Environmental intolerance - Psychological risk and health factors

Eva Palmquist
To all the participants of the VEHS
Acknowledgements

I have been brought up in the Academia by three dads, Steven, Berndt and Greg. My dads are the best, but are kind of different when it comes to parenting.

Steven is the dad that is constantly present, trying to be supportive (even though he is dead nervous when a dead-line is coming up and his beloved PhD student has not yet really signaled that she is going to make it), the one who makes pranks (THE prank call is unforgettable and hilarious), and who always has time, or sets aside time, to answer (or trying to answer) my confused questions (which in many cases are unanswerable or irrelevant but Steven still tries to answer). Steven is the dad that has had to take all the wear and tear in parenting, and even though he gives the impression of being structured and organized, he is just like me... kind of confused.

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[Ps. I think MS Word is prejudiced since it takes “my dads” as a misspelling and wants to correct it to my dad’s. Ds]

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Abstract

Environmental intolerance (EI) is an embracing term for a number of conditions characterized by a wide range of non-specific symptoms attributed to certain environmental exposures (e.g. pungent/odorous chemicals, residing in a certain building, electromagnetic fields and everyday sounds). EI often leads to lifestyle alterations (e.g. not taking part of activities formerly engaged in) and functional impairment (e.g. not being able to work, social deprivation). The etiology of the conditions is largely unknown, though there is growing empirical evidence for associations between mental ill-health and EI. However, mainly cross-sectional studies have been conducted which cannot demonstrate temporality. Further on, the prognosis for EI is not well-known.

This thesis includes four studies based on cross-sectional (Study 1) and longitudinal (Study 2-4) data from the Västerbotten Environmental Health Study (VEHS). The VEHS contains data from three data collections performed on the same set of respondents in 2010 (T1; n=3406), 2013 (T2; n=2336) and 2016 (T3; n=1837). In Study 1 the co-prevalence between EI attributed to chemicals, certain buildings, EMFs and sounds was investigated. The co-prevalence between all types of self-reported EI was greater than predictions based on coincidence, indicating that the different types of EI are associated, possibly sharing the same pathogenesis or that the afflicted individuals share some common predisposition to acquire the conditions. In Study 2 coping strategies and social support in EI were investigated and particularly whether certain combinations of different types of coping and social support may be important in recovering from EI. The participants who recovered from EI showed different combinations of coping strategies and social support than those who did not recover. In Study 3 the temporality between EI (attributed to chemicals, buildings and sounds) and psychological factors was investigated. The results showed that stress, anxiety, depression and burnout are risk factors for EI attributed to chemicals and sounds, but not for EI attributed to buildings. Changing perspective, EI attributed to buildings was a significant predictor of burnout, whereas EI attributed to sounds and chemicals were not. In Study 4 the prognosis of EI during a six-year period was studied. The probability of recovering from a state of specific EI was 44.3%, the probability of a specific EI to spread to other types of EI was 12.8%, and the probability of relapse was 3.9%. The participants who recovered showed lower levels of emotional and behavioral disruption than those who did not recover. The participants who showed spreading from one to several EIs perceived more stress than
those who remained in a state of a specific EI, but had lower levels of burnout.

Based on the findings of the studies in the thesis it is suggested that psychotherapy focusing on reducing the emotional and behavioral reactions of exposure might be helpful. Even though the causation of EI is unknown, negative expectations about exposure might accumulate symptoms, setting a vicious circle into motion. The task of the psychologist might be to break this circle.
List of abbreviations

<table>
<thead>
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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
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<td>CI</td>
<td>Confidence interval</td>
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<td>CNS</td>
<td>Central nervous system</td>
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<td>CSS-SHR</td>
<td>Chemical Sensitivity Scale for Sensory Hyperreactivity</td>
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<td>EI</td>
<td>Environmental intolerance</td>
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<td>EMF</td>
<td>Electromagnetic field</td>
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<td>EMFSS-11</td>
<td>11-item Electromagnetic Field Sensitivity Scale</td>
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<td>HADS</td>
<td>Hospital Anxiety and Depression scale</td>
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<td>HPA</td>
<td>Hypothalamic-pituitary adrenal</td>
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<td>IEI</td>
<td>Idiopathic environmental intolerance</td>
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<td>MANCOVA</td>
<td>Multivariate analysis of covariance</td>
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<td>MCS</td>
<td>Multiple chemical sensitivity</td>
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<td>MI</td>
<td>Multiple imputation</td>
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<td>NS</td>
<td>Noise sensitivity</td>
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<td>NSS-11</td>
<td>11-item Noise Sensitivity Scale</td>
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<td>OR</td>
<td>Odds ratio</td>
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<td>PSS-10</td>
<td>10-item Perceived Stress Scale</td>
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<td>SAM</td>
<td>Sympathetic adrenal-medullary</td>
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<td>SBS</td>
<td>Sick building syndrome</td>
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<td>SD</td>
<td>Standard deviation</td>
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<td>SMBQ</td>
<td>Shirom-Melamed Burnout Questionnaire</td>
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<td>VDU</td>
<td>Visual display unit</td>
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<td>VEHS</td>
<td>Västerbotten Environmental Health Study</td>
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<td>WHO</td>
<td>World Health Organization</td>
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List of papers


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Sammanfattning (summary in Swedish)

Miljöintolerans är ett samlingsnamn för flertalet åkommor som karaktäriseras av en rad symtom som människor upplever när de är exponerade för en viss miljö, eller särskilda faktorer i miljön, såsom doftande/stickande kemikalier, elektromagnetiska fält eller vardagliga ljud. En annan typ av miljöintolerans kännetecknas av att individer får symtom när de vistas i särskilda byggnader. De olika åkommorna har blivit kända för allmänheten som multipel kemisk känslighet, elektromagnetisk överkänslighet (elkänslighet), bullerkänslighet och sjuka-hus-sjukan, men kallas här miljöintolerans och separeras genom den miljöexponering som ger symtom (t.ex. miljöintolerans för kemikalier). Miljöintolerans leder ofta till livsstilsförändringar på grund av att de drabbade individerna inte kan vistas i, eller helt enkelt försöker undvika, miljöer där de vet att de får besvär. Det kan innebära att de avstår från aktiviteter de tidigare uppskattat, och undviker sociala sammanhang där risk för exponering finns. Många får problem att fortsätta arbeta, därför är sjukskrivning och förtidspensionering vanligt. En del av de drabbade upplever problem med social interaktion eftersom de ber omgivningen om vissa saker (t.ex. att undvika parfymerade produkter, inte använda mobiltelefon i deras närhet, eller begäran om utredning av miljöproblem på arbetsplatsen), men att deras värdjan inte får gehör. Andra upplever skam (på grund av de förutfattade meningarna som finns om dessa åkommor) och berättar inte om sina problem för någon, utan lider i ensamhet.


Denna avhandling är baserad på data från Miljöhälsostudie i Västerbotten och omfattar fyra studier. Miljöhälsostudien inbegriper data insamlade från samma uppsättning försöksdeltagare vid tre tillfällen: 2010 (n=3406), 2013 (n=2336) och 2016 (n=1837). I Studie 1 undersökes i hur stor utsträckning olika typer av miljöintolerans samråder. En hög samförekomst kan vara en
indikation på att de olika åkommorna delar samma underliggande mekanismer eller att de individer som drabbar av de olika typerna av miljöintolerans har en gemensam predisposition att förvärva dessa åkommor. Resultatet visade att samförekomsten bland alla typer av miljöintolerans var högre än om inget samband fanns mellan dem. I Studie 2 undersöcktes i vilken utsträckning personer med miljöintolerans använder socialt stöd samt olika coping-strategier för att hantera sin miljöintolerans. Personer som tillfrisknade under en treårsperiod visade sig använda en annan kombination av coping strategier och socialt stöd än de som inte gjorde det. Detta gällde endast de som i hög grad var känslo- och beteendemässigt störda av en specifik exponering. I Studie 3 undersöcktes huruvida psykisk ohälsa föregår eller följer av utvecklandet av miljöintolerans. Resultaten visade att stress, ångest, depression och utbrändhet föregår utvecklandet av miljöintolerans för kemikalier och ljud, men inte för miljöintolerans för byggnader. Omvänt visade sig miljöintolerans för byggnader vara en prediktor för utbrändhet. Ingen av miljöintoleranserna visade sig vara riskfaktorer för ångest eller depression. I Studie 4 undersöcktes prognosen för miljökänslighet under en sexårsperiod. Sannolikheten att tillfriskna från en specifik miljöintolerans var 44.3%, sannolikheten att en specifik miljöintolerans skulle sprida sig till en mer generell miljöintolerans där individer får symtom från olika typer av exponering (t.ex. kemikalier och ljud) var 12.8%, och sannolikheten för återfall var 3.9%. Individer som tillfrisknade var mindre känslo- och beteendemässigt störda av exponeringen än de som inte tillfrisknade. De individer som utvecklade en generell miljöintolerans upplevde mer stress än de med en specifik miljökänslighet, men mindre grad av utbrändhet.

Introduction

What is environmental intolerance?
Environmental intolerance (EI) is an encompassing term for a collection of conditions with the common denominator of attributing several medically unexplained, non-specific symptoms to a certain environmental exposure. Examples of common environmental exposure to which individuals may attribute symptoms are odorous/pungent chemicals (e.g. perfumes, cleaning agents), electromagnetic fields (EMFs; e.g. handheld electrical devices, cell phone towers) and everyday sounds (e.g. wrinkling of paper, the buzz from air conditioners). Another type of EI is the attribution of symptoms to residing in a certain building. The building in question may have known environmental problems such as water damage, mold or poor ventilation, but also include buildings in which investigation of the indoor environment ends up with assessments all within normal, non-hazardous ranges (Barmark, 2014; Hedge, Erickson, & Rubin, 1996; Niven et al., 2000). In general this is the puzzling case for all types of EI, namely that individuals become sick from exposure below hazardous or toxic levels and whilst some individuals get symptoms others do not, even though they are exposed to the same environment (Redlich, Sparer, & Cullen, 1997). Further on, the relationship between the exposure and the symptoms do not in many cases comply with a dose-response relationship, which makes a toxic explanation for EI non-convincing. For example, an afflicted individual may react with severe symptoms from very low level and short duration of exposure, and several sham exposure studies have shown that individuals also report symptoms when they believe they are exposed, but in fact are not (Rubin, Nieto-Hernandez, & Wessely, 2010; B A Sorg, 1999). Another bewildering fact is the heterogeneity when it comes to symptom profiles. The symptom profile of one individual might be totally separate from another afflicted individual’s with the same type of EI (Redlich et al., 1997). One possible reason for this might be that the triggering factor(s) of the symptoms varies. Further on, if one were to list all symptoms reported from a group with a certain EI, indicators from all organ system would be included. However, there are some symptoms that are more commonly reported for each type of EI (which will be presented within shortly). Another question still unanswered when it comes to EI is why it is more common amongst women than men. Female gender is a risk factor for all types of EI (Andersson, Johansson, Millqvist, Nordin, & Bende, 2008; Paulin, Andersson, & Nordin, 2016; Stansfeld & Shipley, 2015; Stenberg & Wall, 1995).
**Multiple chemical sensitivity**

In the past, different types of EI have been investigated separately (and still are) and have been known among the public as multiple chemical sensitivity (MCS), sick building syndrome, electromagnetic hypersensitivity/electrosensitivity and noise sensitivity (NS). MCS is an acquired condition characterized by individuals attributing multiple recurrent symptoms in different organ systems to low concentrations of various odorous/pungent, chemically unrelated substances (e.g. perfumes, cleaning agents, and drying paint) that are tolerated by the majority of people (Hetherington & Battershill, 2013). The most commonly reported symptoms are head-related (foremost headache and head fullness/pressure), airway/mucosal symptoms (foremost nasal congestion/discharge, eye irritation/burning, coughing, sneezing, throat irritation/discharge and shortness of breath), affective (foremost feeling tired/or fatigued, irritable/edgy, depressed and tense/nervous, and sleep difficulties), cognitive (foremost concentration and memory difficulties), gastrointestinal (foremost abdominal swelling/bloating and abdominal gas), and heart-related (foremost heart pounding and chest discomfort; Andersson, Andersson, Bende, Millqvist, & Nordin, 2009).

Functional impairment is often a consequence in individuals with EI attributed to chemicals (Black, Okiishi, & Schlosser, 2000; Gibson, 2010; Skovbjerger, Brorson, Rasmussen, Johansen, & Elberling, 2009; Söderholm, Söderberg, & Nordin, 2011). Avoidance is the main remedy to reduce exposure, resulting in limited social activity (such as dining at restaurants, shopping in stores, using public transportation, visiting friends; Black et al., 2000; Söderholm et al., 2011). Another consequence for individuals with EI attributed to chemicals is early retirement and long-term absence from work because of exposure to odorous chemicals at the workplace (Skovbjerger et al., 2009). In one study, 205 of 268 (76.5%) reported having lost their job or having had to quit their job because of their inability to tolerate chemicals at their workplace (Gibson, Cheavens, & Warren, 1996). In a 9-year follow-up study, 56% had stopped working due to their intolerance (Black et al., 2000).

**Sick building syndrome**

The sick building syndrome is characterized by the manifestation of non-specific symptoms occurring in a particular building, and are distinguished from well-defined building-related illnesses that are caused by specific exposures in indoor environments (e.g. Legionnaires’ disease, hypersensitivity pneumonitis, and allergic dermatitis; Redlich et al., 1997). The symptoms occur during the hours spent in the building (which usually is the work place or home residence) and diminish when spending time away from the building (e.g. during holidays; Burge, 2004). However, the time needed away from the building to show health improvement depends on the individual and the symptom (e.g. might take longer time for skin-related
symptoms to diminish than headache), and severe cases may still report symptoms several years after leaving the building (Edvardsson et al., 2008). Environmental factors in the buildings that have been associated with the sick building syndrome are air contamination (e.g. by microbial contaminants such as fungi and bacteria, dust, volatile organic compounds emitted from building material, building supply such as copy machines and human emission), poor ventilation (air-conditioned buildings often have higher prevalence of symptomatic individuals than naturally ventilated buildings, and low ventilation rates are associated with more symptoms), water damage/dampness, high temperature, and humidity (both too low and too high; Burge, 2004; Norbäck, 2009; Redlich et al., 1997). Symptoms of irritation of the mucous membranes and the upper respiratory tract (such as eye, nose and throat irritation, dry cough, hoarseness of voice), skin related symptoms (dry or itching skin, skin rush/redness), headaches, concentration difficulties and lethargy are commonly present (Burge, 2004; Redlich et al., 1997). Reduced task or work performance and absence from work is related to sick building syndrome (Fisk, Black, & Brunner, 2011; Niemelä, Seppänen, Korhonen, & Reijula, 2006). The non-specific building-related symptoms characterizing the sick building syndrome increase the risk of long-time sick leave and disability (Edvardsson et al., 2008). Distress or worry about more serious health risk is also common (Redlich et al., 1997).

**Electromagnetic hypersensitivity**

Electromagnetic hypersensitivity is characterized by attribution of a variety of symptoms to relatively low-level exposure to non-ionizing EMFs from sources such as mobile phones, overhead power lines and visual display units (VDUs; Baliatsas, Van Kamp, Lebret, & Rubin, 2012). Symptoms most frequently attributed to EMF are fatigue, dizziness, sore muscles, concentration and memory difficulties, sleep disturbances, various skin symptoms, palpitations, tingling sensations, and headaches (Baliatsas, van Kamp, Hooiveld, Yzermans, & Lebret, 2014; Bergdahl, 1995; Hillert, Berglind, Arnetz, & Bellander, 2002; van Dongen, Smid, & Timmermans, 2014; WHO, 2006). The symptoms reported are normally experienced during or shortly after (from 20 minutes to 24 hours) the individual perception, or actual presence of an EMF (Baliatsas et al., 2012). Individuals suffering from EI attributed to EMFs often make lifestyle changes to avoid exposure, such as shielding of the dwelling, disconnecting, shielding and removing electrical devices (Röösli, Moser, Baldinini, Meier, & Braun-Fahrländer, 2004). Physical and social functioning decline (Kjellqvist, Palmquist, & Nordin, 2016). The condition is also associated with occupational impairments, changing of work due to sickness, and increased sick-leave (Carlsson, Karlson, Ørbaek, Osterberg, & Ostergren, 2005). In the
most severe cases entire withdrawal from society has been reported (Boyd, Rubin, & Wessely, 2012).

**Noise sensitivity**

Noise sensitivity (NS; hyperacusis) is a concept composed to describe the individual differences in tolerance and reactions to everyday sounds that are neither threatening nor uncomfortable loud to a typical person (Baguley, 2003). NS is relatively invariant across sound level and is a strong predictor of sound annoyance, capturing attitudes towards a wide range of environmental sounds (such as the sound of someone chewing a gum or wrinkling of paper; Shepherd, Welch, Dirks, & Mathews, 2010). NS can be caused by physical illness, such as constant migraine, and sudden trauma (e.g. head injury; van Kamp & Davies, 2013), but it has also been described as a personality trait (Zimmer & Ellermeier, 1999). The symptoms and signs most often associated with NS are emotional/behavioral (e.g. aggression, anxiety, helplessness, withdrawal), social (e.g. isolation) and cognitive/attentional (e.g. difficulties concentrating; Khalfa et al., 2002). NS may change depending on the individual's age (more common in middle-age) or circumstances (e.g. negative life events; Van Gerven, Vos, Van Boxtel, Janssen, & Miedema, 2009). Strategies used in EI attributed to sounds to reduce exposure are using ear protection supplies and adopting an avoidant behavior (Andersson, Lindvall, Hursti, Carlbring, & Andersson, 2002).

**Idiopathic environmental intolerance - Environmental intolerance**

In a workshop on MCS organized by the World Health Organization (WHO) in 1996, the usage of the term idiopathic environmental intolerance (IEI), instead of MCS, was recommended since this denomination has no causal indications (IPCS/WHO, 1996). It was also suggested that this term could embrace other medically unexplained conditions attributed to environmental exposures, hence all of the conditions described above. However, the term has mostly been used for, and is more or less synonymous with MCS, but is also used to refer to electromagnetic hypersensitivity (but then usually with the suffix EMF: IEI-EMF). Henceforth, the different types of EI will be called EI attributed to chemicals, buildings, EMFs and sounds, respectively.

**Case identification**

There are at the moment no internationally accepted clinical definition or consensus criteria for EI (Das-Munshi, Rubin, & Wessely, 2007; Levallois, 2002; Redlich et al., 1997). The diversity of applied case definitions within the scientific literature is therefore wide. Clinicians urge for diagnostic criteria (since many of them meet these suffering individuals and have no idea how to treat them), but since the afflicted individuals differ substantially
regarding trigger factors eliciting symptoms, symptom profiles, exposure sensitivity, etcetera, it has been proven hard. Researchers constantly debate how cases of EI should be identified, but they have not yet come to an agreement. Depending on the aim or need to identify cases of EI the approach is rather different. For demographic/monitoring/analytic purposes, cases are often identified by the subjects themselves (i.e. self-report), usually by answering “yes” to a question such as: “Are you sensitive to odorous chemicals/EMFs/sounds?”. However, there is still disagreement about how to formulate these kinds of self-assessments, since small semantical changes can lead to dramatic changes in prevalence numbers (see Table 1-3). To identify cases to be enrolled in experimental studies the approach is normally selecting a group of credible cases (for example by contacting support groups or clinics), then (normally) by different inclusion/exclusion criteria choose a subset of them, which are then regarded as cases of EI. Inclusion criteria may include that the potential participants report symptoms regularly and frequently (for example: at least two symptoms once a week during the last three months) which are attributed to the particular environmental exposure, that it is an acquired condition and that they have a normal ability to detect the exposure in question. Exclusion criteria may include comorbidity with neurological or psychiatric diseases which may explain the symptomatology and reactions. The approach for identifying cases of EI also vary depending on the source to which the case attributes the symptoms.

EI attributed to chemicals
Regarding EI attributed to chemicals, the most widely cited case definitions are those by Cullen (1987) and those agreed upon on the MCS consensus conference in 1999 (“Multiple Chemical Sensitivity: A 1999 Consensus,” 1999; Labarge & McCaffrey, 2000). Cullen defined EI attributed to chemicals as an acquired disorder characterized by recurrent symptoms referable to multiple organ systems and occurring in response to exposure to chemically unrelated compounds at doses far below those established in the general population to cause harmful effects. The 1999 consensus criteria defined EI attributed to chemicals as a chronic condition with reproducible symptoms in multiple organ system at low levels of exposure (lower than previously or commonly tolerated) that improve or resolve when incitants are removed. Even though these case definitions are widely used, they are open to interpretation. Due to this, Lacour, Zunder, Schmidtke, Vaith and Scheidt (2005) suggested an extension of the 1999 consensus criteria. The criterion of chronicity of the condition was now specified to have lasted for at least 6 months. The condition also had to cause significant life-style or functional impairments. The reproducible symptoms should, according to the extension, be in the CNS and be associated with self-reported odor
hypersensitivity. Finally, regarding symptoms referable to multiple organ systems, symptoms were defined as being obligatory in the CNS and at least one symptom of another organ system should be present. The above case definitions were foremost intended for diagnostic purposes, and are used to define cases for participating in experiments, but are seldom used in epidemiological research. The most commonly used case definition in epidemiological research is one-item self-report questions.

**EI attributed to buildings**

When it comes to EI attributed to certain buildings it is important to recognize that prevalence data often are based on symptoms patterns at the level of the building, and not necessarily at the level of individual or general population (Hedge et al., 1996). Foremost are buildings with known environmental problems investigated, or separate buildings with different environmental conditions compared (such as natural ventilation versus air-conditioning). Prevalence of “non-specific building related symptoms” are then assessed, and conclusions about the building or some environmental conditions in the building are made based on the total sum of symptoms. Cases of EI attributed to buildings are often identified by a combination of general, mucosal, and skin symptoms according to WHO’s definition of the condition (WHO, 1983). To be regarded an EI case, all three (or sometimes two) types of symptoms (i.e. general, mucosal, skin symptoms) have to be present, and usually be recurrently present within a certain time frame (e.g. every week during the last three months; e.g. Eriksson & Stenberg, 2006). Sometimes additional questions are used to define cases. Such questions might be whether the symptoms improve after leaving the building (e.g. Brightman, Milton, Wypij, Burge, & Spengler, 2008) or if they attribute the symptoms to a specific building or the environment in that building (e.g. Barmark, 2014; Magnavita, 2015).

**EI attributed to EMFs**

The case definition procedure for EI attributed to EMFs is mainly based on self-reports, and only in a small number of investigations are medical and/or psychological assessments used (Baliatsas et al., 2012). Self-reports are often based on a single-item question, asking whether the individual is sensitive to EMFs or is attributing non-specific symptoms to specific EMF sources (such as mobile phones or visual display units).

**EI attributed to sounds**

The operational case definition of EI attributed to sounds are primarily based on three different kinds of questions (or sets of questions; Miedema & Vos, 2003). The first type of question is a single-item self-report question of the form: “In general, how sensitive to sounds are you?” with options such as
“not at all”, “a little”, “moderately”, “considerably” and “extremely”. A problem arises when comparing these studies since the number and content of the response categories vary, and since cases of EI attributed to sounds sometimes are defined according to merely the most extreme response category (e.g. Baliatsas, van Kamp, Swart, Hooiveld, & Yzermans, 2016) whereas others define cases according to (at least) two response categories (e.g. Heinonen-Guzekjev et al., 2000). An alternative used is formulating the question in such a manner that the appropriate response would be restricted to “yes” or “no” (e.g. “Do you consider yourself to be sensitive to everyday sounds?”; Andersson, Lindvall, Hursti, Carlbring, & Andersson, 2002). A second way to identify cases of EI attributed to sounds is assessing the general attitudes to, or the emotional reactions and behavioral disruptions from sounds. Sets of questions have been formulated to measure the attitude to sounds (e.g. Weinstein, 1978) and cases are identified by their sum total exceeding a certain cut-off value. EI attributed to sounds (i.e. noise sensitivity) is also frequently measured in noise annoyance studies since noise sensitivity is regarded as a moderator or mediator of noise annoyance (Schreckenberg, Griefahn, & Meis, 2010). Noise annoyance is a construct separate from noise sensitivity where the former is related to an acoustic variable (e.g. the higher the sound level, the higher the noise annoyance), whereas noise sensitivity is not. In these studies the participants may be asked to rate their reactions to various sound sources (e.g. a dog barking, rustling papers at movies) other than the target noise under investigation (e.g. road traffic noise, airport noise). If individuals score high on these everyday sounds they are considered as noise sensitive (Job, 1999).

**Prevalence**

There is a wide range of estimates of the prevalence of EI attributed to chemicals, EMFs and sounds in the general population, certainly due to the inconsistency of defining cases described in the previous section. Because studies of EI attributed to buildings usually are restricted to buildings with known environmental problems prevalence studies in the general population are few. Though, in one study including office workers (n=4943) from the county of Västerbotten in Sweden the prevalence of EI attributed to buildings¹ was 8.42% (Stenberg et al., 1993), and in a study of indoor workers (n=4029) in the Latium region of Italy the prevalence² was 3.8% (Magnavita, 2015). In Tables 1-3 prevalence rates of EI attributed to chemicals, EMFs and sounds are presented.

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¹ A case was defined as an individual reporting at least one general symptom every month and at least one mucosal and one dermatological symptom every week.

² A case was defined as reporting being bothered by at least five of a total of 18 (five neuropsychological, four mucosal, three dermatological, three musculoskeletal and three sensorial) symptoms during the previous three months and believing the cause of them being due to the work environment.
Table 1. Prevalence studies on EI attributed to chemicals.

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Case definition</th>
<th>Method and sample</th>
<th>Author (year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.6%</td>
<td>One item self-report, answering “yes” to the question: “Are you bothered by strong odours (e.g., perfume, cleaning agents or flower scents)?”</td>
<td>Random sampling. Postal survey. Teenagers, 13-19 years old from the community of Skövde, Sweden (n=326)</td>
<td>Andersson, Johansson, Millqvist, Nordin, &amp; Bende (2008)</td>
</tr>
<tr>
<td>7.5%</td>
<td>Criteria definition</td>
<td>Stratified (age, gender, region) random sampling. National web survey, Japan (n=7245)</td>
<td>Azuma et al. (2015)</td>
</tr>
<tr>
<td>26.7%</td>
<td>Reporting at least one (out of eleven) source of exposure eliciting reactions according to the questions “Have you ever experienced unpleasant reactions elicited by inhalation of odours or chemicals from …”</td>
<td>Random sampling. Postal survey, Copenhagen, Denmark (n=4242)</td>
<td>Berg, Linneberg, Dirksen, &amp; Elberling (2008)</td>
</tr>
<tr>
<td>11.2%, 2.5%</td>
<td>One-item self-report. Confirmative answer to: “Compared with other people, do you consider yourself to be allergic or unusually sensitive to everyday chemicals like those in household cleaning products, paints, perfumes, detergents, insect sprays, and things like that?” Self-report of being physician diagnosed, answering “yes” to: “Have you ever been diagnosed by a medical professional as having MCS?”</td>
<td>Random sampling. National telephone survey, USA (n=1054)</td>
<td>Caress &amp; Steinemann (2004)</td>
</tr>
<tr>
<td>32.7%</td>
<td>One-item self-report, answering “yes” to: “Are you bothered by strong odours (e.g., perfume, cleaning agents or flower scents)?”</td>
<td>Random sampling. Postal survey in the community of Skövde, Sweden (n=1387)</td>
<td>Johansson et al. (2005)</td>
</tr>
<tr>
<td>15.9%, 6.3%</td>
<td>One-item self-report, answering “yes” to: “Do you consider yourself allergic or unusually sensitive to everyday chemicals like those in household cleaning supplies, paints, perfumes, soaps, garden sprays, or things like that?” Self-report of being physician diagnosed, answering “yes” to: “Have you ever been told by a doctor that you had environmental illness or multiple chemical sensitivity?”</td>
<td>Random sampling. Telephone survey in California, USA (n=4046)</td>
<td>Kreutzer, Neutra, &amp; Lashuay (1999)</td>
</tr>
<tr>
<td>32.7%</td>
<td>One-item self-report, answering “yes” to: “Some people get sick after smelling chemical odors like those of perfume, pesticides, fresh paint, cigarette smoke, new carpets, or car exhaust. Other people don’t get sick after smelling odors like these. Do any chemical odors make you sick?”</td>
<td>Random sampling. Telephone survey in North Carolina, USA (n=1027)</td>
<td>Meggs, Dunn, Bloch, Goodman, &amp; Davidoff (1996)</td>
</tr>
</tbody>
</table>
Table 2. Prevalence studies on EI attributed to EMFs.

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Case definition</th>
<th>Method and sample</th>
<th>Author (year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5%</td>
<td>Two-item self-report, answering “quite agree” or “strongly agree” on the statements: “I am sensitive to mobile phone base stations and devices related to communication systems” AND “I am sensitive to electrical devices”</td>
<td>Stratified (age, gender, estimated EMF exposure level) random sampling. Postal survey in the Netherlands (n=5933)</td>
<td>Baliatsas et al. (2015)</td>
</tr>
<tr>
<td>10.3%</td>
<td>Two-item self-report, answering “yes” to the questions: “Are you worried about health effects of mobile phone base stations in general?” AND “Do you believe that your health is adversely affected by mobile phone base stations?”</td>
<td>Random sampling. National postal survey, Germany (n=30047)</td>
<td>Blettner et al. (2008)</td>
</tr>
<tr>
<td>7.1%</td>
<td>One-item self-report, answering “yes” to: “Do you believe you are sensitive to electromagnetic fields?”</td>
<td>Random sampling. Internet survey, the Netherlands (n=1009)</td>
<td>van Dongen et al. (2014)</td>
</tr>
<tr>
<td>1.5%</td>
<td>From a list of factors marking being allergic or hypersensitive to electric or magnetic fields.</td>
<td>Stratified (region) random sampling. Postal survey, the county of Stockholm, Sweden (n=10670)</td>
<td>Hillert et al. (2002)</td>
</tr>
<tr>
<td>3.2%</td>
<td>One-item self-report, answering “yes” to the question: “Are you allergic or very sensitive to being near electrical devices?”</td>
<td>Random sampling. Telephone survey, California, USA (n=2072)</td>
<td>Levallois, Neutra, Lee, &amp; Hristova (2002)</td>
</tr>
<tr>
<td>13.3%</td>
<td>One-item self-report, answering “yes” to the question: “Are you allergic to or very sensitive to being near any EMF?”</td>
<td>Stratified (region, age, sex) random sampling. National telephone survey, Taiwan (n=1251)</td>
<td>Meg Tseng, Lin, &amp; Cheng (2011)</td>
</tr>
<tr>
<td>2.7%</td>
<td>One item self-report responding confirmative to the question: “Do you attribute own health symptoms to electro-smog such as from mobile phones, mobile phone base stations, power lines, cordless phones or other electrical device?”</td>
<td>Random sampling. Telephone interview, Switzerland (n=2048)</td>
<td>Schreier, Huss, &amp; Rössli (2006)</td>
</tr>
<tr>
<td>3.5%</td>
<td>Reporting adverse health effects from EMF sources (“Do you feel disturbed from electromagnetic pollution? If yes, which symptoms do you relate to electromagnetic pollution?”) and suffering to such a high degree that actively seeking for medical help</td>
<td>Random sampling. Telephone survey, Austria (n=460)</td>
<td>Schröttner &amp; Leitgeb (2008)</td>
</tr>
<tr>
<td>Prevalence</td>
<td>Case definition</td>
<td>Method and sample</td>
<td>Author (year)</td>
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<tr>
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<tr>
<td>9% (internet), 8% (post)</td>
<td>One-item self-report, answering “yes” to the question: “Do you consider yourself to be sensitive to everyday sounds?”</td>
<td>Two methods: Internet based and postal survey. Recruitment to the Internet based survey was done by a newspaper advertisement. Stratified (age) random sampling was used for the postal survey. Sweden, (n=563, n=584)</td>
<td>Andersson et al. (2002)</td>
</tr>
<tr>
<td>3.2%</td>
<td>Positive answer to the question “Are you bothered by any kind of sound or noise?” and the description of this sound and identifying at least 10 sounds from a list of 20 sounds (recess, TV, car, toys, firecrackers, classroom noise, radio, motorcycle, balloons, bombs, screams, mixer, truck, whistle, thunder, school bell, telephone, ambulance, musical instruments, dogs) as being annoying</td>
<td>Two stage cluster sampling. The primary cluster was schools (probability proportional to school size), the second cluster was children in school (equal number of children 5–12 years were sampled from each school). Random sampling of children in the schools. Interviews, Lajeado, Brazil (n=506)</td>
<td>Coelho, Sanchez, &amp; Tyler (2007)</td>
</tr>
<tr>
<td>15.2%</td>
<td>Not provided</td>
<td>Interviews, Poland (n=10349)</td>
<td>Fabijanska, Rogowski, Bartnik, &amp; Skarzynski (1999)</td>
</tr>
<tr>
<td>3.7%</td>
<td>Confirmative answer to the question: “Have you ever experienced oversensitivity or distress to particular sounds?”</td>
<td>Random sampling. Interviews (within a hearing session) with children (11 years), UK (n=7093)</td>
<td>Hall, Humphriss, Baguley, Parker, &amp; Steer (2016)</td>
</tr>
<tr>
<td>7.8% (high NS), 38.8% (NS)</td>
<td>Answering “very disturbing” (defined as high NS) and “quite disturbing” to the question: “People experience noise generally as very disturbing, quite disturbing, not especially disturbing, not at all disturbing or can’t say?”</td>
<td>Random sampling. National postal survey, Finland (n=1365)</td>
<td>Hemonen-Guzejev et al. (2000)</td>
</tr>
<tr>
<td>22%</td>
<td>“Are you sensitive to noise?” (Different studies contained different response categories such as “more than average”, “about average” and “less than average”, therefore to obtain comparable categories, they were translated to a 0–100 scale, where a number above 67 were defined as indicating EI attributed to sounds.)</td>
<td>Collection of original data from various field surveys from transportation sources, Australia, Canada, France, Germany, Netherlands, Norway, Sweden, Switzerland, UK, USA (n=15171)</td>
<td>Miedema &amp; Vos (1999)</td>
</tr>
<tr>
<td>23%</td>
<td>Not provided</td>
<td>Random sampling. Sweden (n=1023)</td>
<td>Rubinstein, Alquist, &amp; Bengtsson (1996)</td>
</tr>
</tbody>
</table>
Co-prevalence
The different types of EI have many features in common. The distinguishing characteristic is the environmental exposure or source to which symptoms are attributed. However, there is the possibility that these conditions share the same causal pathway or that the individuals have some predisposition making them more sensitive to low exposure levels of environmental agents in general. High co-prevalence and shifting between conditions (e.g. symptoms are attributed to alternate environmental exposure) can be an indication of this. When studying co-prevalence, it is possible to use two perspectives. One way is to measure how common it is in the general population to suffer from two (or more) EIs. Another approach is to measure how prevalent other types of EI are in a subsample consisting of a specific EI. Using the first perspective, Levallois, Neutra, Lee and Hristova (2002) found the co-prevalence between EI attributed to chemicals and EI attributed to EMFs to be 2%, where the prevalence of EI attributed to EMFs was 3% and 24.4% for EI attributed to chemicals in the same sample. In a Swedish study the co-prevalence between EI attributed to chemicals (defined as a high amount of annoyance from odors) and EI attributed to EMFs was 2.4% (Carlsson et al., 2005). Using the second perspective, Levallois, Neutra, Lee and Hristova (2002) found that among individuals with EI attributed to EMFs 60% also reported EI attributed to chemicals. In another study, 50% of the individuals with EI attributed to sounds also reported sensitivity to warm/cold environment and smells as well (Baliatsas et al., 2016). Further on, the prevalence of reporting disturbance from noise from neighbors, ventilation systems and traffic has been found to be at least twice as common for individuals with intolerance to EMFs compared to referents (Hillert et al., 2002).

Symptom attribution
Perceived or reported causes of actions, feelings or events are called attributions (Marks, Murray, Evans, & Estacio, 2011). Attribution theory is a field within social psychology that deals with how the social perceiver uses information to arrive at causal explanations for events. Essential in the formation of causal judgements, according to attribution theory, is what information is gathered and how it is combined. Attribution theory proposes that individuals are particularly prone to find causal explanations for events if those events are of personal relevance (Jemmott, Ditto, & Croyle, 1986). Symptoms are usually of personal relevance and therefore it is suggested that attribution or the search for causal explanations begins more or less by itself. Symptoms generally occur before a self or professional diagnosis has been made and are associated with a variety of interpretations. Furthermore, symptoms (e.g. headache, gastrointestinal problems, muscle pain) are common experiences among the general population (e.g. Eriksen, Hellesnes,
Staff, & Ursin, 2004; Ihlebaek, Eriksen, & Ursin, 2002; Petrie, Faasse, Crichton, & Grey, 2014). In a Norwegian study only 4% reported not having experienced any symptoms during the last month (Ihlebaek et al., 2002), and in a New Zealand study only 10.6% reported no symptoms during the last week (Petrie et al., 2014). Among the most prevalent symptoms in both studies were headache (reported by 50.6% in Norway and 35% in New Zealand), fatigue (52.8% / 36%) and cold, flu/runny or stuffy nose (53.1% / 34%). This does not hold only for modern civilization. Even more symptoms (100% reported at least one symptom during the past month) were reported when a similar study was conducted with Aborigine Mangyans living under primitive conditions in the jungle (Eriksen et al., 2004). Once again, headache (79.2%), tiredness (88.1%) and cold/flu (73.3%) were among the most prevalent symptoms. Hence, symptoms are common, and when they are troublesome or long-lasting many individuals have an understandable need to find an explanation for them. However, some individuals are more prone to interpret bodily sensations as physical symptoms (Barsky, 1979). These individuals seek medical help more often and will often receive the information that their symptoms are medically unexplained (Barsky, Orav, & Bates, 2005). It is natural for individuals with medically unexplained symptoms to seek causal explanations to them, and if an environmental exposure is present they may start to consider whether this exposure might be the reason for their symptoms (Rubin, Burns, & Wessely, 2014).

Three major dimension within causal attribution of symptoms have been proposed: environmental or normalizing, somatic and psychological styles (Robbins & Kirmayer, 1991). Environmental or normalizing people tend to attribute their symptoms to situational factors, for example to external influences (e.g. environmental irritants) or to normal body processes (e.g. temporary fatigue, lack of sleep). People with a somatizing attribution style suppose pathological body processes behind their symptoms and internal feelings. Finally, those following the psychological style are prone to regard a negative psychological state (e.g. depression or anxiety) as a possible cause of their symptoms. Characteristic for severe cases of EI is attributing their symptoms to a larger extent to environmental causes in comparison with less sensitive individuals who more commonly attribute their symptoms to their psychological state (van Dongen et al., 2014).

Even though EI is described as an intolerance attributed to a certain environmental exposure there are only a few studies on characterization of this attribution process, i.e. what information that is gathered and how it is combined to form causal judgements. However, in a qualitative study on individuals with EI attributed to EMFs, an attribution process consisting of several stages was identified (Dieudonné, 2016). During the first stages the onset of symptoms occur, which are perceived as abnormal since they lead to an inability to fulfill professional and/or domestic duties, leading to the
individuals seeking medical resolution. However, they fail to get a conventional diagnosis, often leading to the individuals feeling distressed and stigmatized. In intermediate stages the afflicted individuals get to know about EI (e.g. through newspaper articles, radio shows, stories from friends/relatives). Regardless of the source of information it consist of the same content: testimony of an afflicted EI individual in which they recognize themselves. This is followed by information gathering. The information individuals seek typically concerns other sufferers’ symptoms and the environmental exposure to which they attribute them. During the final stages the individuals identify themselves as being intolerant to EMFs. Initially they start reasoning as if they were intolerant, while consciously doubting they are. However, as they find more and more relationships between their health status and exposure to EMFs they become more and more convinced of being intolerant to EMFs. Now, every identifiable exposure (whatever its source, power or duration) is regarded as plausible cause of their symptoms. In the last stage the individuals consciously accept being EI sufferers. The afflicted individuals now start adapting their lifestyle, rewriting their personal stories to make them coherent with their new belief system, and sometimes campaigning for official recognition of their condition.

Social factors may influence attribution. One such factor is mass media reports. Mass media reports about EI often portray a severe sufferer of EI, discuss the possible adverse health effects of the environmental factor, and in the majority of cases give a causal explanation which is not in line with the current scientific view (Eldridge-Thomas & Rubin, 2013). This kind of reports might lead to persons being more vigilant when being close to environmental factors mentioned to cause symptoms. If a symptom emerges that has been mentioned in the media report, it is possible that the individual will attribute the symptom to the exposure (Barmark, 2014; Witthöft & Rubin, 2013).

Attribution of symptoms to exposure might also lead to relabeling pre-existing symptoms as being triggered by the exposure. In a study measuring symptoms before and after environmental pesticide spraying, the strongest predictors of symptoms attributed to the spraying were worry and number of symptoms reported at baseline (Petrie et al., 2005).
Suggested etiology of EI

“What is ‘real'? How do you define ‘real'? If you are talking about what you can feel, what you can smell, what you can taste and see then ‘real’ is simply electrical signals interpreted by your brain.”

(Morpheus in The Matrix)

The Bradford Hill criteria for causation has dominated the epidemiology field for half a century (Bradford Hill, 1965). One of the Bradford Hill criteria is that the strength of association, or the effect size, should be high. However, a cause and effect relationship might be slight, and small effect sizes are actually more plausible than large ones (Ioannidis, 2016). Instead, large effect sizes are often due to biases and errors. Often there is just not only one cause, but several factors will lead to the effect. One factor alone might not display a large effect size, but several causative factors together may show a larger effect. Following this argument, another Bradford Hill criterion, namely ‘specificity’, has been questioned. In social science in general, and psychology in particular, the complexity of phenomena and conditions is best approached with multifactorial explanations. A causative factor may be thought as increasing the probability that a certain event will occur (Parascandola, 2011). With this perspective a factor does not have to be necessary nor sufficient to be a causative factor, it is instead contributing to the causation. Take the example of cigarette smoking and lung cancer. Smoking is neither a necessary (lung cancer can develop anyway) nor a sufficient (many smokers will not get lung cancer) cause. However, with today’s knowledge there are few who argue against the claim that cigarette smoking is a causative factor for lung cancer. A risk factor is a circumstance that statistically co-varies with a condition, but for which the importance for the condition is not established. If a risk factor repeatedly and in different settings is associated with a condition, with the probabilistic view of causation, one would argue that it is a causative factor.

Several theories regarding the etiology of EI have been suggested, predominantly immunologic, toxicologic, psychologic and sociologic theories. Opinions about the etiology and pathogenesis have been sharply divided between those researchers suggesting a pathophysiological/toxicological causation and those proposing a psychological/sociological explanation (perhaps with the exception for EI attributed to sounds; e.g. compare Vuokko et al., 2015, and Tuuminen, Haggqvist, & Uusitalo, 2016; Genuis & Lipp, 2012, and Rubin, Hillert, Nieto-Hernandez, van Rongen, & Oftedal, 2011; Miller, 2001 and Van den Bergh, Winters, Devriese, & Van Diest, 2002). Based on clinical and epidemiological data, none of the proposed theories alone has the ability to satisfactorily explain EI (e.g. Das-Munshi et al., 2007; Lahtinen, Huuhtanen, & Reijula, 1998). Therefore, EI is
presumably best conceptualized using multifactorial models, incorporating both physiological and psychological factors. Nevertheless, there is growing empirical evidence for associations between mental ill-health and EI (Bailer, Witthöft, & Rist, 2008b; Kinman & Griffin, 2008; Rubin et al., 2010). The focus here will be on psychological theories of causation, whereas physical/immunological/ toxicological theories of causation such as neurogenic inflammation (Meggs, 1999), toxicant induced sensitivity (Miller, 2001), neurogenic, stapedius reflex dysfunction (Tyler et al., 2014), disrupted 5-HT function (Baguley, 2003) and autoimmune/inflammatory reactions induced by adjuvants (Israeli & Pardo, 2011) will be left out.

**Nocebo effect**
The term nocebo was introduced by Kennedy (1961) as a contrast to the term placebo. Both placebo and nocebo are dealing with effects caused by expectations, but whereas the placebo has a pleasant effect caused by positive expectations, the nocebo is an unpleasant or undesirable effect caused by negative expectations. Both terms were introduced to describe the effects that study participants manifest after receiving an inert dummy drug, and most commonly nocebo effects have been reported during double-blind clinical trials of new drugs in which an inert pill does not only lead to reports of beneficial effects (placebo effect), but also to disadvantageous reports about the side effects associated with the drug (Barsky, Saintfort, Rogers, & Borus, 2002).

A telling example of the nocebo effect comes from New Zealand where television coverage of a reformulated drug lead to a health scare followed by an increase of reported side effects of the drug (Faasse, Gamble, Cundy, & Petrie, 2012). The interesting thing was that the reformulation consisted of changing the color of the tablets from yellow to white and labelling it differently, whereas the active ingredient in the tablets remained the same. The reformulation caused some individuals to report severe symptoms such as blindness, vision loss, memory problems, trembles and unsteadiness which was covered in three television broadcasts some months apart during 2008. In the study by Faasse et al. (2012), first of all the month by month symptom reports to the New Zealand national monitoring center for drug adverse reactions increased after all three television broadcasts. Further on, only the symptoms specifically mentioned in the television news coverages significantly increased, likely by increasing viewers’ expectations that they too would experience similar side effects. Some months after the television news coverage the number of reported symptoms from the medication was more or less back to before the reformulation of the drug. Hence, negative expectations were induced by the television broadcasts leading to the nocebo effect.
In a similar fashion it has been suggested that negative expectations about environmental exposure may lead to the nocebo effect. However, in this case it is not triggered by negative expectations about an inert medicine, rather by an environmental exposure that is perceived as harmful. Expectations/nocebo have in experimental studies been shown to influence symptom reporting of EI individuals. For example, during blank exposure (i.e. no chemical present) individuals with EI attributed to chemicals reported greater symptoms and rated the exposure as more intense than controls (Andersson et al., 2016). Provocation studies have shown that EI individuals report more intense symptoms in both real and sham exposure in comparison with controls (Rubin, Hahn, Everitt, Cleare, & Wessely, 2006). Hence, the expectation of being exposed, rather than the exposure per se, seems to elicit the symptoms. These effects are not only seen in individuals already suffering from EI, but also in individuals who have merely negative expectations about some environmental exposure (Danker-Hopfe, Dorn, Bornkessel, & Sauter, 2010; Job, 1999). The nocebo effect might also be a possible explanation for some outbreaks of EI attributed to buildings (Hedge et al., 1996). Environmental events, such as the emergence of an unpleasant odour after installing a new carpet, could be accompanied with a collective occurrence of negative beliefs and a set of symptoms among several individuals in the absence of any identifiable pathogen. The negative expectations about health outcomes due to the environmental event spread from individual to individual, and consequently also complaints and symptoms.

Negative expectations can be inducted in several ways, for example verbally or experimentally by inducing associations between one (harmless) stimulus and an aversive stimulus, an approach called classical conditioning. In a series of experiments it has been demonstrated that symptoms can be learned by classical conditioning (Leer, Smeets, Bulsing, & van den Hout, 2011; Meulders et al., 2010; Van den Bergh et al., 2001; Van den Bergh et al., 2002). When healthy individuals were presented to an odorous chemical simultaneously with carbon dioxide (which may produce sensations such as headache and fast breathing) or electrical shock, and later were presented to the odorous chemical alone, they displayed the same symptoms as induced by the aversive stimulus. The smell alone was now sufficient to trigger the symptoms. The effect was long-lasting, and did not decrease in a week. Moreover, a spreading phenomenon has been observed, in which the symptoms can be triggered also by other, similar smells. Symptoms attributed to visual display units (VDU), i.e. EMFs, have also been suggested to be explained by classical conditioning (Berg, Arnetz, Lidén, Eneroth, & Kallner, 1992).

Regarding the neurobiology of expectations and the nocebo effect it has been suggested that a “mental representation” of an impending sensory
event significantly can shape neural processes that underlie the actual sensory experience. In an fMRI-study brain areas essential for the expectation of pain was studied (Koyama, McHaffie, Laurienti, & Coghill, 2005). The activation of expected and experienced pain was compared and characterized. The brain areas found to be important for expectation of pain were thalamus, insula, prefrontal cortex and anterior cingulate cortex. In another fMRI-study the brain activity of individuals with EI attributed to EMF and controls were compared when exposed to sham mobile phone radiation (Landgrebe et al., 2008). When anticipating an exposure of mobile phone radiation (which would induce negative expectations in the EI individuals) the EI group showed elevated activation in anterior cingulate cortex, the insular cortex and the fusiform gyrus in comparison with controls. During heat exposure there was no differences in brain activation between the groups. It has been suggested that reward circuitries (dopaminergic, cyclooxygenase-prostaglandins and opioid brain pathways), and decision-making processes play a crucial role in the nocebo response (Mitsikostas, 2016).

It is important to address that the nocebo effect is not uniquely present in medically unexplained conditions, such as EI, but also exists in diseases with known etiology. For example, asthma patients have been shown not only to report increased number of perceived symptoms but also exhibit elevated levels in airway inflammation measures (e.g. broncho-constriction and exhaled nitric oxide) when negative expectations of an exposure were induced by giving the information that the exposure would elicit asthma symptoms (Jaén & Dalton, 2014). Anyhow, the nocebo effect might set a vicious circle into motion, in which symptoms accumulate.

**Dysfunctional cognition**

Cognitive theories of EI emphasize that high level of worry about harmful environmental factors, dysfunctional attribution style, increased symptom-focused attention and negative affectivity will lead to an amplification of perceived bodily sensations into symptoms for which medical treatment is sought (Bailer, Witthöft, & Rist, 2008a; Witthöft, Gerlach, & Bailer, 2006). According to the cognitive model, individuals attribute their symptoms to assumed toxic properties of environmental agents, but the symptoms are mediated by psychological processes (e.g. anxiety, worry, introspection). Hence, the (medically unexplained) symptoms (or bodily sensations) are first present, then an attribution of these symptoms to trigger factors of EI takes place, and finally persons identify themselves as intolerant to certain environmental factors. The symptoms and the cognitive factors interact to form a viscous circle in which increasing symptom-focused attention, catastrophizing and misinterpreting these symptoms and selective attention toward threat-related information lead to chronic hyperarousal which, in
turn, generates and aggravates symptoms (e.g. by stress responses and by altering the perception of bodily sensations into the interpretation of symptoms). Cognitive processes essential in this model are attention (increased selective attention to non-specific symptoms and environmental threat information), attribution (symptoms are attributed to environmental causes), and catastrophizing cognitions about consequences of exposure and the accompanied symptoms (Witthöft et al., 2006; Witthöft & Hiller, 2010).

In an event-related potential study individuals with EI attributed to chemicals displayed shorter chemosomatosensory and olfactory P2 latencies than controls when they were to ignore chemical stimulation during an attention task. The results were interpreted as an attention bias, in which the EI subjects were unable to ignore chemical exposure (Andersson, Bende, Millqvist, & Nordin, 2009). Memory bias to trigger words have also been found in EI individuals (Witthöft et al., 2006). The trigger words were remembered better and evaluated as more unpleasant and arousing in EI individuals compared to controls. Selective attention to symptoms has been found in EI, where EI individuals show longer reaction times in an emotional stroop task in which the color of words are to be mentioned (Witthöft et al., 2006). If the words referred to a symptom the reaction time was longer for EI individuals compared to controls. In a one-year follow-up study the strongest predictors of EI symptoms were somatic attributions (symptoms attributed to a physical rather than psychological or external cause) and cognitions of environmental threat (evaluation of environmental agents for the extent to which they have already harmed their health) (Bailer, Witthöft, Bayerl, & Rist, 2007). Positive associations have been found between attentiveness to bodily responses, somatosensory amplification (responses to bodily sensations generally not indicating disease) and EI (Skovbjerg, Zachariae, Rasmussen, Johansen, & Elberling, 2010). Highly noise sensitive individuals have been found to report significantly higher number and duration of non-specific symptoms and a more negative symptom perception than tolerant individuals (Baliatsas et al., 2016). Direct measures of catastrophizing cognitions or interpretations of bodily complaints has also been found to be elevated in individuals with EI compared to controls, but lower than for individuals with somatoform disorders (Bailer, Witthöft, Paul, Bayerl, & Rist, 2005).
Sensitization

“We should not let the use of the common descriptive term ‘sensitization’ influence us into thinking that things labelled alike are alike and can be understood in the same way. And we should be very open to invoking new, more specific terms to help us properly categorize what is being studied”

(Overmier, 2002)

Learning theory has made a distinction between two classes of learning: associative learning and non-associative learning (Kalivas & Barnes, 1988). In associative learning an association between two stimuli is established (classical conditioning) or between a stimulus and a response (operant conditioning). In non-associative learning, a behavior is changed as a result of the mere repeated presentation of a single stimulus or event. Non-associative forms of learning include habituation, and sensitization. Habituation is a decrease in response amplitude as a function of stimulus delivery, and sensitization is an increase in (non-habituated) response amplitude after repeated stimulation, which is especially prominent when the stimulus is aversive or strong. Both habituation and sensitization makes good sense, from an adaptive perspective. Habituation, since a continuous response to a repeated harmless stimulus may prevent from noticing an important change in the environment (Ursin, 2014). In the case of sensitization, an unexpected or extreme stimulus may signal danger, so an increased response may be helpful and even essential for survival.

Neuronal sensitization

In a pioneer work in which sensitization (or more precisely kindling of the limbic structures) was proposed as a causal explanation for EI, the focus was on EI attributed to chemicals (Bell, Miller, & Schwartz, 1992). Kindling is primarily a model for epilepsy and is described as the process by which repeated application of brief, low-intensity trains of electrical stimulation gradually develop into electrographic and behavioral seizures (Gilbert, 2001). However, kindling can also be induced by chemical stimulation, in which repeated exposures to some pesticides have been shown to induce electrographic signs of hyperexcitability in the amygdala and behavioral seizure. Bell et al. (1992) described kindling (in this perspective) as a special type of time-dependent sensitization of olfactory-limbic neurons, in which drugs or environmental toxicants induce the process. They used the term to refer to limbic neuronal excitability and associated behavior in non-epileptic individuals after repeated subthreshold stimulation with these environmental chemicals. They described the progression of the intolerance
as a “spreading phenomenon”, in which sensitivity generalizes from the original agent to low doses of multiple, chemically unrelated substances, such as perfume, tobacco smoke, car exhaust, etc. This spreading was called cross-sensitization. The intolerance could also spread to other domains such as sensitivities to common foods. Sensitization can, according to Bell and colleagues, take place in the entire nervous system, and depending on where, different symptoms will manifest themselves. Further on, they suggested that it was unlikely that sensitization would occur in only one branch of the nervous system at a time. Once initiated, Bell et al. (1992) claimed that heightened susceptibility to chemicals persist indefinitely, with gradual symptomatic improvement following long-term avoidance of triggering substances (however, since the mechanism suggested is sensitization, symptoms will reoccur if exposed again to the triggering substance). Later on Bell and colleagues broadened their definition of sensitization to include exogenous physical or psychological stressors to be possible triggers of sensitization (Bell, Baldwin, & Schwartz, 2001). Hence, these factors could also initiate the process leading to host response amplification over time. Sensitization is now understood as being initiated by stimuli of threat for the organism, followed by enhanced response to the same or cross-sensitized stimuli.

Cognitive emotional sensitization

Now, before moving on, let us take a step back and spend a moment thinking about what is meant by sensitization. One way to define sensitization (and according to learning theorists the appropriate one) is an increment in response to repeated presentation of the same (noxious or aversive) stimulus. In this sense, sensitization refers to a theoretical (inferential, hypothetical) process raised to explain behaviour (Peeke & Petrinovich, 1984). By this definition the term by itself is not directly measurable, it has to be operationalized into stimulus and response. On the other hand, sensitization is used to describe the observed behavioural outcome. Thus, the explanatory mechanism and the behavioural outcome are both labelled ‘sensitization’, which of course results in confusion. Arguments have been raised to use the term ‘sensitization’ exclusively to describe the cellular process of enhanced excitability in which repetitive stimulation leads to an increase responsiveness of a given neuron (due to synaptic changes) to its normal afferent input (Cervero, 2009). Another outlook argues for a broader definition of sensitization and defines it as a behavioural process of enhanced sensitivity in which cognitive processes such as cognitive bias and illness perception may influence the increased responsiveness to various stimuli (Ursin, 2014). Brosschot (2002) calls this cognitive emotional sensitization in which all types of cognitive bias could be understood. The interpretation is that networks of neurons are too strongly or too easily
activated. The function of cognitive bias, or rather the attentional part of it, is detecting potentially threatening stimuli as early as possible. This emotional information gets priority and is processed “quick and dirty”, thereby initially circumventing higher cognitive processes. Ambiguous internal or external information has a tendency to be interpreted in terms of the individual’s current concerns. A “fear network” is activated causing rapid spread of activation through the CNS. When this network becomes larger and more frequently activated the spread is more massive and causes interference with other cognitive tasks. Brosschot (2002) pinpoints some dissimilarities between neural and cognitive emotional sensitization, namely that neural sensitization involves a relatively low number of neurons with stronger synaptic information transfer, while cognitive emotional sensitization probably involves a larger number of neurons, with more neural interconnections, but with weaker synaptic information transfer. Another difference claimed is that neural sensitization usually is triggered by only one type of sensation, whereas cognitive emotional sensitization is triggered by several. By this definition a variety of stimuli, including stress, may lead to neural plastic changes, resulting in an increased response to, for example, odorous chemicals (Sorg & Prasad, 1997). Hence, the hedonically powerful stimulus that initiate sensitization does not have to be the same stimulus to which an enhanced response emerges. This process is also called cross-sensitization or pseudo-conditioning (Overmier, 2002), but within the research field of EI and other medically unexplained conditions it is usually simply called sensitization (e.g. Bell et al., 2001; Sorg, 1999; Ursin & Eriksen, 2001).

Central sensitization

Further on, another type of sensitization, namely central sensitization, has entered the scene recently as a causal theory for EI. Central sensitization represents an enhancement in the function of neurons in the nociceptive pathways (Latremoliere & Woolf, 2009). As implicated by the name, central sensitization is anatomically located primarily in the CNS. Central sensitization entails several top-down and bottom-up mechanisms (Nijs et al., 2012). To the top-down mechanisms pertain altered sensory processing in the brain, malfunctioning of descending inhibitory mechanisms, increased activity of descending facilitating pathways and temporal summation of sensory stimuli (i.e. wind-up). One example of bottom-up mechanism leading to central sensitization is the release of pro-inflammatory cytokines (signalling molecules) due to, for example, physical injury or infections. Circulating pro-inflammatory cytokines ending up in the spinal cord change the neural transmission by either increasing excitatory synaptic transmission or by decreasing inhibitory synaptic transmission, leading to central sensitization (Kawasaki, Zhang, Cheng, & Ji, 2008).
Central sensitization leads to an increased responsiveness to a variety of stimuli including mechanical pressure, light, sound, chemical substances, cold, heat and electricity, ending up in a decreased load tolerance (Nijs et al., 2012). Central sensitization has been suggested to occur in a variety of medically unexplained conditions such as chronic fatigue syndrome, fibromyalgia, migraine, irritable bowel syndrome (Yunus, 2009). Due to this, a new term has been proposed: central sensitivity syndromes, which embrace a group of conditions that have overlapping signs and symptoms (e.g. pain, fatigue, disturbed sleep, and hypersensitivity to various stimuli including pain, noise, stress and chemicals), lack structural pathology, are based on neuroendocrine-immune dysfunction and are bound by a common pathophysiological mechanism of central sensitization (Yunus, 2009). Many factors are suggested to contribute to central sensitivity syndromes via central sensitization, such as genetic, endocrine, infectious, inflammatory, autonomic, psychological (e.g. stress, anxiety, depression, childhood trauma, catastrophizing) and environmental (e.g. noise) factors. Enhanced pain processing has been found in individuals with EI attributed to chemicals, since intradermal injection of capsaicin (active component of chili pepper) lead to increased area of secondary hyperalgesia and temporal summation in comparison with controls (Holst, Arendt-Nielsen, Mosbech, & Elberling, 2011).

**Mental illness**

"The mind has great influence over the body, and maladies often have their origin there."

(Molière)

“Well, I got a lot of symptoms, but I’m not sick. This [EI] is something that only exists in my mind.”

(Participant)

Judgement of mental malfunctioning is the core of what is called mental illness3 (Busfield, 2011). However, the judgement of mental malfunctioning varies over time and place due to different belief-systems. For example, hearing voices or having visual delusions may in some cultures be considered as special powers rather than more stigmatized, negative perceptions that are typical in our society. For example, these abilities were viewed as bearing shamanic potential in an Eskimo society during the 1950s (Murphy, 1976), whereas they are by most part viewed upon as signs of schizophrenia or

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3 ‘Illness’ is sometimes used interchangeably with ‘disease’, however illness should here be understood as a subjective state of suffering according to the definition by Cassel (1991).
other psychotic illness in modern Western society (Upthegrove et al., 2016). It is important to realize that cultural and lay ideas and beliefs underpin professional (researchers’ and clinicians’) ideas and practices, and these in turn shape lay ideas. Hence, there exists a dynamic interaction between the two. Further on, the boundary between mental and bodily illness is not clear-cut and movements between these two are not uncommon, such as epilepsy moving from being considered a mental illness to a neurological disorder or hysteria moving from being viewed as a bodily illness (i.e. the uterus traveling around the body causing a cascade of symptoms) to a mental one. Another issue arises, when talking about bodily versus mental illness. What is body or medicine and what is mental (i.e. mind) or psychology? The WHO’s definition of (traditional) ‘medicine’ is “the sum total of the knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health, as well as in the prevention, diagnosis, improvement or treatment of physical and mental illnesses.” According to this definition medicine incorporates both body (“physical”) and mind (“mental”). However, the biomedical perspective has dominated medicine for more than a century. At its extreme the biomedical view wishes to disentangle the organic elements of disease from the psychosocial elements of human malfunction, arguing that medicine would deal with the former (the “real” disease) only (Engel, 1977). Since professionals ideas shape lay ideas this biomedical stance may cause mental illness being perceived as something that is not real or something that is not to be taken seriously (Cassel, 1991). This biomedical view may also result in bodily illness being more accepted and perceived as having higher status than mental illness. Following this argument, it should imply that individuals with medically unexplained conditions would seek a bodily rather than a mental explanation to their condition, which also has been found in research (Lian & Nettleton, 2015; Nettleton, 2006). Further on, the issue of medically unexplained conditions being perceived as bodily versus mental illness has become a hot potato for many afflicted persons. For example it has been reported that individuals with EI were upset when introduced to psychological theories about their condition since it would implicate that the problems are in their psyches (perhaps interpreted as not real) rather than in their bodies (Lipson, 2004).

Above from bodily illness (or disease) potentially having a higher status than mental illness, illness (both bodily and mental in various degrees depending on the condition) is marked by stigma. Stigma can be defined as a devalued attribute (in a particular social context) that a person possesses (or is believed to possess) that extensively discredits the individual (Major & O’Brien, 2005). Stigma are associated with negative evaluations and stereotypes, which generally are widely shared and well known among members of a particular culture, and they become a basis for excluding or
avoiding members of the stereotyped category. Some stigma of mentally ill individuals are being unpredictable, hard to talk to/antisocial, dangerous, feeling different, having themselves to blame, and having to pull themselves together (e.g. Crisp, Gelder, Rix, Meltzer, & Rowlands, 2000; Read & Law, 1999). Stigma experienced by individuals with EI include being perceived as crazy, weird, or freaks and that they just make up the symptoms (Lipson, 2004). This stigmatization may lead to other people’s (even family members’ and friends’) avoidance. EI is characterized by medically unexplained symptoms, a label that can be perceived as unacceptable and even offensive by patients, who feel that it carries an implication that their symptoms are imagined or made up (Stone, 2002). That is, that the label confirms the stigma. Perhaps this stigmatization further intensifies the afflicted individual’s urge to convince others that EI is a bodily rather than mental illness.

Several studies have shown that mental illness (such as stress, depression, anxiety and burnout) is associated with EI. The prevalence of psychiatric disorders among individuals with EI attributed to chemicals, EMFs and sounds have been reported to be high (31-75%) (Bornschein, Hausteiner, Zilker, & Förstl, 2002; Jüris, Andersson, Larsen, & Ekselius, 2013; Meg Tseng et al., 2011). Generally, individuals with EI score higher than controls on different scales measuring depression and anxiety (Gomzi et al., 2007; Magnavita, 2015). However, there is sparse documentation as to whether mental illness precedes or follows EI (or if there is a bidirectional relationship). Qualitative studies have reported that the informants insist that they are mentally ill because they suffer from EI (i.e. EI being the cause of mental illness) and not the other way around (Lipson, 2004).

**Stress**

Living organisms survive by maintaining a complex and harmonious equilibrium, or homeostasis, that is constantly threatened by inner or outer forces, or stressors (Chrousos & Gold, 1992). The steady state required for successful adaptation is maintained by counteracting forces, consisting of a magnitude of physical and mental reactions that attempt to counteract the effects of the stressors in order to reestablish homeostasis. Stress may be defined as an actual or perceived biological, social or psychological load or demand that threatens homeostasis, accompanied by an evaluation (conscious or unconscious) with the aim to distinguish what is threatening or noxious from what is benign, the activation of coping processes to deal with these stressful demands and a complex pattern of responses often referred to as the stress response (Lazarus, 1993). However, this definition of stress is not universally accepted since stress is still not fully understood, nor are the detailed mechanisms of the activation of the stress response under various specific stressors (Kvetnansky, Sabban, & Palkovits, 2009). The above
definition of stress may be divided into four parts: i) the load or demand, or the stressor, ii) the evaluation also called appraisal, iii) coping processes, and iv) the stress response. In this section stressors and the stress response will be covered. Appraisal and coping will be covered under the section ‘Coping’.

Stressor
When it comes to the stressor, it can be defined as a stimulus that disrupts homeostasis. Most researchers look upon the stress response as having a degree of specificity, depending, among other things, on the particular stressor (Kvetnansky et al., 2009). Stressors may be divided into four major categories: physical stressors (e.g. cold, heat, radiation, noise, vibration, chemical stressors, pain, immobilization), psychological stressors (e.g. anxiety, fear, frustration), social stressors (e.g. unemployment, marital separation, death of partner), and stressors that challenge cardiovascular and metabolic homeostasis (e.g. exercise, hypoglycemia, hemorrhage, hunger; Pacák & Palkovits, 2001). Stressors may also be divided according to duration into either acute stressors (single, recurrent, time-limited exposure) or chronic or repeated stressors (continuous long-term exposure, recurrent long-term exposure). Certain characteristics of a stressor is associated with greater stress responses, for example high intensity or severity and uncontrollability of the stressor (Schneiderman, Ironson, & Siegel, 2005). Multiple stressors that work synergistically are more powerful than those working alone; for example high demand in combination with low control result in higher stress response (Karasek & Theorell, 1990). Besides various stressors having a tendency to elicit different stress responses, there are also individual differences in stress response to the same stressor. In a particular situation some individuals tend to show stress responses associated with increased autonomic and hormonal activities that maximize the possibilities for muscular exertion, whereas others tend to show stress responses more associated with vigilance that involves sympathetic nervous system (SNS) arousal accompanied by an active inhibition of movement and shunting of blood away from the periphery (Schneiderman et al., 2005).

The stress response
The stress response consist of a cascade of changes in the nervous, cardiovascular, endocrine, and immune systems (Chrousos & Gold, 1992; Schneiderman et al., 2005; Tsigos & Chrousos, 2002). If a situation is appraised as stressful, forebrain integrative centers, such as the hypothalamus (the command center of the stress response), the limbic system, and cerebral cortical areas are activated (Dickerson & Kemeny, 2004; Kvetnansky et al., 2009). Efferent neuronal pathways carry the stress response signals from these forebrain centers to the periphery by two major routes: humoral (activation of the hypothalamic-pituitary-adrenal – HPA-
轴) 和神经 (交感神经)。肾上腺-脑干轴以及交感-副交感神经系统的活动。肾上腺皮质类固醇（主要为皮质醇）是HPA轴的最终效应者。皮质醇具有广泛的生理效应，如动员能量、抑制免疫系统功能，并且对于儿茶酚胺和其他交感神经产品的效果在心血管系统（Dickerson & Kemeny, 2004）起作用。肾上腺皮质类固醇在终止应激反应中起着关键作用，通过在外侧结构、边缘系统、脑干神经元，下丘脑和垂体腺的负反馈环路。此负反馈环路限制了皮质醇的总暴露，最小化了这些激素的分解代谢、反生殖和免疫抑制效应。总的来说，HPA轴对于支持正常的生理功能和调节其他系统，如免疫系统、SAM轴、心血管系统以及情感和认知过程至关重要。神经路径从下丘脑开始，通过脊髓的背根神经元终止在肾上腺髓质和交感神经节细胞。根据它们的终止和功能作用，神经路径被分为SAM轴，主要负责血中肾上腺素的合成和约30%的去甲肾上腺素，以及交感神经系统，在其中交感神经节细胞合成和释放大部分血中去甲肾上腺素。循环中的肾上腺素提高了心血管张力（导致血压和心率升高）和呼吸频率。去甲肾上腺素水平导致糖异生和脂肪分解，为全身提供能量。

应激反应是有益的，一般在有益的方式下。术语应激状态已被引入来描述身体适应各种应激物的过程（McEwen, 2004, 2007）。主要应激介质，例如HPA轴的激素，儿茶酚胺和细胞因子，通过相互作用来创建一个相互影响的网络，通过这种相互影响达到稳态。然而，当应激介质（如皮质醇或儿茶酚胺）在应激期间未充分激活，当应激结束后未停止，或者由于许多同时的应激物过分产生时，会产生累积变化，导致应激状态。这些应激状态被称为症状如炎症、皮肤条件、疼痛、心相关疾病、抑郁、焦虑和消化、睡眠和认知问题。进一步，应激状态描述为一种主要介质的不平衡，反映了某些介质的过分产生和某些介质的不足产生。例如，慢性疲劳综合症已被解释为应激状态。
state in which there is a chronic elevation of inflammatory cytokines and low cortisol.

Subjective measures of stress, or perceived stress, has been associated with EI attributed to chemicals EMFs and sounds (Hill, Billington, & Krägeloh, 2014; Ljungberg & Neely, 2007; Nordin, Ljungberg, Claeson, & Neely, 2013; Osterberg, Persson, Karlson, Carlsson Eek, & Orbaek, 2007; Persson, Carlsson Eek, Osterberg, Orbaek, & Karlson, 2008). EI attributed to buildings is associated with occupational/organizational stress (Crawford & Bolas, 1996; Hedge, Erickson, & Rubin, 1995; Lukcsó, Guidotti, Franklin, & Burt, 2016; Mendelson, Catano, & Kelloway, 2000). Two prospective studies have investigated the temporality between EI and mental illness, demonstrating conflicting results. EI attributed to sounds was, in one study, found to be a consistent predictor of psychological distress (Stansfeld & Shipley, 2015), whereas perceived stress was found to be a predictor of EI attributed to chemicals in another study (Eek, Karlson, Osterberg, & Ostergren, 2010).

Concerning endocrine measures of stress, conflicting results have been found regarding the hypothesis of elevated cortisol levels (indicating an increased stress reaction) in highly NS individuals compared to low NS individuals (Ljungberg & Neely, 2007; Waye et al., 2002). Ljungberg and Neely (2007) did not find differences in cortisol levels between the different NS groups, even though the groups differed regarding perceived stress. This is in line with studies on EI attributed to chemicals and EMFs in which no significant differences has been found between intolerant groups versus controls regarding cortisol secretion, but in which higher levels of self-reported stress were seen in EI groups (Bornschein et al., 2008; Carlsson et al., 2006).

**Depression**

Depression is a cluster of signs and symptoms (e.g. feelings of sadness or emptiness, pessimistic thoughts, hopelessness, loss of motivation, loss of interest in usual activities, fatigue or loss of energy, concentration difficulties, reduced self-esteem and confidence, disturbed sleep, weight loss or gain, self-criticism, ideas about self-harm and suicidal wishes) that last a long time and affects normal, everyday functioning such as social and occupational impairment (American Psychiatric Association, 2013). Depression is a complex illness and one of the leading causes of disability in our society (Alonso et al., 2004; Kessler et al., 2003; Kessler & Bromet, 2013). Symptoms of depression vary between persons. One depressed person may display a symptom profile totally separate from another depressed person. The severity and time course of the symptoms also vary between persons. Risk factors for depression are multiple, but acute and chronic psychological stress, severe early trauma experiences, somatic disease, and
genetic factors are some of them (Swaab, Bao, & Lucassen, 2005). It has been suggested that a systematic cognitive bias in information processing is present in depression (Beck, 2008). This cognitive bias would lead to selective attention to negative aspects of experiences, negative interpretations, and blocking of positive events and memories (Beck, 2008). Concerning the pathophysiology of depression, associations have been found between depressive symptomology and a hyperactive HPA-axis, induced by alterations at different levels of the axis (Dantzer, O’Connor, Freund, Johnson, & Kelley, 2008; Dickerson & Kemeny, 2004; O’Keane, Frodl, & Dinan, 2012). There has also been multiple findings tying amygdala hyperactivity to depression (Abler, Erk, Herwig, & Walter, 2007; Drevets et al., 1992; Fu et al., 2008; Jenkins et al., 2016; Sawamoto et al., 2000; Sheline et al., 2001). It has been shown that the part of the amygdala that is hyperactive in depression is associated with the processing of anticipation of negative emotional stimuli (Abler et al., 2007). This supports the notion that anticipation of future events is altered in individuals with depression. Hence, a cognitive bias towards negative interpretations and selective attention to negative aspects of experiences are present in depression. Further on, depression has been associated with reduced prefrontal activity that is important for down-regulation of amygdala responses to negative stimuli (Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007; Siegle, Thompson, Carter, Steinhauer, & Thase, 2007). This can be interpreted as the top-down process of reappraisal being defective in depressed individuals, which may account for the importance of reappraisal in cognitive therapy of this illness.

Depression has been reported to be more pronounced than stress and anxiety in EI patients (Bergdahl & Bergdahl, 2001), and several cross-sectional studies have reported an association between EI and depression. This holds for EI attributed to chemicals (Azuma et al., 2015; Caccappolo-van Vliet, Kelly-McNeil, Natelson, Kipen, & Fiedler, 2002; Katerndahl, Bell, Palmer, & Miller, 2012), buildings (Bjornsson, Janson, Norback, & Boman, 1998; Kinman & Griffin, 2008; Magnavita, 2015), EMFs (Johansson, Nordin, Heiden, & Sandström, 2010; Rubin, Cleare, & Wessely, 2008) and sounds (Milenković & Paunović, 2015; Paulin et al., 2016). However, in one study, the relationship with NS and depression was accounted for by the variance explained by neuroticism (Hill et al., 2014). In a prospective study depression was associated with the development and persistence of EI attributed to chemicals (Skovbjerg et al., 2015), whereas in another prospective study EI attributed to sounds was found to be a consistent predictor of depressive symptoms (Stansfeld & Shipley, 2015).

**Burnout**
The concept of burnout was first used within the human service sector to describe the gradual emotional depletion/exhaustion, loss of motivation and
commitment, negative perceptions and feelings about clients/patients, and experiences of diminished professional competence seen in some workers (Freudenberger, 1974; Maslach, 1976). Maslach’s conceptualization of burnout embraces three dimensions: exhaustion, cynicism (depersonalization), and inefficacy (Maslach, Schaufeli, & Leiter, 2001). Exhaustion is seen as the cornerstone of burnout and means depletion of energy and emotional resources. Cynicism is described as a way to distance oneself emotionally and cognitively from one’s work, by for example depersonalizing individuals that one is working with (since their demands are easier to deal with if they are impersonal objects), and/or by developing an indifferent (cynical) attitude. Inefficacy stands for diminished professional/personal accomplishment by which the person comes to a negative self-assessment. Another definition comes from Melamed, Kushnir and Shirom (1992) who conceptualize burnout as consisting of three dimensions: physical fatigue, emotional exhaustion and cognitive weariness. Physical fatigue refers to feelings of tiredness and lack of energy in performing daily tasks. Emotional exhaustion refers to lacking energy to display empathy or to invest in relationships. Cognitive weariness refers to feelings of “slow thinking”. According to this definition the dimensions of burnout covers the draining and depletion of an individual’s energetic resources in different domains, and is thought to be a consequence of chronic stress and depletion of coping resources (Melamed et al., 1999). Despite some dissimilarities between the different definitions of burnout, they agree on the role of exhaustion as the key component of the construct (Schaufeli, Leiter, & Maslach, 2009). From the beginning burnout was thought of as only existing in professions working with people, above all within health care and social work, but later on the term was extended and was recognized to exist in other professions with intense requirements (Schaufeli et al., 2009). The notion of burnout has been broadened further to refer, not only to work-related, but to any long lasting stressful situation that is emotionally demanding and features high levels of interpersonal contact (e.g. marital conflicts; Bianchi, Truchot, Laurent, Brisson, & Schonfeld, 2014). Common symptoms of burnout are except for mental and physical exhaustion and cognitive problems (concentration difficulties and memory problems), sleep difficulties (e.g. insomnia, early awakening), irritability, specific somatic problems such as headaches, gastro-intestinal disturbances and increased infection sensitivity (Kahill, 1988; Melamed et al., 1999). There is at the moment no biomarker for burnout, the results from studies on HPA-axis activity are inconsistent sometimes indicating elevated and sometimes decreased activity (Grossi, Perski, Osika, & Savic, 2015).

Only a few previous studies have been conducted to test whether there exists associations between burnout and EI. However, EI attributed to EMFs
(Johansson et al., 2010) and buildings (Redman, Hamilton, Malloch, & Kleymann, 2011) have been found to be associated with burnout.

**Anxiety**
The core feature of anxiety is “the anticipation of danger”, which means persistent, excessive and unrealistic worry about everyday things (Hausteiner, Bornschein, Zilkcr, Henningsen, & Förstl, 2007). Anxiety is associated with a high proportion of somatic symptoms and is characterized by symptoms such as restlessness or feeling tense, being easily fatigued, difficulty concentrating or the mind going blank, irritability, muscle tension, and sleep disturbance. Anxious individuals overestimate the dangerousness of various stimuli, and have an attentional bias to threat stimuli (i.e. cognitive processing priority for information related to their fears or worries) which may result in showing automatic vigilance, constantly scanning the environment for potential threats (Brosschot, 2002; Clark, 1999). Emotional reasoning, safety-seeking behavior and selective retrieval of negative memories do also play a major role in maintaining anxiety (Clark, 1999). Stressful life events often precede anxiety disorders (Schneiderman et al., 2005). In general, HPA hyperactivity (demonstrated by elevated cortisol levels) has been found in the anxious population. Constant or chronic anxiety disrupts social activities and interferes with work, school, family and relationships.

Associations between anxiety and EI attributed to chemicals, buildings, EMFs and sounds have been found in cross-sectional studies (Bergdahl & Bergdahl, 2001; Björnsson et al., 1998; Hausteiner et al., 2007; Jüris et al., 2013; Milenković & Paunović, 2015). An increase in symptom score has been associated with anxiety in individuals with EI attributed to buildings (Runeson & Norbäck, 2005). However, there might be a difference between men and women in this regard since job related depression has been found to be a stronger predictor of SBS symptoms than anxiety for men, whereas for women, anxiety has been found to be a stronger predictor (Kinman & Griffin, 2008). Differences between men and women have also been observed in EI attributed to sounds in which NS index was highly correlated with anxiety in women but not in men (Nivison & Endresen, 1993). Additionally, the association between anxiety and EI attributed to chemicals was found not to persist when adjusting for background variables (including gender; Azuma et al., 2015). In a prospective study anxiety was associated with the development and persistence of EI attributed to chemicals (Skovbjerger et al., 2015). In another study anxiety predicted the number of symptoms, perceived intensity of trigger factors and functional impairment in individuals with EI attributed to chemicals 32 months later (Bailer et al., 2008b).
Coping and social support

Coping
The process of handling or managing specific demands, which are appraised as exceeding available resources, and the accompanying emotions, is called coping (Lazarus & Folkman, 1984). Hence, coping, defined in this way, is the cognitive and emotional efforts to manage, regardless of how good or poorly it actually works. Managing embraces everything from tolerating, avoiding, reprioritizing, minimizing and accepting stressful circumstances. To be able to understand the coping process it is essential to know with what the person actually is coping. What a person thinks or does depends on the specific context. For example, how a person manages a stressful encounter such as a student examination certainly differs from how the same person handles the news of a life-threatening illness. However some strategies of coping are often more stable and are used across different stressful encounters (Lazarus, 1993). Yet, rather than being an individual trait, coping is instead conceptualized as a transactional process (Lazarus, 1993; Lazarus & Folkman, 1984). Concepts important for understanding this transactional process are cognitive appraisal and reappraisal. Cognitive appraisal is an evaluative or interpretative process of demands and available resources that decides whether or not a certain transaction is stressful. It is this appraisal of transactions that can explain individual and situational differences regarding the stress reactions (Lazarus & Folkman, 1984). Appraisal hence shapes the stress reaction and is influenced by variables in the environment (such as controllability and predictability) and within the person (such as commitments and beliefs; Lazarus, 1993; Lazarus & Folkman, 1984).

Cognitive appraisal is taking place continuously, and the evaluation of a threat may alter as time goes by. A threat previously evaluated as not harmful might be re-evaluated on the basis of new information, and may hereafter be appraised as harmful (or the other way around). This process is called reappraisal. The new information altering the appraisal of a stressful circumstance might stem from sources “from the outside”, such as mass media or information from co-workers, or “from the inside”, that is information from the individual’s own reactions and experiences. In other words, reappraisals follow and modify an earlier appraisal. As the stressful event unfolds, with accompanying appraisals and reappraisals, different coping strategies may be used and perceived as effective (Lazarus & Folkman, 1984). Coping is hence a shifting process in which different strategies, in the form of thoughts and acts, are used over time. Individual differences are also fundamental to take into consideration. The specific coping strategy used and perceived as effective depends on the particular person. Accordingly, there may not be a universally good or poor coping
strategies, though some coping strategies are more effective more frequently (Lazarus, 1993).

Coping can be oriented toward emotion-regulation, and is then called emotion-focused coping, or towards altering or relieving the problem, called problem-focused coping. Most stressors (or stressful situations) elicit both types of coping. However, problem-focused coping tends to dominate when people feel that something constructive can be done, and emotion-focused coping tends to dominate when people feel that the stressor is unmanageable (Lazarus & Folkman, 1984). The categorization of coping into problem-focused (solving or altering the source of stress) and emotion-focused (managing or reducing the emotional reaction to the stressor) was suggested by Lazarus and Folkman (1984). Even though this categorization is perhaps the most used one, there is little agreement concerning the optimal conceptualization of coping. Another way to conceptualize coping is separating engagement from disengagement (Carver & Connor-Smith, 2010). Engagement seeks to deal with a stressor and the accompanied emotions by actively working to solve the problem or acknowledging the feelings and take action to handle them. This involves both problem-focused and emotion-focused strategies such as seeking support, emotional regulation and cognitive restructuring. In disengagement, on the other hand, the person seeks to escape from his/her feelings of anxiety, which includes coping responses such as avoidance, denial and irrational thinking.

Sex or gender differences in coping have been observed, in which women generally use more coping strategies than men, both problem-focused and emotion-focused strategies (Tamres, Janicki, & Helgeson, 2002). The largest effects of the sex differences have to do with expressions of feelings (seeking emotional support, positive self-talk and rumination) for which women are more likely than men to use these strategies. Men may engage in more avoidant or withdrawal behavior for stressors having to do with others’ health or relationship, that is, stressors that are more uncontrollable. Gender socialization might play a role in these differences between women and men (Ryle, 2011). Women are expected to express and communicate their feelings, and men to suppress and control their emotions. Stressor appraisal can also be an explanation for the sex difference in the use of coping strategies. Women tend to appraise stressors as more threatening, hence leading them to engage more in coping behavior (Tamres et al., 2002).

Generally, the most used coping strategy among EI individuals is avoidance. Between 43 and 52% of individuals with EI attributed to sounds have been reported to stay away from activities and places in which potential exposure was anticipated (Andersson et al., 2002; Hall et al., 2016). Even though avoidance lead to temporary prevention of discomfort, it has been suggested that it may result in increased hyperacusis (i.e. EI attributed to sounds; Baguley, 2003). This could be explained by the central gain theory in
which loudness perception depends on the average level of sensory input. The auditory system adapts to changes in the input it receives, and to compensate for loss of sensory input (as a consequence of avoiding sounds) a neural amplification of the central auditory system takes place that modulates the loudness perception (Diehl & Schaette, 2015). Individuals with EI attributed to sounds would in this case be caught in a vicious circle of sound avoidance and increased discomfort to sounds. Avoidance has also been reported to be used extensively by individuals with EI attributed to chemicals (Gibson, Elms, & Ruding, 2003; Nordin, Andersson, & Nordin, 2010) and EMFs (Hagström, Auranen, & Ekman, 2013). Avoidance has also been reported to be a strategy used by individuals with EI attributed to buildings (Söderholm, Öhman, Stenberg, & Nordin, 2016). Learning to accept the condition and reprioritizing are emotion-focused coping strategies used by EI individuals (Nordin et al., 2010; Söderholm et al., 2016).

Social support
Social support is related to both psychological well-being (Turner, 1981) and physical health (Uchino, 2009). It can be defined as the perception that one is being cared for, accepted and esteemed by others (Pierce, Lakey, Sarason, & Sarason, 1997), and can be divided into emotional, instrumental and informative support (House, 1981). Emotional support includes empathy, caring and consideration. Instrumental support includes practical supportive behaviors such as assisting with a certain task, doing the grocery shopping or loaning money. Informative support involves the provision of information and advice. Emotional, instrumental and informative support can be seen as functional aspects of social support, but there is also structural aspects (Thoits, 1995). Structural aspects of social support refers to the organization of the social network or an individual’s ties to others. It includes number of relationships and closeness to the persons in the social network. Social support can be seen as a psychosocial coping resource (Thoits, 1995). With this view, when an individual is under stress, social support can be seen as a social fund from which the individual can draw to handle the stressor.

Different age groups may require social support in different ways. Younger people tend to require more unconditional support from their network, whereas older people tend to require more specific support (such as feedback on a certain behavior adopted to deal with their everyday life; Aldwin, 2009). In adulthood, the size of the social network steadily decreases by age (Wrzus, Hänel, Wagner, & Neyer, 2013). However, emotional closeness to significant others increases with age (Carstensen, 1992).

Low levels of social support has been found to be associated with EI (Runeson-Broberg & Norbäck, 2013; Skovbjerg et al., 2012). Employees perceiving low levels of organization support has been reported to evaluate
their health as being adversely affected by their place of work and also predicted perceptions of poor air quality, which is of importance for EI attributed to buildings (Mendelson et al., 2000). In a prospective longitudinal study individuals who had developed EI between baseline and follow-up had at baseline reported less social support in comparison to those who had not developed EI (Eek et al., 2010). Social support has also been suggested to be useful in treatment of EI attributed to sounds (Pienkowski et al., 2014). Patients are then encouraged to expose themselves to environmental sounds in the company of a trusted counselor. The idea is that the social support would be helpful in decreasing the anxiety of being exposed.
The empirical studies

General methods

*Västerbotten Environmental Health Study*
The Västerbotten Environmental Health Study (VEHS) is a large questionnaire-based, longitudinal survey with focus on environmental intolerance. Västerbotten is a county in northern Sweden with approximately 260 000 inhabitants (about 195 000 between 18 and 79 years) and with an age and sex distribution similar to the general Swedish population (Figure 1).

![Figure 1](image-url)

*Figure 1.* Distribution of the population of Sweden (dark bars) and Västerbotten (light bars) for each age strata.

Data for VEHS has been collected at three occasions with three years in between (2010, 2013, and 2016). Altogether, the VEHS questionnaire consists of (i) demographic inquiries, (ii) an inventory on diagnosed cases of illness of relevance for EIs, (iii) questions on self-reported intolerance and symptoms attributed to environmental factors (odorous/pungent chemicals, certain buildings, sounds, EMFs), asthma and allergy, (iv) inquiries on affective and behavioral consequences of noise, odorous/pungent chemicals and EMFs, (v) inventories on somatic symptoms and symptoms associated with EIs, (vi) sets of items for assessing mental ill-health (perceived stress, burnout, anxiety, depression, hopelessness and helplessness (only at T1), modern health worries), (vii) questions concerning sleep, (viii) inquiries on...
certain environments and sources eliciting problems, (ix) a section, only answered by those with self-reported EI containing questions on coping and social support, and (x) inquiries on illness perception only answered by those with self-reported EI, asthma and allergy (only at T3).

**Questionnaire instruments and single questions**

Regarding **Environmental intolerance**, VEHS contains two types of self-reports for its identification. The first type is constituted by a set of listed medical conditions/diseases/illnesses that are to be checked if the respondents have been diagnosed by a physician with the particular illness. Checking either (or both) of ‘sensory hyperreactivity’ or ‘hypersensitivity to odorous/pungent chemicals / multiple chemical sensitivity’ resulted in that individual being classified as a diagnosed case of EI attributed to chemicals. In the same manner, diagnosed cases of EI attributed to buildings, EMFs or sounds were classified by checking ‘hypersensitivity by residing in certain buildings / building related unhealthiness’, ‘hypersensitivity to switched on electrical devices / electrosensitivity’ or ‘hypersensitivity to sounds / noise’, respectively (these cases are called diagnosed cases in Study 1). The other type of self-report to identify cases of EI is constituted by yes/no questions (Table 4), in which an affirmative answer leads to the respondent being classified as an EI case (these cases are called self-reported cases in Study 1 and cases in Studies 3 and 4). Further on, since the different types of EI seem to co-occur, a query was included in the VEHS to be answered only by those giving a confirmative answer to more than one of the questions in Table 4, in which they were to check the EI causing most symptoms. This question was the basis for the variable ‘main intolerance’ used in Study 2.

**Table 4. Questions to assess self-reported intolerance to certain environmental factors.**

<table>
<thead>
<tr>
<th>Environmental intolerance</th>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemicals</td>
<td>Are you getting symptoms from odorous/pungent chemicals (not limited to certain buildings), such as perfumes and cleaning agents, in doses that you were not getting symptoms from before or that you believe most other people are not getting symptoms from?</td>
</tr>
<tr>
<td>Certain buildings</td>
<td>Are you getting symptoms from residing in certain buildings (non-specific building related symptoms) that you were not getting symptoms from before or that you believe most other people are not getting symptoms from?</td>
</tr>
<tr>
<td>EMFs</td>
<td>Are you getting symptoms from certain switched-on electrical devices that you believe most other people are not getting symptoms from?</td>
</tr>
<tr>
<td>Sounds</td>
<td>Do you have a hard time tolerating everyday sounds that you believe most other people can tolerate?</td>
</tr>
</tbody>
</table>

**The Hospital Anxiety and Depression Scale (HADS)** is a well-established questionnaire instrument that was developed to identify anxiety and depression amongst patients in non-psychiatric hospital clinics (Zigmond & Snaith, 1983). HADS is composed of 14 statements which
respondents are to evaluate to what extent they are true for the individual according to a four-point response scale (ranging between 0 and 3). The scale consist of an anxiety subscale and a depression subscale. Both subscales consist of seven items that are intermingled in the HADS. Total scores on the scales are obtained by adding the seven questions for each subscale, respectively, hence the total scores range between 0 and 21.

The Shirom Melamed Burnout Questionnaire (SMBQ) consist of 22 items and measures three dimensions of burnout; physical fatigue, cognitive weariness, and emotional exhaustion (Melamed et al., 1992). All items are scored on a 7-point scale (1 = almost never to 7 = almost always). A global value, the SMBQ-global, of burnout is calculated by taking the means of all values (after reversing some of the items).

The perceived Stress Scale comprised of ten questions (PSS-10) measures the degree to which life situations are appraised as stressful by the respondent (Cohen, Kamarck, & Mermelstein, 1983; Cohen & Williamson, 1988). Each question concerns how frequently certain events or feelings have emerged the past month and is answered on a five-point Likert scale, ranging from “Never=0” to “Very often=4”. Total score for perceived stress is calculated by adding the 10 items (after reversing some of the items) of the scale, resulting in a total score ranging between 0 and 40.

The Noise Sensitivity Scale comprised of 11 items (NSS-11; Nordin, Palmquist, & Claeson, 2013), the Chemical Sensitivity Scale for Sensory Hyperreactivity (CSS-SHR; Nordin, Millqvist, Löwhagen, & Bende, 2004) and the 11-item Electromagnetic Field Sensitivity Scale (EMFSS-11; Nordin, Palmquist, et al., 2013) assess affective reactions to and behavioral disruptions by sounds, chemicals and electromagnetic fields, respectively. The Noise Sensitivity Scale (NSS) developed by Weinstein (1978) is the precursor of these scales. As an analogue to the NSS, the 21-item CSS was developed (Nordin, Millqvist, Löwhagen, & Bende, 2003). Each item of the CSS was constructed to resemble the questions in the NSS as closely as possible, only, when possible, substituting the environmental trigger (sounds/odors). From the CSS, 11 items were selected according to the highest sensitivity and specificity for differentiating individuals who were sensitive to odorous/pungent chemicals from the non-sensitive. The items of the EMFSS-11 were constructed as analogues to the items in the CSS-SHR, and 11 items from the NSS (constituting the NSS-11) was chosen to map the questions in CSS-SHR (e.g. “I am more aware of... odors/pungent chemicals | noise | possible electric fields... than I used to be”). Each scale consists of 11 statements, of which 10 statements are answered on a 6-point (zero to five) Likert scale and one statement on a 5-point scale. The items’ scores of each scale are added (after reversing some of the items) resulting in a total score ranging between 0 and 54, with a high score indicating high emotional and behavioral disruption from the environmental exposure in question.
Eight statements about how individuals with EI cope with their condition is included in VEHS. The statements have previously been used by Nordin, Andersson and Nordin (2010), and are based on the conceptualization into problem-focused and emotion-focused coping strategies by Lazarus and Folkman (1984). Of the eight statements, four of each of problem-focused and emotion-focused strategies are represented as intermingled items in the set of coping questions (Table 5). For each statement, the participants are instructed to rate to what extent the strategy is used by him/her to cope with the EI. The ratings are performed on a seven-point scale ranging from 'Not at all' (0) to 'To a very large extent' (6). The measures of emotion-focused and problem-focused coping strategies are the sum of the ratings for the four items addressing problem-focused and emotion-focused question, respectively, ranging from 0 to 24. Only individuals with EI are instructed to respond to these statements.

<table>
<thead>
<tr>
<th>Coping strategy</th>
<th>Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problem-focused</td>
<td>You ask others to explore the environment before you go to a place you suspect will affect your EI.</td>
</tr>
<tr>
<td></td>
<td>You seek information about your EI.</td>
</tr>
<tr>
<td></td>
<td>You seek health care for your EI.</td>
</tr>
<tr>
<td></td>
<td>You avoid environments you know will affect your EI.</td>
</tr>
<tr>
<td>Emotion-focused</td>
<td>You try to accept your situation with your EI and make the best of it.</td>
</tr>
<tr>
<td></td>
<td>You try to re-prioritize how important different things are to you.</td>
</tr>
<tr>
<td></td>
<td>You try not to think about your EI.</td>
</tr>
<tr>
<td></td>
<td>You make yourself feel better by eating, drinking or smoking.</td>
</tr>
</tbody>
</table>

Three questions are included in the VEHS questionnaire operationalizing emotional, instrumental and informational support: “To what extent do you think that... others show understanding for | you get help with information about | you get practical help with... your EI?” The questions are to be answered with regard to seven sources of support: ‘partner’, ‘other family members’, ‘friends’, ‘co-workers’, ‘health professionals’, ‘accountable authorities’ and ‘support groups’ according to a seven-point scale ranging from ‘Not at all’ (0) to ‘To a very large extent’ (6). The measures of emotional support, instrumental support and informational support are the mean of the ratings for the available sources of support for each support type, ranging between 0 and 6.

Participants
The sample size needed for the VEHS was based on the lowest expected prevalence for a specific environmental intolerance by sex, which was EI attributed to EMFs for men (1.1%; Hillert, Berglind, Arnetz, & Bellander, 2002). Precision was set to 0.55% (Naing, Winn, & Rusli, 2006) and with a level of confidence of 95% the sample size was calculated according to Daniel
(1999) to 1382 men. Since the sex distribution in Västerbotten was nearly equally distributed (50.3% men) in 2010 (Statistics Sweden) the amount of women needed was rounded up to the same number as for men. With an expected response rate of 60% the sample size was estimated to 4607 participants. Further on, since the present study is the first part of a longitudinal study, with expected accessibility of 90% and expected response rate of 60% at follow-up, the sample size was estimated to fully 8530 participants. This number was rounded up to the nearest hundred. Hence, in the first data collection (T1) 8600 adults (aged 18 to 79 years) from the county of Västerbotten were randomly selected from the population registry after stratification for sex and six age strata: 18 to 29 years (n=1990; males=1035, females=955), 30 to 39 years (n=1377; males=717, females=660), 40 to 49 years (n=1452; males=741, females=711), 50 to 59 years (n=1467; males=746, females=721), 60 to 69 years (n=1395; males=702, females=693) and 70 to 79 years (n=919; males=426, females=493). Eighty persons were excluded from the sample because they could not be reached by post, resulting in a sample size of 8520 persons. Of these, 3406 (40%) replied (Figure 2). The second data collection was done in 2013 (T2) for which respondents from the first data collection, who still were alive and lived in Västerbotten, received the follow-up questionnaire (n=3181), giving an accessibility rate of 93.4%. Of these, 2336 (73.4%) responded (Figure 2). For the third data collection, 2226 participants who were still alive and lived in Västerbotten remained. The accessibility rate was 95.3%. Of these, 1837 (82.5%) responded.
Procedure
The questionnaire, together with written information concerning confidentiality, intended use of the data and voluntariness, were sent to the participants by mail. A reminder was sent to non-responders after fully three weeks. An additional reminder and a new copy of the questionnaire were sent after another three weeks. The data collections, with the same procedure, were conducted between Mars and May on all three occasions.

Data management
Filled in questionnaires were scanned and a database was created from the responses. A data-entry verification test was performed to check the accuracy of the scanning procedure. One percent of the filled in paper questionnaires were randomly selected and each item in these questionnaires was compared with the corresponding entry in the database, revealing an error rate of 0.11%, 0.13% and 0.12% for the three data collections, respectively. The error rates were considered negligible. Cases in the database with missing values for all variables (participants had sent in the questionnaire without answering it) were removed, and were treated as non-responders.

In the scanning procedure each item with double response (i.e. two or more checkboxes checked instead of one) was given a certain code. All items
with this code was inspected and in cases where participants had “crossed out” their “faulty” answers or the scanner had interpreted a wrinkle in the paper as an answer, the scores were corrected in the database.

All missing values were given a specific code in the scanning procedure. However, the questionnaire contains certain questions which only should be answered by some (e.g. “Have you during the last four weeks experienced menstrual cramps or other problems with your periods” should only be answered by women). These missing values were recoded, enabling separation of correctly missing values and true missing values.

Range checks were performed for all entries in the database (e.g. the items of the variable ‘Age’ should range between 18-79 at T1). If some entry in the database did not comply with the range check it was inspected and corrected when possible (e.g. the respondent had reported the age of birth instead of age). A number of logic tests were performed (e.g. the number of years that a person has suffered from EI cannot exceed the age of the person) and if some record in the database did not pass the tests it was inspected and corrected when possible. All records that had been inspected because of not fulfilling the range checks, the logic tests or being coded as a double response, and that were not correctable were recoded as true missing values. True missing values were then imputed by multiple imputation for questionnaire instruments. After imputation the total scores of the different scales in the questionnaire were computed. The data management steps described were performed independently for each database in the separate data collections. In a final step the databases from the different data collections were merged into one.

Multiple imputation (MI) is a method to deal with missing data in which values are imputed in several copies of a database. The basic idea underlying MI is to replace each missing data with a set of values generated from its predictive distribution based on the observed data, and to generate multiple imputed datasets to account for the uncertainty of imputation (Schafer & Olsen, 2010). Hence, MI can be viewed as a device for representing missing data uncertainty, since it overcomes the issue of lost error variance seen in, for example, regression-based single imputation (Graham, 2009; Schafer, 1999). Imputed values from single regression-based imputation lie right on the regression line, but real data always deviate from the regression line by some amount.

There exists different methods for imputing data in MI, of which one is the Markov chain Monte Carlo (MCMC) method (Schunk, 2008). The MCMC algorithm creates a distribution of observed data for a variable with a collection of predefined variables as predictors. In a first step, missing data are simulated by pseudo-random draws from the distribution of observed data. The draws are called pseudo-random since it may be compared with rolling a biased dice, all numbers of the dice might turn up, but the
probability for each number turning up varies. That is, the probability of simulating a certain value depends on a probability function based on the distribution of the observed variables. In a next step, the distribution from which values are drawn is updated, including the simulated values from the first step. The procedure from the first step is now performed again, and the two steps are iterated long enough for a stationary distribution to appear. The final draws of the missing data constitute a single imputed dataset. The process is then repeated to create as many imputed datasets as desired. This stochastic procedure results in the imputed values to vary across each of the MI datasets.

Concerning how many imputations that are enough, a rule of thumb is that the number of imputations should at least equal the percent of missing values (Bodner, 2008). Each of the complete, imputed datasets is analyzed by standard methods, and the results are then pooled (i.e. combined) to produce single estimates and confidence intervals that incorporate missing data uncertainty. Measures of spread of values (such as standard error) are estimated by considering both the between-imputation and the within-imputation variance.

The variables in the VEHS which are part of different established scales (including HADS, SMBQ, PSS-10, CSS-SHR, NSS-11 and EMFSS-11) were considered for MI, assuming that the data were missing at random. The total percentage of missing values of the data that was intended to be imputed was 2.25% at T1, 2.26% at T2 and 3.44% at T3. For the VEHS database a MCMC procedure with 10 iterations was performed in which all variables were used as independent (predictors) variables including the demographic variables, reported physician diagnosed diseases/illnesses/conditions, self-reported EIs and symptoms, whereas the rest of the variables were used as both independent (predictors) and dependent (data to be imputed) variables. Based on the rather low proportion of missing values five imputations were performed, creating a database with six copies of the data (one original and five imputed datasets).

**Ethical considerations**

The VEHS did not intend to affect or harm the participants in any way. However, personal data were collected as well as questions concerning health, which might be perceived as an invasion of privacy. The participants were though informed that no unauthorized individuals would take part of this personal data, and that none of the individual participants could be identified or linked to particular results presented in research reports or manuscripts. Personal information such as personal names, addresses, and personal identity number (the Swedish national identificat) was substituted with an identification code in the database. The participants were informed about the content of the questionnaire and the purpose and benefits of the
Statistical analyses

MANCOVA is used to ask whether a linear combination of multiple outcome variables varies as a function of two or more grouping variables (factors) after adjusting for the effects of covariates. The adjusted linear combination of the outcome variables is the combination that would be obtained if all participants had the same value on the covariates. It is conceptually desirable when choosing to perform MANOVA/MANCOVA that there exists a pattern of relations among the outcome variables that could be explained in terms of a construct (Huberty & Petoskey, 2000). MANCOVA is basically a two-step process, in which the first step is to test whether there are differences in mean centroids between groups, and the second is to make follow-up tests to explain the result of the first step (Bray & Maxwell, 1982). Whereas the first step is relatively straightforward, there is some controversies about how to perform the second step. Historically a significant MANOVA has been followed with multiple ANOVAs for the dependent variables. These separate ANOVAs are insensitive to the interivariate correlation. If the researcher is interested in a linear combination of variables as they potentially represent some underlying construct different follow-up tests have to be performed to explain how this linear combination separates between the groups (Bray & Maxwell, 1982; Grice & Iwasaki, 2007). Discriminant analysis does exactly this and is preferentially used as a post-hoc test in circumstances such as this. Hence, discriminant analysis describes the resultant MANOVA/MANCOVA grouping variable effects.

Discriminant analysis has as mathematical objective to weight and linearly combine information from a set of variables in a manner that forces groups to be as distinct as possible (Brown & Wicker, 2000). Discriminant analysis can be used as a post-hoc method for interpreting significant MANCOVAs (Bray & Maxwell, 1982; Grice & Iwasaki, 2007). This method is appropriate when the hypothesis is that a combination of a set of variables represent an underlying construct or dimension. The aim of discriminant analysis as a post-hoc method to MANCOVA is elucidating the individual contributions of the original variables to the underlying dimension (Borgen & Seling, 1978). When it comes to interpretation of discriminant analysis, three important concepts are essential: discriminant coefficients, discriminant function and discriminant scores (Brown & Wicker, 2000). Discriminant analysis calculates weights (the discriminant coefficients) for scores on each discriminator variable that reflect the degree to which scores on that variable differ among the groups being discriminated. The
Discriminant coefficients represent the unique contribution of a single variable to the combination of discriminator variables (Bray & Maxwell, 1982). The discriminant coefficients with the most weight indicate the discriminator variables on which the groups differ most. To eliminate scaling differences among the discriminator variables standardized discriminant coefficients, which have been converted to z scores (i.e. $m=0, sd=1$), can be used. Discriminant analysis forms one or more weighted linear combinations of discriminator variables called discriminant functions. The discriminant function gives a discriminant score which is calculated by multiplying the coefficients weights for each discriminator variable with an individual’s separate score for that particular discriminator variable, then calculating the sum of each of these for each individual (Grice & Iwasaki, 2007). The discriminator scores are used to calculate the average discriminant score of the cases belonging to a group.

**Logistic regression** is a method suitable when an outcome variable is dichotomous (e.g. sickness present/absent) and the aim is to determine the odds of falling into one of the two outcome categories based on qualitative and/or quantitative characteristics (e.g. life-style factors such as smoking and exercise, personality factors, and psychological/social factors) (Imrey, 2000). The non-linear model produced by logistic regression is based on the natural logarithm of the odds (i.e. occurrence/non-occurrence) (Peng, Lee, & Ingersoll, 2002). The goal of logistic regression is to model the best combination of predictors to maximize the likelihood of obtaining the observed outcome frequencies (Tabachnick & Fidell, 2007). Multinomial logistic regression is an extension of binary logistic regression and is suitable when the outcome variable is categorical with more than two levels. Model evaluation is performed by comparing the model with a constant only model (i.e. the most simple and worst fitting model).
Study 1

Overlap in prevalence between various types of environmental intolerance

Aims and methods
Due to similarities between the different types of EI it seems plausible that they are associated in some way. If this is the case the overlap between the conditions would be larger than by chance. Previous studies have found this to be the case between pair of EIs (Carlsson, Karlson, Ørbaek, Osterberg, & Ostergren, 2005; Hillert, Berglind, Arnets, & Bellander, 2002; Levallois, Neutra, Lee, & Hristova, 2002). However, no previous study has simultaneously investigated the overlap between EI attributed to odorous/pungent chemicals, certain buildings, EMFs and sounds, which motivated the present study. The question to be answered was whether the overlap in prevalence between these four types of EI was larger than the expected overlap if no association existed between them. Data from T1 were used to classify cases of EI as either self-reported cases or diagnosed cases.

Prevalence values for the four types of EI (with or without overlaps) were calculated as proportions expressed as percentages of the sample, or of subsamples of a particular EI. The Wilson method was used to calculate 95% confidence intervals (Altman et al., 2000). Chi-square tests were performed to assess whether the overlaps between the different types of EI were greater than by chance. Yate’s (continuity) correction was used when at least one cell had an expected count less than 5.

Results and discussion
Proportions of the sample reporting at least one, two or three types of EI are reported in Table 6. The prevalence of, and co-prevalence between the specific types of EI in the sample are presented in Figure 3, in which co-prevalence is obtained by adding the areas shared by the different EIs of interest (e.g. the co-prevalence between self-reported EI attributed to chemicals and buildings, which is 2.9%, is obtained by adding 1.8, 0.3, 0.2 and 0.6).

Table 6. Proportion of the sample reporting at least one, two or three types of environmental intolerance (EI).

<table>
<thead>
<tr>
<th></th>
<th>Self-reported EI</th>
<th>Diagnosed EI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence % (n)</td>
<td>95% CI</td>
</tr>
<tr>
<td>At least one EI</td>
<td>21.6 (736)</td>
<td>20.3-23.0</td>
</tr>
<tr>
<td>At least two EI</td>
<td>5.8 (197)</td>
<td>5.1-6.6</td>
</tr>
<tr>
<td>At least three EI</td>
<td>1.3 (44)</td>
<td>1.0-1.7</td>
</tr>
</tbody>
</table>

The overlaps between subsamples of EI attributed to chemicals, buildings, EMFs and sounds and one (of any kind), two or three other types of EIs are
presented in Table 7. Figures 4–7 illustrate the distribution of the overlaps in subsamples of EI attributed to chemicals, buildings, EMFs and sounds, respectively.

![Venn-diagrams](image)

Figure 3. Venn-diagrams representing the overlap, n (%), between self-reported and diagnosed cases of EI attributed to chemicals, certain buildings, EMFs and sounds.

The overlaps between subsamples of EI attributed to chemicals, buildings, EMFs and sounds and one (of any kind), two or three other types of EIs are presented in Table 7. Figures 4–7 illustrate the distribution of the overlaps in subsamples of EI attributed to chemicals, buildings, EMFs and sounds, respectively.

### Table 7. Overlap, % (95% CI), between subsamples of a specific environmental intolerance (EI) with one, two or three of the other types of EI.

<table>
<thead>
<tr>
<th>Overlaps with</th>
<th>Type of intolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chemicals</td>
</tr>
<tr>
<td></td>
<td>Self-reported</td>
</tr>
<tr>
<td>At least one other EI</td>
<td>39.9 (35.3-44.6)</td>
</tr>
<tr>
<td>At least two other EIs</td>
<td>9.7 (7.2-12.9)</td>
</tr>
<tr>
<td>All other EIs</td>
<td>1.4 (0.7-3.1)</td>
</tr>
</tbody>
</table>
Figure 4. Venn diagrams representing the distribution of and overlap, n (%), between environmental intolerance (EI) attributed to buildings, EMFs and sounds in self-reported and diagnosed cases of EI attributed to chemicals.

Figure 5. Venn diagrams representing distribution of, and the overlap, n (%), between environmental intolerance (EI) attributed to chemicals, EMFs and sounds in self-reported and diagnosed cases of EI attributed to buildings.

Figure 6. Venn diagrams representing the distribution of, and overlap, n (%), between, EI attributed to chemicals, buildings and sounds in self-reported and diagnosed cases of EI attributed to EMFs.
Figure 7. Venn diagrams representing the distribution of, and overlap, n (%), between environmental intolerance (EI) attributed to chemicals, buildings and EMF in self-reported and diagnosed cases of EI attributed to sounds.

Table 8 and 9 present the results from the Chi-square tests between the different types of self-reported and diagnosed cases of EI, respectively.

Table 8. Results from Chi-square tests and observed and expected overlaps between the different types of self-reported environmental intolerance.

<table>
<thead>
<tr>
<th>Environmental intolerance</th>
<th>Chemicals</th>
<th>Certain buildings</th>
<th>EMFs</th>
<th>Sounds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed/ Expected</td>
<td>Observed/ Expected</td>
<td>Observed/ Expected</td>
<td>Observed/ Expected</td>
</tr>
<tr>
<td>Chemicals</td>
<td>96/19.5</td>
<td>359.2***</td>
<td>30/10.7</td>
<td>40.4***</td>
</tr>
<tr>
<td>Certain buildings</td>
<td></td>
<td>26/4.3</td>
<td>117.6***</td>
<td>38/15.2</td>
</tr>
<tr>
<td>EMFs</td>
<td></td>
<td></td>
<td>28/8.4</td>
<td>51.6***</td>
</tr>
</tbody>
</table>

Note. ***=p< 0.001

Table 9. Results from Chi-square tests and observed and expected overlaps between the different types of diagnosed environmental intolerance.

<table>
<thead>
<tr>
<th>Environmental intolerance</th>
<th>Chemicals</th>
<th>Certain buildings</th>
<th>EMFs</th>
<th>Sounds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed/ Expected</td>
<td>Observed/ Expected</td>
<td>Observed/ Expected</td>
<td>Observed/ Expected</td>
</tr>
<tr>
<td>Chemicals</td>
<td>25/1.5</td>
<td>357.5***</td>
<td>6/0.5</td>
<td>52.8***</td>
</tr>
<tr>
<td>Certain buildings</td>
<td></td>
<td>4/0.2</td>
<td>53.4***</td>
<td>10/1.3</td>
</tr>
<tr>
<td>EMFs</td>
<td></td>
<td></td>
<td>2/0.4</td>
<td>2.8NS</td>
</tr>
</tbody>
</table>

Note. ***=p< 0.001. NS = non-significant. Yate’s continuity correction is used in calculating $\chi^2$-tests.

The results revealed that the overlap between all types of EI was greater than predictions based on coincidence, except for the overlap between diagnosed cases of EI attributed to EMFs and sounds. The overlaps between different types of EI may be an indication of sharing the same or similar underlying mechanism, or at least that the environmentally intolerant persons share some predisposition to acquire the conditions.
Study 2
Coping and social support in environmental intolerance

Aims and methods
Both coping and social support are related to psychological well-being as well as physical health (Penley, Tomaka, & Wiebe, 2002; Siedlecki, Salthouse, Oishi, & Jeswani, 2014; Uchino, 2009). However, the literature is sparse concerning how coping and social support can change the outcome of EI.

The present study investigated whether individuals with EI cope/perceive social support differently depending on how much they are emotionally and behaviorally disrupted by a certain environment, and whether individuals who had recovered from EI at follow-up (from a state of intolerance at baseline) used a different combination of coping strategies and social support at baseline than those who had not recovered. Cases of EI attributed to chemicals, EMFs and sounds were identified by self-report. If an individual had reported several EIs, classification into EI attributed to either chemicals, EMFs or sounds was done in accordance with their answer to the main intolerance question.

To answer the first research question, data from T1 were used. The scores on the CSS-SHR, EMFSS-11 and NSS-11 were used to divide individuals with EI attributed to chemicals, EMFs and sounds into high (n=183) and low (n=118) emotionally and behaviorally disrupted groups. To answer the second research question the cases of EI at T1 were divided into non-recovered (n=145)/recovered (n=68) groups (constituting the factor ‘prognosis’ in the MANCOVA) according to whether they still reported the intolerance or not at T2. MANCOVAs were used to answer the two research questions with problem-focused and emotion-focused coping, as well as emotional, instrumental and informational support as dependent variables. Discriminant analyses were used as post-hoc method. One way analyses of variance (ANOVAs) were used to analyze the group differences of the discriminator scores.

Results and discussion
The MANCOVA, with which the main effect of intolerance severity was tested, showed a significant, Λ = 0.85, F(5, 293) = 10.43, p < 0.001, and large effect, multivariate η²= 0.15. Univariate means and standard deviations and the raw and standardized discriminant function coefficients for the discriminator factors are reported in Table 10. The coefficients indicate that problem-focused coping contribute most to group (i.e. low and high intolerance severity) discrimination on the discriminant function and in a positive direction. Instrumental support, informational support and
emotion-focused coping are moderately related to group discrimination, in which instrumental support contribute in a positive direction, and informational support and emotion-focused coping in a negative direction. Emotional support contributed only slightly to group discrimination on the discriminant function and did so in a negative direction.

Table 10. Means, standard deviations, and discriminant function coefficients for intolerance severity groups (Low/High) on the dependent variables.

<table>
<thead>
<tr>
<th>Severity</th>
<th>M (SD)</th>
<th>Raw discriminant function coefficients</th>
<th>Standardized discriminant function coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emotion-focused coping</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>10.65 (4.65)</td>
<td>-0.069</td>
<td>-0.312</td>
</tr>
<tr>
<td>High</td>
<td>11.04 (4.47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Problem-focused coping</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>6.08 (4.41)</td>
<td>0.218</td>
<td>1.050</td>
</tr>
<tr>
<td>High</td>
<td>9.95 (5.24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional support</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>3.20 (1.61)</td>
<td>-0.068</td>
<td>-0.101</td>
</tr>
<tr>
<td>High</td>
<td>3.50 (1.42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informational support</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1.86 (1.90)</td>
<td>-0.219</td>
<td>-0.372</td>
</tr>
<tr>
<td>High</td>
<td>2.23 (1.79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Instrumental support</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>2.11 (1.77)</td>
<td>0.281</td>
<td>0.463</td>
</tr>
<tr>
<td>High</td>
<td>2.59 (1.68)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 8. Mean (SE) of the discriminant scores for the low and high intolerance severity groups.

Figure 8 illustrates the group averages of the discriminant scores. The results from the discriminant analysis indicate that the low and high sensitivity groups were optimally separated by positive values on problem focused coping and instrumental support and negative values on
informational support, emotion focused coping and emotional support, for which the higher the value of the discriminant score, the more likely the individual will be classified as belonging to the high sensitivity group.

The MANCOVA, with which the main effect of prognosis was tested, showed a significant, $\Lambda = 0.93$, $F(5, 206) = 2.99$, $p = 0.012$, and medium effect, multivariate $\eta^2 = 0.07$. Univariate means and standard deviations and the raw and standardized discriminant function coefficients for the discriminant factors are reported in Table 11. The coefficients indicate that instrumental support and problem-focused coping contributed highly to group discrimination on the discriminant function in a positive direction. Emotional support and informational support are moderately related to group discrimination on the function in a negative direction. Emotion-focused coping contributed slightly to group discrimination on the discriminant function in a negative direction.

<table>
<thead>
<tr>
<th>Prognosis</th>
<th>M (SD)</th>
<th>Raw discriminant function coefficients</th>
<th>Standardized discriminant function coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Raw</td>
<td>Standardized</td>
</tr>
<tr>
<td></td>
<td></td>
<td>discriminant function</td>
<td>discriminant function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>coefficients</td>
<td>coefficients</td>
</tr>
<tr>
<td>Emotion-focused</td>
<td>Non-recovered</td>
<td>10.91 (4.53)</td>
<td>-0.039</td>
</tr>
<tr>
<td></td>
<td>Recovered</td>
<td>10.76 (4.52)</td>
<td></td>
</tr>
<tr>
<td>Problem-focused</td>
<td>Non-recovered</td>
<td>8.79 (5.23)</td>
<td>0.134</td>
</tr>
<tr>
<td></td>
<td>Recovered</td>
<td>7.00 (4.70)</td>
<td></td>
</tr>
<tr>
<td>Emotional support</td>
<td>Non-recovered</td>
<td>3.40 (1.49)</td>
<td>-0.335</td>
</tr>
<tr>
<td></td>
<td>Recovered</td>
<td>3.31 (1.45)</td>
<td></td>
</tr>
<tr>
<td>Informational support</td>
<td>Non-recovered</td>
<td>2.21 (1.84)</td>
<td>-0.340</td>
</tr>
<tr>
<td></td>
<td>Recovered</td>
<td>1.88 (1.89)</td>
<td></td>
</tr>
<tr>
<td>Instrumental support</td>
<td>Non-recovered</td>
<td>2.58 (1.69)</td>
<td>0.822</td>
</tr>
<tr>
<td></td>
<td>Recovered</td>
<td>2.00 (1.79)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 9 illustrates the group averages of the discriminant scores. The results from the discriminant analysis indicate that the non-recovered and recovered groups were optimally separated by positive values on instrumental support and problem-focused coping, and negative values on informational support, emotional support and emotion-focused coping, for which the higher the value of the discriminant score, the more likely the individual will be classified as belonging to the non-recovered group.
Furthermore, the prognosis groups were split into high and low intolerance severity. The results revealed that prognosis had a significant effect for the individuals with high intolerance severity; \( F(1, 127)=6.74, p = 0.011 \), but not for those with low intolerance severity; \( F(1, 82)=0.04, p = 0.85 \). Figure 10 illustrates the difference between the prognosis groups split into high/low intolerance severity of the discriminant scores.

Results from this study indicate that combinations of different coping strategies and social support is of importance in recovering from EI, at least
for those individuals who are highly emotionally and behaviorally disrupted by a certain environmental exposure. Particularly, lower levels of instrumental support and problem-focused coping together with higher levels of emotion-focused coping strategies, emotional and informational support were of importance for recovery in the present study. High degrees of problem-focused coping and instrumental support could potentially be balanced with emotion-focused strategies, emotional and informational support.
Study 3

Environmental intolerance and mental ill-health – Which comes first?

Aims and methods
Previous studies have found associations between EI and mental ill-health such as stress, anxiety and depression (Johansson, Nordin, Heiden, & Sandström, 2010; Magnavita, 2015; Milenković & Paunović, 2015; Nordin, Körning Ljungberg, Claeson, & Neely, 2013; Osterberg, Persson, Karlsson, Carlsson Eek, & Orbaek, 2007). However, the number of prior prospective studies investigating the temporality between the two is sparse and none has investigated the possibility of a bidirectional relationship. The aim of the present study was to investigate whether mental ill-health (in the form of perceived stress, anxiety, depression and burnout) is a predictor of developing EI, and whether the opposite holds; EI being a predictor of developing anxiety, depression or burnout. Data from T1 and T2 of the VEHS were used. Binary variables were constructed by dividing individuals who self-reported not having EI attributed to chemicals, buildings or sounds at T1 based on whether they reported the current EI at T2 or not (developed EI – 1=yes, 0=no). These variables were then used as the outcome variables in logistic regression analyses. Crude odds ratios were calculated using the global score of the SMBQ, HADS-A, HADS-D and PSS-10 as continuous predictors (assessed at T1) in separate logistic regression analyses for the binary outcome variables developed EI attributed to chemicals, buildings and sounds, respectively. Adjusted odds ratios were calculated for which sex, age, co-occurrence of EI attributed to another source and asthma (the latter not for EI attributed to sounds) were controlled. Further on, dichotomous variables (1=yes, 0=no) were constructed based on cutoff values of the SMBQ (≥4.47), HADS-A (>8) and HADS-D (>8) indicating caseness of burnout, anxiety and depression at T1, respectively. Separate logistic regression analyses were then performed with these variables as predictors for the outcome variables developed EI attributed to chemicals, buildings and sounds.

Changing perspective, to answer the question whether EI predicts mental illness, binary variables (developed burnout, anxiety and depression) were constructed for which the value 1 was assigned to cases fulfilling the criteria: SMBQ < 4.47 at T1 and SMBQ ≥ 4.47 at T2, HADS-A ≤ 8 at T1 and HADS-A > 8 at T2 and HADS-D ≤ 8 at T1 and HADS-D > 8 at T2, respectively. The value 0 was assigned to cases who had values below the cut-off scores at both T1 and T2. The dichotomous predictors EI attributed to chemicals, certain buildings and sounds, as well as the continuous predictors NSS-11 and CSS-SHR (all assessed at T1) were used in logistic regression analyses with the outcome variables developed burnout, anxiety and depression, respectively.
Results and discussion
Of the 2336 respondents at follow-up the number of developed cases of EI attributed to chemicals, certain buildings and sounds were 115, 64 and 102, respectively. Results from the logistic regression analyses examining whether mental-illness predicted the development of EI are presented in Tables 12 and 13. The results suggest that burnout, anxiety, depression and perceived stress are risk factors of EI attributed to chemicals and sounds, but not to EI attributed to certain buildings. Caseness of burnout is a risk factor of EI attributed to chemicals and sounds, and caseness of anxiety and depression are risk factors of EI attributed to chemicals only. None of the psychopathological predictors reached significance for EI attributed to certain buildings.

Table 12. Results from logistic regression analyses with the continuous predictors burnout (SMBQ), anxiety (HADS-A), depression (HADS-D) and perceived stress (PSS-10), and the outcome variables developed environmental intolerance attributed to chemicals, certain building and sounds, respectively.

<table>
<thead>
<tr>
<th></th>
<th>Crude OR</th>
<th>95% CI</th>
<th>P-value</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemicals</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMBQ</td>
<td>1.40</td>
<td>1.20-1.64</td>
<td>&lt;0.001</td>
<td>1.31</td>
<td>1.11-1.55</td>
<td>0.006</td>
</tr>
<tr>
<td>HADS-A</td>
<td>1.09</td>
<td>1.04-1.14</td>
<td>0.002</td>
<td>1.06</td>
<td>1.01-1.12</td>
<td>0.046</td>
</tr>
<tr>
<td>HADS-D</td>
<td>1.10</td>
<td>1.05-1.16</td>
<td>&lt;0.001</td>
<td>1.10</td>
<td>1.04-1.16</td>
<td>0.004</td>
</tr>
<tr>
<td>PSS-10</td>
<td>1.05</td>
<td>1.02-1.08</td>
<td>0.004</td>
<td>1.03</td>
<td>1.00-1.07</td>
<td>0.037</td>
</tr>
<tr>
<td><strong>Certain buildings</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMBQ</td>
<td>1.24</td>
<td>1.01-1.54</td>
<td>0.088</td>
<td>1.10</td>
<td>0.88-1.38</td>
<td>0.804</td>
</tr>
<tr>
<td>HADS-A</td>
<td>1.08</td>
<td>1.01-1.15</td>
<td>0.066</td>
<td>1.04</td>
<td>0.97-1.11</td>
<td>0.828</td>
</tr>
<tr>
<td>HADS-D</td>
<td>1.05</td>
<td>0.97-1.13</td>
<td>0.262</td>
<td>1.02</td>
<td>0.94-1.11</td>
<td>0.631</td>
</tr>
<tr>
<td>PSS-10</td>
<td>1.05</td>
<td>1.01-1.09</td>
<td>0.076</td>
<td>1.03</td>
<td>0.99-1.07</td>
<td>0.852</td>
</tr>
<tr>
<td><strong>Sounds</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMBQ</td>
<td>1.58</td>
<td>1.33-1.87</td>
<td>&lt;0.001</td>
<td>1.47</td>
<td>1.23-1.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HADS-A</td>
<td>1.12</td>
<td>1.06-1.18</td>
<td>&lt;0.001</td>
<td>1.09</td>
<td>1.03-1.15</td>
<td>0.002</td>
</tr>
<tr>
<td>HADS-D</td>
<td>1.12</td>
<td>1.06-1.19</td>
<td>&lt;0.001</td>
<td>1.11</td>
<td>1.05-1.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PSS-10</td>
<td>1.07</td>
<td>1.03-1.10</td>
<td>&lt;0.001</td>
<td>1.05</td>
<td>1.02-1.09</td>
<td>0.004</td>
</tr>
</tbody>
</table>

† Adjusted for age, sex, asthma, and EI attributed to another source for EI attributed to chemicals and buildings, and adjusted for age, sex and EI attributed to another source for EI attributed to sounds.

a Adjusted for multiple comparisons according to Holm’s correction.

Table 13. Results from logistic regression analyses with the categorical predictors burnout (SMBQ≥4.47), anxiety (HADS-A > 8), and depression (HADS-D > 8), and the outcome variables developed environmental intolerance attributed to chemicals, certain building and sounds, respectively.

<table>
<thead>
<tr>
<th></th>
<th>Chemicals</th>
<th>Certain buildings</th>
<th>Sounds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>P-value</td>
</tr>
<tr>
<td><strong>Burnout</strong></td>
<td>2.14</td>
<td>1.24-3.68</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
<td>2.14</td>
<td>1.31-3.50</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td>2.61</td>
<td>1.39-4.88</td>
<td>0.006</td>
</tr>
</tbody>
</table>

a Adjusted for multiple comparisons according to Holm’s correction.

The number of cases that had developed burnout, anxiety and depression between T1 and T2 were 134, 137 and 88, respectively. Results from the
logistic regression analyses examining whether EI attributed to chemicals, buildings and sounds predicted the development of burnout, anxiety or depression are presented in Tables 14 and 15. EI attributed to chemicals or sounds were not predictors of burnout, anxiety or depression. EI attributed to certain buildings was found to be a risk factor of burnout only. Noise sensitivity (assessed with the NSS-11) and chemical sensitivity (assessed with the CSS-SHR) were not risk factors of anxiety, depression or burnout when controlled for age and sex.

Table 14. Results from logistic regression analyses with the categorical predictors EI to chemicals, certain buildings and sounds, and developed burnout (SMBQ < 4.47 at T1, SMBQ ≥ 4.47 at T2), anxiety (HADS-A =< 8 at T1, HADS-A > 8 at T2) and depression (HADS-D =< 8 at T1, HADS-D > 8 at T2) as outcome variables.

<table>
<thead>
<tr>
<th></th>
<th>Burnout</th>
<th>Anxiety</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>EI</td>
<td>OR</td>
<td>95% CI</td>
<td>P-valuea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemicals</td>
<td>1.24</td>
<td>0.71-2.19</td>
<td>0.894</td>
</tr>
<tr>
<td>Certain buildings</td>
<td>2.35</td>
<td>1.22-4.53</td>
<td>0.033</td>
</tr>
<tr>
<td>Sounds</td>
<td>1.14</td>
<td>0.60-2.16</td>
<td>0.700</td>
</tr>
</tbody>
</table>

a Adjusted for multiple comparisons according to Holm’s correction.

Table 15. Results from logistic regression analyses with the continuous predictors NSS-11 and CSS-SHR, and developed burnout (SMBQ < 4.47 at T1, SMBQ ≥ 4.47 at T2), anxiety (HADS-A =< 8 at T1, HADS-A > 8 at T2) and depression (HADS-D =< 8 at T1, HADS-D > 8 at T2) as outcome variables.

<table>
<thead>
<tr>
<th></th>
<th>Burnout</th>
<th>Anxiety</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>EI</td>
<td>OR</td>
<td>95% CI</td>
<td>P-valuea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSS-SHR</td>
<td>1.01</td>
<td>0.99-1.03</td>
<td>0.467</td>
</tr>
<tr>
<td>NSS-11</td>
<td>1.03</td>
<td>1.00-1.05</td>
<td>0.044</td>
</tr>
<tr>
<td>CSS-SHR</td>
<td>1.00</td>
<td>0.98-1.02</td>
<td>0.848</td>
</tr>
<tr>
<td>NSS-11</td>
<td>1.02</td>
<td>0.99-1.04</td>
<td>0.354</td>
</tr>
<tr>
<td>CSS-SHR</td>
<td>0.99</td>
<td>0.96-1.02</td>
<td>0.402</td>
</tr>
<tr>
<td>NSS-11</td>
<td>1.02</td>
<td>1.00-1.05</td>
<td>0.210</td>
</tr>
</tbody>
</table>

† Adjusted for age and sex
a Adjusted for multiple comparisons according to Holm’s correction.

An interpretation of the results is that there seems to be different mechanisms at play when it comes to EI attributed to certain buildings, in comparison to EI attributed to chemicals and sounds. Mental illness seems to precede the development of EI attributed to chemicals and sounds, whereas it follows (in the form of burnout) the development of EI attributed to buildings.
Study 4

Who recovers from environmental intolerance?

Aims and methods

Etiological theories of EI suggest that increased responsiveness to an environmental stimulus may spread or generalize into other domains (Bell, Miller, & Schwartz, 1992). Hence, a specific type of EI, e.g. EI attributed to sounds, may generalize into EI attributed to sounds and chemicals. Further on, EI attributed to chemicals is according to some definitions stated as a chronic condition and EI attributed to sounds a rather stable personality trait (Lacour et al, 2005; Zimmer & Ellermeier, 1999). To date few studies have reported the prognosis of EI, and in those conducted patients or severe cases have been studied showing poor recovery and improvement rates (Bailer, Witthöft, & Rist, 2008; Edvardsson et al., 2008). No previous study has investigated the probability of a specific EI to spread into generalized EI. This motivated the present study in which the following research questions were asked: i) What are the chances for recovery from a specific EI among the general population during a six-year period? ii) What are the chances of a specific EI to spread into generalized EI during the same period? iii) Are levels of stress, burnout, anxiety, depression and emotional/behavioral disruption from environmental exposure able to predict recovery from EI?

Participants self-reporting EI attributed to chemicals, certain buildings, EMFs or sounds at T1 were included in the study. Depending on whether they: i) still reported the same type of EI, but no other type of EI, ii) reported the same EI plus one or more additional types of EI, iii) did not report the specific EI or any other type of EI, or iv) if they did not report the same EI as at T1 but another type, they were divided into different states (specific EI, general EI, recovered, or other EI) at T2 and T3. A state transition diagram was constructed to be able to track the participants’ transitions between states. Probability estimates were based on two types of calculations. The first calculation considered only those individuals who responded to the questionnaire on all three occasions. The second calculation was based on all participants from T1, hence taking attrition into account. Since it is possible to reach a certain state at T3 via different trajectories, the probabilities of each transition along a certain trajectory were multiplied to obtain the probability of taking this particular trajectory to reach the specific state. The probabilities of different trajectories for reaching the state in question were then added to obtain the total sample probability (independent of trajectories) for being in that state at T3.

Multinomial logistic regression was performed to predict recovery and spreading with the SMBQ, HADS-A, HADS-D, PSS-10, CSS-SHR, EMFSS-11 and NSS-11 as predictors.
Results and discussion
Of the 539 participants reporting a specific type of EI at T1, 282 remained at T3. The transition between states (recovered, specific EI, general EI and other EI) for these individuals are illustrated in Figure 13. The probability of recovering from EI at T3 from a state of specific EI at T1 was 44.3% according to the probability calculation based on the participants that remained in the study at T3. The probability of specific EI to spread into general EI was 12.8% for the same set of respondents. When the probability was calculated based on all participants from T1, 23.2% recovered and 6.7% reported general EI. The probability of relapse was 3.9%.

Figure 13. Tree diagram representing the probability space of transitions between states. The squares represent states at the three time points, and ovals represent subsamples remaining from a previous time point. Numbers aligning lines represent probabilities. Numbers within parentheses represent the number of individuals with EI attributed to chemicals, buildings, EMFs and sounds (in that order).

The multinomial logistic regression analysis revealed best model fit for the model containing the predictors CSS-SHR, SMBQ and PSS-10 (Table 15). The only significant predictor of recovery in this model was CSS-SHR, in which one step increase of the scale reduced the odds of recovering 0.94 times. PSS-10 and SMBQ were significant predictors of general EI. One step increase of the PSS-10 increased the odds of spreading 1.12 times. One step increase in the SMBQ global score decreased the odds of spreading 0.61 times.
Table 15. Results from the multinomial logistic regression presenting the predictors in the model with the best model fit.

<table>
<thead>
<tr>
<th></th>
<th>Recovered versus specific EI (reference)</th>
<th>General versus specific EI (reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>PSS-10</td>
<td>1.04</td>
<td>0.99-1.10</td>
</tr>
<tr>
<td>SMBQ</td>
<td>0.88</td>
<td>0.66-1.16</td>
</tr>
<tr>
<td>CSS-SHR</td>
<td>0.94</td>
<td>0.92-0.97</td>
</tr>
</tbody>
</table>

The results from the present study indicate that the prognosis of EI is fairly good. In a six-year period fully one out of five of the individuals with a specific EI recovered. However, being recovered is not a stable state. The probability to relapse (going from a state of specific EI to the recovered state and then back to the state of specific EI) was 3.9%. The probability of spreading from a specific EI into general EI was 6.7%. Hence, the course of EI is difficult to predict. Additionally, when interpreting the results which are based on the general population it is important to remember that they may not hold for patients with EI. The severity of the condition (e.g. how much it impacts on daily functioning) probably varies considerably when identifying cases by self-report, and logically, less severe cases may have a higher chance of recovery. Consequently, the chances of recovery are probably smaller for patients, which also has been found by Edvardsson et al. (2008).

The less emotionally and behaviorally disrupted a person was by odorous chemicals at T1, the higher were the odds of recovery. According to etiological theories of EI, medically unexplained symptoms (such as increased sensitivity to sensory stimuli) may result in increased worry about, and attention toward, environmental factors. This hypervigilance towards environmental exposure may set a viscous circle into motion in which symptoms aggravate and obstruct recovery. Therapies focusing on reducing the emotional and behavioral reactions towards environmental exposure might be helpful.
General discussion

Study 1 showed that the overlap between different types of EI is extensive. This raised the question as to whether the different types of EI share the same underlying mechanisms or whether the afflicted individuals share some predisposition of acquiring these conditions. One etiological theory of EI is the neural sensitization theory. According to this theory a specific type of EI may spread into generalized EI. This spreading phenomenon is called cross-sensitization in which the neuronal response is amplified, not only in response to the original stimulus (e.g. an odor), but also to a stimulus of another domain or modality (e.g. a sound). The neural sensitization theory further claims that the heightened susceptibility to the sensitized stimulus persists indefinitely. In Study 4 the prognosis of EI was studied. About 7% of the individuals with a specific type of EI had in six years developed a generalized EI. Hence, spreading seems to exist. Hypervigilance to environmental threat information may contribute to this spreading phenomenon. However, when it comes to duration of EI fully one out of five recovered, which would be an argument against the neural sensitization theory. Though, relapse was quite common (present in 3.9%), which obstructs total rejection of the neural sensitization theory. Additionally, in Study 4, factors important for recovering from EI were studied. The more emotionally and behaviorally disrupted the individuals were, the less likely they were to recover. In Study 2 the importance of coping and social support in recovering from EI was studied. Combinations of coping and social support differed between the individuals who recovered from EI and those who did not recover. Those individuals who did not recover perceived more instrumental support (i.e. more practical help) and/or were more prone use problem-focused coping strategies (i.e. seek healthcare, seek information, avoid a certain environment, and ask others to explore a certain environment) in combination with, to a lesser extent use emotion-focused strategies (i.e. accepting the situation and do the best out of it, trying to reprioritize, trying not to think about it, and making themselves feel better by eating, drinking or smoking) and/or perceived less emotional and/or informational support, in comparison with EI individuals who did recover. However, a similar difference in combinations of coping strategies and social support was seen in high versus low severity groups. Therefore, the sample was split by high and low severity (i.e. emotional and behavioral disruption), showing that the differences found in combinations of coping and social support between the recovered versus the non-recovered groups were due to differences within the high severity group. In merging the results from Studies 4 and 2, those individuals who to a lesser degree were emotionally and behaviorally disrupted by an environmental exposure had a greater
chance of recovering. However, with the right coping strategies and social support even those individuals who were highly disrupted by the exposure could recover. In Study 3 stress, anxiety, depression and burnout were found to be risk factors of EI attributed to chemicals and sounds, but not for EI attributed to buildings. Conversely, EI attributed to chemicals, buildings and sounds were not found to be risk factors of anxiety or depression. EI attributed to buildings was found to be a significant predictor of burnout, whereas this was not true for EI attributed to chemicals or sounds. The causality of EI attributed to buildings, with this result, seems to be separate from the causality of EI attributed to chemicals and sounds, since in the former case psychological factors were not found to be causative factors, but in the latter case they were. However, there might be other factors, not included in the VEHS, such as psychosocial occupational factors that are of more relevance for EI attributed to buildings. Altogether, the studies indicate that psychological factors are relevant both concerning the causality of and the recovery from EI.

**Some ideas about identifying cases of EI**

The group of EI individuals is heterogeneous. First of all the individuals with EI differ depending on what kind of environmental exposure they react to. This difference is not only observed between different types of EI, but also within the separate types of EI. For example, within a group of individuals reporting EI attributed to EMFs, some of the participants comment that they only get symptoms from handheld devices, others report symptoms from different electrical sources of light (e.g. VDUs, fluorescent tubes), others report symptoms from EMFs emitted by digital wireless systems, and some individuals report symptoms from all of the sources mentioned. In terms of sensation these different sources might be processed by different senses. In the case of handheld devices, it may actually be the vibrations from the electrical equipment rather than the EMFs that lead to symptoms. In the case of VDUs and fluorescent tubes, symptoms might be caused by the light per se (which actually is electromagnetic radiation), processed by our sense of vision. In the third case, in which individuals report symptoms from digital wireless systems, potentially, EMF energy could lead to a temperature rise in body tissue causing symptoms, hence processed by our thermoreceptors (Wessapan & Rattanadecho, 2016). Taking this into consideration one way to identify cases could be by the sense (or modality) that processes the environmental exposure information. If, for a moment, disregarding the cognitive or psychological processes involved in EI (which in practice is impossible), solely the different types of sources of exposure might lead to different symptoms and symptom profiles. Since the objective of this thesis not was to investigate either the exposure leading to symptoms or the physical symptoms and symptom profiles, but instead how
psychological factors effects the risk of developing, as well as the chances of recovering from EI, this might not be crucial to take into account. However, to be able to fully understand the causality of EI, and the individuals suffering from the condition, this is suggested to be of importance.

Not only do individuals with EI react to different kinds of exposures in the environment, and show different types of symptom patterns, they also vary concerning attribution style. Suppose that individuals get symptoms from environmental exposure (e.g. an odor), there seems to be different opinions among the participants of the cause for this. Some of the participants comment\(^4\) that they are sensitive to a specific environmental exposure because they are stressed or depressed, implying a psychological attribution style. The seemingly greatest proportion of the participants seem to embrace an environmental or normalizing attribution style. They attribute their symptoms to environmental exposure without the interpretation of the exposure being pathological. Thus they simply describe themselves as being sensitive. Finally, there are participants who describe themselves as being intoxicated or who think the cause of the symptoms is pathological body processes induced by the environmental exposure, thus having a somatizing attribution style. Worrying about things in the environment believed to be harmful may elicit more symptoms, since symptoms can be induced or reduced by expectations and beliefs, a phenomenon called the nocebo effect. The nocebo effect might set a vicious circle into motion, in which symptoms accumulate. Increased worry, accumulating symptoms, selective attention to symptoms and environmental health hazards may lead to lifestyle alterations and impairment in daily functioning seen in EI individuals. Regarding EI attributed to chemicals a distinction has been made between pre-clinical and clinical cases, in which a pre-clinical case is characterized by a subjective manifestation of experiencing an altered sense of smell and feeling ill (e.g. nausea, headache, difficulties breathing) from environmental chemicals, whereas a clinical case is described as someone that chronically experiences multiple symptoms from various organ systems attributed to exposures to extremely low doses of various chemically unrelated substances, leading to functional impairment (Szarek, Bell, & Schwartz, 1997). Perhaps what best separates these two groups are their attribution styles and the degree of functional impairment (which could be applicable to other types of EI as well). Many of the clinical cases have a somatizing attribution style, whereas the pre-clinical CI cases have an environmental or normalizing attribution style (Bailer, Rist, Witthöft, Paul, & Bayerl, 2004). At T1 and T2 the VEHS did not contain questions concerning attribution style or illness perception.

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\(^4\) The VEHS, at all three data-collection waves, includes a section in which respondents are free to comment on whatever they like. Additionally at T3, the brief illness perception questionnaire is included, containing an open-ended question in which individuals with EI are to list the three most important factors they believe caused their EI.
Hence, there are no means that enable separation of pre-clinical from clinical cases. Based on the comments from the participants it seems as if the majority of the cases included in the studies of this thesis are pre-clinical cases with an environmental/normalizing attribution style. However, all analyzes are probably based on a mixture of pre-clinical and clinical cases, which is a limitation. The results would probably have been different if it had been possible to separate these two groups. From a psychological perspective, this separation of cases is indeed interesting. However, separating cases according to this argument is not common. Most studies have only used single item questions to identify cases (see Tables 1-3). Hence, the results from most studies are based on a mixture of pre-clinical and clinical cases, which could be contributing to the heterogeneity characterizing the EI group. A suggestion for future studies is separating these cases.

A psychological or physiological condition?
The split between mind and body stem from the philosophical work by René Descartes during the 17th century. According to the Cartesian thesis the soul (the mind) was an immaterial entity without any connection with life and unsolvable to mathematics and physics, and the body a matter incapable of thought and bound to the laws of nature (Berhouma, 2013). Descartes suggested that the pineal organ (with the argument that this gland is the only organ of the brain that is not duple) was the place where mind and body could interact. By separating the mind from the body, the mind’s impact on health was denied. The dualistic stance has influenced medicine, in which disease has been defined as a deviation from biological norms, caused by some physical or chemical event (Mehta, 2011). A reductionism approach has been adapted, examining the parts instead of the entire individual. In contrast, ancient philosophical outlooks on health did not separate the mind and the body (Daruna, 2012). Major traditions stemming from the Chinese, the Indian and the Greek civilizations all argued that balance of substances within an individual was fundamental to sustain health. Imbalance made an individual susceptible to illness. In the Chinese tradition imbalance (of “Qi”) was said to make the person unable to cope with changing circumstances arising from both external as well as internal sources. In the Indian ideology it was said that a predominance of focusing on external events suppressed the natural state of an individual. The Greek ideology acknowledged the importance of lifestyle factors and personality traits in health and disease. For example, it was said that individuals who became passionate (for whatever reason), frequently became ill, and it was difficult to heal these persons.

Mind and body are inseparable, how can they not be? Where is a mind if not in a body? And how can a body function without a mind? In the same
way, how can we think or feel without neurons or signaling substances? What is an emotion if not changes in the body? Is it possible to feel pain, to go through an infection or recover from stroke, without it affecting our mind or mood?

With the progress of psychoneuroimmunology it has been obvious that psychological processes affect physiological and immunological processes and the other way around. Finding psychological factors being risk factors (Study 3) of EI is not the same as implying that EI is a “psychological condition”. The susceptibility of developing diseases with known pathology such as cancer, ischemic heart disease and asthma also increases if a person is under stress or mental strain. One way to look at EI is to describe it as an imbalance in the body (using an ancient term of illness) or that it is an allostatic state (using a modern term). We are constantly bombarded with sensory information, and one of the brain’s tasks is to filter out the essential information which makes us able to interact with the surrounding world. This regulatory function is called sensory adaptation and costs a lot of energy (Lan, Sartori, Neumann, Sourjik, & Tu, 2012). A hypothesis is that when resources are needed elsewhere (e.g. to handle high work demands or recover from an injury) or when the energy demand of the adaptation itself is too high, the regulatory function of filtering sensory input collapses or deteriorates, leading to an unfiltered perception of sensory stimuli. Consequently, sensory stimuli are perceived as more intense and enduring. The allostatic overload leads to symptoms such as insomnia, cognitive and digestive problems, as well as inflammatory, epidermal and heart-related symptoms. When the individual experiences these changes there is no wonder that they start to fear or worry about, and have negative expectations of, the environmental exposure, which in turn can lead to dysfunctional cognitions about the exposure and to the nocebo effect. This in turn may accumulate symptoms, setting a vicious circle into motion.

**Ideas about treatment of EI**

When it comes to understanding and treating medically unexplained conditions a biopsychosocial approach is recommended (Edwards, Stern, Clarke, Ivbijaro, & Kasney, 2010; Witthöft & Hiller, 2010). The biopsychosocial approach considers symptom reporting to be the outcome of complex interactions between biological, psychological and social factors. Additionally, in the case of EI an environmental exposure factor is needed (Brand et al., 2009). Due to the heterogeneity of the group constituting EI, medical, psychological/psychiatric, environmental and social assessments may guide treatment. Preferentially, physicians, psychologists/psychiatrists, and environmental engineers/analysts should work in teams. From a psychological perspective, when meeting EI patients it is recommended to acknowledge the symptoms, confirming that they are real. For successful
treatment it is also important to gain knowledge about the patients’ attribution style/illness perception/health belief model. For example, if persons believe that there might be a psychological component to their EI they are potentially more susceptible to psychological treatment or therapy. In these cases the focus could be on relieving the emotional and behavioral disruption these persons experience from different environmental exposures (in accordance with Study 4). Mindfulness-based cognitive therapy focusing on making patients aware of their thoughts and feelings without reacting to them has been suggested (Hauge, Bonde, Rasmussen, & Skovbjerg, 2012). This type of therapy may provide emotion-focused, and reduce the usage of problem-focused coping strategies (e.g. avoidance) which, in Study 2, was found to be important for recovery. It might be helpful to explain the nocebo effect to these patients, explaining that negative expectations of exposure might aggravate symptoms. Explaining the nocebo effect has previously been found to reduce symptoms (Crichton, Dodd, Schmid, & Petrie, 2015). Further on, the therapy might extend into other domains of life causing mental illness since stress, anxiety, depression and burnout has been found to be risk factors of EI (Study 3). If persons instead do not believe that there is a psychological component to their EI, but only consider biological or environmental factors as important, a different approach has to be taken. The majority of these patients tend to discount physicians’, psychiatrists’ and environmental engineers’ suggestion of psychogenic influences on their EI, instead holding on to a somatic disease model and resisting psychological interventions (Brand et al., 2009). You cannot force anyone to undergo psychotherapy if they do not want to, but many of these patients have experienced traumatizing interactions with other people due to their EI, and psychotherapy can be offered to alleviate these kinds of problems (instead of focusing on treatment). If trust is established between the patient and the therapist, one way to approach these patients is to give a biological or physiological explanation of psychological processes (in accordance with their biological disease model), explaining that these processes will affect the immune system and neural signaling. If patients are willing to accept this explanation they might consider to work with their emotional and behavioral reactions to certain environmental exposures.

There is probably no golden recipe or gold standard for successful treatment. In some cases reduction of exposure might be enough, whereas in other cases long-term psychotherapy could relieve symptoms. In whatever case though, patients who have not yet made lifestyle alterations, adopted the label of EI (i.e. MCS, SBS, IEI-EMF and NS), or a somatic attribution style will probably recover more easily. Hence, intervention at an early stage is advised. However, strikingly many of the respondents who report some kind of EI in the VEHS comment that they have not yet told anyone, since
they feel “ridiculous” or “ashamed”, hence these individuals are less likely to seek medical attention.

**Limitations of the thesis**

The response rate of the VEHS was moderate, which raises the question whether the result may be generalizable. Generally, participation rates are decreasing in epidemiological studies. One possible explanation is the increasing number of requests to participate in studies or investigations. The number of research studies have increased, and at the same time there has been a proliferation in marketing research, which may intrude on personal life and perhaps have reduced the sense of meaningfulness in answering. Another reason for low participation rates in epidemiological studies is that they in general have become increasingly demanding for the participants, with, for example, numerous assessments. Anyhow, a comparison between studies with participation rates ranging between 30% and 70% has revealed very few significant differences, and the lower participation rates were at most weakly associated with bias (Galea & Tracy, 2007). A greater issue is the unequal distribution of non-response in the different age and sex strata. Non-response was more common among the younger participants and among men (with the exception for the age stratum 70-79 years in which non-response was more common in women; see Figure 2). EI is more common in women (Andersson et al., 2008; Paulin et al., 2016; Stansfeld & Shipley, 2015; Stenberg & Wall, 1995), hence there is probably a overrepresentation of EI cases in VEHS. Additionally, individuals with a certain condition may be more likely to participate in studies where the particular condition is investigated (Dunn, Jordan, Lacey, Shapley, & Jinks, 2004; Groves et al., 2006). Since the topic of the current questionnaire was environmental issues and health it is likely that an overrepresentation exists of environmental intolerant persons or at least of individuals who are more conscious or concerned about these issues. In Study 2 and 4 this does not implicate a problem, since only participants with EI were investigated. In Study 3 development of EI was investigated and the drop-out between T1 and T2 was similar for those individuals who did and did not develop EI. In Study 1, caution is warranted regarding generalizing the prevalence values for separate EIs, since they might be too high following this argument. However, when considering the overlap between different types of EI, it might not be as affected.

Research on response rates in mail surveys has found that the most important factors for maximizing the response rate are follow-up mailings and incentives (Church, 1993; Edwards et al., 2007; Yammarino, Skinner, & Childers, 1991). In the VEHS there were two reminders sent out if participants had not yet responded to the first mailing for each data collection wave. No incentives were used in the VEHS, which potentially
could have increased the response. Ethical regulations in Sweden did not allow a complete drop-out analysis (Prop, 2007/08:44), however some participants announced that they were not answering the questionnaire because it was too extensive. Some of the respondents also complained about the length of the questionnaire. Length of a questionnaire has been found to reduce the response rate (Sahlqvist et al., 2011). When constructing a questionnaire the researcher has to weight the number of variables against the possibility of increased non-response. In the design phase of VEHS all variables included were carefully selected, and it was a deliberate choice to opt a lengthier questionnaire to be able to make multivariable predictions, with the potential cost of increased non-response.

Attribution of symptoms may be affected by the focus of a study. For example, Brauer and Mikkelsen (2003) found that changing the information of a study influenced the attribution, but not the prevalence of symptoms. For reducing the effect of the information given on the attribution of symptoms, it was not explicitly stated in the information sheet of the VEHS about symptom attribution to environmental exposure. In the information to the participants it was stated that the survey contained questions on physical and mental health, as well as reactions to different environments. Further on, it has been suggested that the context of questions (near before or after, certain other questions) may affect validity (Crosby, DiClemente, & Salazar, 2006). Hence, the sections containing physical symptoms, diagnosed diseases/conditions, mental health and questions concerning reactions to environmental factors and EI were placed separately in the questionnaire, as a mean to reduce bias.

Preferentially, EI attributed to chemicals, certain buildings, EMFs and sounds should have been investigated in all four studies. However, in Study 2 EI attributed to buildings was not included. One aim of this study was to examine whether the individuals with high versus low emotional and behavioral disruption by exposure used different combinations of coping strategies and social support. Emotional and behavioral disruption by exposure was assessed by the CSS-SHR, EMFSS-11 and NSS-11 for EI attributed to chemicals, EMFs and sounds respectively. The items of these scales correspond. However, there is no corresponding scale for EI attributed to buildings, hence this type of EI was left out. In Study 3 EI attributed to EMFs was not included since the number of participants who had developed EI attributed to EMFs between T1 and T2 were few, and performing statistical analyses on this subsample would probably lead to biased results (Cepeda, 2003; Peduzzi, Concato, Kemper, Holford, & Feinstein, 1996).

**Future directions**
The tradition within psychology in general is studying between-person differences or effects discovered through aggregate (e.g. mean, median,
variance, covariance) statistical analysis (Speelman & McGann, 2013). Hence, conclusions drawn are based on group-level analyses and not on the individual level. However, between-person differences or effects discovered through aggregate statistical analysis do not necessarily exist at the level of the individual. With the heterogeneity of the group constituted by individuals with EI in mind this might be especially prominent (Bailer et al., 2004). Therefore individual-based statistical analyses are recommended. Such statistical analyses in which patterns of multi-facet characteristics can be found might be especially helpful in understanding EI (such as observation oriented modeling; Grice, 2014). Furthermore, if there are financial means and it is practically viable, measures of exposure, biomarkers, and symptoms, as well as genetic, social and psychological factors should all be included when modeling EI, since they all have the potential of being causal factors.

More qualitative studies are needed. Especially when it comes to coping strategies and the attribution process. The qualitative studies could be a basis for developing a coping questionnaire customized for individuals with EI. Which coping strategies that are used are dependent on the individual (or the personality of the individual) and the certain demand placed on the individual (Folkman & Moskowitz, 2004). Hence, coping is problem-specific. Not much is known of the certain coping strategies used by individuals with EI, except for the coping strategy of avoidance which seems to be pervading. Since coping is problem-specific and standardized checklists of coping are not, it has been recommended to develop tailored questions reflecting how individuals of interest deal with the particular, characteristic problems they face (Coyne & Gottlieb, 1996). Hence, tailored questions of how EI individuals deal with their condition are warranted, and qualitative studies are suggested for deciding which questions that should be considered. Further on, after obtaining a set of questions reflecting strategies used by individuals to cope with their EI, categorization of these strategies is needed. Perhaps, the optimal conceptualization of coping strategies is not by emotion-focused and problem-focused coping, but engagement and disengagement coping (or another conceptualization). Concerning the attribution process, more knowledge is needed and qualitative studies could be a hypothesis generator in how the attribution process unfolds and the accompanied implications of this process.

Another idea, which is in line with Hetherington and Battershill (2013), is to recruit individuals who are intolerant to some environmental exposure, but who do not yet display lifestyle alterations nor comorbid psychiatric features (called pre-clinical cases by Szarek et al., 1997), and then follow these individuals to find out what the essential factors contributing to the lifestyle alterations are. Once again, if feasible, multiple factors should be
measured; exposure, biomarkers, symptoms, and genetic, social and psychological factors.

More intervention studies are needed, and mindfulness-based cognitive therapy could be a candidate for such interventions. Important when designing these kind of studies is to recruit participants with care. The participants must believe that there might be a psychological component to their EI and also be committed to recover. If they do not believe the therapy might be helpful nor are committed to it, it would probably not be effective.
References


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