practical point of view it is well justified to propose that psychological distress should be addressed and treated as part of the clinical management of respiratory health complaints and IE-related PPS to enhance the HRQoL of symptomatic individuals. Finally, a shared understanding of the treatment aims is required to prevent deterioration of HRQoL among symptomatic individuals in cases of comorbidities.

## 7 CONCLUSIONS

This thesis aimed to study the psychological factors influencing the self-regulation of health in cases that have a discrepancy between self-perceived health complaints and objective, i.e. clinical health factors. The specific aims were to assess the magnitude of psychological factors in the respiratory symptom burden at the population level and further, rehabilitation for PPS in a specific population of patients with a biomedically contested health condition. The results of this thesis add to findings from previous studies that self-perceived respiratory-health complaints are highly prevalent in the general population, and that they are not attributable to common mood, anxiety, substance-use, or psychotic and respiratory disorders. The studies of this thesis provide novel findings regarding the independent contribution of psychological factors to the medical burden, and their associations with respiratory complaints and even with the incidence of new respiratory diseases during a considerably long follow-up period, again independently of psychiatric comorbidities.

The results of the randomized clinical trial in this thesis show that individuals with IE-related PPS had poorer HRQoL than individuals in the general population with globally burdensome diseases such as depression, anxiety disorder or asthma. Psychological distress and self-regulatory factors were also associated with HRQoL among these individuals, suggesting that they should be considered when making decisions about the treatment of these patients. Although our results suggest that CBT for PPS or PE might not have a robust effect on HRQoL among individuals with PPS associated with IE, they might prevent the deterioration of their HRQoL.

Although our findings regarding the treatment of PPS are limited by modest statistical power and await replication in larger samples, our results show that individual factors associate with poor respiratory health outcomes at the population level. Thus, it would be worthwhile further assessing their impact on the specific population of patients with IE-related PPS. The multifactorial background of symptom perception should be considered an essential aspect in the diagnosis and treatment of bodily symptoms related to environmental factors. Our results underline the fact that IE-related PPS requires extensive and multidisciplinary care to prevent deterioration.

So far, information on the mechanisms related to the treatment outcomes and the acceptance of treatments among symptomatic individuals is scarce. The specific focus of further intervention studies should include research on the mechanisms of the shared understanding of the objectives of the intervention, aiming to validate experiences related to health complaints and to prepare patients for treatment. It is also important to conduct further research on the sociocultural factors that explain disease initiation and treatment processes. If individual self-regulatory factors influence how one

anchors the symptom explanations on various factors, the contributing cultural factors should be taken into account in the incidence of PPS. It is also important to enhance the discussion and research on individual case formulation in conceptualizing self-regulatory factors that may enhance our understanding of change mechanisms in PPS.



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## **APPENDIX A: ORIGINAL PUBLICATIONS**