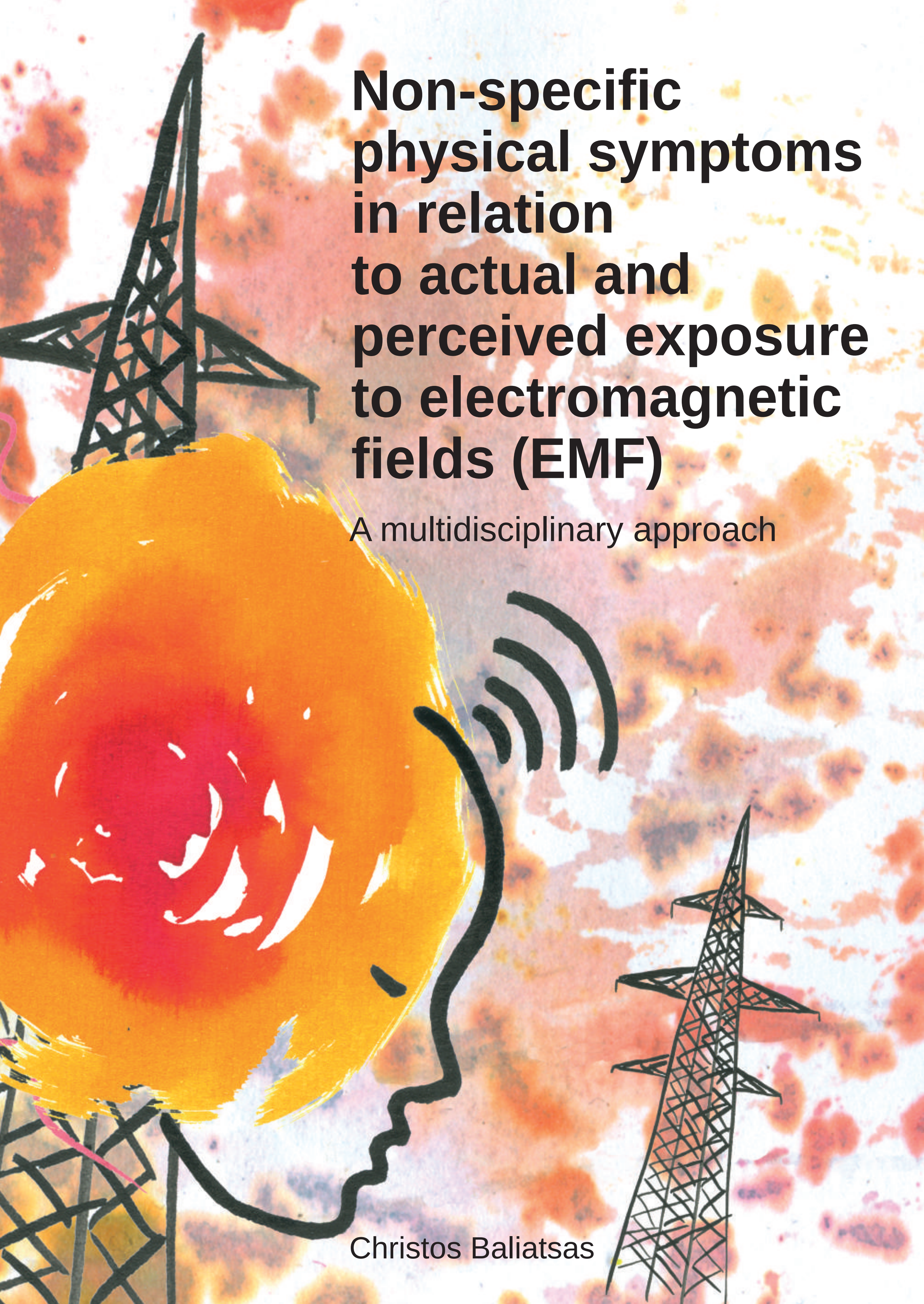
Non-specific physical symptoms in relation to actual and perceived exposure to electromagnetic fields (EMF)

A multidisciplinary approach

Christos Baliatsas



Non-specific physical symptoms in relation to actual and perceived exposure to electromagnetic fields (EMF): A multidisciplinary approach

Christos Baliatsas

2015

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Non-specific physical symptoms in relation to actual and perceived exposure to electromagnetic fields (EMF): A multidisciplinary approach

Niet-specifieke lichamelijke klachten in relatie tot werkelijke en waargenomen blootstelling aan elektromagnetische velden (EMV): Een multidisciplinaire benadering

(met een samenvatting in het Nederlands)

Proefschrift

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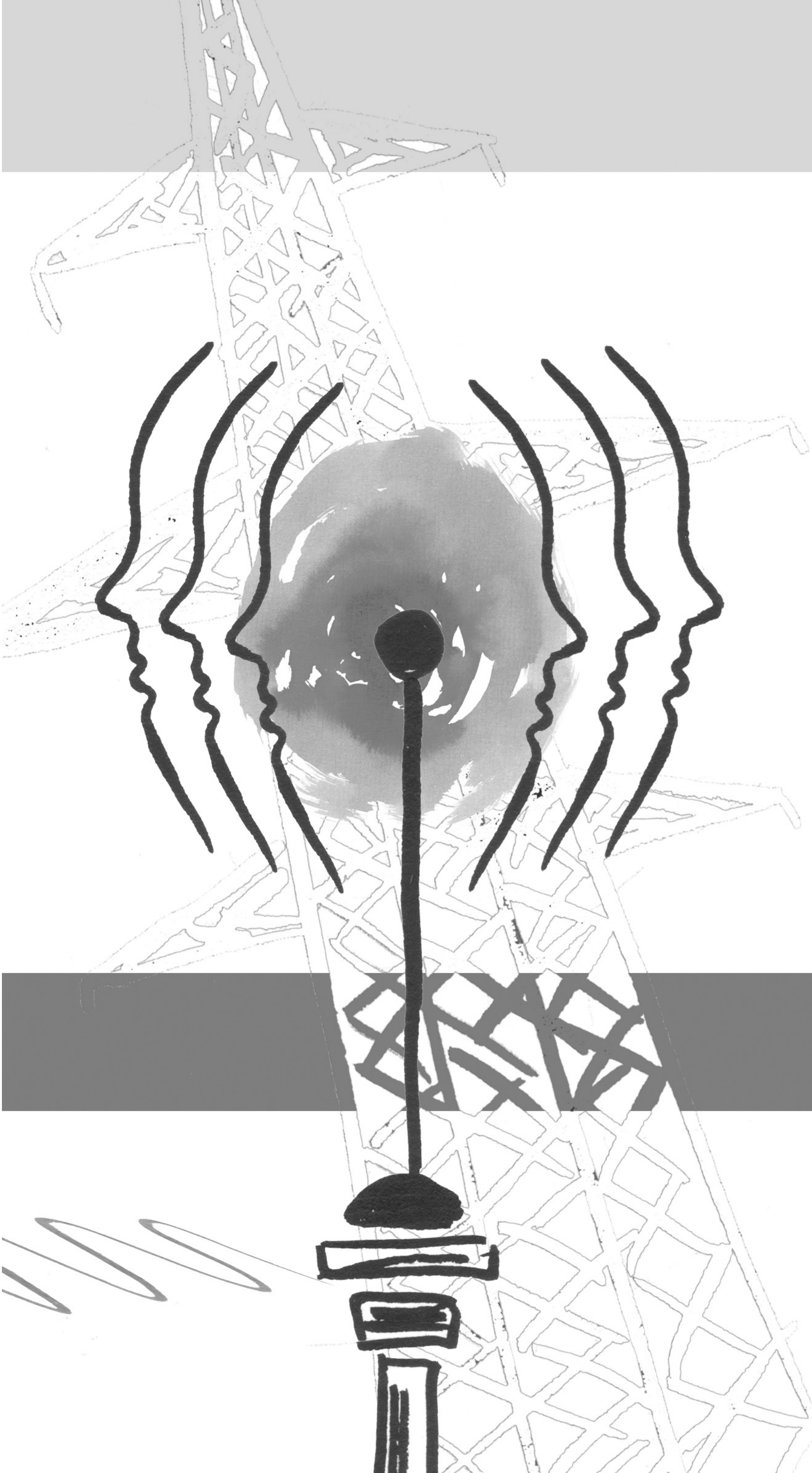
Contents

Chapter 1

General Introduction



Non-specific physical symptoms

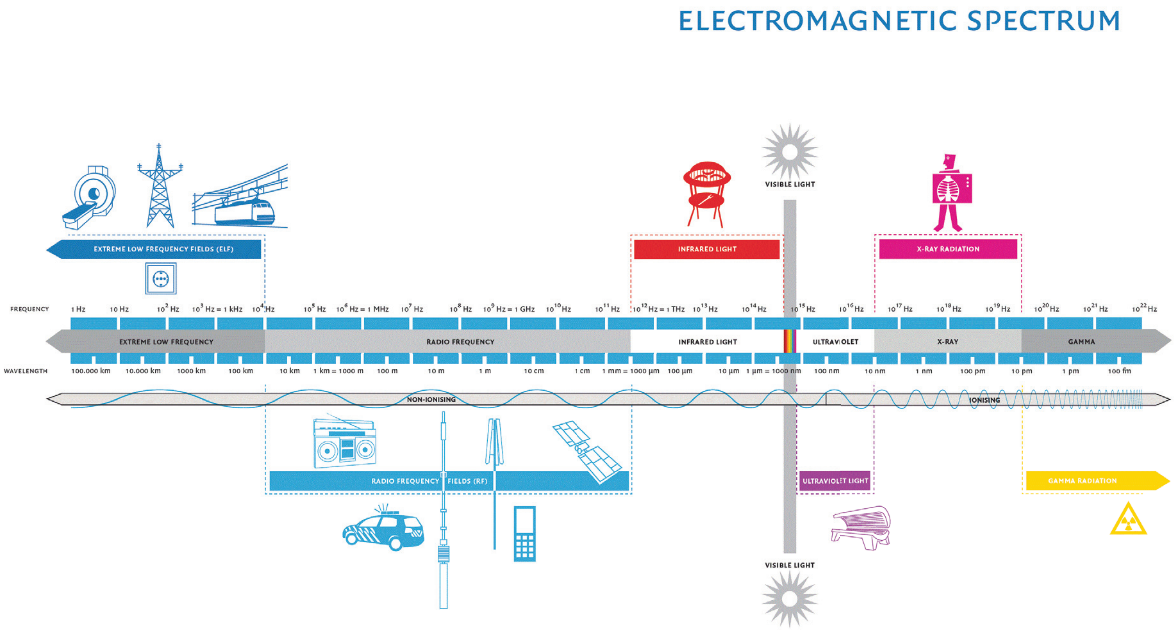
Symptoms such as headache, fatigue, disturbances of sleep, skin rashes and stomach ache are very common in the general population [1,2]; an estimated 80% of the general population experiences at least one of these symptoms in any given month[3]. These symptoms are called "non-specific" (Non-specific physical symptoms, NSPS) when they occur in different organ systems and can be caused by a variety of factors, often unknown [4]. When presented in primary care, between 30% and 50% of NSPS cannot be associated with a medical diagnosis. For this reason the term "medically unexplained" is widely used to describe such complaints in clinical practice and research [5,6]. Furthermore, clusters of NSPS are referred to as functional somatic syndromes or somatoform disorders [7,8], such as irritable bowel syndrome, fibromyalgia and chronic fatigue syndrome [7]. Due to the substantial overlap and common features between these syndromes, it is still controversial whether they should be considered as separate conditions or not [7,9]. Non-specific physical symptoms in healthcare are associated with functional impairment similar to that of patients with medical disorders [10], increased sick leave and medication use [11,12], lower perceived control over their situation and/or environment [13], maladaptive coping behavior [14], higher levels of psychological distress [15,16] and negative symptom perceptions [17-18].

Sufferers often attribute their NSPS to exposure to environmental agents at lower levels than the established safety standards, such as chemical substances, noise, odors and food additives [19]. However, the attributed cause(s) of such symptomatic conditions is often not adequately supported by scientific evidence [20-22]. Terms such as "sick building syndrome", "multiple chemical sensitivity" and "idiopathic environmental intolerance" are regularly used in the literature to describe clusters of NSPS attributed to environmental sources [19,20].

NSPS in relation to electromagnetic fields (EMF)

An issue that remains controversial is the association of NSPS with EMF [23] emitted from outdoor far-field sources such as mobile phone base stations and high voltage overhead power lines and near-field sources such as mobile phone devices and electric domestic appliances [24] (Figure 1). Although exposure to high levels of EMF could affect human health, e.g. via thermal effects caused by high-intensity radiofrequency (RF)-EMF, such exposure levels do not exist in everyday life [24,25].

Figure 1: The electromagnetic spectrum and associated sources (from the Dutch Knowledge Platform EMF)



Despite public concern and a continuing scientific debate, evidence regarding a causal association between EMF and NSPS is scattered, inconsistent and primarily based on laboratory experiments with small sample sizes and short-term exposure sessions [26,27].

An epidemiological design allows for the investigation of everyday life/long-term EMF exposure and NSPS but relatively few epidemiological studies have been performed. First, the association between ELF-MF exposure and NSPS in the population has been scarcely investigated. Second, the majority of studies on RF-EMF and NSPS rely exclusively on self-reported exposure by e.g. asking respondents to estimate their daily exposure to EMF or to recall the history of mobile phone use [28,29]. This might introduce considerable misclassification; in the light of findings indicating that self-reported (perceived) exposure is a poor proxy of the actual exposure levels [30]. Only a limited number of studies has employed more objective methods such as geocoded distance to the nearest base station [31], spot measurements [32], use of personal expositmeters [33] or prediction modeling [34].

Considering these issues and also the fact that a biological mechanism for NSPS in relation to residential EMF levels is unknown, it is imperative to take into account exposure from different relevant sources. A prediction model based on exposure from mobile phone base stations and exposure-relevant activities seems to combine representativeness of daily life exposure and cost-effectiveness [30].

Another methodologically important issue in this research field is proper outcome measurement. Since only a clinical examination can exclude medical disorders and determine whether a symptom has an organic explanation or not [4], it is still unknown whether the symptoms reported in the existing epidemiological studies can be reliably defined as unexplained. Furthermore, epidemiological research on EMF and NSPS is frequently confronted with limitations such as selection and information bias and in some cases insufficient adjustment for confounders [35].

There are competing, but not necessarily exclusive, theories about the possible underlying mechanisms for a relationship between EMF exposure and NSPS. For instance, one school of thought is that a bio-electromagnetic mechanism could exist through pathways related to cellular damage or immune dysregulation [23,36]. Another theory argues in favor of the role of psychological factors and a (neuro)physiological mechanism of stress responses that could lead to symptoms [37-39]. Part of the debate about EMF and NSPS concerns the existence of a subgroup of highly sensitive individuals who may suffer effects when exposed to levels that lay well below current exposure limits and well below levels where effects in the general population would occur.

Idiopathic environmental intolerance attributed to EMF

Despite the lack of evidence for a bioelectromagnetic mechanism, between 1.5% and 5% of the population internationally, attributes adverse health effects to exposure to EMF [40-43]. The attribution of NSPS to residential levels of EMF exposure is mainly referred to as "electromagnetic (hyper)sensitivity" (EHS). The term "idiopathic environmental intolerance attributed to EMF" (IEI-EMF) has been recommended by the World Health Organization (WHO) [44], as a more etiologically neutral one. Attributed symptoms seem to be mainly neurovegetative and dermatological, such as headache, fatigue, low sleep quality, lack of concentration, skin problems and burning sensations, although no clear patterns of symptoms in relation to EMF have been observed yet [44,45].

Idiopathic environmental intolerance attributed to EMF can be associated with social, occupational and mental impairment [46,47] and increased avoidance behavior related to exposure [40,45]. In contrast to the experiences of sufferers, short-term experiments have failed to scientifically document a direct association between exposure to EMF and effects [35,48]. Only one epidemiological study has investigated the association between EMF and NSPS in people with IEI-EMF, showing no evidence for an association [49]. Moreover, evidence regarding the clinical profile and symptom characteristics of this potentially susceptible group is missing at the population level.

Psychological factors in symptom report; towards a multidisciplinary framework

In addition to the investigation of physical explanations of symptom report, other potentially explanatory variables should be taken into account when studying determinants of NSPS. Several studies that have examined NSPS attributed/related to environmental exposures have shown that psychological factors may have a prominent role. For example, studies after the Gulf War showed that psychological distress was an important predictor of symptoms such as fatigue, gastrointestinal complaints and pain in muscles among veterans [50]. Studies among patients with the chemical sensitivity syndrome have also shown strong relationships with somatization and mood and anxiety disorders [51].

A strong body of experimental studies has demonstrated that NSPS occur when people believe they are exposed to EMF, irrespective of whether this belief is accurate or not [35, 52-59]. Since people cannot accurately estimate the magnitude of their exposure to EMF [30,60-62], the suggested association between NSPS and perceived exposure, apart from being a possible byproduct of information bias [27], could also indicate the presence of a so-called ”nocebo” effect, in which perceived exposure triggers a self-fulfilling expectation of occurrence of NSPS [27,52]. Considering that environmental stressors are often outside individual control (Campbell 1986), this could be suggestive of a generic mechanism of environmental stress.

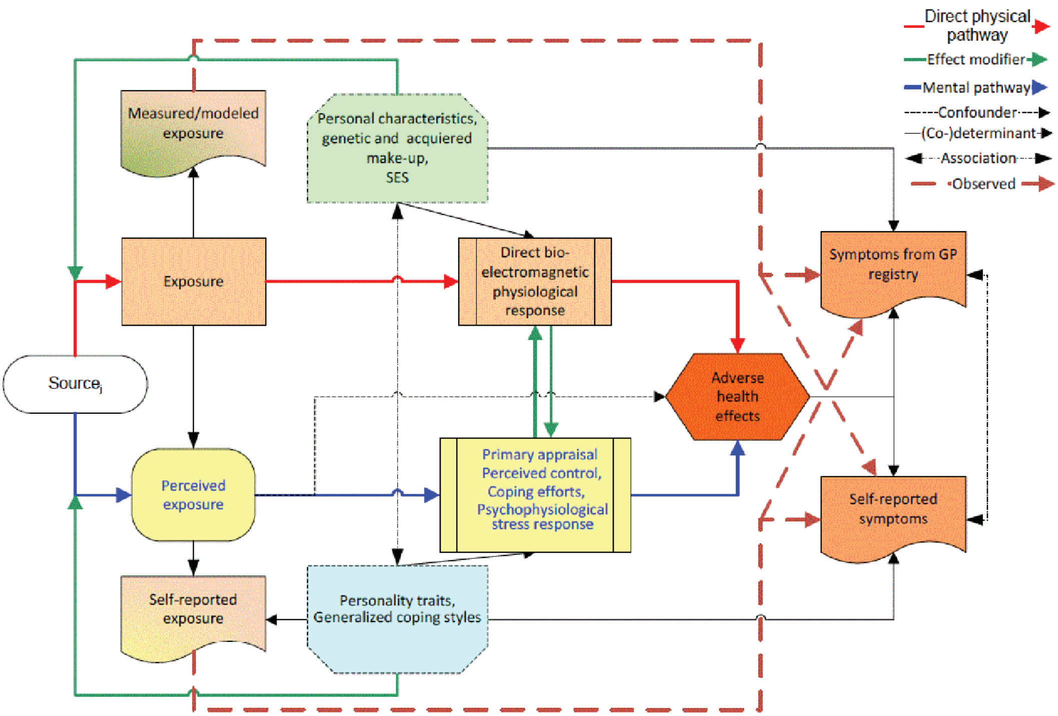
A theory of stress has been established by Selye [63], Lazarus and Folkman [64] and Ursin [65] and has to date shown to be broadly applicable in the exploration and explanation of the relationship between stress reactions and health, also in the context of environmental exposures [66]. When individuals are confronted with an environmental stressor, they engage in two types of cognitive processes: First a process of primary appraisal, whereby the stressor is evaluated in terms of threat, depending on the individual and context.

This threat can also be appraised in relation to the extent to which a person can control it. This process is referred to as secondary appraisal, representing the evaluation of the individual capacity to confront/deal with the stressful situation. Not only the environmental stressor itself determines the experience of physiological reactions, but also psychological/behavioral mediating factors, such as coping strategies [64,67]. These are employed by the individual to adapt to the stressful situation and can be divided into two main strategies: Active-focused (or problem-focused) such as problem-solving and emotion-focused such as avoidance [68].

Variants of this model have been previously used to examine the relationship between several environmental stressors and health, such as noise, odor and soil pollution [66,69,70]. These studies have shown that the model is a very useful approach to get insight into the process of appraisal of and coping with environmental stressors and its health consequences via stress reactions. The question is, whether such a stress model could be applicable for the case of EMF as main environmental stressor, at population level. The majority of existing studies investigating psychological determinants of NSPS within the EMF context, have focused on small samples of environmentally sensitive subgroups and in many cases, actual exposure was not taken into account. Considering that multiple factors may play a role in the triggering and maintenance of NSPS and associated conditions, such as biological, psychological and social [4,71,72] EMF-related NSPS could be defined as the possible outcome of a complex mechanism between actual and perceived exposure to environmental factors and individual characteristics [73-75] (Figure 2).

In order to enhance our understanding of the physical and psychological factors and mechanism underlying the relationship between NSPS and EMF in the population, a broad epidemiological approach is proposed, employing a) both questionnaire and medical record data on NSPS, b) estimates of actual and perceived exposure and c) assessment of psychological factors. Such an approach demands expertise from different fields of study by combining physic, epidemiological, sociological, psychological, environmental, statistical and geographical expertise, in line with a multidisciplinary framework.

Figure 2: A generic conceptual model with possible pathways from EMF to NSPS



Aim of this thesis

The key objectives are:

A. To study NSPS (including sleep quality) in relation to actual and perceived exposure to EMF in the general population, including potentially susceptible people such as those with IEI-EMF.

B. To provide insight into determinants of NSPS and psychological factors that could modify the relationship between perceived exposure to EMF and NSPS.

Research questions to achieve objective A

1. Do residents who live closer to mobile phone base stations and high-voltage overhead power lines report more NSPS?
2. Do respondents with higher levels of actual exposure to EMF report more NSPS and a higher prevalence of symptoms associated with no medical diagnosis based on the clinical judgment of the general practitioner (GP-registered NSPS)?
3. Do respondents who report higher levels of perceived exposure to EMF have more NSPS and a higher prevalence of GP-registered NSPS?
4. Does IEI-EMF moderate the association between actual and/or perceived exposure and NSPS?

Research questions to achieve objective B

1. What is the association between self-reported NSPS and functional impairment, illness behavior and GP-registered NSPS among (EMF) sensitive and non-sensitive individuals?
2. Are stress-related psychological factors such as perceived control and coping behavior related to levels of self-reported and GP-registered NSPS?
3. Do these psychological variables moderate the association between perceived exposure and NSPS?

To answer these research questions, a PhD thesis project has been conducted in five main stages (see Table 1 for the corresponding datasets, categorized per chapter). The project comprised two systematic reviews, a pilot epidemiological study and a main study (divided into two parts; the first focusing on the symptomatic profile of different groups and the second on the exposure-outcome associations). For the development of the prediction models for RF-EMF exposure in the main study, input from an external project was used [76]. The main study consisted of 5933 participants, combining survey data with GP-registry data. The results of the study are reported in separate chapters of this thesis.

Outline of this thesis

In chapter 2 a systematic review and meta-analysis of epidemiological studies is presented, to gain insight into the quality and strength of evidence for an association between actual and perceived exposure to EMF and NSPS in the general population.

In chapter 3 the results of the pilot study are reported with the aim to explore whether self-reported NSPS are associated with actual and perceived proximity of home address to mobile phone base stations and high-voltage overhead power lines, taking into account demographic, residential and area characteristics. The potential role of perceived environmental sensitivity, coping styles and perceived control in symptom report is also investigated.

In chapter 4 a systematic evaluation of the scientific literature is provided regarding the case definition criteria and methodology to identify individuals with IEI-EMF in epidemiological research.

In chapter 5 part of the results of the main study are reported: a) Definition of the prevalence of IEI-EMF and general environmental sensitivity/IEI in a large population sample b) Estimation of the prevalence and duration of self-reported NSPS in people with IEI-EMF, general environmental sensitivity and the broader population, addressing their association with GP-registered NSPS, functional impairment, illness behavior and psychological aspects c) Identification of between-group differences and potential clinically relevant characteristics of people with environmental sensitivities.

In chapter 6 the primary results of the main study are presented: a) The association between actual and perceived exposure to EMF and self-reported and GP-registered NSPS b) The moderating role of IEI-EMF in these associations c) The association of the aforementioned health outcomes with psychological variables such as perceived control and avoidance coping 3) The moderating role of psychological variables in the association between perceived exposure and NSPS.

In chapter 7 a general discussion of the main findings is presented, in which methodological considerations are addressed along with implications for future research.

Table 1: Overview of datasets that are used to address the research questions of the different chapters of the thesis

Chapter	Design	Data
Chapter 1 *		
Chapter 2	Systematic review & meta-analysis	Epidemiological data on the association between NSPS and EMF published between January 2000 and April 2011
Chapter 3	(Pilot) epidemiological health survey combined with proxies of actual and perceived EMF exposure to EMF sources	Data on NSPS, psychological variables, perceived proximity to EMF sources and geo-coded distance to mobile phone base stations and high-voltage overhead power lines, collected in 2006, within the framework of an RIVM project (Centre for Environmental Health Research) entitled “Living Environment: Quality of Life in relation to residential area” (VROM, 830950)
Chapter 4	Systematic review	Quantitative data on case definitions for IEI-EMF in the relevant scientific literature published up to June 2011
Chapter 5	Epidemiological health survey combined with electronic medical records from patients registered in 21 general practices	Data on NSPS, psychological variables, healthcare utilization, medication prescriptions and somatic and psychological morbidity. collected in 2011, within the framework of the “EMPHASIS” project (ZonMw 85100002)
Chapter 6	Epidemiological health survey combined with electronic medical records from patients registered in 21 general practices and estimates of actual and perceived exposure to EMF sources	Data on NSPS, psychological variables, healthcare utilization, medication prescriptions, somatic and psychological morbidity, modeled exposure to RF-EMF, geo-coded distance to high-voltage overhead power lines and use of electric devices collected in 2011 within the framework of the “EMPHASIS” project (ZonMw 85100002)
Chapter 7 *		

* Not applicable, general introduction and discussion

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Chapter 2

Non-specific physical symptoms and electromagnetic field exposure in the general population: Can we get more specific? A systematic review

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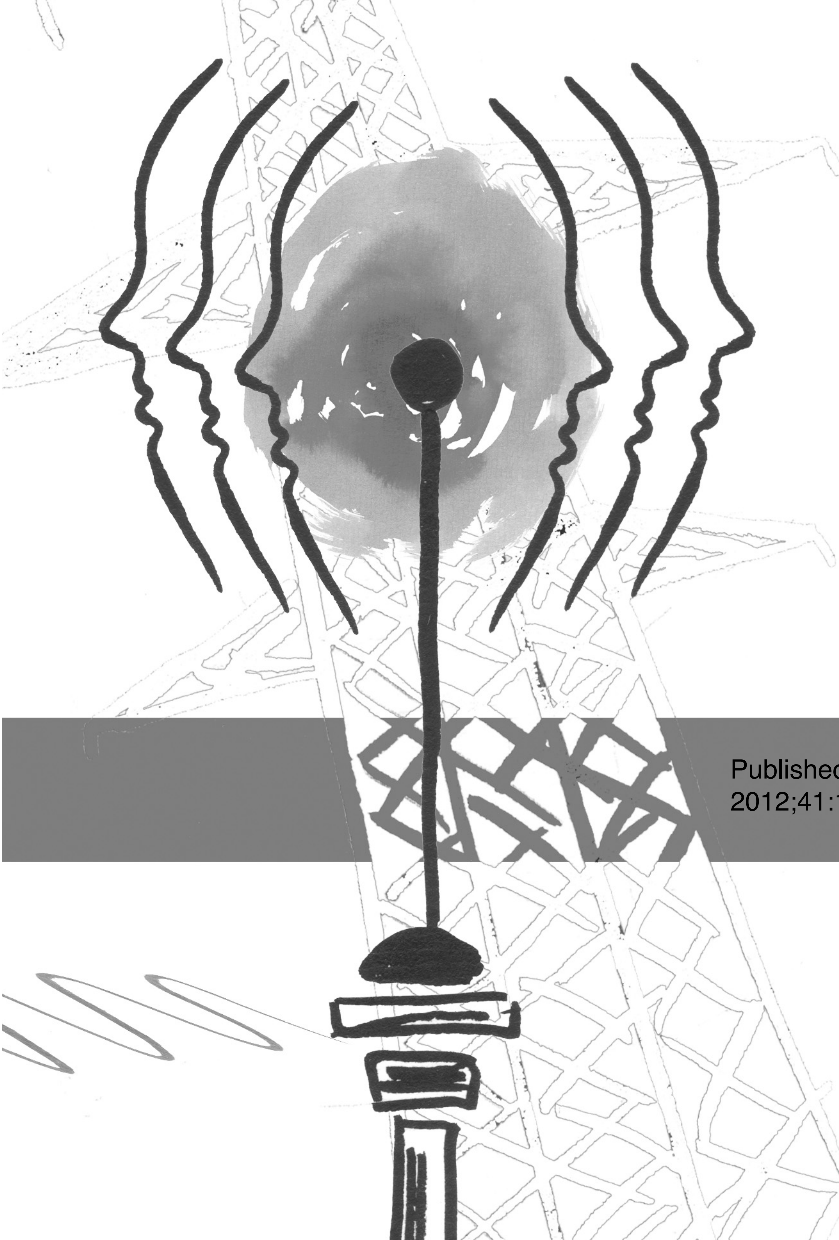

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Summary

Objective: A systematic review of observational studies was performed to address the strength of evidence for an association between actual and perceived exposure to electromagnetic fields (EMF) and non-specific physical symptoms (NSPS) in the general population. To gain more insight into the magnitude of a possible association, meta-analyses were conducted.

Methods: Literature databases Medline, Embase, SciSearch, PsychInfo, Psyndex and Biosis and additional bibliographic sources such as reference sections of key publications were searched for the detection of studies published between January 2000 and April 2011.

Results: Twenty-two studies met our inclusion criteria. Qualitative assessment of the epidemiological evidence showed either no association between symptoms and higher EMF exposure or contradictory results. To strengthen our conclusions, random effects meta-analyses were performed, which produced the following results for the association with actual EMF; for symptom severity: Headache odds ratio (OR) = 1.65; 95% confidence interval (CI) = 0.88–3.08, concentration problems OR = 1.28; 95% CI= 0.56–2.94, fatigue-related problems OR = 1.15; 95% CI = 0.59–2.27, dizziness-related problems OR = 1.38; 95% CI = 0.92–2.07. For symptom frequency: headache OR = 1.01; 95% CI= 0.66–1.53, fatigue OR = 1.12; 95% CI= 0.60–2.07 and sleep problems OR= 1.18; 95% CI= 0.80–1.74. Associations between perceived exposure and NSPS were more consistently observed but a meta-analysis was not performed due to considerable heterogeneity between the studies.

Conclusions: This systematic review and meta-analysis finds no evidence for a direct association between frequency and severity of NSPS and higher levels of EMF exposure. An association with perceived exposure seems to exist, but evidence is still limited because of differences in conceptualization and assessment methods.

Introduction

Ongoing environmental exposures related to technological development such as air pollution, toxic substances and radiation give rise to people's worries about possible impact on health (Petrie et al., 2001). A part of the general population has concerns about potentially harmful effects from electromagnetic fields (EMF) emitted either by sources of near-field exposure such as mobile phones or from far-field exposure sources such as base stations for mobile telecommunication and high-voltage overhead power lines (Blettner et al., 2009; Hutter et al., 2004; Schreier et al., 2006); in the latter case, exposure is often continuous and people perceive it as less controllable (Schreier et al., 2006). Not only concerns about increased risk for long-term conditions such as cancer are reported, but also a variety of symptoms without a clear pathological basis is attributed to relatively low-level exposure to EMF, such as redness, tingling and burning sensations (in the facial area), fatigue, tiredness, lack of concentration, dizziness, nausea, heart palpitation and digestive disturbances (Mild et al., 2006; WHO, 2005). The estimated prevalence of these non-specific physical symptoms (NSPS) ranges between 3.5% and 10% (Blettner et al., 2009; Schreier et al., 2006; Schrottner and Leitgeb, 2008).

Although evidence that could support a causal association between exposure and outcome seems to be insufficient and inconsistent (Röösli and Hug, 2011; Röösli et al., 2010; Rubin et al., 2009), a possible effect of higher exposure levels cannot be ruled out yet because of methodological obstacles, primarily regarding bias related to exposure assessment and study design (Röösli, 2008; Röösli et al., 2010). Systematic reviews focusing mainly on experimental evidence suggest rather a nocebo effect, which could imply an underlying psychological mechanism that leads to physiological responses and subsequent symptoms (Rubin et al., 2009). Therefore, perceived/self-reported exposure, even poorly correlated with actual exposure levels (Inyang et al., 2008; Vrijheid et al., 2009) could be an important factor to investigate, since it is associated with NSPS (Baliatsas et al., 2011) and might have a distinct role in symptom report via concerns about possible health effects caused by EMF (Röösli, 2008).

Despite the fact that the vast majority of EMF research focuses on possible associations with chronic medical conditions such as leukemia and glioma, during the last years the international scientific literature on EMF and NSPS has grown, both with respect to objectively measured and self-reported exposure.

In order to elucidate the pathways that lead to the report of EMF-related NSPS it is necessary to systematically examine these two aspects of exposure. Observational studies are highly important due to the investigation of long-term exposure and effects in large population samples. Taking into consideration the methodological obstacles that epidemiological research on EMF and health is confronted with, important conclusions can be drawn from comprehensive reviews and meta-analyses rather than from a single study, as has been recently highlighted by Rothman (2009).

No systematic review has been conducted yet concentrating exclusively on observational studies on various sources of general population exposure to EMF and NSPS, assessing the existing evidence in terms of both actual and perceived exposure. In addition, no meta-analysis has been performed in the past on epidemiological data on EMF and NSPS.

The present paper attempts to identify the relevant observational epidemiological studies conducted in the last eleven years (2000–2011), in order to systematically assess the strength of evidence for an association between objectively measured (actual) and self-reported (perceived) exposure to EMF and NSPS.

Methods

Data sources and searches

The following electronic databases were searched to detect relevant studies that were published between January 2000 and April 2011: Medline (US National Library of Medicine, Bethesda, Maryland), Embase (Elsevier B.V., Amsterdam, The Netherlands), SciSearch (Institute for Scientific Information, The Thomson Corporation, Stamford, Connecticut), PsychInfo (American Psychological Association, Washington, DC), Psyndex (German Institute of Medical Documentation and Information, Cologne, Germany) and Biosis (The Thomson Corporation, Stamford, Connecticut). There was no language restriction.

A wide range of keywords was used, related to EMF exposure and symptoms, which is presented in Table 1. In addition to the electronic database searches, the reference sections of previous systematic reviews, key papers, international reports on EMF and health and research databases of websites focused on the issue of EMF such as the “EMF Portal” and the WHO webpage were checked for potentially relevant articles.

Table 1: Key search terms

Health outcome	Non-specific physical symptoms, Physical symptoms, Somatic symptoms, Health symptoms, Medically unexplained symptoms, unexplained symptoms, somatic symptoms, subjective symptoms, Health problems, Health effects, Self-reported symptoms, Psychosomatic symptoms, Ill health, Well-being, Quality of life.
Exposure	EMF, Electromagnetic fields, Base stations, Powerlines, Transmitters, Fixed transmitters, Mobile phones, Electromagnetic exposure, Wireless, Electricity, Mobile phone frequencies, Perceived exposure, Self-reported exposure, Actual exposure, Cell towers, Antenna(e), UMTS, GSM, DECT, VDU, Cellular phones.
Design	Epidemiological, Observational, Cross-sectional, Cohort, Prospective, Case-control.
Time period	2000 – 2011

Inclusion criteria

For paper selection, four criteria were used:

I. *An exposure criterion*. Only studies examining symptom report in relation to general population exposure to radio-frequency (RF) EMF which did not exceed the levels established by the International Commission of Non-ionizing Radiation (ICNIRP) (1998) were considered as eligible for the review, covering a wide range of frequencies such as GSM, UMTS, FM radio, TDAB, WiMAX/LTE, analog TV and DVB-T, TETRA, DECT and WLAN/WIFI. The exposure could be either actual/objectively measured when an indicator of actual exposure levels was assessed (e.g. field strength), or perceived/self-reported when it was assessed by self-reported instruments. Studies on occupational exposure are not covered in this review.

II. *A symptom report criterion*. Studies should examine a range of self-reported physical/somatic symptoms without a diagnosed pathological or psychopathological cause. Since this review focuses on somatic symptoms as an outcome, results regarding mental health outcomes (e.g. depression) that are possibly presented by some of the reviewed studies are not included. Studies focusing on a possible association between EMF and chronic medical conditions (e.g. cancer) were also excluded. Moreover, studies focusing exclusively on ergonomic problems (such as musculoskeletal symptoms related to posture of computer users) are not covered in this paper.

III. *A population criterion*. The eligible studies recruited samples of healthy individuals being at least 12 years old. Studies focusing only on individuals with self-reported idiopathic environmental intolerance attributed to EMF (IEI-EMF) were not included.

IV. *A study criterion*. Only primary observational studies (not reanalyses, conference presentations or reviews) from the peer-reviewed literature, investigating a potential exposure– response relationship (and not being restricted to descriptive analyses) were considered as suitable for inclusion. The term “observational” refers to non-experimental studies such as cross-sectional, case control and cohort studies, in which the possible association between EMF and NSPS was investigated without an attempt to affect the exposure or the outcome. In the case of so-called “natural experiments” which combine both experimental and observational design, only the baseline results were included (if given). Case (individual) studies were excluded.

Evaluation of the quality of information

The adequacy of the information provided in the articles was assessed based on the “Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)” statement (Vol Elm et al., 2007). Minimal quality criteria were:

a) Provision of adequate information regarding study design, sample size, recruitment and characteristics.
b) Clear description of the methods that were followed for the assessment of the exposure and outcome.
c) Provision of adequate information regarding the performed statistical analyses including confounding adjustment (which should be at least for age and gender).
d) In case a selected article did not meet the forenamed basic criteria, further information was requested from the original authors. If there was no response, the article was excluded.

Procedure

For each included study, the following data were abstracted: references, study design, respondents' characteristics (including selection, sample size, response rate, age range or mean, gender distribution and country), exposure source and intensity recalculated in volts per meter (V/m), exposure assessment, outcome assessment, variables included as potential confounders and statistically significant associations between exposure and outcomes (Tables

2 and 3). The literature search, evaluation of inclusion and exclusion criteria and evaluation of the quality of information in the articles were conducted by the first two authors, with uncertainties resolved through consultation with the rest of the co-authors. More specifically, in the first stage the titles and abstracts that were derived from the search process were independently screened, to evaluate whether they met the exposure and symptom criteria. The abstracts or titles were examined. Next, the hard copies of the publications fulfilling the inclusion criteria were assessed in terms of the population and study criteria. Finally, an article quality evaluation was performed.

Data synthesis and analysis

After paper selection and data extraction, the included studies were screened for meta-analysis suitability. Studies were considered eligible if they assessed the same symptoms, or outcomes of similar meaning (e.g. fatigue and exhaustion), employed comparable methods to assess exposure and used comparable instruments and cut-off points to assess the outcome(s). Based on these parameters, it was decided to conduct meta-analyses on the effect of objectively measured electromagnetic field strength on different NSPS. The risk of bias due to exposure misclassification, selective participation and confounding was assessed for the relevant studies (Table 4), as proposed by Grimes and Schulz (2002). Studies with a high risk of one or more of the basic categories of bias were not included in the meta-analyses; the method of rating was broadly based on schemes used by previous systematic reviews (Röösli et al., 2010). Finally, studies were included only if the adjusted odds ratios (OR) (risk for reference exposure category versus risk for highest exposed category) and 95% confidence interval (95% CI) for the association were given or derivable.

Studies were grouped on the basis of the investigated symptoms and assessment (frequency/chronicity or severity/acuteness). For each reported outcome the log-transformed OR value and standard error were calculated. Effect sizes were weighted using the inverse variance method (Sutton et al., 2000). DerSimonian–Laird random effects meta-analyses (DerSimonian and Laird, 1986) were performed to calculate the pooled OR estimates and their 95% CI. Two measures of heterogeneity were used: The Squared tau (τ^2) value which indicates the underlying between-study variability (Rücker et al., 2008) and the I^2 quantity which describes the percent variation across studies due to heterogeneity rather than chance (Higgins et al., 2003); low, moderate and high heterogeneity levels correspond to I^2 values of 25%, 50% and 75% respectively.

Publication bias was assessed by Egger's regression test (level of significance: $p < 0.05$) (Egger et al., 1997). Where possible, we also performed a number of sensitivity analyses to evaluate the stability of the results. Meta-analyses were performed using the MIX software version 1.7 (Bax et al., 2006).

Definitions

In the present paper, three main terms are consistently used to describe the exposure and outcome: Actual EMF Exposure, Perceived EMF Exposure and Non-specific Physical Symptoms (NSPS). Actual Exposure refers to EMF levels assessed by objective exposure indicators/proxies such as measurements of field strength. Perceived Exposure is determined as the subjective estimation of the magnitude of being exposed to EMF (sources), assessed by self-reported instruments. In this review, perceived exposure is investigated as an indicator of a nocebo effect and not as a proxy for actual exposure. *NSPS* refers to the health outcomes, as a general and neutral term which does not imply any causal link with a particular pathogenic source.

Results

Study characteristics

The database investigation yielded 640 abstracts in total: 400 from Medline and 240 from the other 5 electronic databases. The citations that were derived from Medline were complete including both title and abstract, while only the title was available for a considerable amount of citations in the other databases.

Whenever necessary, we sought for further information by requesting the full articles. Overall, 608 studies were excluded, because they did not meet the inclusion criteria (Fig. 1). A further search in additional bibliographic sources yielded 9 studies, which all appeared to be eligible. Forty-one articles were found to be eligible for the review; evaluation with regards to article quality of reporting led to a further exclusion of 21 studies (Appendix A). Finally, 20 research articles from the peer-reviewed literature were accepted for this review, representing 22 studies (Tables 2 and 3); eighteen of cross-sectional design, three longitudinal and one case–control study.

Ten studies investigated NSPS in relation to actual exposure, 9 studies on perceived exposure and 3 studied both aspects. Response rates were given in 17 studies, ranging from 37% to 88% for the studies on actual exposure and from 36% to 75% for the studies on perceived exposure. Sample sizes ranged between 54–420 095 (actual exposure studies) and 132–4520 subjects (perceived exposure studies). The percentage of female participants ranged between 15%–66% and 10%–66% respectively. In most of the studies on actual exposure, mobile phone base stations constituted the EMF source of primary concern in the investigation (n= 8), while most of the studies providing data on the effect of perceived exposure on NSPS, focused on mobile/wireless phone use (n= 9). The majority of the studies was conducted in Europe (n= 20).

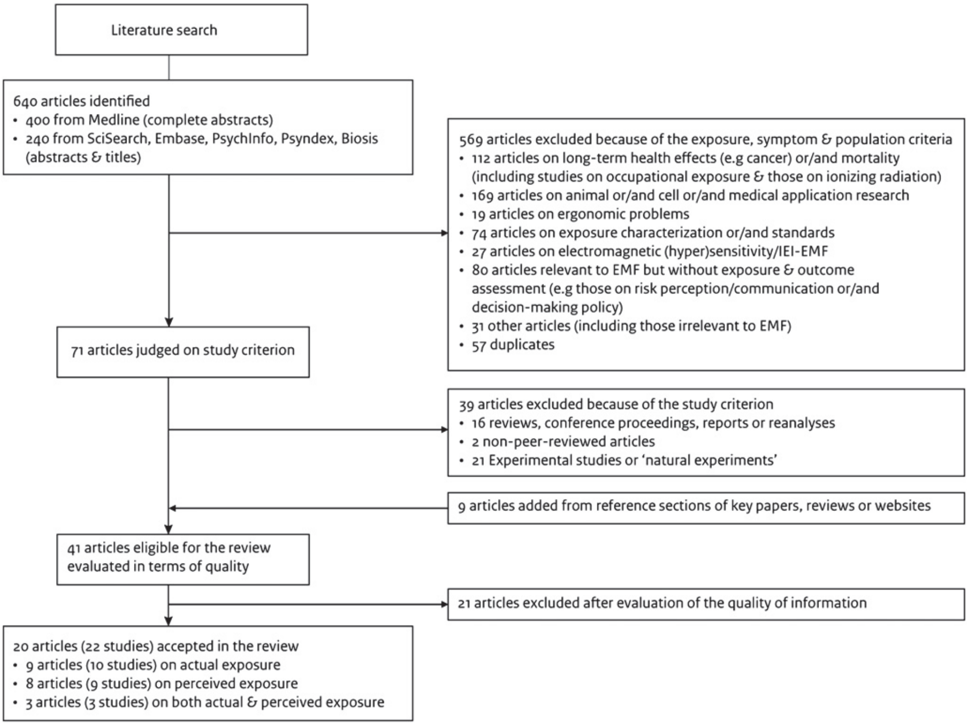


Figure 1: Flow diagram outlining the study selection process

Actual exposure and NSPS

Thirteen studies in total provided data on the association between actual exposure and NSPS; eleven of cross-sectional design, one longitudinal study and one registry-based cohort (Table 2). Exposure (24 h) assessment was based on field strength spot measurements (n=7 studies), use of personal dosimeters during waking hours (n=4), exposure prediction modeling (n=1) and geo-coded distance to base stations (n=1). The time weighted average electric field strength in these studies could be approximately estimated as ≤ 0.1 V/m for the reference (low/unexposed) group of participants and did not exceed the 5 V/m for the individuals being considered as highly exposed.

Eight studies used standardized instruments to assess NSPS (Altpeter et al., 2006; Berg-Beckhoff et al., 2009; Blettner et al., 2009; Heinrich et al., 2010; Heinrich et al., 2011; Hutter et al., 2006; Mohler et al., 2010; Thomas et al., 2008). The “Von Zerssen complaint list” (Von Zerssen, 1976) was the most consistently used symptom scale. Overall, the most frequently investigated outcomes were headache, sleep problems, dizziness-related symptoms (such as vertigo), fatigue-related symptoms (such as exhaustion) and concentration problems.

The majority of the studies did not show a significant effect of exposure on fatigue related-symptoms (n=4 versus n=1) and concentration difficulties (n=3 versus n=1). Findings for headache were contradictory, since n=4 studies reported a significant association with higher exposure levels, while n=3 suggested no association. Results for sleep problems and dizziness-related symptoms were also found to be contradictory (n=4 versus n=5 and n=3 versus n=3 respectively). Two studies used symptom total scores as outcome (Berg-Beckhoff et al., 2009; Blettner et al., 2009); one did not find any exposure effect while the other showed a weak association, although only geo-coded distance to base stations was employed (Blettner et al., 2009), which is a not a sufficient proxy for actual exposure (Frei et al., 2010).

Evidence regarding other NSPS (e.g. migraine and memory problems) was limited and inconsistent. Studies employing more advanced exposure characterization methods such as personal dosimeters and exposure prediction modeling were less likely to find significant associations (Heinrich et al., 2010, 2011; Mohler et al., 2010; Thomas et al., 2008). Apart from age, gender and socio-economic status, the most examined potential confounders were perceived mobile phone use, urbanization level, smoking habits and risk perception/concerns related to possible health effects caused by EMF exposure. It should be mentioned that although the studies of Heinrich et al. (2010, 2011) and Milde-Busch et al. (2010) investigate different outcomes (e.g. acute versus chronic symptoms), they are based on the same sample.

Perceived exposure and NSPS

Twelve studies provided data on the association between perceived exposure and NSPS; ten of cross-sectional design, one case–control study and one cohort (Table 3). Perceived exposure was measured based mainly on the daily mobile phone use.

Seven studies used standardized instruments to assess symptoms (Heinrich et al., 2010, 2011; Herr et al., 2005; Hutter et al., 2010; Milde-Busch et al., 2010; Mohler et al., 2010; Thomée et al., 2011). The most consistently examined outcomes were headache, dizziness, sleep problems, fatigue-related symptoms, concentration problems, burning sensations in the facial area, ears or body and tinnitus. Most of the studies showed an effect of perceived exposure on concentration problems (n=4 versus n=2) and headache (n=5 versus n=3), while no statistically significant effect was demonstrated for the majority of the studies on sleep problems (n=4 versus n=1) and dizziness (n=5 versus n=2). Results were contradictory for fatigue-related symptoms (n=4 studies reported significant associations versus n=3 that did not report significant results), tinnitus (n=2 versus n=1) and burning sensations (n=2 versus n=2). Again, evidence regarding other NSPS was limited and inconsistent. Apart from age, gender and socio-economic status, there was a quite consistent adjustment for video display terminal (VDT) use, stress-related variables and urbanization level as potential confounders.

Table 2: Observational studies on actual 24h EMF exposure and NSPS

Reference	Study design	Actual Sample characteristics (response rate)	Exposure source & average field strength range	Exposure assessment	Outcome assessment	Variables included as possible confounders	NSPS significantly associated with the highest actual exposure levels
[a] Abelin et al., 2005 (1992)	Cross-sectional	404 (60%) subjects with mean age=45 y.o living in the vicinity of a broadcast transmitter in Switzerland. F.g=57.6%.	Short-wave broadcast transmitter, ≤0.38 V/m (reference category) to <3.8 V/m.	Field strength measurements in different outdoor locations based on actual distance from the exposure source.	Self-constructed symptom questionnaire on sleep problems.	Age, gender, education, attribution, duration of time lived at the same location.	Nervousness (OR=2.77; 95% CI=1.62-4.74), difficulties in falling asleep (OR=3.35; 95% CI=1.86-6.03), difficulties in maintaining sleep (OR=3.19; 95% CI=1.84-5.52), joint pain (OR=2.46; 95% CI=1.37-4.43), limb pain: (OR=2.51; 95% CI=1.15-5.50), cough and sputum (OR= 2.80; 95% CI=1.18-6.64).
Abelin et al., 2005 (1996)	Cross-sectional	399 (77%) subjects with mean age=49 y.o living in the vicinity of a short-wave broadcast transmitter in Switzerland. F.g=57%.	Short-wave broadcast transmitter, ≤0.38 V/m (reference category) to <3.8 V/m.	Field strength measurements in different outdoor locations based on actual distance from the exposure source.	Self-constructed symptom questionnaire on sleep problems.	Age, gender, education, attribution, duration of time lived at the same location.	Difficulties in falling asleep (p=0.006), difficulties in maintaining sleep (p=0.001), nervousness/restlessness (p=0.024).
Abdel-Rassoul et al., 2006	Cross-sectional	165 subjects (80 controls) with mean age=39 y.o living or/and working in a building in the vicinity of a mobile phone base station in Egypt. F.g=42.4%.	Mobile phone base station, <0.61 V/m (reference category) to 0.614 – <5.0 V/m (highest exposure).	Spot field strength measurements in locations within and outside the "exposed" building.	Self-constructed symptom questionnaire on various NSPS.	Age, gender, education, smoking habits, mobile phone use.	Headache (OR=2.77; 95% CI=1.06-7.4), memory changes (OR=7.48; 95% CI=2.29-26.98), dizziness (OR=4.41; 95% CI=1.29-16.46), sleep disturbances (OR=2.77; 95% CI=1.06-7.4), tremors (p<0.01).
Altpeter et al., 2006 (baseline phase)	Longitudinal	54 subjects 24-70 y.o living in the vicinity of a short-wave broadcast transmitter in Switzerland. F.g=61%.	Short-wave broadcast transmitter, 0.15 V/m (reference category) to 0.98 V/m (highest exposure).	Spot field strength measurements & calculations.	Sleep log (VIS-M, Collegium Internationale Psychiatriae Scalarum, 4th edition) (Ott et al., 1981).	Age, gender.	Sleep quality (morning tiredness versus freshness) (regression coefficient=3.85; 95% CI=1.72-5.99).
Hutter et al., 2006	Cross-sectional	336 (64%) subjects 18-	Mobile phone base	Spot field strength	Items from Von	Age, gender, mobile	Headache (OR=3.06; 95% CI=1.22-7.67),

Reference	Study design	Actual Sample characteristics (response rate)	Exposure source & average field strength range	Exposure assessment	Outcome assessment	Variables included as possible confounders	NSPS significantly associated with the highest actual exposure levels
		91 y.o randomly selected from telephone register entries, living in urban & rural areas near mobile phone base stations in Austria. F.g=59%.	stations (GSM), 0.08 V/m (reference category) to 2.5 V/m (highest exposure).	measurements in bedrooms.	Zerssen complaint list (Von Zerssen, 1976) & PSQI (Pittsburgh Sleep Quality Index) (Buysse et al., 1989).	phone use, worry about health effects from mobile phone base stations.	cold hands or feet (OR=2.57; 95% CI=1.16-5.67), concentration difficulties (OR=2.55; 95% CI=1.07-6.08).
Preece et al., 2007	Cross-sectional	1870 (87%) subjects 18≤ y.o living in three villages differently exposed to a military antenna in Cyprus. F.g=66.2%.	Military antenna systems, <0.01 V/m (reference category) to >0.57 V/m (highest exposure).	Field strength measurements in different locations in the regions close to the antenna.	Self-constructed symptom questionnaire on various NSPS & SF-36 (Ware et al., 1993).	Age, gender, education, smoking habits, mobile phone use, perceived risk of health.	Migraine (OR=3.32; 95% CI=2.14-5.15), headache (OR=4.16; 95% CI=2.96-5.84), dizziness (OR=5.64; 95% CI=3.69-8.62), HRQoL scores ($p<0.05$).
Thomas et al., 2008	Cross-sectional	329 (40%) randomly selected subjects 18-65 y.o from registration offices of four cities on Germany. F.g=52.7%.	Mobile phone base stations (GSM, UMTS), DECT, WLAN, 0.05 – 0.075 V/m (reference category) to 0.05 – 0.3 (highest exposure).	Field strength measurements based on personal dosimeters during waking hours.	For acute symptoms: Items from Von Zerssen complaint list (Von Zerssen, 1976). For chronic symptoms: Freiburg symptom list (Fahrenberg, 1975).	Age, gender.	N.S

Reference	Study design	Actual Sample characteristics (response rate)	Exposure source & average field strength range	Exposure assessment	Outcome assessment	Variables included as possible confounders	NSPS significantly associated with the highest actual exposure levels
Berg-Beckhoff et al., 2009	Cross-sectional	1326 (85%) subjects 15-71 y.o randomly selected from a nationwide panel sample mainly from urban regions in Germany. F.g=50.8%.	Mobile phone base stations (GSM, UMTS), FM radio, analogue TV & DVB-T, TETRA, DECT, WLAN & Bluetooth, <0.1 V/m (reference category) to 0.1 – 1.41 V/m (highest exposure).	Spot field strength measurements in bedrooms.	Von Zerssen complaint list (Von Zerssen, 1976), PSQI (Buysse et al., 1989), HIT-6 (Headache Impact Test) (Kosinski et al., 2003) & SF-36 (Ware et al., 1993).	Age, gender, education, mobile phone use, urbanization level, chronic stress.	N.S
Blettner et al., 2009	Cross-sectional	26 039 subjects (58.6%) 14-69 y.o randomly selected nationwide via email communication, address publishers & snow-ball systems in Germany. F.g=52%.	Mobile phone base stations.	Objectively measured distance to base stations based on geo-coding.	Frick symptom list (Frick et al., 2006).	Age, gender, education, family income, region, urbanization level, concerns/attribution.	Actual distance to mobile phone base stations (≤500 m) with NSPS total score (regression coefficient=0.34; 95% CI=0.32-0.37).
Schuz et al., 2009	Registry-based cohort	Data for 420 095 subjects ≥18 y.o in Denmark over a period of 10 years. F.g=15%.	Mobile phones.	Years of mobile phone use based on subscription records.	Hospital contacts for migraine & vertigo.	Age, gender, time period.	For the total time period: Migraine (SHR=1.2; 95% CI=1.1-1.3), vertigo (SHR=1.1; 95% CI=1.1-1.2).
[b, c] Heinrich et al., 2010	Cross-sectional	1508 (52%) subjects 13-17 y.o randomly selected from registration offices of four cities in the south of Germany. F.g=51.5%.	Mobile phone base stations (GSM, UMTS), DECT, WLAN, ≤0.05 V/m (reference category) to 0.12 – 0.62 V/m (highest exposure).	Field strength measurements based on personal dosimeters during waking hours.	Items from Von Zerssen complaint list (Von Zerssen, 1976) on various (acute) NSPS.	Age, gender, education, urbanization level, environmental worries, mobile phone use, DECT phone use, perceived distance to mobile phone base station.	Headache with exposure during morning hours (OR=1.50; 95% CI=1.03-2.19), irritation with exposure during afternoon (OR=1.79; 95% CI=1.23-2.61).
Mohler et al., 2010	Cross-sectional	1212 (37%) subjects 30-60 y.o randomly	Mobile phone base stations (GSM,	Geospatial modeling &	Questions on general	Age, gender, education, marital	N.S

Reference	Study design	Actual Sample characteristics (response rate)	Exposure source & average field strength range	Exposure assessment	Outcome assessment	Variables included as possible confounders	NSPS significantly associated with the highest actual exposure levels
		selected from population registries in the city Basel in Switzerland. F.g=58%.	UMTS), FM radio, analogue TV & DVB-T, TETRA, DECT, WLAN, 0.004 – 0.052 V/m (reference category) to 0.01 – 0.49 V/m (highest exposure).	exposure prediction model based on exposure-related characteristics & behaviours.	subjective sleep quality from the Swiss Health Survey questionnaire (Schmitt et al., 2000) & Epworth Sleepiness Scale (Johns, 1991).	status, BMI, stress perception, physical activity smoking habits, alcohol consumption, self-reported disturbance due to noise, urbanization level, belief in health effects due to RF-EMF exposure.	
[b] Heinrich et al., 2011	Cross-sectional	1508 (52%) subjects 13-17 y.o randomly selected from registration offices of four cities in the south of Germany. F.g=51.5%.	Mobile phone base stations (GSM, UMTS), DECT, WLAN, ≤0.05 V/m (reference category) to 0.12 – 0.62 V/m (highest exposure).	Field strength measurements based on personal dosimeters during waking hours.	Items from the HBSC Survey (Haugland and Wold, 2001) on various (chronic) NSPS.	Age, gender, education, urbanization level, environmental worries, mobile phone use, DECT phone use, perceived distance to mobile phone base station.	N.S

[a] Results are provided after personal communication with the original authors.
[b] Results from participants under the age of 12 years were excluded.
[c] The studies of Heinrich et al., (2010) and Heinrich et al., (2011) were based on the same sample.
Abbreviations: CI, Confidence interval; OR, Odds ratio; SHR, Standardized hospitalization ratio; N.S, no statistical significance; y.o, Years old; F.g, Female gender distribution; NSPS, Non-specific physical symptoms; GSM, Global system for mobile communications; NMT, Nordic mobile telephone; DECT, Digital enhanced cordless telecommunications; UMTS, Universal mobile telecommunications system; WLAN, Wireless local area network; DVB-T, Digital video broadcasting-Terrestrial; TETRA, Terrestrial trunked radio; HRQoL, Health-related quality of life; BMI, Body mass index.

Table 3: Observational studies on perceived EMF exposure and NSPS

Reference	Study design	Actual Sample characteristics (response rate)	Exposure source	Self-reported exposure assessment	Outcome assessment	Variables included as possible confounders	NSPS significantly associated with the highest perceived exposure levels
Chia et al., 2000	Cross-sectional	808 (45%) randomly selected subjects 12-70 y.o living in an urban area in Singapore. F.g=52.7%.	Mobile phones (GSM, NMT).	Daily calling duration in minutes, daily number of calls.	Self-constructed symptom questionnaire on symptoms related to the central nervous system.	Age, gender, ethnicity, occupational status, VDT use.	For calling duration: Headache (p=0.038). Users versus non-users: Headache (PR=1.31; 95% CI=1.0-1.70).
[a]Sandstrom et al., 2001 (Norway)	Cross-sectional	1872 (58%) randomly selected registered mobile phone users ≥18 y.o in Norway. F.g=10%.	Mobile phones (GSM, NMT).	Daily calling duration in minutes, daily number of calls.	Self-constructed symptom questionnaire on various NSPS.	Age, gender, occupational status, workplace location, work-related psychosocial factors, VDT use.	Daily calling duration (GSM): Dizziness (OR=11.8; 95% CI=3.08-45.6), fatigue (OR=4.16; 95% CI=1.87-9.24), headaches (OR=6.84; 95% CI=2.44-19.1), warmth behind ear (OR=15.6; 95% CI=6.2-39.3), warmth on ear (OR=8.21; 95% CI=3.24-20.8), burning skin (OR=9.21; 95% CI=2.68-31.7). Daily number of calls (GSM): Dizziness (OR=2.85; 95% CI=1.25-6.48), concentration difficulties (OR=2.28; 95% CI=1.19-4.38), fatigue (OR=2.27; 95% CI=1.41-3.65), headaches (OR=3.23; 95% CI=1.70-6.11), warmth behind ear (OR=3.43; 95% CI=2.01-5.85), warmth on ear (OR=4.22; 95% CI=2.48-7.19), burning skin (OR=2.90; 95% CI=1.43-5.89).
[a]Sandstrom et al., 2001 (Sweden)	Cross-sectional	4520 (66%) randomly selected registered mobile phone users ≥18 y.o in Sweden. F.g=14%.	Mobile phones (GSM, NMT).	Daily calling duration in minutes, daily number of calls.	Self-constructed symptom questionnaire on various NSPS.		Daily calling duration (GSM): Headaches (OR=2.63; 95% CI=1.22-5.67), warmth behind ear (OR=26.9; 95% CI=10.0-72.2), warmth on ear (OR=26.4; 95% CI=10.3-66.9). Daily number of calls (GSM): Dizziness (OR=2.85; 95% CI=1.25-6.48), concentration difficulties (OR=2.28; 95% CI=1.19-4.38), fatigue (OR=2.27; 95% CI=1.41-3.65), headaches (OR=3.23; 95% CI=1.70-6.11), warmth behind ear (OR=3.34; 95% CI=2.01-5.85), warmth on ear (OR=4.22; 95%

Reference	Study design	Actual Sample characteristics (response rate)	Exposure source	Self-reported exposure assessment	Outcome assessment	Variables included as possible confounders	NSPS significantly associated with the highest perceived exposure levels
							CI=2.48-7.19), burning skin (OR=2.90; 95% CI=1.43-5.89).
Herr et al., 2005	Cross-sectional	132 subjects ≥18 y.o voluntarily selected in Germany. F.g=54%.	Mobile phones (GSM).	Daily calling duration in minutes.	PSQI (Buysse et al., 1989)	Age, gender, daily working time, stress, score on psychosomatic symptoms.	N.S
Mortazavi et al., 2007	Cross-sectional	518 (75%) voluntarily selected university students ≥18 y.o in Iran. F.g=66.2%.	Computer monitors, mobile phones, cordless phones.	Possession of a device and/or daily use at least for 30 seconds the last 3 months (for mobile phones) and 1 minute for computer monitors.	Self-constructed symptom questionnaire on various NSPS.	Age, gender, occupational status, VDT use, medical history.	For cordless phones: Concentration difficulties ($p<0.05$), attention difficulties ($p<0.05$).
Soderqvist et al., 2008	Cross-sectional	1269 (63.5%) randomly selected young subjects 15-19 y.o in Sweden. F.g=52.2%.	Mobile phones (GSM, NMT, digital 3G), wireless phones (DECT).	Daily calling duration in minutes.	Self-constructed symptom questionnaire on various NSPS.	Age, gender, hands-free equipment use.	For mobile phones (total use): Asthmatic symptoms (OR=1.8; 95% CI=1.1-3.0), headache (OR=1.5; 95% CI=1.1-2.0), concentration difficulties (OR=1.4; 95% CI=1.1-1.9). For DECT (total use): Asthmatic symptoms (OR=1.9; 95% CI=1.01-2.2), headache (OR=1.5; 95% CI=1.2-2.1), concentration difficulties (OR=1.4; 95% CI=1.03-1.9), tiredness (OR=1.3; 95% CI=1.01-1.8).

Reference	Study design	Actual Sample characteristics (response rate)	Exposure source	Self-reported exposure assessment	Outcome assessment	Variables included as possible confounders	NSPS significantly associated with the highest perceived exposure levels
[b] Milde-Busch et al., 2010	Cross-sectional	1025 (51.5%) subjects 13-17 y.o randomly selected from population registries in for cities in Germany; 489 meeting criteria for increased headache report and 536 reporting no headache. F.g=51.2%.	Mobile phones, VDT/computer monitors & related activities.	Daily use in minutes.	Item on Headache screening (King et al., 1996) & self-constructed questionnaire on different types of headache based on the International Classification of Headache Disorders (ICHD-II).	Age, gender, socio-economic status, family condition.	N.S
[c] Heinrich et al., 2010	Cross-sectional	1508 (52%) subjects 13-17 y.o randomly selected from registration offices of four cities in the south of Germany. F.g=51.5%.	Mobile phones.	Daily calling duration in minutes.	Items from Von Zerssen complaint list (Von Zerssen, 1976) on various (acute) NSPS.	Age, gender, education, urbanization level, environmental worries.	For mobile phone use: Headache (OR=1.55; 95% CI=1.05-2.29), irritation (OR=1.64; 95% CI=1.10-2.44), fatigue (OR=1.76; 95% CI=1.22-2.56).
Hutter et al., 2010	Case-control	200 subjects (100 controls) 18-60 y.o enrolled as tinnitus patients of a medical department in Vienna, Austria.	Mobile phones.	Past and/or present mobile phone use in terms of possession, daily average call duration, cumulative hours of use & number of calls & years of use.	Clinical examination, self-reported questionnaire on tinnitus (Structured Tinnitus Interview) (Hiller et al., 2000) & psychoacoustic measurements.	Age, gender, education, urbanization level.	For long-term mobile phone use in years (4≤) on the side of the head that tinnitus occurred: Tinnitus (OR=1.95; 95% CI=1.00-3.80).
Mohler et al., 2010	Cross-sectional	1212 (37%) subjects 30-60 y.o randomly	Mobile phones, mobile	Calling duration,	Questions on general	Age, gender, education, marital status, BMI,	N.S

Reference	Study design	Actual Sample characteristics (response rate)	Exposure source	Self-reported exposure assessment	Outcome assessment	Variables included as possible confounders	NSPS significantly associated with the highest perceived exposure levels
		selected from population registries in the city Basel in Switzerland. F.g=58%.	phone base stations, cordless phones.	perception of being generally exposed.	subjective sleep quality from the Swiss Health Survey questionnaire (Schmitt et al., 2000) & Epworth Sleepiness Scale (Johns, 1991).	stress perception, physical activity smoking habits, alcohol consumption, self-reported disturbance due to noise, urbanization level, belief in health effects due to RF-EMF exposure.	
[c] Heinrich et al., 2011	Cross-sectional	1508 (52%) subjects 13-17 y.o randomly selected from registration offices of four cities in the south of Germany. F.g=51.5%.	Mobile phones, DECT phones.	Daily use.	Items from the HBSC Survey (Haugland and Wold, 2001) on various (chronic) NSPS.	Age, gender, education, urbanization level, environmental worries, perceived distance to mobile phone base station.	For mobile phone use: Irritation (OR=1.48; 95% CI=1.13-1.93). For DECT phone use: Irritation (OR=1.30; 95% CI=1.02-1.64).
[d] Thomee et al., 2011	Prospective cohort	4156 (36%) subjects 20-24 y.o randomly selected from population registries in Sweden. F.g=65%.	Mobile phones.	Frequency of daily calls & SMS-type messages.	Items from the Karolinska Sleep Questionnaire (Keeklund and Akerstedt, 1992).	Gender, education, occupational status, relationship status (the sample was homogeneous regarding age).	At baseline: Sleep problems (PR=1.4; 95% CI=1.30-1.62). At follow-up: Sleep problems (PR=1.3; 95% CI=1.06-1.66).

[a] Analyses yielded similar associations for NMT use.
[b] The studies of Milde-Busch et al., (2010), Heinrich et al., (2010) and Heinrich et al., (2011) were based on the same sample.
[c] Results from participants under the age of 12 years were excluded.
[d] Results are provided after personal communication with the original authors.
Abbreviations: CI, Confidence interval; OR, Odds ratio; PR, Prevalence ratio; N.S, no statistical significance; y.o, Years old; F.g, Female gender distribution; NSPS, Non-specific physical symptoms; GSM, Global system for mobile communications; NMT, Nordic mobile telephone; DECT, Digital enhanced cordless telecommunications; VDT, Video display terminal; 3G, Third generation digital phone; BMI, Body mass index.

Table 4: Risk for three basic categories of bias* in observational studies on objectively measured EMF strength and NSPS

Reference	Exposure measurement bias	Selection bias	Confounding
Abelin et al., 2005 (1992)	+ +(although exposure assessment was relatively adequate for that specific frequency no indoor measurements were performed)	+ + + (possibility for awareness bias, increased possibility for non-response bias)	+ + (a few variables were considered)
Abelin et al., 2005 (1996)	+ + (although exposure assessment was relatively adequate for that specific frequency no indoor measurements were performed)	+ + + (increased possibility for awareness bias & nonresponse bias)	+ + (a few variables were considered)
Abdel-Rassoul et al., 2006	+ + + (crude exposure assessment, no recent measurements were available)	+ + + (increased possibility for awareness bias & nonresponse bias)	+ + (a few variables were considered)
Altpeter et al., 2006 (baseline)	+ + (although exposure assessment was relatively adequate for that specific frequency no indoor measurements were performed)	+ + + (increased possibility for awareness bias)	+ + (a few variables were considered)
Hutter et al., 2006	+ + (small exposure contrast)	+ + (subjects that agreed to participate might constitute a selective population group with increased EMF-related concerns)	+
Preece et al., 2007	+ + + (no indoor measurements were performed, conservative calculation methods)	+ + + (increased possibility for awareness bias, increased prevalence of EMF-related concerns in the “exposed”groups)	+
Thomas et al., 2008	+ + (small exposure contrast)	+ + (subjects that agreed to participate might constitute a selective population group with increased EMF-related concerns)	+ + (a few variables were considered)
Berg-Beckhoff et al., 2009	+ + (small exposure contrast)	+ + (increased prevalence of EMF-related concerns among subjects participating in measurements)	+
Blettner et al., 2009	+ + + (use of poor exposure proxies)	+ + (subjects that agreed to participate might constitute a selective population group with increased EMF-related concerns)	+
Heinrich et al., 2010	+ + (small exposure contrast)	+ + (subjects that agreed to participate might constitute a selective population group with increased EMF-related concerns)	+
Mohler et al., 2010	+ + (small exposure contrast)	+ + (possibility for nonresponse bias)	+
Heinrich et al., 2011	+ + (small exposure contrast)	+ + (subjects that agreed to participate might constitute a selective population group with increased EMF-related concerns)	+

*Note: + low risk for bias, + + medium risk for bias, + + + high risk for bias.

Meta-analyses

Overall, 5 studies were excluded from the meta-analyses (Abdel-Rassoul et al., 2006; Abelin et al., 2006; Altpeter et al., 2006; Blettner et al., 2009; Preece et al., 2007), primarily due to high risk for bias and lack of comparability. One study was excluded because it was not possible to obtain the OR and 95% CI (Berg-Beckhoff et al., 2009). Finally, depending on the outcome, 2 to 4 studies of cross-sectional design were included in the meta-analyses (Heinrich et al., 2010, 2011; Hutter et al., 2006; Mohler et al., 2010; Thomas et al., 2008) (Table 5).

Most of the studies characterized exposure levels using personal dosimeters (Heinrich et al., 2010, 2011; Thomas et al., 2008). The investigated NSPS were headache, concentration problems, fatigue-related problems, dizziness-related problems and sleep problems. Since studies used self-reported scales to measure either the frequency of symptoms (labeled as "chronic") or severity (labeled as "acute"), apart from the classification of the studies on the basis of the investigated symptom, they were also grouped based on these types of measures in order to enhance their comparability. All the "acute" NSPS were measured with items from the "Von Zerssen complaint list" (Von Zerssen, 1976). Among the 3 studies assessing these symptoms (Heinrich et al., 2010; Hutter et al., 2006; Thomas et al., 2008), two used the same cut-off points (Heinrich et al., 2010; Hutter et al., 2006); a symptom was considered to be present if it was "at least of weak intensity", while in the study of Thomas et al. (2008) if it was "at least moderate". Regarding the "chronic" NSPS, although the two eligible studies (Heinrich et al., 2011; Thomas et al., 2008) employed different standardized scales (Fahrenberg, 1975; Haugland and Wold, 2001) they used similar cut-off points (a symptom was considered to be present if occurred "nearly once every week" and "at least twice a month" respectively) and the same time reference ("during the last six months"). For the assessment of sleep problems, most of the analyzed studies used summarized items on sleep quality (Hutter et al., 2006; Mohler et al., 2010; Thomas et al., 2008).

In the study of Hutter et al. (2006) a median split was applied for the total score of sleep quality (OR and 95% CI were available after personal communication with the original authors). In the study of Mohler et al. (2010) a number of questions about subjective sleep quality were summarized into a binary sleep quality score (ranging between 0 and 12); a score of ≤ 8 was considered as an indication of having sleep problems. The time reference for these two studies was "during the last month" and "during the last four months" respectively.

The scales and cut-off points for the studies of Thomas et al. (2008) and Heinrich et al. (2011) were the same as for the measurement of "chronic" NSPS, which were previously described.

There were between 919 and 1897 study participants included in each analysis. The publication dates of the studies included ranged between 2006 and 2011. The forest plots for summarizing the meta-analyses for the 7 outcomes are shown in Figs. 2 and 3. Heterogeneity was negligible to moderate for the NSPS that were measured based on their severity (acute) and negligible to low for the NSPS that their assessment was based on their frequency (chronic). There was no publication bias apparent.

Analyses did not show a significant effect of higher exposure levels on any of the examined outcomes (Table 5, Figs. 2 and 3). Two of the analyzed studies on acute NSPS investigated symptom report in relation to exposure during both morning and afternoon hours (Heinrich et al., 2010; Thomas et al., 2008); since in the abovementioned meta-analyses we used the ORs for symptoms occurring during morning hours, additional analyses were performed replacing these ORs with the ones for symptoms reported in the afternoon. Statistically significant results were observed for headache (OR = 1.9; 95% CI = 1.07–3.49, p = 0.03) and dizziness-related problems (OR = 1.54; 95% CI = 1.02–2.31, p = 0.04), while the risk estimate for the rest of the acute outcomes remained non-significant (concentration problems: OR = 1.4; 95% CI = 0.81–2.41, p = 0.22, fatigue-related problems: OR = 0.92; 95% CI = 0.48–1.77, p = 0.82).

Table 5: Odds ratio of self-reported NSPS based on their severity (acute) and frequency (chronic), according to random-effect meta-analyses of observational studies on the association between actual EMF exposure and NSPS.

Outcome	Studies n	Reference group n*	Highly exposed Group n*	Combined OR (95% CI)	*P*	τ^2	I^2 %	Egger's test *P*
Acute NSPS								
Headache	3	626	544	1.65 (0.88-3.08)	0.11	0.13	40.3	0.97
Concentration problems	3	626	544	1.28 (0.56-2.94)	0.55	0.28	57.5	0.91
Fatigue-related problems	3	626	544	1.15 (0.59-2.27)	0.66	0.23	66.7	0.78
Dizziness-related problems	2	544	461	1.38 (0.92-2.07)	0.11	0.00	0.00	N.A
Chronic NSPS								
Headache	2	459	460	1.01 (0.66-1.53)	0.96	0.00	0.00	N.A
Fatigue	2	459	460	1.12 (0.60-2.07)	0.71	0.11	0.00	N.A
Sleep problems	4	1248	649	1.18 (0.80-1.74)	0.40	0.03	24.7	0.28

Note: OR, Odds ratio; CI, Confidence interval; *P*, p value, τ^2, square tau value for heterogeneity; I^2, statistic for heterogeneity; Egger's test, Regression test for publication bias; N.A, not applicable due to limited number of analysed studies.
*Data regarding the number of participants for the exposure categories are provided after personal communication with the original authors.

An extra sensitivity analysis was performed by integrating the OR of the studies excluded from the meta-analyses (based on the quality and comparability criteria) into the principal analyses. This was possible for 2 studies assessing headache based on its frequency (Abdel-Rassoul et al., 2006; Preece et al., 2007) and 2 assessing sleep problems (Abdel-Rassoul et al., 2006; Abelin et al., 2006); the recalculated pooled estimate remained non-significant for chronic headache (OR = 2.03; 95% CI = 0.79– 5.19, p = 0.14) and for sleep problems was OR=1.65; 95% CI=1.00–2.72, p=0.05. In line with the qualitative evaluation, there were very high levels of statistical heterogeneity (I^2 = 89% and I^2 = 70%), which demonstrate the incomparability of these studies, since the exposure characterization methods, self-reported symptom scales and especially the cut-off points varied considerably.

Figure 2: Forest plots of random-effect meta-analyses of observational studies on the association between actual EMF exposure and NSPS for 4 self-reported outcomes based on severity.

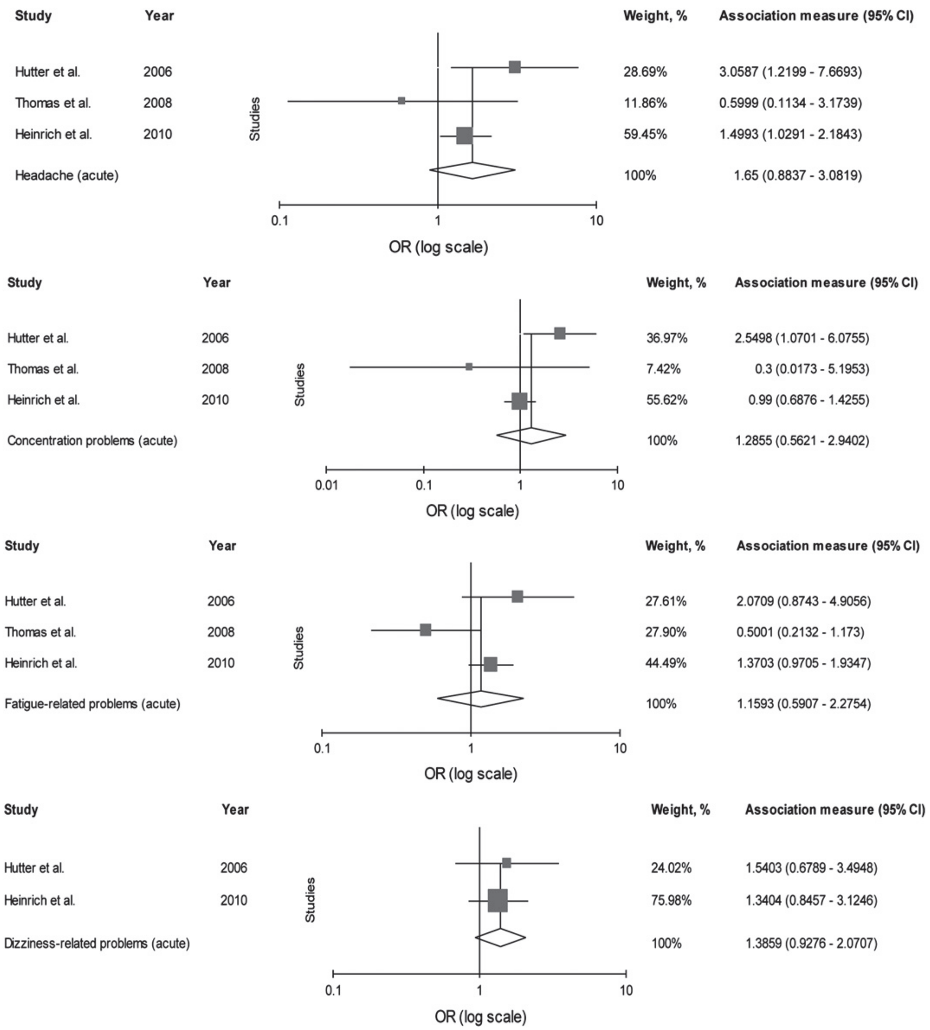
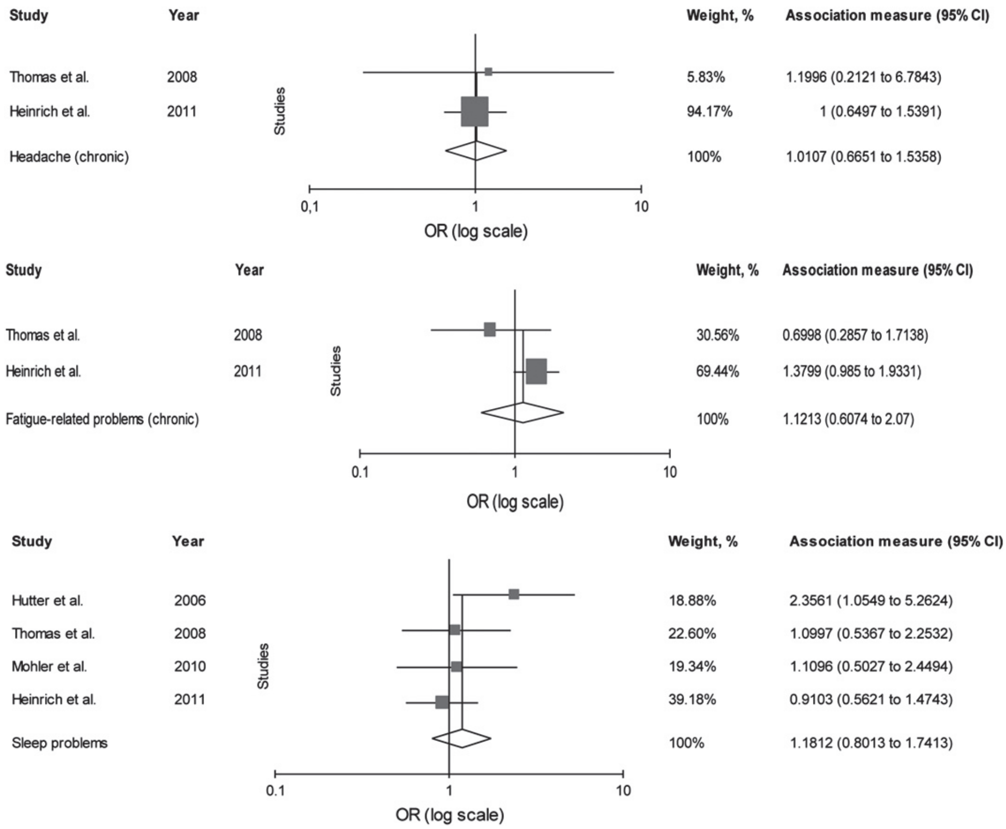


Figure 3: Forest plots of random-effect meta-analyses of observational studies on the association between actual EMF exposure and NSPS for 3 self-reported outcomes based on frequency.



Discussion

The present systematic review identified the observational epidemiological studies conducted during the last eleven years on the effect of actual and perceived EMF exposure on the report of NSPS in the general population. Using sensitive search strategies and strict quality criteria, we distinguished the most examined NSPS and assessed the strength of evidence for an association with higher exposure levels. Meta-analyses were conducted to quantify the associations.

The review showed that there is no consistent association between actual exposure to EMF and occurrence of NSPS in the general population. Most of the studies suggested either no significant effect of higher exposure levels as in the case of fatigue-related symptoms and concentration difficulties, or contradictory results as in the case of dizziness-related symptoms, sleep problems and headache. It was also observed that methodological quality was an important component for the strength of the associations, since studies with a higher risk of bias, mainly regarding exposure assessment and sample selection, reported more significant associations.

More recent studies which tend to employ advanced exposure characterization methods did not suggest a significant effect; this is in agreement with the findings of Röösli and Hug (2011). Studies on perceived exposure showed generally stronger symptomatic effects and more consistent patterns, indicating an association with concentration problems and headache, while most of them yielded non-significant or contradictory results for sleep problems, dizziness, fatigue-related symptoms and tinnitus. Differences in the conceptual framework of perceived exposure and variation in symptom and exposure assessment prevented us from conducting a meta-analysis of these studies.

Pooling the risk estimates of studies with a smaller chance of exposure misclassification and selection and confounding bias, the performed meta-analyses yielded no significant risk difference between low exposed and highly exposed individuals regarding symptom frequency and severity. In a sensitivity analysis of "acute" symptoms, when we pooled the ORs for exposure measurements "during afternoon hours" instead of exposure "during morning hours" for two of the studies, analyses yielded statistical significance only for headache and dizziness-related problems. This is probably due to the nearly significant OR in the study with the most power (Heinrich et al., 2010). Since this was the case for a number of associations in that study, the authors attributed it to multiple testing, stating that after considering exposure as a 90% cut-off in the analyses (data were not available), any significant association disappeared.

It is notable that while 9 out of 13 reviewed studies on actual exposure data suggest an association for at least one symptom, when we qualitatively examined these associations per symptom group, only the effect on headache was slightly more often significant. In this qualitative assessment we did not exclude studies of higher chance of bias which are prone to effect overestimation. In the meta-analysis, where those studies were excluded, all the associations were found to be non-significant.

Since quality assessment in meta-analysis is often controversial, in an additional sensitivity analysis, we pooled the risk ratio of studies with higher probability of bias in the principal analyses; the summary effect was higher but heterogeneity was striking. Despite the non-significant results, it is noteworthy that the vast majority of the exposure–symptom associations in the studies on actual exposure show a positive association. Independently of the study quality, exposure and outcome measures and examined symptoms, people who are exposed to higher levels of EMF, tend to report NSPS more frequently or severely than their “unexposed” counterpart. Possible explanations for this phenomenon could be just chance, selection bias leading to overestimation of the effect, positive-outcome bias in peer-review literature (Emerson et al., 2010), the lack of sufficient exposure contrast which could mask an exposure–outcome association, if one existed, or the small prevalence in the general population of people sensitive to EMF, which could reduce the power for the detection of a significant effect. Additionally, possible exposure misclassification effects cannot be dismissed due to the existing limitations in exposure characterization (Röösli and Hug, 2011).

The strengths of this systematic review include a comprehensive search strategy, the examination of studies on both actual and perceived exposure and the performance of meta-analyses. Important publication bias as a result of preferential publication of studies with significant findings is unlikely to have occurred as Eggers's test on bias also indicated. However, in some cases Egger's test could not calculate the bias risk due to the limited number of studies. Among the articles excluded due to inadequacy of the provided information and lack of minimal confounding adjustment, only one concerned actual exposure, suggesting a positive significant association with various NSPS (Eger and Jahn, 2010). All the other excluded studies focused on perceived exposure, with the vast majority reporting a significant effect, which was not adjusted for confounders (Appendix A).

This is the first time that a meta-analytic study is conducted for the effect of EMF on NSPS. The only formal meta-analysis to date in this research field focused on the individual ability to perceive short-term EMF exposure tested by randomized double-blind trials (Röösli, 2008; Röösli et al., 2010), including only a small number of studies. In the present meta-analyses, a considerable number of subjects were included, and all the analyzed studies were considered comparable in terms of study design, type of exposure source, exposure and outcome assessment. Although there was some variation in the measured exposure levels across the studies, they all were much lower than the safety limits as established by ICNIRP (1998).

Our meta-analysis has a number of limitations, such as the small number of comparable studies available for analysis, which however reflects that there are only a few comparable high quality studies addressing this issue. This prevented us from performing a meta-regression with other explanatory variables. Another shortcoming might be the fact that the study with the most statistical power was restricted to the age groups between 13 and 17 years old, which could constitute a source of heterogeneity. Nevertheless, epidemiological studies on actual exposure often set the 15 years of age or even lower as age limit for participation (Berg-Beckhoff et al., 2009; Blettner et al., 2009) and no important differences between adolescents and young adults have been shown in terms of symptom patterns, even for larger age contrasts (Yzermans and Oskam, 1990). Finally, some between-study variation was expected due to the classification of symptoms in groups and a few differences in cut-off points as was described in detail in the Results section.

This review included studies on actual as well as perceived exposure to EMF. Since people are not able to accurately self-estimate the magnitude of personal exposure to EMF sources (Frei et al., 2010; Inyang et al., 2008; Vrijheid et al., 2009), we used perceived exposure as an indicator of a nocebo phenomenon that could possibly indicate underlying psychological processes. The subjective belief of being exposed to a hazardous environmental source could reinforce the alertness for the presence of potential exposure indicators, the expectations of symptom occurrence and consequently the development and report of symptoms (Landgrebe et al., 2008). In the broader literature a number of studies have accentuated the role of psychologically-oriented factors in the report of NSPS attributed to environmental exposures (Johansson et al., 2010; Landgrebe et al., 2008; Osterberg et al., 2007; Persson et al., 2008; Rubin et al., 2006, 2008). However, most of the reviewed studies used perceived exposure as a proxy for actual exposure. This may explain the inconsistency across results. More recently published studies on actual exposure (Heinrich et al., 2010, 2011; Mohler et al., 2010) investigated the effect of perceived exposure as well, together with some psychological components such as environmental worries as confounders, but evidence regarding psychological determinants of NSPS related to EMF is still very limited and consensus about a conceptual framework on their mediating or moderating role is lacking.

Although, in terms of design, experimental studies are preferable for the clarification of causal relationships, observational studies allow the investigation of longer-term exposures and outcomes and evaluation of possible mediating determinants in larger population samples. Exposure assessment remains a major challenge.

On the one hand, methods such as self-reported exposure or geo-coded distance are not sufficient surrogates for personal exposure, and spot measurements provide only limited knowledge on exposure for specific locations (Frei et al., 2010). On the other hand, personal exposure measurements with exposimeters come with biases due to calibration issues, arrival angle dependent response, and body shielding, which lead to underestimation of the actual exposure (Bolte et al., 2011; Mann, 2010). Also, performing personal exposure measurements in large groups is very time-consuming and expensive and therefore may not be feasible for large, especially cohort, studies. Nevertheless, personal exposure measurements are recommended, as they are actually measuring one's exposure during all activities at all locations (Neubauer et al., 2007). If it is not feasible to measure every group member, a prediction model based on modeled exposure of fixed transmitters and exposimeter measurements may be the best compromise (Frei et al., 2009, 2010).

Since the restriction of sources of bias is of vital importance, future epidemiological studies should be particularly careful regarding the sample selection and data collection; the combination of electronic medical records from general practices and self-reported health data in conjunction with exposure data, would be an important step forward in this field of research. For future research, it is also suggested that instead of adopting either the psychogenic or the bioelectromagnetic hypothesis for the explanation of NSPS in relation to EMF, the exposure–outcome association should be considered as a product of an interaction between actual exposure, the perception of the magnitude of being exposed and psychological factors, consonant to a psychobiological approach.

In light of this systematic review, and taking findings from systematic evaluation of experimental evidence into account (Röösli and Hug, 2011; Röösli et al., 2010; Rubin et al., 2009) it is concluded that there is no direct association between actual exposure to EMF and NSPS. An association between NSPS and perceived exposure seems to be stronger and more consistent, but striking heterogeneity regarding the conceptual framework and assessment of exposure and outcome prevents from more solid conclusions. The establishment of an international protocol of harmonization of concepts and exposure–outcome characterization would minimize the methodological obstacles in epidemiological research on EMF and NSPS and strengthen the interpretations of future meta-analytic studies.

Conclusions

There are no indications for an association between higher levels of actual EMF exposure and frequency or severity of NSPS in the general population. An association with perceived exposure seems to exist, but evidence is still scarce mainly because of between-study differences in the conceptual framework and measurement. More epidemiological studies are needed, using comparable methods and instruments to assess exposure and outcome and investigating the role of perceived exposure and mediating psychological components in conjunction with actual exposure. Studies on long-term effects of residential EMF exposure are of particular importance in order to enhance our knowledge.

Acknowledgments

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Appendix: List of excluded articles (based on the evaluation of the quality of information) and reasons for exclusion

Reference	Exposure (based on the assessment method)	Primary reason(s) for exclusion*
Santini et al., 2002	Perceived	1, 2
Navarro et al., 2003	Perceived	1, 2
Santini et al., 2003	Perceived	1, 2
Al-Khlaiwi and Meo, 2004	Perceived	1, 2, 3
Balikci et al., 2005	Perceived	1, 2, 3
Balik et al., 2005	Perceived	1, 2, 3
Meo and Al-Drees, 2005a	Perceived	1, 2, 3
Meo and Al-Drees, 2005b	Perceived	1, 2, 3
Szyjkowska et al., 2005	Perceived	1, 2
Al-Khamees, 2007	Perceived	1, 2
Davidson et al., 2007	Perceived	1
Koivusilta et al., 2007	Perceived	1
Pennarola et al., 2007	Perceived	1, 2
Punamäki et al., 2007	Perceived	1
Thomée et al., 2007	Perceived	1
Al-Abduljawad, 2008	Perceived	1, 2, 3
Al-Khamees, 2008	Perceived	1, 2, 3
Khan, 2008	Perceived	1, 2, 3
Kucer, 2008	Perceived	1, 2, 3
Augner and Hacker, 2009	Perceived	1
Eger and Jahn, 2010	Actual	1

*Note: 1=No (report of) adjustment for confounding variables, 2= lack of important information regarding study design and/or sample recruitment/size/characteristics, 3=lack of important information regarding the methods/instruments that were used for the exposure and outcome assessment.

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Chapter 3

Non-specific physical symptoms in relation to actual and perceived proximity to mobile phone base stations and powerlines

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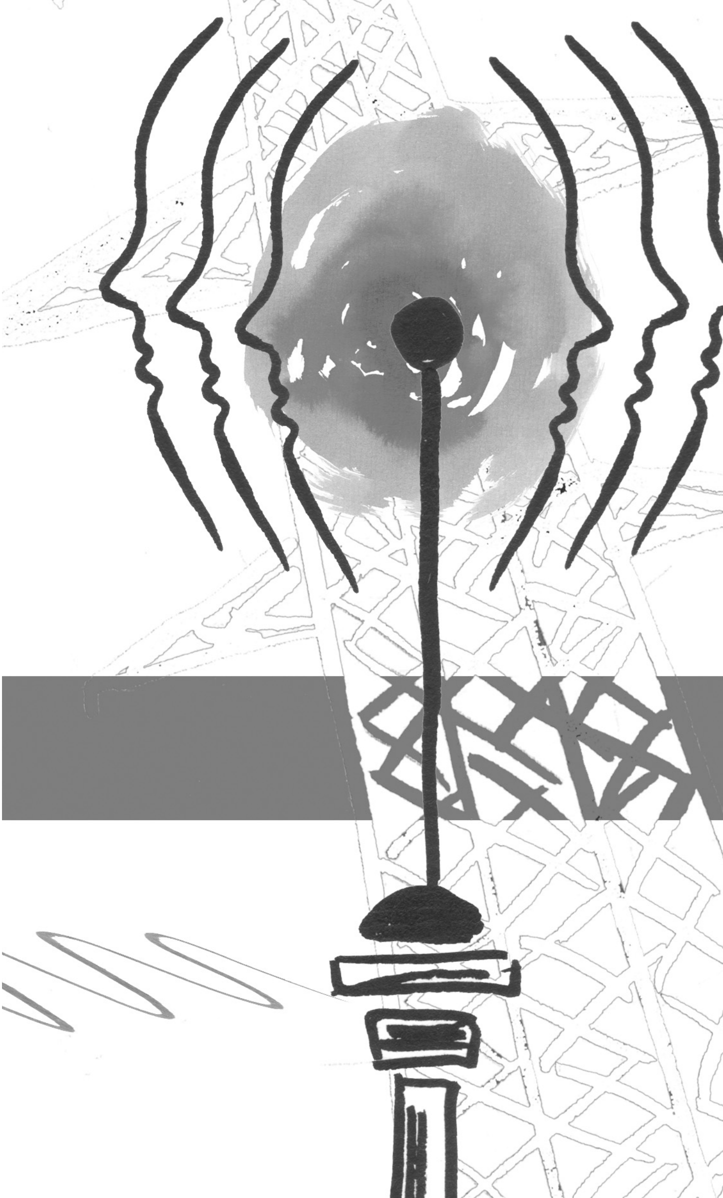

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Summary

Background: Evidence about a possible causal relationship between non-specific physical symptoms (NSPS) and exposure to electromagnetic fields (EMF) emitted by sources such as mobile phone base stations (BS) and powerlines is insufficient. So far little epidemiological research has been published on the contribution of psychological components to the occurrence of EMF-related NSPS. The prior objective of the current study is to explore the relative importance of actual and perceived proximity to base stations and psychological components as determinants of NSPS, adjusting for demographic, residency and area characteristics.

Methods: Analysis was performed on data obtained in a cross-sectional study on environment and health in 2006 in the Netherlands. In the current study, 3611 adult respondents (response rate: 37%) in twenty-two Dutch residential areas completed a questionnaire. Self-reported instruments included a symptom checklist and assessment of environmental and psychological characteristics. The computation of the distance between household addresses and location of base stations and powerlines was based on geo-coding. Multilevel regression models were used to test the hypotheses regarding the determinants related to the occurrence of NSPS.

Results: After adjustment for demographic and residential characteristics, analyses yielded a number of statistically significant associations: Increased report of NSPS was predominantly predicted by higher levels of self-reported environmental sensitivity; perceived proximity to base stations and powerlines, lower perceived control and increased avoidance (coping) behavior were also associated with NSPS. A trend towards a moderator effect of perceived environmental sensitivity on the relation between perceived proximity to BS and NSPS was verified ($p = 0.055$). There was no significant association between symptom occurrence and actual distance to BS or powerlines.

Conclusions: Perceived proximity to BS, psychological components and socio-demographic characteristics are associated with the report of symptomatology. Actual distance to the EMF source did not show up as determinant of NSPS.

Introduction

Technological development does not only improve people's quality of life but is often accompanied by increased worry about potential health effects related to environmental exposures [1]. A considerable part of the general population does not only express serious concerns but also attributes various health complaints and symptoms to relatively low-level exposure to Electromagnetic fields (EMF), emitted by sources such as mobile phone devices, base stations and powerlines [2-5]. This phenomenon of symptom attribution to EMF exposure is often referred to as "Electromagnetic Hypersensitivity" (EHS) and more recently as "Idiopathic Environmental Intolerance attributed to Electromagnetic Fields" (IEI-EMF) [6].

According to the World Health Organization (WHO) IEI-EMF is characterized by physical symptoms such as redness, tingling and burning sensations in the face, fatigue, tiredness, lack of concentration, dizziness, nausea, heart palpitation and digestive disturbances [7]. These complaints are estimated to be prevalent in 1.5% of the general population in Sweden [2], 3.2% in California [8], 5% in Switzerland [3], 3.5% in Austria [4] and 10.3% in Germany [5] and seem to be frequently accompanied by occupational, social and mental impairment [9,10]. Age, gender, education, occupational status and ethnicity have been recognized as stable predisposing factors for the NSPS attributed to EMF [2,3,5,11].

Results from well-designed epidemiological studies indicate no consistent associations between various symptoms and residential EMF exposure [12-16]. Recent reviews strengthen the aforementioned evidence, concluding that a causal relationship between health complaints and exposure to EMF cannot be adequately and consistently supported [17-19]. Additionally, the need of improvement in major methodological aspects such as exposure characterization, symptom assessment, study design, population selection, sample size and the investigation of possible confounders has been highlighted.

Since the causes of EMF-attributed symptoms are unspecified and so far there is a lack of objective findings that could support a causal mechanism, these subjective complaints belong to the domain of the so-called "Non-specific physical symptoms" or "Medically Unexplained (Physical) Symptoms" which are often attributed to environmental exposures [20]. In the current paper the term "Non-specific physical symptoms" (NSPS) is used to refer to the symptoms, as a broader and more neutral term which does not imply a link with particular etiologic agents, especially since similar symptoms are very common in the general population [21]. The most recent systematic review focusing (exclusively) on experimental evidence was based on the examination of 46 studies involving 1117 subjects [19]. It was suggested that symptoms attributed to EMF might be a result of underlying psychological processes related to the nocebo effect. The latter reflects the triggering of symptoms under blind experimental conditions, due to individual's expectations of harmful health effects produced by a sham exposure source. Perceived exposure to EMF sources such as BS might be associated with elevated symptom scores [22] and could comprise an important element in this process; the subjective belief of being exposed to a hazardous source can reinforce the alertness for the presence of potential exposure indicators, the expectations of symptom occurrence and consequently the development and report of symptoms [23].

Although a number of studies have accentuated the role of psychological factors in unexplained environmental intolerances [23-28] evidence regarding a psycho-physiological process underlying this phenomenon is still scarce and consensus on a conceptual framework is lacking. In view of the possible overlap between diverse environmental sensitivities [29], it is also questionable whether IEI-EMF constitutes a unique condition or should be considered as a part of a broader syndrome. It has been shown that subjects with IEI-EMF report increased self-reported sensitivity to several other environmental stressors apart from EMF [2]. Approaches from the area of health psychology support the notion that investigation of both the individual and environmental context can elucidate the mechanisms behind the occurrence of ill health, including socioeconomic, geographic, demographic and psychological components [30]. In line with this perspective, research in environmental epidemiology has indicated that NSPS attributed to environmental exposures might be the result of an interaction between biological, psychological and social pathways [31]. This exploratory study aims to a better understanding of the pathways through which exposure to EMF could be associated with increased report of non-specific physical symptoms, by introducing potential determinants and moderators of this relationship. More specifically, adjusting for demographic, home and area characteristics, the present analysis was performed to subsequently test:

- Whether actual (objectively measured) distance and perceived (self-reported) proximity to BS are associated with report of NSPS, controlling for actual and perceived proximity to powerlines.
- The impact of psychological components such as self-reported environmental sensitivity, lack of perceived control and coping styles (problem oriented versus avoidance) on NSPS report.

Methods

Selection and recruitment

The study makes use of data which were collected in 2006 in the Netherlands. Residents were selected from twenty two residential areas with varying levels of urbanization, socioeconomic status (SES) and clustering of environmental problems (air pollution, noise and green area). After selecting areas with contrasting levels of urbanization, SES and accumulation of environmental problems (irrelevant to EMF), a random sample of inhabitants age 18 and over was drawn via the registration offices of the selected municipalities. More people from one household could be selected. The initial (gross) sample consisted of N = 9502 persons.

In the period between May-September 2006, people were invited to participate in a study about environmental quality, residential satisfaction and subjective health by either filling out a written questionnaire or a web based version. A small reward of 5 Euros was offered for participation. A press report was released in local newspapers. Two reminders were sent to non-responders. The total response rate was 37% (N = 3611). Among the respondents, 85% used the written questionnaire, while 15% participated via the website. For each included neighborhood, an equal number of non-respondents was extracted; short telephone interviews were performed for this non-response group (N = 255, response rate: 41%) in order to determine the degree of selection bias. The questionnaire data from the full sample were used in the current study, after linking the home addresses of the respondents to the location of BS and powerlines.

Ethics

The current study was approved by the Dutch Medical Ethics Review Committee (METC). The data set was collected in 2006 following the privacy guidelines of the Dutch Privacy Law regarding the use of personal data (WBP) of the National Institute for Public Health and the Environment. All data were treated anonymously and confidentially.

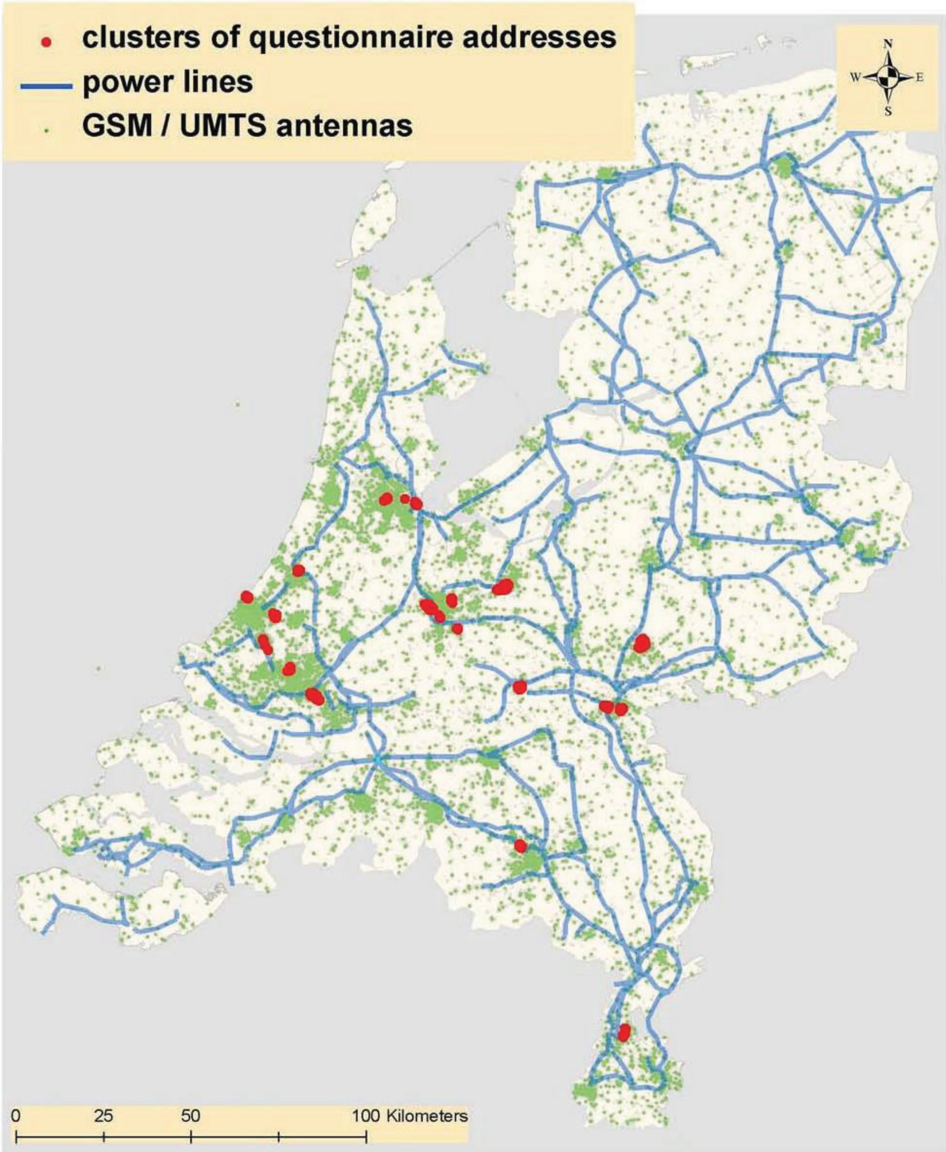
Procedure

The 3611 respondents lived at 2921 different addresses, determined by zip/postal code, house number and an optional house number extension. These were matched with the Address Coordinate File Netherlands (ACN) of the Dutch Land Registry which contains all the addresses of the Dutch dwellings as well as the Dutch standard co-ordinates of the dwellings.

Records of the Antenna Bureau of the Netherlands for each base station, the Dutch standard co-ordinates and the type of communication were involved (GSM900, GSM1800, UMTS). The GIS-EMV information system operated by the Laboratory of Radiation Research at the National Institute for Health and the Environment (RIVM) was used to determine the base stations close to a respondent's address. Both the distance of the address to the base station and an identification of the base station itself were added as an attribute to the respondents' addresses.

The data on the location of the powerlines were derived from the same geographical information system. In a collaboration of RIVM and KEMA (a technical consultancy with expertise in the energy sector) the Dutch network of overhead powerlines has been digitized in 2002 from topographic maps (1:25000) [32]. The overhead high-voltage powerlines have five voltage levels ranging from: 50 kilovolts to 380 kilovolts (kV). The total length of overhead high-voltage powerlines amounts to nearly 4000 km. These powerline data were used to select the powerline closest to a sample address and to determine the shortest (perpendicular) distance of the sample address to that powerline. Both the distance of the address to the powerline and an identification of the powerline itself were added as an attribute to the sample address. An overview of the position of the addresses, BS and powerlines is illustrated in Figure 1.

Figure 1: Distribution over the Netherlands of the house addresses, mobile phone base stations and powerlines that were included in the study (clusters refer to groups of addresses)



Material

The Somatization scale of the Four-Dimensional Symptom Questionnaire (4DSQ or 4DKL) [33] was used to measure NSPS. It contains 16 items, with a score range of 0-32. Responses are based on the individual experience during the period of "last week", categorized as "no", "sometimes", "regularly", "often", "very often" and "constantly". They are scored as 0 for "no", 1 for "sometimes" and 2 for the rest response categories. The cut-off points divide the scores into "low" (0-10), "moderately high" (11-20) and "very high" (21-32). The scale measures a variety of physical symptoms that could be related to distress or psychopathologic conditions. A moderate score might indicate the presence of increased levels of distress, while higher scores can reflect psychological mechanisms that involve maladaptive health beliefs and focusing attention on symptoms. The scale is characterized by high internal consistency (Cronbach's a = 0.84).

To assess self-reported environmental sensitivity, a list of 9 items based on the Sydney Airport Survey [34] was used, representing perceived sensitivities to environmental stressors such as noise, light, specific materials, color, smells, temperature changes, cold or warm environment. The answers are formatted in a 5-point scale ranging from strongly disagree (0) to strongly agree (4). The reference period was "during the previous week". A higher score indicates a higher perceived sensitivity.

Perceived Proximity to BS and powerlines was evaluated with two positive statements; "I live in the vicinity of a mobile phone base station" and "I live in the vicinity of a powerline" ("vicinity" was defined as neighborhood). Answers were categorized as "yes" (1) and "no"(0) reflecting a high and low perception of proximity respectively.

Coping Styles were assessed using the subscales of Active problem-solving (5 items) and Avoidance (2 items) of the Utrecht Coping List (short version) [35]. The first subscale illustrates a direct and logical approach towards problematic situations and the second one describes the effort to avoid to deal with a stressful stimulus. All items are scored on a 4-point Likert scale (1 = Seldom or Never, 2 = Sometimes, 3 = Often, 4 = Very often). These two subscales have been demonstrated to be reliable in the general Dutch population, with Cronbach's a = 0.81 for the Active problem-solving scale and a = 0.67 for the Avoidance scale.

Lack of Perceived Control was identified using two items from a Dutch version of the Life Orientation Test (LOT) [36]: "I am always optimistic about my future" and "I hardly ever expect things to go my way". Furthermore, an extra item was added and combined, namely “If I try I can influence the quality of my living environment”, in order to enhance the individual sense of control that can lead to a positive outcome. The score is rated on a 5-point Likert scale ranging from strongly disagree (0) to strongly agree (4). After proper reversals the included items were summed, with higher scores indicating less perceived control. Good validity has been demonstrated in Dutch population samples [36].

Finally, the questionnaire included questions on socio-demographic characteristics such as age, gender, ethnicity, education, occupational status, type of residence and home ownership status.

Statistical analysis

Variables representing distance measures were log-transformed in order to obtain normally distributed variables. Multilevel linear regression models were used to determine the effect of actual distance and perceived proximity to BS and powerlines, psychological components and demographic and home characteristics on the occurrence of NSPS which was included as a continuous score in the analysis.

Taking into account the hierarchical nature of the data, a selection of levels of random effects was made in a model (random intercepts) describing the relation between the (log) actual distance to BS and NSPS. The selection used tests based on the Restricted Maximum Likelihood (REML). Once the levels for random effects were chosen they were included in all subsequent analyses for comparison reasons. It is recommended for epidemiological studies to use a multilevel approach for confounding, since specific contextual characteristics such as SES may influence the associations between exposure and health [37]. In the current study each PC4 level contains a large but varying number of PC6 areas with a range 1 to 132 participants per code. Based on the results of the analysis of the random effects on NSPS it appeared that PC4 and PC6 were relevant to include in the multilevel analysis. Therefore, all models were adjusted for these random effects, plus SES (cross classification). Statistical significance of fixed effects was tested by comparing the goodness of fit of different models using a chi-square test of deviance.

The estimation of effects on NSPS included five steps, which are presented as separate models.In the primary analysis, the relationship between (log) actual distance to BS and NSPS was examined. A second linear mixed model tested the same relation while adjusting for demographic characteristics. In the following analysis (log) perceived proximity to BS and powerlines and (log) actual distance to powerlines were included.

Next, the model was extended with variables related to home characteristics. In the final model, psychological variables were added to evaluate the relative contributions of coping styles, perceived control and self-reported environmental sensitivity.

In order to verify a possible moderating effect of psychological components on the relation between perceived proximity to BS and NSPS, the interaction term between each psychological component (avoidance, problem-solving, control, perceived sensitivity) and perceived proximity to BS were entered in the final model. This was based on the hierarchical moderated regression approach [38]. Descriptive statistics were produced using the Statistical Package for Social Sciences (SPSS), version 17. Linear mixed models and the moderated regression were conducted within the statistical software package R, version 2.10.0.

Results

Descriptive analyses and non-response

Table 1 presents the demographic structure and other key characteristics of the respondents. Descriptive analyses (using one-way ANOVA and t-test analyses) demonstrated a number of statistically significant differences in symptom report between different groups: Female participants had a higher score in NSPS $t\ (3516) = -9.05$, $p = 0.00$ compared to men. Significant differences were found between different age groups $F(5, 3548) = 7.52$, $p = 0.00$; the highest scores were reported by the youngest (mean = 7.1, SD = 5.52) and the oldest category (mean = 6.31, SD = 5.47).

Table 1: General characteristics of the individuals included in the analysis.

Characteristic	Analytic sample (n = 3611)
Age in years (%)	
18-24	208 (5.8)
25-34	702 (19.4)
35-44	799 (22.3)
45-54	733 (20.5)
55-64	586 (16.4)
65 <	550 (15.4)
Missing	33
Gender	
Male (%)	1580 (44.1)
Female (%)	2002 (55.9)
Missing	29
Ethnicity	
Native (%)	2860 (79.7)
Non-native (%)	730 (20.3)
Missing	21
Education*	
Lower (%)	581 (16.6)
Middle (%)	1292 (36.9)
Higher (%)	1629 (46.5)
Missing	109
Occupational status	
> 20 hours per week (%)	2045 (56.6)
< 20 hours per week (%)	256 (7.1)
Unemployment/Retirement (%)	635 (17.6)
Work incapacity (%)	143 (4)
Students/Housewives	532 (14.7)
Missing	0
Type of residency	
Separate (detached) house/Villa	235 (6.8)
Semi-detached house	900 (26)
Townhouse/Terraced house/Unit or flat with own Entrance	1341 (38.7)
Unit or flat (with shared entrance or front door at walkway - covered/non-covered)	988 (28.5)
Missing	147
Home ownership status	
Owned (%)	2195 (61.2)
Rented (%)	1391 (38.8)
Missing	25
Perceived proximity (subjects answering "yes")	
Base Stations (%) (total missing: 111)	1197 (34.2)
Powerlines (%) (total missing: 103)	523 (14.9)
	Mean(*SD*)
Actual distance to BS (in metres)	347.3 (259.9)
Actual distance to powerlines (in metres)	2381 (1508.5)
Non-specific physical symptoms	6.1 (5.43)
Missing	28

*Note: Higher: scientific education; Middle: professional education; Lower: lower than professional.

Differences were also observed across the categories of educational level F (2, 3476) = 88.7, p = 0.00, with people of lower education reporting the highest symptom score (mean = 8.18, SD = 6.75). Symptom report also differed in terms of occupational status F (4, 3578) = 67.7, p = 0.00; the highest symptom score was reported by people unable to work (mean = 11.84, SD = 7.4) and unemployed individuals (mean = 7.04, SD = 5.9). Finally, non-native participants scored significantly higher in NSPS t(984) = -3.04, p = 0.002 than natives. Information about the prevalence of each of the 16 examined symptoms is provided in Figure 2.

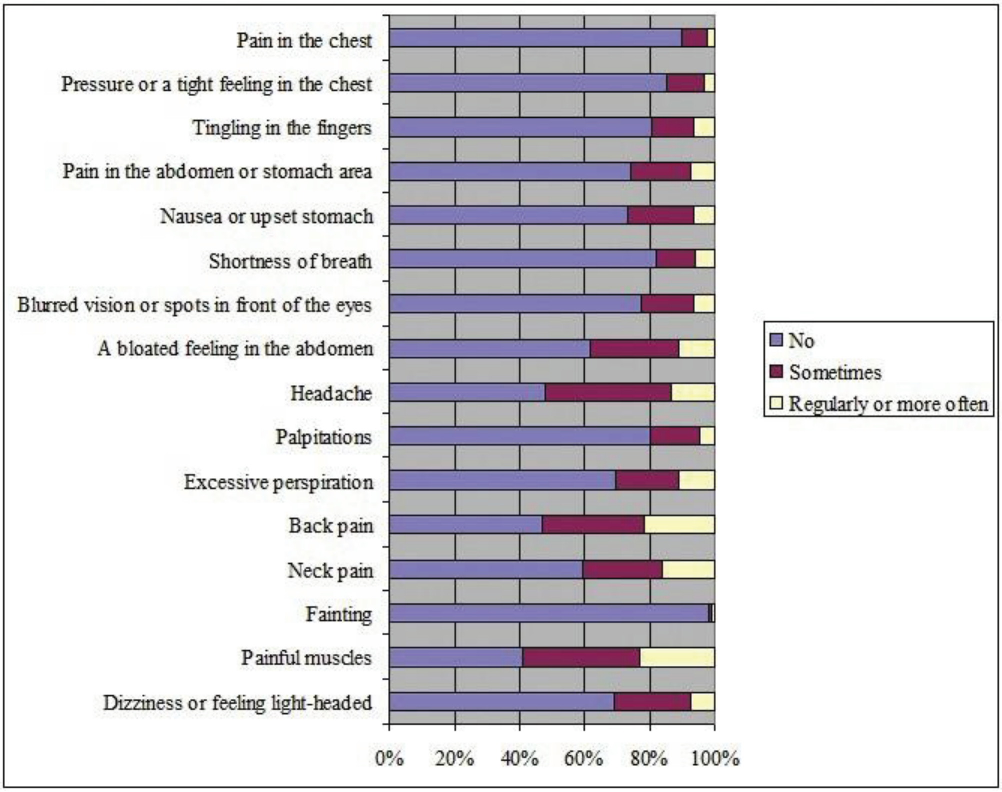


Figure 2: Frequencies (%) of the 16 self-reported symptoms in the sample

The associations between actual distance and perceived proximity for BS and powerlines are shown in Figures 3 and 4; the non-parametric Wilcoxon test yielded no significant results ($p = 0.15$ and $p = 0.17$ respectively).

A comparison of the 3611 respondents with 255 people (response rate 41%) who did not participate in the study, indicated small differences in demographic structure between the two groups: Participants were in general younger (mean age: 47 years) and had a higher level of education (46.5%) compared to non-participants (mean age: 50 years, higher education: 30%). In addition, participants were significantly less satisfied with their residential situation than the non-respondents (80% versus 90%, $p < 0.05$) and scored significantly lower on perceived health (68% versus 73%, $p < 0.05$). There were no differences in the male/female ratio. Based on these findings a moderate non-response bias might exist, which can be explained by the fact that part of the distribution is inherent to the study design and sampling process.

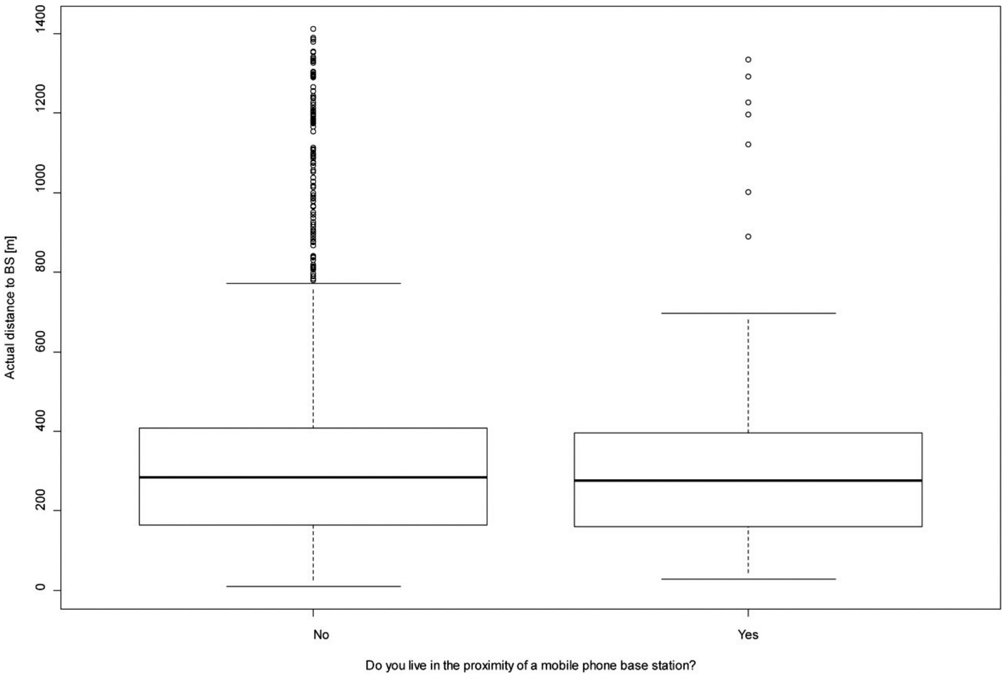


Figure 3: Box plot indicating the non-significant correlation between actual distance and perceived proximity to mobile phone base stations

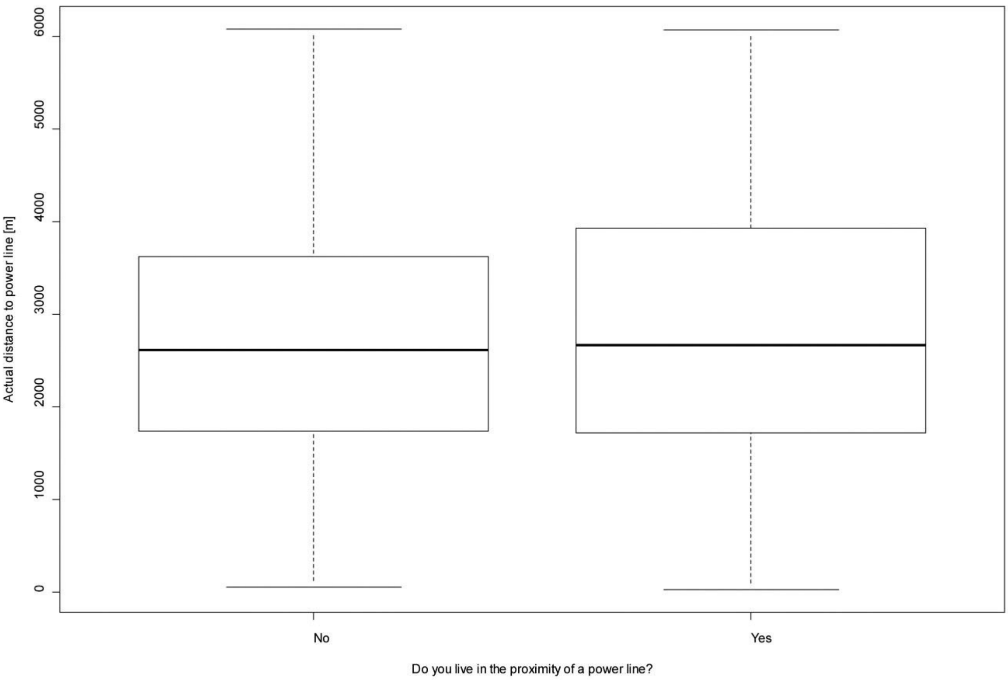


Figure 4: Box plot indicating the non-significant correlation between actual distance and perceived proximity to powerlines

Multivariate analysis

Table 2 summarizes the results of the steps followed for the development of the full multilevel model.

In the unadjusted model the effect of actual distance to BS was not significant (Model 1, Table 2). Results did not change after controlling for demographic characteristics. A significant effect was observed for gender, education and occupational status (Model 2).

In the next model (Model 3) the variables of actual distance and perceived proximity to powerlines were entered; although there was no relation between actual distance to powerlines and symptoms (estimate = 0.13, 95% CI -0.28 to 0.54), increased perceived proximity towards both BS and powerlines was associated with increase of symptom report. The fixed effect of actual distance to BS was increased but remained non-significant as in the previous equations. When aspects related to the home environment were included, only the effect of renting a home was found to be significant (Model 4).

In the final model, the added contribution of psychological variables such as lack of perceived control, self-reported environmental sensitivity and the coping styles of problem-solving and avoidance was evaluated; a significant impact on NSPS was found for lack of perceived control and increased environmental sensitivity and avoidance, but not for problem-solving. Table 2 gives an overview of the final model estimates (Model 5).

In this fifth step, an analysis of interaction terms showed that there was a trend towards a moderator effect of perceived environmental sensitivity on the relation between perceived exposure to BS and NSPS ($\chi^2 = 3.66$, df = 1, p = 0.055). The other terms had no significant influence. It is also noteworthy that after the inclusion of the fixed effects, the random effects of PC4 and PC6 were no longer significant. Dichotomization of actual distance to base stations (≤500 m., >500 m.) in line with the approach of Blettner et al. [5] did not change the results.

Table 2: Effects of actual distance and perceived proximity to BS and psychological components on NSPS

		Beta estimate (95% CI)*				
		Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**
Fixed effects						
log Actual distance to BS		-0.02 (-0.35 – 0.34)	-0.004 (-0.33 – 0.32)	0.14 (-0.19 – 0.45)	0.28 (-0.05 – 0.6)	0.25 (-0.037 – 0.57)
Female Gender			1.46 (1.05 – 1.87) ‡	1.48 (1.09 – 1.9) ‡	1.46 (1.04 – 1.85) ‡	0.97 (0.57 – 1.36) ‡
Age			-0.04 (-0.20 – 0.12)	-0.07 (-0.25 – 0.08)	-0.10 (-0.27 – 0.06)	-0.06 (-0.22 – 0.09)
Education			-1.91 (-2.6 – -1.27) ‡	-1.93 (-2.59 – -1.29) ‡	-1.76 (-2.4 – -1.05) ‡	-1.44 (-2.07 – -0.82) ‡
Occupational status						
(Work Incapacity)			4.54 (3.44 – 5.65) ‡	4.48 (3.39 – 5.6) ‡	4.33 (3.23 – 5.44) ‡	3.8 (2.72 – 4.9) ‡
(< 20 hours/week)			-1.02 (-1.93 – -0.16) ⊤	-1.05 (-1.97 – -0.20) ⊤	-0.94 (-1.84 – -0.07) ⊤	-1 (-1.85 – -0.17) ⊤
(> 20 hours/week)			-0.69 (-1.3 – -0.09) ⊤	-0.66 (-1.25 – -0.05) ⊤	-0.56 (-1.16 – 0.06)	-0.27 (-0.90 – 0.27)
Students/housewives			0.14 (-0.65 – 0.88)	0.15 (-0.61 – 0.91)	-0.01 (-0.72 – 0.78)	0.001 (-0.71 – 0.74)
Ethnicity			0.29 (-0.22 – 0.79)	0.31 (-0.20 – 0.82)	0.32 (-0.17 – 0.83)	0.36 (-0.14 – 0.83)
Perceived proximity to BS				0.91 (0.24 – 1.58) ┼	0.90 (0.23 – 1.58) ┼	0.75 (0.08 – 1.37) ⊤
Perceived proximity to powerlines				0.99 (0.57 – 1.44) ‡	0.99 (0.54 – 1.42) ‡	0.87 (0.44 – 1.3) ‡
log Actual distance to powerlines				0.10 (-0.28 – 0.54)	-0.0002 (-0.39 – 0.42)	-0.05 (-0.40 – 0.25)
Home ownership status (Rented)					1.16 (0.64 – 1.64) ‡	0.84 (0.35 – 1.33) ┼
House type					0.78 (-0.09 – 1.61)	0.57 (-0.22 – 1.38)
Perceived environmental sensitivity						0.16 (0.13 – 0.19) ‡
Lack of Perceived control						0.43 (0.32 – 0.54) ‡
Problem-solving						-0.05 (-0.12 – 0.02)
Avoidance						0.18 (0.09 – 0.28) ‡
Random effects (variances)						
Postcode level						
PC4	1.09 † ‡	1.12	0.36	0.35	0.31	0.11
PC6	1.1 † ⊤	0.85	0	0.21	0	0
Neighborhood level						
SES	1.35 †	1.31	0.62	0.64	0.22	0.21
Measurement level						
Residual	26.4 †	26.4	25.1	24.4	24.5	22.3

*95% CI = 95% Confidence interval calculated by means of the standard error. ⊤ $p < 0.05$. ┼ $p < 0.01$. ‡ $p < 0.001$. † Effects of random parameters on NSPS before adjusting for individual characteristics.

Discussion

The results of this study show that the actual distance to mobile phone base stations and powerlines did not predict non-specific physical symptoms, while socio-demographic and psychological factors have a significant effect on symptom report. Higher self-reported environmental sensitivity, perceived proximity to base stations and powerlines, lower perceived control, increased avoidance, living in a rented home, female gender, lower educational level and incapacity for work were significantly associated with increased NSPS report.

Comparing the symptom frequency in our sample with previous studies using the somatization scale of 4DSQ in the working population [39], we observed an average increase between 3%-6% (per symptom) for people reporting symptoms “regularly or more often” ("Fainting” was the only exception, reported almost in the same frequency). This increase can be explained if we take into account that in the current study more demographic categories are included (such as people being unemployed/retired or unable to work who are prone to symptom report). Therefore we consider these symptom rates as representative for the general population. This can be also supported by the fact that the mean symptom scores in the current sample (83% scored between 0-10, 14% 11-20 and 2.8% 21-32) were lower compared to general practice patients [40] and higher compared to the working population [40].

Previous cross-sectional studies investigating the link between actual distance to an EMF source and NSPS, showed inconclusive results due to methodological differences. A study solely based on female participants didn’t detect any effect of distance from powerlines on the report of NSPS [41] while a recent epidemiological study determining actual distance from BS using geo-coding, demonstrated a statistically significant but very small impact of actual distance on NSPS [5]. A possible explanation could be that in our study the association between actual distance and symptoms was tested for a greater range of other possible determinants than in the earlier studies. In addition, in the current analyses we adjusted for area effects (PC4 and PC6) and SES levels. Still, the effect of actual distance in our study was increased considerably in the fourth model and almost reached borderline significance. This is unlikely to be caused by collinearity among the examined variables, since the Variance Inflation Factor (VIF) indicated a low possibility for multicollinearity. Nevertheless, an effect overestimation due to overadjustment for (similar) socio-demographic characteristics cannot be ruled out. It is notable that after adjustment for house characteristics, the effect of “full-time” employment (> 20 hours/ week) was no more significant.

Additionally, the unadjusted effect of actual distance to BS (measured per meter) on NSPS is negligible compared to the unadjusted effects of the other examined variables (data are not shown). The fact that we found strong determinants of NSPS in the analyses, especially in the last model, reduces the possibility of residual confounding. However, other potentially strong determinants of symptomatology such as obesity and smoking habits were not taken into account.

A main outcome was the significant effect yielded for perceived proximity to both BS and powerlines on NSPS, which was stronger for powerlines compared to BS. This might be partly explained by the visual aspects of powerlines. Even though previous findings have suggested a relation between NSPS and self-reported distance/proximity [42], the latter was not examined as a psychologically-oriented determinant but rather as a proxy of the actual exposure and there was a lack of proper confounding investigation.

Another important finding was the contribution of psychological characteristics to symptom report; increased perceived environmental sensitivity, lack of perceived control and an avoidant coping style were associated with elevated report of NSPS even after adjusting for actual distance and perceived proximity to BS and powerlines, demographic, home and area characteristics. The role of these psychological factors as determinants of NSPS related to EMF has to date not been extensively investigated in epidemiological studies therefore there are no previous results for comparison. However, there is some evidence that IEI-EMF samples tend to report also other sensitivities [2]. In addition, avoidance behavior has been suggested as a possible characteristic of sensitive to EMF people [6] and perceived control as a determinant of subjective pain experience [43]. No effect was observed in the current study for the problem oriented coping strategy, the improvement of which comprises an important element in psychological treatments of NSPS [44]. Possibly, this does not hold for environmental stressors which are typically outside the control of individuals [45].

This is the first study in which the possible relation between actual distance and perceived proximity to BS and powerlines, perceived environmental sensitivity, coping strategies, perceived control and NSPS was investigated in a relatively large population sample. An important strength is the limited possibility of awareness bias, since the sample was not originally derived from subjects residing in varying vicinities of BS but was stratified based on areas with contrasting risk of environmental problems such as air and noise pollution and limited availability of green.

Apart from the two questions on perceived proximity to BS and powerlines, the issue of EMF exposure was not addressed in the original study nor included in the questions regarding environmental sensitivities. The limited possibility for such bias could be also supported by the non-significant association between actual and perceived proximity for both BS and powerlines, although this association could be influenced by the definition used to describe “vicinity”, which leaves some room for subjective interpretation.

Besides the cross-sectional nature of the present study, further limitations should be acknowledged. One weakness is related to the utilization of actual distance to BS as a proxy for exposure. Geo-coded distance might be a useful component in an EMF exposure prediction model but it is moderately correlated with residential exposure from fixed transmitters [46]; it is considered as a too simplistic proxy of the actual exposure level [46,47] which is a function of the square root of the Equivalent Isotropic Radiated Power divided by the distance. In a better approximation the power level and the antenna characteristics, e.g. the direction of the main beam of the transmitter, as well as the reflections and absorptions along the path from antenna to the home of the participant, as the housing parameters should be taken into account. Also the contribution of other EMF sources is of prior importance [46,47]. Another limitation of the study is the relatively low response rate which could increase the risk for non-response bias. Possible reasons could be the length of the study questionnaire and the small reward for participation. Non-response analysis however did not reveal large differences. Finally, at the time of this study only data on BS location as far back as June 2008 were available. Therefore the sample addresses in 2006 could only be compared with the base stations of 2008. This implies that for some addresses the closest base station did not exist yet or was not yet operable in 2006. More specifically, in June 2006 the total number of base stations (GSM900, GSM1800 and UMTS) amounted to 20.821; for June 2008 this number was 24.240 indicating an increase of 16% (data derived from the website of the Dutch ‘Antennebureau’, http://www.antennebureau.nl/antenneregister, consulted on March 15 2011). We judged this 16% mismatch in the number of base stations as acceptable and had no means to reduce it. Thus, we realize that this mismatch resulted in an underestimation of the distance of the sampled addresses to the base stations.

Bearing these limitations in mind, this analysis has laid the ground for future studies into the effects of actual and perceived exposure to EMF by pinpointing the influence of individual and environmental factors when examining the link between environmental risks and health. The findings suggest that the report of NSPS in EMF studies should be approached as the outcome of a complex interaction between aspects such as actual exposure to environmental factors, the perception of being exposed and psychological factors.

Definition and outcome measurement issues are still under debate, such as the consideration of IEI-EMF as syndrome, disorder or set of symptoms, and its differentiation from somatoform disorders and NSPS. Under a common conceptual ground in terms of diagnostic criteria, future studies have to target on the reduction of recall and selection bias in EMF studies by the combination of the electronic medical records of general practitioners and self-reported health data, and the separate examination of actual and perceived exposure. Appropriate methods for rating symptoms as EMF-related are required, taking into consideration measurement determinants that have been proposed by the broader research field of medically unexplained symptoms such as population type, use of validated symptom checklists and frequency, severity and duration of the symptoms [48]. This should be accompanied with testing the significance of psychological variables that have been proposed as relevant to the report of NSPS while adjusting for psychiatric comorbidity.

The possible role of external influential factors such as media in the perception of risk and the magnification of related worries can additionally be a dimension of research on EMF and NSPS. It is also necessary to conduct more longitudinal and prospective research to address which variables constitute stable determinants of NSPS.

Conclusions

The present cross-sectional epidemiological study in the Netherlands is an exploration of potential determinants of symptom report related to distance to mobile phone base stations and powelines. It shows no relation between actual distance to these EMF sources and NSPS. Perceived environmental sensitivity, perceived proximity, lower perceived control, increased avoidance behavior and particular demographic characteristics and home aspects were significantly associated with increased symptom report. Further analyses showed a trend towards a moderator effect of perceived environmental sensitivity on the relation between perceived proximity to BS and NSPS. These components should be introduced in future epidemiological studies as potential moderating factors in order to comprehend the causal pathways that lead to the activation of somatic responses and subsequent symptoms.

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Chapter 4

Idiopathic environmental intolerance attributed to electromagnetic fields (IEI-EMF): A systematic review of identifying criteria

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Summary

Background: Idiopathic environmental intolerance attributed to electromagnetic fields (IEI-EMF) remains a complex and unclear phenomenon, often characterized by the report of various, non-specific physical symptoms (NSPS) when an EMF source is present or perceived by the individual. The lack of validated criteria for defining and assessing IEI-EMF affects the quality of the relevant research, hindering not only the comparison or integration of study findings, but also the identification and management of patients by health care providers. The objective of this review was to evaluate and summarize the criteria that previous studies employed to identify IEI-EMF participants.

Methods: An extensive literature search was performed for studies published up to June 2011. We searched EMBASE, Medline, Psychinfo, Scopus and Web of Science. Additionally, citation analyses were performed for key papers, reference sections of relevant papers were searched, conference proceedings were examined and a literature database held by the Mobile Phones Research Unit of King's College London was reviewed.

Results: Sixty-three studies were included. "Hypersensitivity to EMF" was the most frequently used descriptive term. Despite heterogeneity, the criteria predominantly used to identify IEI-EMF individuals were: 1. Self-report of being (hyper)sensitive to EMF. 2. Attribution of NSPS to at least one EMF source. 3. Absence of medical or psychiatric/psychological disorder capable of accounting for these symptoms 4. Symptoms should occur soon (up to 24 hours) after the individual perceives an exposure source or exposed area. (Hyper)sensitivity to EMF was either generalized (attribution to various EMF sources) or source-specific. Experimental studies used a larger number of criteria than those of observational design and performed more frequently a medical examination or interview as prerequisite for inclusion.

Conclusions: Considerable heterogeneity exists in the criteria used by the researchers to identify IEI-EMF, due to explicit differences in their conceptual frameworks. Further work is required to produce consensus criteria not only for research purposes but also for use in clinical practice. This could be achieved by the development of an international protocol enabling a clearly defined case definition for IEI-EMF and a validated screening tool, with active involvement of medical practitioners.

Introduction

Although the issue of idiopathic intolerances attributed to environmental exposures (IEI) first appeared in the scientific literature more than five decades ago [1], the possible underlying causes, as the term “idiopathic” suggests, remain unclear [2] and there is no widely accepted protocol for the identification of patients and treatment [3]. A representative example is the variety of physical symptoms without a clear pathological basis that are attributed by the patients to relatively low-level exposure to non-ionizing electromagnetic fields (EMF), emitted by sources such as mobile phone devices and base stations, high-voltage overhead powerlines, computer equipment and domestic appliances [4]. This phenomenon is better known within the public and scientific context as "electromagnetic hypersensitivity"(EHS), although since 2005 the term “Idiopathic Environmental Intolerance Attributed to EMF" (IEI-EMF) has been proposed by the World Health Organization (WHO) as an etiologically neutral description [5]. In this paper, the descriptive term “IEI-EMF” is used.

According to the WHO [5], people with IEI-EMF are mainly characterized by the report of non-specific physical symptoms (NSPS), without a consistent pattern [6], such as redness, tingling, burning sensations in the facial area, fatigue, tiredness, lack of concentration, dizziness, nausea, heart palpitation and digestive disturbances. IEI-EMF is often accompanied by occupational, social and mental impairment [4,7] and its estimated prevalence varies considerably, probably due to different methodological approaches; 1.5% in Sweden [6], 3.2% in California [8], 3.5% in Austria [9], 5% in Switzerland [10] and 13.4% in Taiwan [11]. Demographic characteristics such as age, gender and occupational status have repeatedly been associated with IEI-EMF [6,10].

The experience and belief of IEI-EMF patients is in contrast with the scientific state of the art; results from systematic assessment of experimental and epidemiological evidence are consistent, concluding that a causal association of EMF exposure with symptomatic and other physiologic or cognitive reactions cannot be adequately supported [12-17]. IEI-EMF has been associated with psychological components [18-23] but their exact role is not clear. Although a possible effect of exposure cannot yet be ruled out because of methodological obstacles in research primarily regarding exposure assessment and study design [14,16], more recent approaches stress the importance of looking into the interaction of environmental, biological, psychological and social pathways [24].

However, it is still controversial who should be categorised as having IEI-EMF. The lack of a validated, mutually accepted case definition and diagnostic instrument affects the quality of the research outcomes and increases the methodological heterogeneity, resulting in limited comparability between the studies. That stands in the way of a reliable estimation of the prevalence of IEI-EMF in the general population, proper meta-analysis of etiological evidence, the identification of health outcome patterns/profiles and contributes to a great deal of uncertainty regarding the characteristics, identification and management of this sensitivity by health care providers [25-27].

No systematic review has been performed yet focusing on the existing definitions and criteria for the identification of people with IEI-EMF. In light of the need to inform health care profesionals about relevant aspects of IEI-EMF and prepare the ground for discussion and consensus in the research community on widely supported case definition criteria, the present paper identified the relevant studies on IEI-EMF published to date, in order to summarize:

- The descriptive terms used to define IEI-EMF.
- The inclusion criteria and procedure for the identification of individuals with IEI-EMF.

Methods

Search strategy for the identification of studies

Initially, the following electronic databases were searched to detect relevant studies that were published from inception to April 2010: Embase (Elsevier B.V., Amsterdam, The Netherlands), Medline (US National Library of Medicine, Bethesda, Maryland), PsychInfo (American Psychological Association, Washington, DC). Web of Knowledge (Institute for Scientific Information, The Thomson Corporation, Stamford, Connecticut) and Scopus (Elsevier B.V., Amsterdam, The Netherlands). A wide range of (combined) keywords was used with regards to EMF exposure, sensitivity and related health outcomes, which is presented in Table 1.

In addition to the electronic database searches, the reference sections of previous systematic reviews, key papers, international reports on EMF and health and research databases of websites focused on the issue of EMF such as the “EMF Portal” and the WHO webpage were checked for potentially relevant articles.

A wide literature database held by the Mobile Phones Research Unit of King's College London was also consulted. A second literature search was carried out in order to update our review with studies published from May 2010 to June 2011.

Table 1: Key search terms

Sensitivity:	Electrosensitivity, Electromagnetic hypersensitivity, Electrical sensitivity, Electromagnetic sensitivity, Electric hypersensitivity, IEI-EMF, Environmental intolerance, environmental illness.
Exposure:	EMF, ELF, Electromagnetic field(s), Electromagnetic exposure, mobile telephones, mobile phone(s), Base stations, Powerlines, Celltowers, Antenna(e), UMTS, GSM, DECT, VDU, cell phones.
Health Outcome:	Symptom(s), well-being, attributed symptoms, headache, fatigue.
Time period	From inception – 2011

Inclusion criteria

Only primary studies written in English and published in the peer-reviewed literature were considered as suitable for inclusion in the current review. Conference presentations, brief communications and reviews were excluded. The primary condition to include a study was the report of use of at least one criterion to identify individuals with IEI-EMF. Studies focusing on health effects from wider environmental exposures (such as chemicals) were eligible as long as they attempted to identify sensitivity to EMF in their investigation. Studies recruiting exclusively "healthy" individuals without any attempt to assess IEI-EMF or identify relevant individuals were excluded. Since the "attribution" of health complaints to EMF is not necessarily synonymous with IEI-EMF and it is not an established prerequisite for its existence, studies relying solely on "attribution" without any mention of and explicit conceptual link with IEI-EMF or synonymous terms were not considered eligible for this review. Among papers based on the same sample and identifying criteria of IEI-EMF, the first publication was included.

Data extraction

For each included study, the following data were abstracted: reference and country, study design, methods and source of sample recruitment, IEI-EMF sample characteristics (such as sample size, age mean or range and gender distribution), type of sensitivity based on the triggering EMF source(s), the criteria used to identify individuals with IEI-EMF, exclusion criteria (based on self-report/interview or clinical examination) and the case definition procedure followed for the identification of IEI-EMF (such as self-report and/or medical examination to exclude the possibility that a diagnosed disorder was responsible for the reported health complaints) (Tables 3 & 4). The data provided in the tables were derived from the information that was given or could be inferred from the original publications. However, in some cases (part of) the necessary information was not provided in the reviewed articles.

Review Process

The literature search was performed by the first author and the evaluation of inclusion criteria by CB, IVK and GJR, with uncertainties resolved through consultation among all the authors. The initial screening was based on the titles and/or abstracts. Next, the hard copies of the potentially eligible publications were examined to assess whether they met the inclusion criteria.

Results

Search results

Figure 1 illustrates the literature search process. We examined 5328 citations in total and identified 35 experimental and 28 observational studies that met our inclusion criteria.

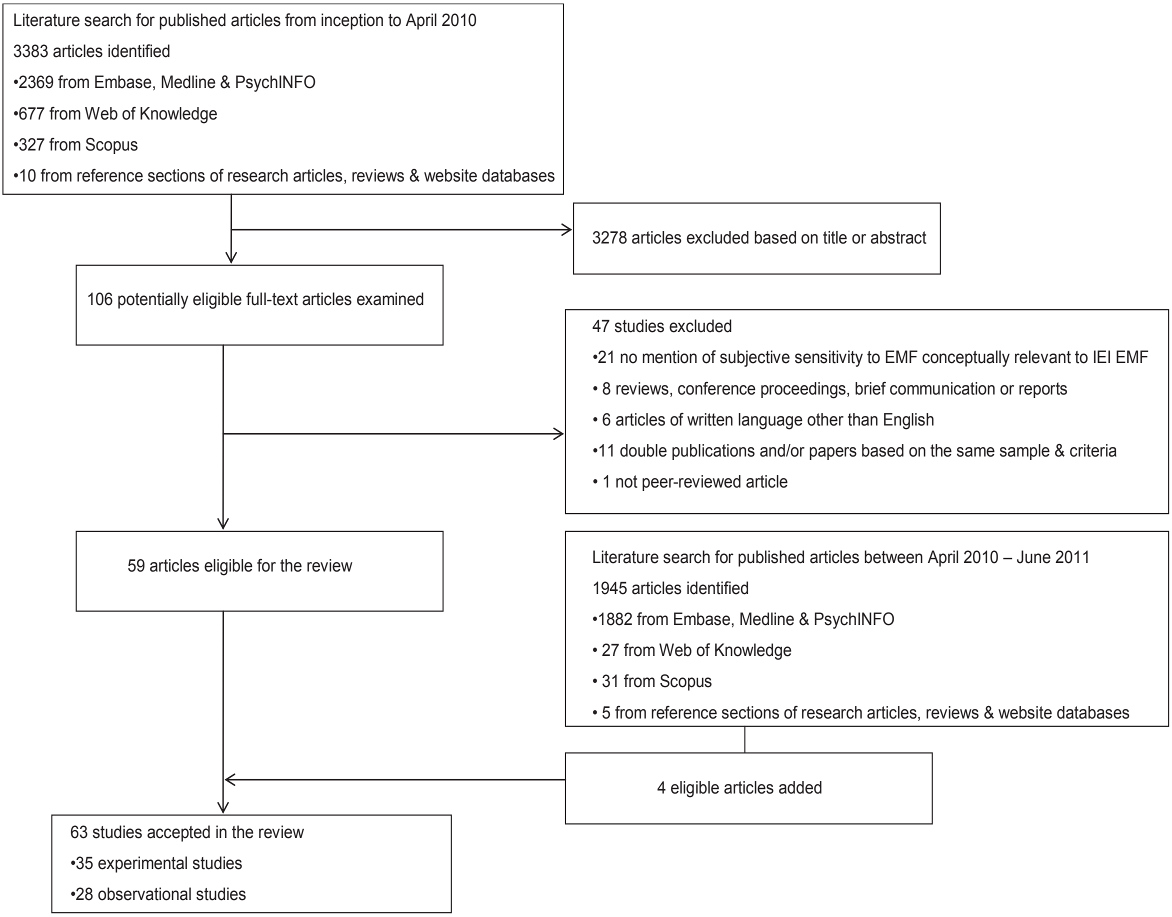

Figure 1: Flow diagram outlining the study selection process.

Study characteristics

When reported, sample sizes of subjects with IEI-EMF ranged between 1 to 100 in the experimental studies and from 2 to 2748 in the observational studies. The percentage of female participants (exempting case-studies) ranged between 0 to 81.3% and 50% to 100% respectively. In all studies, the reported mean age of IEI-EMF individuals varied between 26.1 and 55.5 years.

IEI-EMF triggered by several different EMF sources ("general") was the sensitivity type of primary focus in the included investigations (n=48), while 14 studies concentrated exclusively on "source-specific" IEI-EMF and three on both "general" and "source-specific" IEI-EMF.

Despite the large variation of synonyms of IEI-EMF in the literature (Table 2), "Hypersensitivity to EMF" (and its variants) was by far the most frequently used definition/descriptive term (Figure 2).

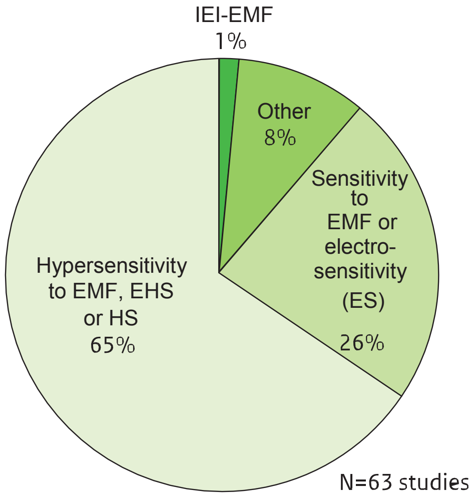

Figure 2: Distribution (%) of terms used to describe IEI-EMF in the reviewed literature.
Abbreviations: IEI-EMF, Idiopathic environmental intolerance attributed to EMF; EHS, Electrohypersensitivity; HS, Hypersensitivity

In 35 studies the case definition procedure was solely based on the subjective report of the respondents. In 28 studies it was mentioned that objective assessment (e.g medical and/or psychological assessment) was additionally taken into account. The principal method of sample recruitment was via study description in advertisements and/or local or national media (22 studies). The vast majority of the reviewed studies were conducted in Europe (58 studies).

Experimental studies

The major inclusion criteria used by experimental studies to identify individuals with IEI-EMF were:

- Attribution of NSPS to either various or specific sources of EMF (being reported 13 times).

- Self-reported IEI-EMF (or synonymous terms) (n=14).
- Experience of symptoms during or soon (from 20 minutes to 24 hours) after the individual perception or actual presence or use of an EMF exposure source (n=10).
- High score on a symptom scale (n=6).

In addition, two studies used limitation in daily functioning of the individual due to the attributed health effects as an inclusion criterion. The main exclusion criterion was the existence of a medical and/or psychiatric or psychological condition that could account for the reported health complaints (n=20). Other exclusion criteria included undergoing treatment for somatic or psychiatric conditions (n=8), pregnancy (n=5), history of severe injuries (n=3) and regular smoking (n=2).

In 16 studies the case definition procedure did not only rely on subjective report, but also on medical and/or psychiatric and/or psychological examination. In eight studies, the sample recruitment was based on participants who were already referred or registered to a health care institution (such as a university hospital) for their health complaints. All extracted data from the experimental studies are presented in Table 3.

Observational Studies

The major inclusion criteria used by observational studies to identify individuals with IEI-EMF were:

- Self-reported IEI-EMF (or synonymous terms) (n=16).
- Attribution of NSPS to either various or specific EMF sources (n=12)
- Experience of symptoms during or soon (from 20 minutes to 24 hours) after the individual perception or actual presence or use of an EMF exposure source (n=3).
- Limitation in daily functioning of the individual due to the attributed health effects (n=2).

The main exclusion criteria were a medical and/or psychiatric or psychological condition that could account for the reported health complaints and undergoing treatment for somatic or psychiatric condition (n=4). Eleven studies included medical and/or psychiatric and/or psychological examination to assess whether a pathological condition was responsible for patients' complaints.

In nine studies the sample was based on participants who were already referred or registered to health care institutions for their complaints. All extracted data from the observational studies are listed in Table 4.

The prevalence of IEI-EMF in randomly selected samples of population-based epidemiological studies varied and seemed to be influenced by the number and degree of strictness of the applied identification criteria. This is illustrated in Figure 3. These differences could also be due to the population under study, year of study and sample stratification (e.g age range).

Figure 3: Prevalence (%) of IEI-EMF based on the identifying criteria employed by population-based observational studies

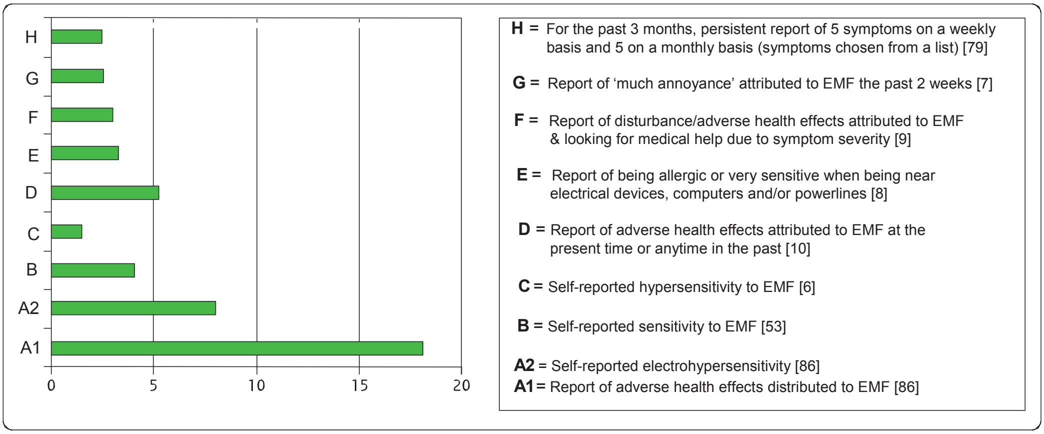

Table 3: Experimental studies on IEI-EMF

Reference	Study design	Recruitment	Type of sensitivity	IEI-EMF sample characteristics	Identifying criteria for IEI-EMF	Main exclusion criteria	Identification/Case definition methods for IEI-EMF
Rea et al., 1991 (USA) [28].	Provocation	Voluntary participation.	General	N=100.	Self-reported sensitivity to EMF.	N.R/E.	Subjective report, medical examination.
Hamnerius et al.,1993(Sweden) [29].	Provocation	IEI-EMF subjects referred to a health care service/institution.	VDU-specific	N=30.	Report of "distinctive" symptoms, occurrence of the symptoms within an hour from being exposed to VDU and disappearance or substantial reduction within a few hours after exposure termination.	Somatic or psychiatric disorder that could account for the reported symptomatology.	Subjective report, medical, psychiatric & psychological examination.
Arnetz et al., 1995 (Sweden) [30].	Intervention	IEI-EMF subjects referred to a health care service/institution.	General	N=20, m.a= 45, f.g=75%.	Report of symptoms attributed to EMF exposure.	Somatic or psychiatric disorder that could account for the reported symptomatology.	Subjective report, medical & psychiatric examination.
Andersson et al., 1996 (Sweden) [31].	Provocation	IEI-EMF subjects referred to a health care service/institution.	General	N=17, m.a=41.7, f.g=70.6%.	Experience of "typical" symptoms of "electric hypersensitivity" when being in an "electrical environment", duration of at least 6 months, limitations in daily functioning, experience of symptomatology within less than 30 minutes after exposure to electric equipment under experimental testing.	Somatic or psychiatric disorder that could account for the reported symptomatology.	Subjective report, medical & psychiatric examination.
Bertoft et al., 1996 (Sweden) [32].	Provocation	Voluntary participation of IEI-EMF subjects.	General	N=5, a.r=46-60, f.g=80%.	Self-reported hypersensitivity to EMF.	N.R/E.	Subjective report.
Toomingas, 1996 (Sweden) [33].	Provocation (case study)	Voluntary participation of a medical patient.	General	N=1 male, age=35.	Fear of a negative impact of health caused by EMF exposure, report of symptoms attributed to EMF such as fatigue, headache, lack of concentration, numbness & paresthesia in the arms, greasy feeling in the palms, inability to work due to	N.R/E.	Subjective report, medical & neurological examination.

Reference	Study design	Recruitment	Type of sensitivity	IEI-EMF sample characteristics	Identifying criteria for IEI-EMF	Main exclusion criteria	Identification/Case definition methods for IEI-EMF
					the reported symptoms.		
Sandström et al., 1997 (Sweden) [34].	Provocation	IEI-EMF subjects treated to a health care service/institution.	VDT & fluorescent light-specific	N=10, m.a=47, f.g=70%.	Self-report of a combination of skin (mucous), eye & neurological symptoms, attribution of these symptoms to EMF emitted from VDT work, fluorescent light or TV.	Somatic or psychiatric diseases severe enough to require medical treatment.	Subjective report, medical examination.
Hillert et al., 1998 (Sweden)[35].	Intervention	IEI-EMF subjects referred to a health care service/institution.	General	N=10, m.a=40, f.g=60%.	Self-reported hypersensitivity to EMF, age between 18-65 y.o, being employed for at least 1 week during the past 3 months, symptoms had to show some variation due to perceived exposure to EMF or proximity to relative equipment.	Medical or mental disorder that could account for the reported symptomatology, long period of sick leave, unemployment.	Subjective report, medical examination.
Trimmel et al., 1998 (Austria) [36].	Provocation	Voluntary participation.	General	N=36, a.r=18-36.	Individual belief of an "exceptional reaction to EMF", a score of >50 on a continuous rating scale between 0-100.	N.R/E.	Subjective report.
Flodin et al., 2000 (Sweden)[37].	Provocation	IEI-EMF subjects who were members of a relative self-group or registered to a health care service/institution.	General	N=15, m.a=48.3, f.g=73.3%.	Attribution of symptoms to named EMF sources, mean reaction should occur within 60 minutes of exposure, there was no experience of symptoms at home or workplace when the subject was considered as "unexposed", symptoms should disappear within a few days after exposure.	Slow reaction or denial for participation because of symptom severity, undergoing treatment for medical conditions.	Subjective report, medical examination (registered IEI-EMF subjects).
Lohne-Rahm et al., 2000 (Sweden) [38].	Provocation	Voluntary participation after description of the study in newspaper advertisements or IEI-EMF subjects referred to a health care	General	N=12.	Report of skin symptoms during a 30-minute exposure to EMF & symptom duration of at least 6 months.	Diagnosed skin diseases, slow, excessive or no reactions during the experiment.	Subjective report, medical examination (referred IEI-EMF subjects).

Reference	Study design	Recruitment	Type of sensitivity	IEI-EMF sample characteristics	Identifying criteria for IEI-EMF	Main exclusion criteria	Identification/Case definition methods for IEI-EMF
		service/institution.					
Hillert et al., 2001 (Sweden) [39].	Intervention	IEI-EMF subjects referred to a health care service/institution.	General	N=16, m.a=39.5, f.g=81.3%.	Self-reported hypersensitivity to electricity, experience of change in symptoms within 24 hours after a perceived change in exposure to EMF, a history of VDU or fluorescent lights as the initial triggering factors.	Somatic or psychological disorder that could account for the reported symptomatology.	Subjective report, medical & psychological examination.
Lyskov et al., 2001 (Sweden) [40].	Provocation	IEI-EMF subjects referred to a health care service/institution.	General	N=20, m.a=45.8, f.g=75%.	Self-reported hypersensitivity to EMF	N.R/E.	Subjective report, medical examination.
Hietanen et al., 2002 (Finland) [41].	Provocation	Voluntary participation.	General	N=20, m.a=49, f.g=65%.	Self-reported hypersensitivity to EMF, experience of symptoms during a 30-minute (provocation) test period.	N.R/E.	Subjective report, medical examination.
Hillert et al., 2002 (Sweden) [42].	Intervention	IEI-EMF subjects referred to a health care service/institution.	General	N=22, m.a=42, f.g=64%.	Report of symptoms assumed to be caused by sensitivity to EMF.	Medical or psychological condition that could account for the symptoms.	Subjective report, medical & psychiatric examination.
Mueller et al., 2002 (Switzerland) [43].	Provocation	Voluntary participation.	General	N=63, m.a=49.5, f.g=51%.	Self-reported sensitivity to EMF or “Electrical Hypersensitivity Syndrome (EHS)”.	N.R/E.	Subjective report.
Leitgeb et al., 2003(Austria) [44].	Provocation	Randomly selected sample from general population (N=708).	General	a.r=17-60.	Increased levels of “electrosensibility”, defined as the individual ability to perceive electric or electromagnetic exposures without necessarily developing health symptoms.	N.R/E.	Measurement of EMF perception thresholds.
Österberg et al., 2004 (Sweden) [45].	Provocation	Randomly selected sample from general population (N=13381), based on Östergren et al. (report) [46].	General	N=16, m.a=41.8, f.g=50%.	Individual experience the past 2 weeks of “very much” physiologic “annoyance” attributed to FTL, and/or VDU and/or other electrical equipment.	Report of long-term sick leave, disability pension, subjects diagnosed with severe medical condition that required medication	Subjective report, medical examination.

Reference	Study design	Recruitment	Type of sensitivity	IEI-EMF sample characteristics	Identifying criteria for IEI-EMF	Main exclusion criteria	Identification/Case definition methods for IEI-EMF
						(e.g diabetes), age of >58 y.o	
Belyaev et al., 2005 (Sweden) [47].	Provocation	Voluntary participation.	General	N=7, m.a=44.8, f.g= 71.5%.	Self-reported hypersensitivity to EMF.	Smoking, regular medication	Subjective report.
Frick et al., 2005 (Germany) [48].	Provocation	Voluntary participation after description of the study in a local newspaper.	General	N=30, m.a=41.7, f.g=77%.	Self-reported hypersensitivity to named EMF sources, attribution of severe symptoms that limited daily functioning & age between 18-64 y.o.	Not complaining or not experiencing limitations to daily living due to the reported symptomatology.	Subjective report.
Wenzel et al., 2005 (Germany) [49].	Provocation	Voluntary participation.	VDU & powerline-specific	N=3 male subjects, m.a=37.	Concern about the effects of EMF exposure, report of various symptoms attributed to VDU and/or powerlines, abstinence from smoking.	N.R/E.	Subjective report.
Regel et al., 2006 (Switzerland) [50].	Provocation	Voluntary participation after description of the study in advertisements in a local newspaper, flyers & use of databases of two previous studies with IEI-EMF subjects willing to participate in future research projects.	Base station-specific	N=33, m.a=37.7, f.g=57.5%.	Self-reported sensitivity to EMF emitted by mobile or cordless phones & antennas.	Regular consumption of narcotics or psychoactive drugs in the last 6 months, smoking, diagnosed with a chronic disease, pregnancy, medical history of head injuries, neurologic/psychiatric diseases, sleep disturbances, average alcohol consumption of >10 drinks per week, average consumption of caffeinated beverages amounting to >450 milligrams caffeine per day, shift workers,	Subjective report.

Reference	Study design	Recruitment	Type of sensitivity	IEI-EMF sample characteristics	Identifying criteria for IEI-EMF	Main exclusion criteria	Identification/Case definition methods for IEI-EMF
						undertaking long-haul flights of >3 hours time zone difference within the last month.	
Rubin et al., 2006 (UK) [51].	Provocation	Through mailshots organised by an IEI-EMF support group, advertisements & articles in health care institutions & practices.	MP-specific	N=71, m.a=37.1, f.g=56%.	Frequent experience of headache-related symptoms within 20 minutes of using a 900 MHz GSM MP.	Age of <18 or >75 y.o, pregnancy, psychotic illness, use of antidepressants, report of severe symptoms at baseline while in the testing room.	Subjective report.
Eltiti et al., 2007 (UK) [52].	Provocation	Voluntary participation through local advertising, IEI-EMF action groups & word of mouth.	MP & base station-specific	N=56, m.a=46.1, f.g=42.9%.	Individual experience of negative health effects attributed to EMF emitted from mobile phone devices and/or base stations, based on the “Electromagnetic Hypersensitivity Questionnaire” [53].	History of brain injury, currently suffering from epilepsy or claustrophobia, undergone treatment for mental disease or psycho-active medication within 4 months before the study.	Subjective report.
Schröttner et al., 2007 (Austria) [54].	Provocation	Three different recruitment sources: 1. EMF self-help groups. 2. Through advertisements in local newspapers & inviting patients that contacted a health care service/institution for their EMF-attributed symptoms. 3. Subjects reporting severe sleep	General	Recruitment 1: N=37, a.r=27-81, f.g=67.6%. Recruitment 2: N=29, a.r=32-63, f.g=79%. Recruitment 3: N=24, a.r=37-73, f.g=62.5%.	Self-reported hypersensitivity to electricity, attribution of symptoms to EMF, active avoidance behavior to EMF sources.	Sensitivity only to sources of flickering light such as VDU fluorescent tubes.	Medical examination (for part of the group of “Recruitment 2”).

Reference	Study design	Recruitment	Type of sensitivity	IEI-EMF sample characteristics	Identifying criteria for IEI-EMF	Main exclusion criteria	Identification/Case definition methods for IEI-EMF
		problems being deeply convinced that these were caused by EMF exposure.					
Bamiou et al., 2008 (UK) [55].	Provocation	Voluntary participation after description of the study through advertisements at a health care services/institutions & relative website & short film shown on the national television.	MP-specific	N=9, m.a=36.7, f.g=66.7.	Report of headache and/or disorientation, dizziness, muzziness, nausea attributed to mobile telephone use, age between 20–55 y.o, normal tympanometry & normal pure tone audiometric thresholds in both ears.	N.R/E.	Subjective report, audiometric examination.
Hillert et al., 2008 (Sweden) [56].	Provocation	Voluntary participation after description of the study in newspapers, or individual initiative.	MP-specific	N=38, m.a=28, f.g=63.2%.	Report of headache, vertigo or other kind of pain or discomfort in the head attributed to MP use.	Attribution of symptoms to sources other than MP, medical or psychological illness, undergoing medication, sleep disorders, hypertension, pregnancy, history of severe injury.	Subjective report.
Kwon et al., 2008 (Finland) [57].	Provocation	Voluntary participation after description of the study in an advertisement that announced a monetary prize.	MP-specific	N=2 male subjects, m.a=37.	Report of suffering from severe symptomatology after use of a mobile phone, high score on a scale on EMF sensibility (defined as the individual ability to perceive EMF without necessarily developing symptoms).	Neurological disease, auditory abnormality, being on permanent medication.	Subjective report.
Landgrebe et al., 2008a (Austria & Germany) [58].	Provocation	Voluntary participation after description of the study in newspapers and informative events at public locations and	General	N=88, m.a=50.5, f.g=58.4%.	A symptom score of at least 19 points on the “Regensburger EMF complaint list” [59], attribution of health symptoms to named EMF sources & age between 18-75 y.o	Unstable medical condition.	Subjective report.

Reference	Study design	Recruitment	Type of sensitivity	IEI-EMF sample characteristics	Identifying criteria for IEI-EMF	Main exclusion criteria	Identification/Case definition methods for IEI-EMF
		institutions.					
Leitgeb et al., 2008 (Austria & Germany) [60].	Crossover field study	Voluntary participation after description of the study in media.	General	N=43, m.a=55.5, f.g=60.5%.	Personal conviction on a causal role of EMF indicated by the employment of precautionary activities and/or measures (e.g reducing fields, measuring exposure in the household etc), above-normal symptom scores on standardized questionnaires such as the “Freiburger Personality Inventory” [61] and “PSQI” [62] (at least 5 points on the latter).	Neurological & psychiatric disorders, somatic conditions that could account for sleep disturbances, drug consumption less than 2 weeks before the study, medical treatment for severe conditions.	Subjective report.
Augner et al., 2009 (Austria) [63].	Provocation plus cross-sectional data	Voluntary participation.	General	N=8, a.r=18-67.	Self-reported electromagnetic hypersensitivity (rated as “strong” or “very strong”).	N.R/E.	Subjective report.
Furubayashi et al., 2009 (Japan) [64].	Provocation	Randomly selected female subjects (N=2472).	MP & base station-specific	N=11, m.a=37.3.	Report of symptoms attributed to MP use and/or exposure to base stations, symptoms should persist “always” or “almost always”	History of myocardial infarction epilepsy or other (psycho)pathological condition, undergoing medical treatment for severe medical conditions.	Subjective report.
Nam et al., 2009 (South Korea) [65].	Provocation	Voluntary participation after description of the study through advertisements at a health care service/institution.	MP-specific.	N=18, m.a=26.1, f.g=55.5%.	Self-reported hypersensitivity to EMF emitted only by CDMA cellular phones.	Self-reported hypersensitivity to other EMF sources, subjects concerned with payment for volunteering,	Subjective report.
Szemerszky et al., 2010 (Hungary) [66].	Provocation	Voluntary participation of university students.	General	N.R.	Self-reported electrosensitivity (rated from “not at all” to “fully”).	Severe medical disorders, health conditions such as premenstrual syndrome	Subjective report.

Reference	Study design	Recruitment	Type of sensitivity	IEI-EMF sample characteristics	Identifying criteria for IEI-EMF	Main exclusion criteria	Identification/Case definition methods for IEI-EMF
						and common cold that could account for the reported symptomatology	
Nieto-Hernandez et al., 2011 (UK) [67].	Provocation	Voluntary participation after description of the study within UK Police Forces with the use of circular emails, notices in police newsletters and intranet sites & advertisements in police-related magazines & websites.	TETRA-specific	N=60, m.a=35.6, f.g=11.7%.	Report of symptoms attributed to TETRA, report of being at least 70% sure that the radio signal was the responsible source, occurrence of symptoms/sensations within an hour of radio use and when the radio was used near the head.	Pregnancy/trying to conceive, medical or psychological condition which could account for similar symptoms.	Subjective report.

*Although the studies of Österberg et al. [45] and Carlsson et al. [7] are based on the same sample [46], they have some differences in terms of inclusion criteria and/or identification methods.
Abbreviations: N.R., Not reported; N.R/E, Not reported or employed; EMF, Electromagnetic fields; IEI-EMF, Idiopathic environmental intolerance attributed to EMF; m.a, Mean age; a.r, Age range; f.g, Female gender distribution; y.o; Years old; MP, Mobile phone(s); VDT, Video display terminal: VDU, Video display units; GSM, Global system for mobile communications; CDMA, Code division multiple access; TETRA, Terrestrial trunked radio; PSQI, Pittsburgh sleep quality index.

Table 4: Observational studies on IEI-EMF

Reference (Country)	Study design	Recruitment	Type of sensitivity	IEI-EMF sample characteristics	Identifying criteria for IEI-EMF	Main exclusion criteria	Identification/Case definition methods for IEI-EMF
Bergdahl et al., 1998 (Sweden) [68].	Cross-sectional	IEI-EMF subjects referred to a health care service/institution.	General, VDU-specific	N=28, m.a= 45.5, f.g=50%.	Report of symptoms assumed to be caused by VDU and/or other EMF sources.	N.R/E.	Subjective report, medical examination.
Hocking, 1998 (Australia) [69].	Cross-sectional	Voluntary participation after description of the study in a medical journal.	General	N=0 (people identified with IEI-EMF)	Self-reported electrosensitivity.	N.R/E.	Subjective report
Hillert et al., 1999 (Sweden) [70].	Case-control	Subjects selected from an older occupational health survey & IEI-EMF subjects referred to a health care service/institution.	General	N=62, a.r=20≤.	Self-reported hypersensitivity to EMF.	N.R/E.	Subjective report, medical examination (referred IEI-EMF subjects).
Stockenius et al., 2000 (Switzerland) [71].	Cross-sectional	Voluntary participation of male subjects (mostly university students) after description of the study through advertisements.	General	N.R.	Self-reported electrosensitivity to named sources (ranked from "very insensitive" to "very sensitive").	N.R/E.	Subjective report.
Bergdahl et al., 2001 (Sweden) [72].	Cross-sectional	IEI-EMF subjects referred to a health care service/institution.	General	N=44, m.a=47, f.g=57%.	Report of symptoms assumed to be caused by "abnormal sensitivity to EMF".	N.R/E.	Subjective report, medical interview & examination.
Hillert et al., 2001 (Sweden) [73].	Cross-sectional	IEI-EMF subjects referred to a health care service/institution.	General	N=14, m.a=46, f.g=64.3%.	Self-reported hypersensitivity to EMF including disabling fatigue attributed to EMF exposure.	Medical condition that could account for the reported symptomatology.	Subjective report, medical examination.
Lyskov et al., 2001 (Sweden) [74].	Case-control	IEI-EMF subjects referred to a health care service/institution.	General	N=20, m.a=47, f.g=55%.	Report of a combined pattern of skin, general and ocular symptoms & attribution to EMF exposure.	Chronic diseases, acute illness the last 6 months, undergoing hormonal, hypotensive or sedative therapy.	Subjective report, medical examination.

Reference (Country)	Study design	Recruitment	Type of sensitivity	IEI-EMF sample characteristics	Identifying criteria for IEI-EMF	Main exclusion criteria	Identification/Case definition methods for IEI-EMF
Hillert et al., 2002 (Sweden) [6].	Cross-sectional	Randomly selected sample from general population (N=10605).	General	N=167, a.r=19-80, f.g=62.8%	Self-reported hypersensitivity to named EMF sources.	N.R/E.	Subjective report.
Levallois et al., 2002 (USA) [8].	Cross-sectional	Randomly selected sample from general population (N=2072).	General	N=68, m.a=43.4, f.g=58.8%.	Report of being allergic or very sensitive when being near electrical devices, computers and/or powerlines.	N.R/E.	Subjective report
Stenberg et al., 2002 (Sweden) [75].	Cross-sectional	IEI-EMF subjects referred to a health care service/institution.	General, VDT-specific.	General sensitivity: N=50, m.a=49, f.g=62%. VDT specific: N=200, m.a=50, f.g=78.5%.	General: Experience of symptoms attributed to EMF sources in general within 24 hours after being exposed. VDT-specific: Experience of (mainly skin) symptoms attributed to VDT, TV screens & fluorescent light within 24 hours after being exposed. For all subjects, the possible association between exposure & symptoms could not be ruled out.	Lack of medical records or examination, diagnosed medical condition, no symptom attribution to EMF within 24 hours after being exposed.	Subjective report, medical records & examination.
Sandström et al., 2003 (Sweden) [76].	Case control	IEI-EMF subjects registered to a health care service/institution.	General	N=14, m.a=48.9, f.g=64.3%.	Individual perception that exposure to VDT, FTL, TV and/or other EMF sources causes symptoms within 24h, the possible exposure-outcome association could not be ruled out.	Symptoms indicating autonomic nervous dysregulation, undergoing hormonal or hypotensive therapy, having arrhythmia due to frequent non-sinus beats or severe cardiac conduction disturbances.	Subjective report, medical examination.
Bergdahl et al., 2004 (Sweden) [77].	Case-control	IEI-EMF subjects referred and registered to a health care service/institution.	General	N=250, m.a=49.1, f.g=75.2%.	Individual perception that exposure to VDT, TV and/or other EMF sources causes symptoms within 24h.	N.R/E.	Subjective report, medical examination.
Röösli et al., 2004 (Switzerland) [4].	Cross-sectional	The survey was described to various	General	N=394, m.a=51, f.g=57%.	Report of symptoms (open question) attributed to EMF exposure.	N.R/E.	Subjective report.

Reference (Country)	Study design	Recruitment	Type of sensitivity	IEI-EMF sample characteristics	Identifying criteria for IEI-EMF	Main exclusion criteria	Identification/Case definition methods for IEI-EMF
		local institutions and organizations which informed & encouraged IEI-EMF subjects to participate.					
Bergdahl et al., 2005 (Sweden) [78].	Case-control	IEI-EMF subjects referred to a health care service/institution.	General	N=33, m.a=47, f.g=51.5%.	Report of symptoms assumed to be caused by sensitivity to EMF.	N.R/E.	Subjective report, psychological examination.
* Carlsson et al., 2005 (Sweden) [7].	Cross-sectional	Randomly selected sample from general population (N=13381), based on Östergren et al. (report) [46].	General	N=2748 ("some annoyance" by EMF), N=354 ("much annoyance" by EMF), a.r=18≤.	Individual experience the past 2 weeks of "some" or "much" physiologic "annoyance" attributed to FTL, and/or VDU and/or other electrical equipment.	N.R/E.	Subjective report.
Eriksson et al., 2006 (Sweden) [79].	Cross-sectional	Random sample from general population (N=2154).	General	N=46, a.r=18-64, f.g =76%.	For the past 3 months, report of 5 symptoms on a weekly basis and 5 on a monthly basis: These symptoms could be: fatigue, feeling heavy-headed, headache, concentration difficulties, itching, burning or irritation of the eyes, dry eyes, dry facial skin, flushed facial skin, itching/stinging/tight or burning sensation in facial skin & cold hands or feet.	N.R/E.	Subjective report.
Schreier et al., 2006 (Switzerland) [10].	Cross-sectional	Randomly selected sample from general population (N=2048).	General	N=107, a.r=14<, f.g=54.5%.	Report of adverse health effects (open question) attributed to EMF at the time of the interview or anytime in the past.	N.R/E.	Subjective report.
Schüz et al., 2006 (Germany) [80].	Cross-sectional	Voluntary participation from EMF self-help & action groups, internet & media advertisements,	General	N=107, f.g=54%.	Self-reported hypersensitivity to EMF.	N.R/E.	Subjective report.

Reference (Country)	Study design	Recruitment	Type of sensitivity	IEI-EMF sample characteristics	Identifying criteria for IEI-EMF	Main exclusion criteria	Identification/Case definition methods for IEI-EMF
		invitation letters.					
Eltiti et al., 2007 (UK) [53].	Three cross-sectional investigations.	Investigation 1&3: IEI-EMF subjects through local self-help & action groups or personal contact. Investigation 2: Random selection from the general population (N=3633) .	General	Investigation 1: N=50, m.a=52.5, f.g=66%. Investigation 2: N=698. Investigation 3: N=88, m.a=48.7, f.g=53.4%.	Investigation 1: Self-reported sensitivity to EMF, attribution of symptoms to EMF. Investigation 2 &3: Self-reported sensitivity to EMF.	N.R/E.	Subjective report.
Landgrebe et al., 2007 (Germany) [81].	Case-control	Voluntary participation after description of the study in a local newspaper.	General	N=23, m.a=41.3, f.g=74%.	Report of severe symptoms that limited daily functioning, attribution of these symptoms to named EMF sources & age between 18-64 y.o.	N.R/E.	Subjective report.
Hardell et al., 2008 (Sweden) [82].	Case-control	Voluntary participation.	General	N=13 female subjects, m.a=53.	Report of symptoms attributed to EMF.	Severe medical condition.	Subjective report, medical examination.
Lidmark et al., 2008 (Sweden) [83].	Cross-sectional, plus qualitative data	Voluntary participation of members of an IEI-EMF self-help group.	General	N.R.	Report of symptoms attributed to EMF	N.R/E.	Subjective report, medical & psychiatric examination.
Schröttner et al., 2008 (Austria) [9].	Cross-sectional	Randomly selected sample from general population (N=526).	General	N=16, a.r=15-80, f.g=50%.	Report of disturbance/adverse health effects (open question) attributed to named EMF sources, looking for medical help because of symptom severity.	N.R/E.	Subjective report.
Dahmen et al., 2009 (Germany) [84].	Case-control	Sample selected from EMF self-help groups, an internet-based survey on EMF and health & local advertisements.	General	N=132, m.a=51.5, f.g=68.2%.	A symptom score of at least 14 points on the “Regensburger EMF complaint list” [85], attribution of health symptoms to named EMF sources & age between 18-56 y.o	Acute psychiatric disorder (after psychiatric examination).	Subjective report.

Reference (Country)	Study design	Recruitment	Type of sensitivity	IEI-EMF sample characteristics	Identifying criteria for IEI-EMF	Main exclusion criteria	Identification/Case definition methods for IEI-EMF
Johansson et al., 2010 (Sweden) [23].	Case-control	Voluntary participation after description of the study in newspaper advertisements.	General, MP-specific, VDT-specific	MP-specific sensitivity group: N=45, m.a=45.7, f.g=62%. General sensitivity group: N=71, m.a=51.6 f.g=82%.	Report of symptoms attributed to: 1. MP use only, 2. VDT use only or 3several types of electrical equipment.	N.R/E.	Subjective report.
Mohler et al., 2010 (Switzerland) [86].	Cross-sectional	Randomly selected sample from general population (N=1212).	General	N=253.	Self-reported electrohypersensitivity or report of adverse health effects attributed to EMF.	Consumption of sleeping pills, night shift workers, severe disability.	Subjective report.
Nordin et al., 2010 (Sweden) [87].	Cross-sectional	Voluntary participation of IEI subjects after description of the study in a local and a national newspaper.	General	N= 2, a.r=18-69.	Report of being intolerant to EMF.	Pregnancy.	Subjective report.
Röösli et al., 2010 (Switzerland) [88].	Cross-sectional	Randomly selected sample from general population (N=1122).	General	N=130, a.r=30-60, f.g=72.3%.	Self-reported hypersensitivity to EMF.	N.R/E.	Subjective report.

*Although the studies of Carlsson et al. [7] and Österberg et al. [45] are based on the same sample [46], they have some differences in terms of inclusion criteria and/or identification methods. This was the case also for the studies of Mohler et al. [86] and Röösli et al. [88].

Abbreviations: N.R., Not reported; N.R/E, Not reported or employed. FTL, Fluorescent tube light; EMF, Electromagnetic fields; IEI-EMF, Idiopathic environmental intolerance attributed to EMF; m.a, Mean age; a.r, Age range; f.g, Female gender distribution; y.o; Years old; MP, Mobile phone(s); VDT, Video display terminal: VDU, Video display units.

Discussion

The present systematic review based on an extensive literature search, summarized the case definition criteria and methods that have been used in the published literature to date for the identification of subjects with IEI-EMF. It is noteworthy that only 1% of the reviewed studies used the term "IEI-EMF" as a descriptive term, despite the fact that it has been proposed by WHO since 2005 [5]. Sixty-five percent of the studies used the description "Hypersensitivity to EMF" which seems to be mainly characterized by the following aspects: Self-reported sensitivity to one or more sources of EMF, attribution of NSPS to either several or specific EMF sources (such as mobile phones and VDUs), experience of symptoms during or soon after (from 20 minutes to 24 hours) the individual perception or actual presence or use of an EMF source and absence of a (psycho)pathological condition accounting for the reported health complaints. In the majority of the studies the case definition procedure was based exclusively on self-report. In a smaller number of investigations, medical and/or psychiatric and/or psychological assessment was included.

In most of these studies participants were recruited from registries to a health care institution for their symptoms and for whom medical data were available. Although there were no important differences between observational and experimental studies in the most frequently employed criteria, experimental studies used a larger number of criteria per investigation compared to observational studies. Moreover, the demographic profile of the recruited individuals with IEI-EMF in terms of age and gender was quite consistent; the frequency of female gender and age over 40 years were considerably higher in most of the studies.

Despite previous attempts to bring order to this field [6,53,70], as it appears in the literature, IEI-EMF is still predominantly a self-reported sensitivity without a widely accepted and validated case definition tool. This could be due to the absence of a bioelectromagnetic mechanism [17] or because of the varying patterns regarding the symptom type, frequency and severity [6,41]. The other way around could also be the case: The lack of validated case definition criteria could have hindered the identification of homogeneous patient groups and consequently the recognition of symptom profiles and a physiologic mechanism.

Furthermore, the application of very broad criteria could dilute the power of the studies and make difficult the detection of those individuals that really suffer from IEI-EMF. For example, although "Attribution" of NSPS to EMF could be considered as a first indication of suffering from IEI-EMF, it is questionable whether it comprises a sufficient identifying criterion when used alone.

Possible subgroups

Several subdivisions may exist within IEI-EMF that may be of relevance to clinicians and researchers. One such division is that between patients for whom an alternative diagnosis exists, which might account for their symptoms and those for whom it does not. The absence of screening for pathological conditions which might underlie the symptoms reported by participants in many studies was notable. Previous studies have identified occasionally high levels of other diagnoses in such patients, such as somatoform and anxiety disorders which might account for their ill-health [89,90]. Including these individuals in the same sample as those for whom there is no clear explanation for their symptoms may reduce our ability to identify causal factors for IEI-EMF.

An additional distinction that we may need to take into account is between patients who attribute symptoms to short-term exposure to EMF and those for whom longer-term exposure is relevant. Furthermore, it remains unclear whether generalized and source-specific IEI-EMF should be assessed separately or not. Exposure from far-field sources such as high-voltage overhead powerlines and mobile phone base stations is mostly continuous and people often perceive it as less controllable compared to near-field sources such as mobile phones [10] but there is still no convincing evidence for source-specific sensitivities [13]. As differences may exist between IEI-EMF patients in terms of their psychological and health-related characteristics, division into subgroups for the purposes of research may be of use [22-23]. Perhaps the most complicated issue is to figure out whether self-reported-NSPS and objectively assessed physiologic reactions are preceded by events of the relevant (EMF) exposures, distinguishable from other random exposure events experienced during the day. Use of a prediction model based on modelled exposure from various sources [91-92] could be a solution; however it is questionable whether and how it could be systematically incorporated in a case definition tool. Table 5 illustrates a number of proposed aspects for IEI-EMF, based on a synthesis of the existing identifying criteria in the reviewed literature.

Table 5: Proposed case definition aspects for IEI-EMF

Dimensions of IEI-EMF	**Case definition assessment/identification of IEI-EMF**	
	Research	*Clinical practice*
Health effects	- Subjective report of symptoms/physiologic reactions. - The possibility that a known medical or psychiatric condition is the cause of the reported health complaints should be excluded with the use of standardized interview and patient history. - Current status of residential and occupational exposure to harmful environmental agents that could be related to the reported complaints (other than non-ionizing EMF).	- Subjective report of symptoms/physiologic reactions. - The possibility that a known medical or psychiatric condition is the cause of the reported health complaints should be excluded after thorough physical and psychiatric examination and detailed patient history.
Triggering factors	- Attribution of NSPS or other physiologic reaction(s) to either all/several EMF sources (General IEI-EMF) or one specific EMF source (such as VDU, MP or FTL) and/or - Subjective report of being sensitive to specific or various EMF sources.	
Cognition & behavior (optional)	- Symptoms occur during or after the individual perception or actual exposure, presence or use of an EMF source. - Regular avoidance behavior towards EMF source(s) due to the fear of a negative impact of EMF on health.	

Considering the fact that the reported symptoms are quite common in the general population and also the lack of symptom patterns [6,53] and etiology, the only parameter that clearly distinguishes sensitive from control individuals is the causal attribution of symptomatology to EMF exposure. Therefore, the attribution of health outcomes and self-reported sensitivity to EMF inevitably constitute, at the moment, the cornerstone of IEI-EMF case definition in research and clinical practice. Additional aspects such as medical examination/history would elucidate whether the reported health outcomes can be explained by underlying pathology.

Cognitive and behavioral aspects could be complementarily included in the case definition, since evidence on their role in IEI-EMF is promising [18] but not yet established. Moreover, taking into account potentially harmful environmental agents other than EMF would be an important addition for research.

This is the first time that a systematic review is conducted on definitions and identifying criteria for IEI-EMF. Given the large number of included articles, it is unlikely that any missing (or even excluded) studies would alter the results or increase any publication bias, especially since the aim of the current paper was not to assess etiologic associations. It is a challenge how all the different case definition parameters for IEI-EMF can be concisely embodied in one international operational tool which could be used in research and clinical practice, and how this instrument could be adjusted to the possible cultural differences (e.g in terms of wording/phrasing questions on health outcomes). Nevertheless, without the harmonization of the conceptual framework and validation of identifying criteria, the value of the case definition standards for IEI-EMF will remain insufficient and possibly unreliable. Apart from research, this has an important impact also in primary care; physicians, who are often the first to be contacted by the sufferers, are usually not adequately informed about IEI-EMF, which can affect the patient-doctor interaction and the management of the patient [26].

In order to properly construct an operational tool, a proposed two-phase approach can be briefly described as follows: In the first phase, a case definition and case selection tool should be developed, taking into account sources such as the published literature, expert opinions (e.g based on a Delphi procedure [93]) and information on IEI-EMF patient characteristics from available datasets/ongoing research. At this stage, EMF measurements or provocation tests should not be a priority since a provocation study will only have added value after the formulation of a proper case definition and participant selection. Additionally, if the aim of a “case selection tool” is to routinely test cases where symptoms occur without a clear underlying pathology, then that tool should be concise, inexpensive and easy to implement, such as a short questionnaire or checklist. In the second phase, the case definition tool should be validated in terms of practical usability and the ability to differentiate between subgroups of IEI-EMF and patients with other conditions (e.g chronic fatigue) who report similar symptoms. Based on the findings, the requirements for a follow up study could be outlined.

Conclusions

IEI-EMF is a poorly defined sensitivity. Heterogeneity and ambiguity of the existing definitions and criteria for IEI-EMF show the necessity to develop uniform criteria that will be applicable both in research and clinical practice. Broader criteria identified in the published literature such as attribution of NSPS to EMF and subjective report of being EMF sensitive could be used as a working definition for IEI-EMF which will serve as a basis for the development of a case selection tool. However, further optimization is required, testing its reliability and validity in several different patient groups, leading to an international multidisciplinary protocol with the active involvement of health care providers. This could also be a stepping stone for the harmonization of concepts and case definition for the broader condition of IEI.

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Chapter 5

Comparing non-specific physical symptoms in environmentally sensitive patients: Prevalence, duration, functional status and illness behavior

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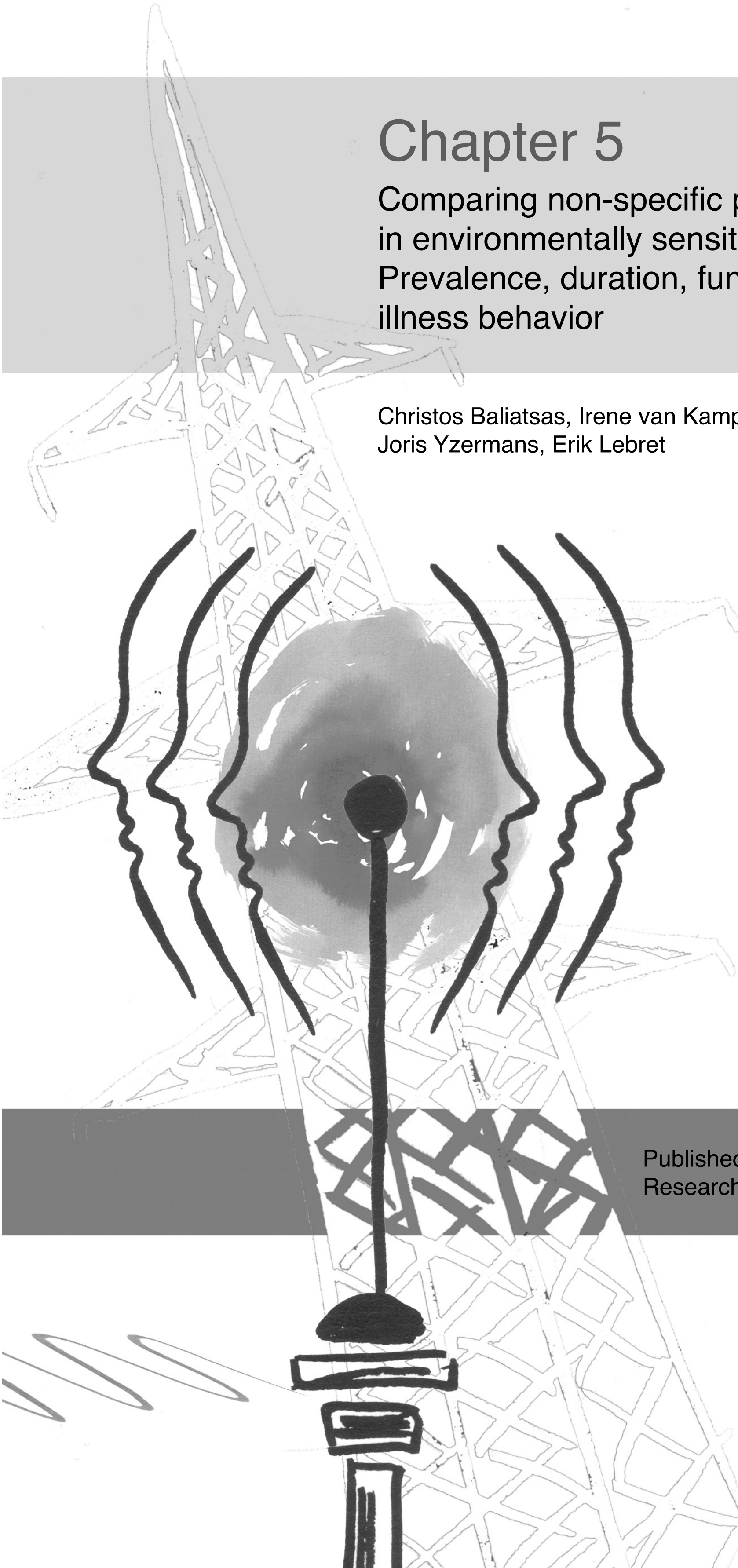

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Summary

Objective: Little is known about the potential clinical relevance of non-specific physical symptoms (NSPS) reported by patients with self-reported environmental sensitivities. This study aimed to assess NSPS in people with general environmental sensitivity (GES) and idiopathic environmental intolerance attributed to electromagnetic fields (IEI-EMF) and to determine differences in functional status and illness behavior.

Methods: An epidemiological study was conducted in the Netherlands, combining self-administered questionnaires with the electronic medical records of the respondents as registered by general practitioners. Analyses included n = 5789 registered adult (≥18 years) patients, comprising 5073 non-sensitive (NS) individuals, 514 in the GES group and 202 in the IEI-EMF group.

Results: Participants with GES were about twice as likely to consult alternative therapy compared to non- sensitive individuals; those with IEI-EMF were more than three times as likely. Moreover, there was a higher prevalence of symptoms and medication prescriptions and longer symptom duration among people with sensitivities. Increasing number and duration of self-reported NSPS were associated with functional impairment, illness behavior, negative symptom perceptions and prevalence of GP-registered NSPS in the examined groups.

Conclusion: Even after adjustment for medical and psychiatric morbidity, environmentally sensitive individuals experience poorer health, increased illness behavior and more severe NSPS. The number and duration of self-reported NSPS are important components of symptom severity and are associated with characteristics similar to those of NSPS in primary care. The substantial overlap between the sensitive groups strengthens the notion that different types of sensitivities might be part of one, broader environmental illness.

Introduction

People often experience symptoms such as headaches, fatigue, musculoskeletal pain, sleep problems and bowel disturbances, which are not necessarily related to a medical condition. More than 80% of the general population experiences at least one of such non-specific physical symptoms (NSPS) in any given month [1,2]. When presented to the general practice (GP), between 30% and 50% of NSPS cannot be sufficiently explained by a pathological cause and are often labeled as medically unexplained [3,4]; according to more recent evidence, these rates can be even higher [5]. However, the term "medically unexplained" is perceived as negative by patients [6] or ambiguous, connoting that the health provider is not able to help or that the symptoms can only be psychiatrically explained [7]. For these reasons and considering that such symptoms are usually reported in different organ systems [8], the term NSPS will be used in the following. In medical care, NSPS are associated with functional impairment similar to that of patients with medical disorders [9], increased illness behavior [10], high levels of psychological distress [11,12] and negative symptom perceptions [13,14].

Experiencing NSPS is a main characteristic of self-declared sensitivities attributed to low (in relation to established effect thresholds) levels of exposure to environmental agents such as electromagnetic fields (EMF). However, there is no convincing evidence for a causal dose– response association and a broadly accepted case definition for patients is missing [15–22]. Although not well-established, there is the notion that self-reported sensitivity to EMF sources, described by the WHO as idiopathic environmental intolerance attributed to EMF (IEI-EMF) [23] and other diverse environmental sensitivities, such as those to odorous chemicals, food additives and noise, may constitute dimensions of just one condition; a generalized environmental sensitivity which is usually referred to as idiopathic environmental intolerance (IEI) [24–27]. This notion is mainly based on evidence that patients tend to be sensitive to more than one environmental sources [28,29] and the lack of symptom patterns [28]; IEI has been considered as part of the broader spectrum of functional somatic syndromes [12] and can co-occur with syndromes such as fibromyalgia and chronic fatigue [30]. However, evidence on the clinical pertinence of symptoms reported by environmentally sensitive individuals is still scarce. Important information regarding the clinical profile of the patients such as prevalence of registry-based medical and psychiatric morbidity and prescribed medication is also missing at the population level.

On the one hand, only a diagnostic evaluation could sufficiently determine whether underlying pathology accounts for the symptoms [31,32]. On the other hand, persistent presentation of NSPS to the GP is relatively rare [33–35] and patients who seek health care are not always those with increased functional impairment [32,36–38]. This means that a large pool of symptomatic cases in the population has not been studied in primary care research [39]. Evidence from studies in the general population and among disaster survivors suggests that NSPS reported in surveys share several features with NSPS in medical care, showing that increased number of self-reported NSPS is a strong indicator of functional impairment and illness behavior [2,7]. However, it is not clear yet whether this is the case for NSPS reported by individuals with environmental sensitivities, such as IEI-EMF and the broader condition of IEI. Additional components of symptom severity, such as duration, should also be considered to understand the clinical importance of symptomatology [32].

The following research questions were addressed in the present study: 1) Do people with IEI-EMF and those with general environmental sensitivity experience more NSPS and NSPS of longer duration compared to participants without such sensitivities? 2) Do the examined groups differ in terms of symptom patterns, functional status and illness behavior? 3) What is the association between self-reported NSPS and functional impairment, illness behavior and GP-registered NSPS among sensitive and non-sensitive individuals?

Methods

Study design and participants

Data were collected within the framework of an epidemiological study into NSPS in relation to actual and perceived exposure to EMF (EMPHASIS). The study was carried out between January 21 and 23 June 2011 in the Netherlands, combining self-administered questionnaires and electronic medical records (EMR) of health problems, registered in GPs within the Dutch Information Network of General Practices (LINH) [40]; every Dutch citizen is obliged to be registered at one GP, so the population listed in family practice can be used as the denominator in epidemiological studies [40–42]. Data collection within the LINH network is carried out according to the Dutch legislation on privacy. Each patient is coded with an anonymous administrative number. The key to this coding number is only with the general practitioner. The privacy regulation of the study was approved by the Dutch Data Protection Authority. Based on the Law on Medical Scientific Research (WMO), the Dutch Medical Ethics Committee decided that an ethical approval was not required.

Twenty-one practices, varying in terms of number of patients and level of urbanization were selected from the primary care database of the Netherlands Institute for Health Services Research (NIVEL). Registered patients were listed according to postal codes and house number; a geographical information system (GIS) layer of these addresses was then created, resulting to a total pool of 76,684 eligible addresses. A random sample among the adult population (≥ 18 years) was drawn from the GP registry data set, initially stratified by age, gender and preliminary estimates of EMF exposure from mobile phone base stations [43]. Only one adult was sampled from each household. All invitees (n = 13,007) received a letter from their GP to fill out a questionnaire, either electronically or in a paper version, entitled "Living environment, technology and health", along with an information leaflet and informed consent form. If a completed questionnaire had not been received, a reminder letter was sent two weeks after the first invitation and a second reminder two weeks later. This resulted in n = 5933 respondents (response rate: 46%). Twenty percent of the respondents filled out the survey online. A non-response follow-up on a shorter version of the questionnaire was also conducted, including n = 505 individuals.

Case definitions

Selection of individuals with IEI-EMF was based on findings from a recent systematic evaluation of the relevant literature [21], considering that: 1) IEI-EMF is a highly heterogeneous condition in terms of severity and associated EMF sources; 2) self-reported (hyper) sensitivity to EMF is the most often used criterion for patient identification in the literature; 3) most people with IEI-EMF tend to be sensitive to more than one EMF source. Therefore, two items were used to assess IEI-EMF in the study sample, asking the extent to which people agree with the following statements: 1) "I am sensitive to mobile phone base stations and devices related to communication systems (e.g. mobile phones, wireless internet etc.)" and 2) "I am sensitive to electrical devices (e.g. domestic appliances etc.)"; answers were scored on a five-point scale, ranging from "strongly disagree" to "strongly agree". Those who indicated "quite agree" to "strongly agree" were included in the IEI-EMF group.

A list of nine items assessing sensitivity to several environmental stressors (other than EMF) such as chemical substances, smells in general and in relation to scented detergents, noise, light, various materials, color, temperature changes and cold or warm environment was used to assess general environmental sensitivity (GES), adapted from Stansfeld et al. [44].
Answers were scored in a similar format as the items on IEI- EMF mentioned above. Respondents with a score at or above the 90th percentile of the score distribution (which

corresponds to an average per-item response of at least "quite agree"), were included in the GES group. Participants who had more than one items missing were excluded from subsequent analyses.

Assessment of self-reported non-specific physical symptoms (NSPS)

To assess NSPS, 23 items from the recently developed Symptoms and Perceptions (SaP) scale [45] were selected. These correspond to physical symptoms similar to those reported by patients in general practice, based on the International Classification of Primary Care (ICPC-1) [46]. The included items ask respondents on a binary scale whether they experienced any of the examined symptoms in the past month; if so, respondents are asked about how long they have been bothered by these symptom(s), with responses formed on a 5-point scale, with "over 6 months" as the highest value. A higher total score in the corresponding characteristics indicates increased number of NSPS and related duration (Internal consistency based on the total analyzed sample: Cronbach's $\alpha = .80$ for and $\alpha = .82$ respectively).

Moreover, the sum scores were added together and categorized into four ranges, based on the approach of van den Berg et al. [8], to present more explicitly the relationship between graded increases in NSPS and the different indicators of functional status and illness behavior: The first range was 0 to 1 symptom, the second 2 to 9 symptoms, the third 10–14 symptoms and the fourth 15 or more symptoms. Following similar methodology, the total score on duration was categorized into 4 ranges as well, corresponding to different percentiles (50th, 50th–79th, 80th– 94th and 95th), based on the distribution reported by the NS group.

Assessment of GP-registered NSPS

Non-specific physical symptoms in EMR were registered by the GP according to the ICPC-1 [46]. The evaluation of the clinical judgment of the GP on the symptoms was based on "episodes of care", representing the period from the first presentation of a health problem to a general practice until the completion of the last encounter for the same problem [47]. An episode was defined as "non-specific" if no medical diagnosis had been registered as an explanation for the symptoms, during the year before the completion of the present study.

In order to evaluate the association between self-reported and registry based NSPS, we compared the 23 self-reported NSPS with potentially corresponding NSPS in the medical records of the participants [8].

For example, the symptom "headache" corresponded to the ICPC codes N01 (headache) and N02 (tension headache). The total prevalence of registered-NSPS was treated as a dichotomous variable.

Assessment of functional status

For the same period, the GP-registered prevalence of prescriptions related to painkillers, tranquilizers (benzodiazepines) and antidepressants were examined, classified according to the Anatomical Therapeutic Chemical Classification system (ATC) [48].

Participants also completed the General Health subscale of the RAND-36 Health Survey questionnaire [49], which is scored from 0 to 100. A higher score represents better physical functioning.

Sleep quality was assessed using a 10-item version of the Groningen Sleep Quality Scale (GSQS) [50,51]. Answers were formatted on a binary scale, with a higher sum score demonstrating lower self-reported sleep quality.

Psychological distress was assessed with the 12-item version of the General Health Questionnaire (GHQ-12) [52–54]. The 4-point Likert-type scoring method was used in the present analyses; a higher total item score indicates increased distress.

Measures of illness behavior and symptom perceptions

Participants were asked whether they consulted a GP, a psychologist/ psychotherapist and/or an alternative therapist (e.g. homeopathist, acupuncturist or paranormal therapist) and also whether they used any unprescribed medication within the past year.

Symptom perceptions were assessed using the items related to consequences and emotional response of the Brief Illness Perceptions Questionnaire (Brief-IPQ) [55,56]. The items were scored on a 10-point Likert scale and referred to the symptom perceived as the most important. Higher scores indicate a greater perceived influence of the reported symptom on life and a stronger, negative emotional response.

Finally, information was obtained on socio-demographic characteristics, lifestyle indicators and GP-registered (based on the ICPC-1) medical (co)morbidity and psychiatric (co)morbidity.

Data analysis

To examine potential differences between the three groups in terms of symptom report, functional status, illness behavior and symptom perceptions, linear (for the continuous outcomes) and logistic (for the dichotomous outcomes) regression analyses were used to control for socio-demographic characteristics and medical and psychiatric morbidity. None of the examined continuous scores exceeded the suggested acceptable values for skewness [57]. No risk for multicollinearity was observed. Analysis of variance (one-way ANOVA), the chi-squared test, Cramer's V, and the unpaired samples *t*-test were performed for the descriptive analyses and to examine the associations between symptom categories and indicators of functional status, illness behavior and perceptions.

Depending on the type of analyzed variables, effect sizes (regression coefficient, ORs, Cramer's V statistic, Pearson r coefficient) are presented for the main results. The non-parametric equivalent of the ANOVA (Kruskal–Wallis test) was employed to verify the consistency of the findings. To determine whether medical morbidity affected the results, analyses were repeated for participants without registered medical conditions. Post-hoc comparisons were also performed to verify differences between the symptom groups, using the Games–Howell and Bonferroni procedures [58,59]. In all tests, the significance level was set at $p < .05$. When self-reported NSPS were examined as a sum score, respondents who had more than five items on the 23-symptom list missing were excluded from the analyses.

Missing values in the rest of the self-reported measures were treated according to the guidelines or previous publications on these measures. Statistical analyses were carried out using IBM SPSS Statistics (SPSS Inc. version 19, Chicago IL, USA).

Results

Descriptive analyses and non-response

Based on the employed case definition criteria and after exclusion of associated incomplete items (n = 144), a total sample of 5789 respondents was available for analysis; n = 202 (3.5%) and n = 514 (8.8%) met the criteria for the IEI-EMF and GES group respectively, while the rest of the participants (n = 5073) formed the “control”, non- (environmentally) sensitive (NS) sample. Seventy-seven (38%) of participants in the IEI-EMF group also met the criteria for GES. Demographic characteristics, lifestyle indicators and medical and psychiatric morbidity for the three groups are presented in Table 1.

Table 1: Basic demographic characteristics, morbidity and lifestyle indicators of the three investigated groups (valid cases)

	NS group (n=5,073)	GES group (n=514)	IEI-EMF group (n=202)
Demographic characteristics			
Age (%)			
18 – 24	6.4	3.3 [1]	3.0
25 – 44	32.2	23.0 [1]	20.8 [2]
45 – 64	39.8	42.8	39.6
65 – 74	12.3	16.1 [1]	14.8
75 +	9.3	14.8 [1, 3]	21.8 [2, 3]
Mean age (SD)	51.0 (17.0)	56.5 (16.5) [1]	58.5 (17.7) [2]
Female gender (%)	56.0	78.0 [1, 3]	61.4 [3]
Education [a] (%)			
Lower	22.4	27.0 [1]	34.2 [2]
Middle	44.8	45.2	41.3
Higher	32.8	27.8 [1]	24.5 [2]
Marital status (%)			
Unmarried	20.2	19.0	23.6
Married, living together	64.8	60.0 [1]	57.8 [2]
Divorced	7.0	12.4 [1]	7.5
Widowed	8.0	8.6	11.1
Occupational status (%)			
Employed, school, housewife/man	73.5	62.5 [1]	62.9 [2]
Unemployed, incapacitated	7.8	13.0 [1]	10.4
Retired	18.7	24.5 [1]	26.7 [2]
Born in the Netherlands (%)	93.8	89.8 [1]	84.4 [2]
Medical morbidity (registered) (%)			
Asthma	3.5	5.4 [1]	4.5
Acute myocardial infarction	.9	.4	2.5 [2, 3]
Chronic obstructive pulmonary disease (COPD)	2.6	4.7 [1]	3.0
Diabetes	5.7	8.4 [1]	8.9
Duodenal/peptic ulcers	.2	.0	.6
Hypertension (uncomplicated)	12.0	15.4 [1]	14.9
Rheumatoid arthritis	.6	1.2	.5
Herpes zoster	.5	1.4 [1]	.5
Psoriasis	.9	.6	2.5 [2, 3]
Cancer (malignant neoplasm)	2.6	5.1 [1]	3.5
Psychiatric morbidity (registered) (%)			
Anxiety disorder	1.0	3.1 [1]	1.0
Depressive disorder	2.3	4.5 [1]	3.0
Lifestyle indicators			
Mean BMI (Body mass index) (SD)	25.4 (4.8)	25.4 (5.1)	26.0 (4.6)
Smoking (%)			
No, never	42.7	43.3	46.5
No, in the past	36.8	40.5	34.5
Yes	20.5	16.2 [1]	19.0
Alcohol abuse > 6 months (%)	1.8	3.0	2.3

Note: Significance level set at $p < .05$.
[1] Significant difference between GES & NS group.
[2] Significant difference between IEI-EMF & NS group.
[3] Significant difference between GES & IEI-EMF group.
[a] Lower: No education or primary school or lower secondary education ; Middle: Intermediate vocational or intermediate general secondary or higher general secondary education; Higher: Higher vocational or university education.

Compared to non-respondents, participants in the total sample were younger (mean age 51.8, SD 17.1 versus 55.0 SD 18.9, p = .001), higher educated (higher vocational education or university 32% vs. 21.5%, Cramer's V =.096, p = .00) and with better perceived health (good, very good or excellent perceived health 82% vs. 73.5%, OR .6, 95% CI .48–.76, p = .00). There was no significant difference in gender distribution (female gender 58% vs. 59.5%, OR 1.05, 95% CI .86–1.29, p = .61). Among the non-respondents, 89% provided reasons for not participating in the study: (26%) stated that they had no time, 22.5% had no interest to participate, 14.5% had no health complaints and 26% provided various other (additional) reasons.

NSPS, functional status and illness behavior: differences between GES, IEI-EMF and controls (NS)

Controls reported a mean number of 5.0 (SD 3.8) NSPS in the past month, which was significantly lower than the mean number of 6.9 (SD 4.5) symptoms in the IEI-EMF group and the mean number of 7.7 (SD 4.5) symptoms in the GES group (p = .00). The total prevalence of registry-based NSPS was 35% in the NS group, 42% in the IEI-EMF and 43% in the GES group (p = .001).

There was a higher prevalence and longer duration of all self-reported symptoms among people with environmental sensitivities, especially those with GES, compared to the NS group (Tables 2 & 3, Fig. 1); symptoms in particular organ systems such as the digestive and cardiovascular, were strikingly pronounced in the GES and IEI-EMF group respectively.
Participants in the sensitive groups had higher levels of functional impairment, symptom scores, negative symptom perceptions and illness behavior; the latter was more related to alternative therapies rather than consulting a GP (Table 4).

Association between self-reported NSPS and indicators of functional status and illness behavior

With increasing number and duration of self-reported NSPS in the three groups, there was an increase in GP-registered NSPS and the examined indicators of functional impairment and illness behavior (Fig. 1, Tables 5 & 6). Significant associations were verified by post-hoc comparisons (data not shown).

In the two environmentally sensitive groups, not all associations reached statistical significance. For instance, although there was a significantly higher prevalence of registered NSPS with increasing number and duration of self-reported NSPS in the NS group (Cramer's $V_{number} = .17$, $p = .00$ & $V_{dur} = .21$, $p = .00$) and with increasing symptom duration in the GES group ($V_{number} = .12$, $p = .07$, $V_{dur} =.16$, $p = .01$), such associations were not observed for the IEI-EMF group ($V_{number} = .15$, $p = .3$, $V_{dur} = .17$, $p = .2$) (Fig. 1). The results of ANOVA did not change after repeating the analyses with non-parametric tests. Overall, the two highest categories of symptom number and duration (≥10 and 80th percentile respectively) remained the ones with the highest scores on functional impairment, illness behavior and negative symptom perceptions after exclusion of respondents with medical and psychiatric morbidity (data not shown).

Table 2: Prevalence of 23 self-reported NSPS in the NS, GES & IEI-EMF group and between-group differences [a]

Self-reported NSPS	Corresponding ICPC code(s)	NS [b]	GES [c]	OR (95% CI)	IEI-EMF	OR (95% CI)
Fatigue/tiredness	A04	52.4	68.5	1.8 (1.5 – 2.3)*	62.2	1.5 (1.1 – 2.1) ⊤
Abdominal/stomach pain	D01 – D02, D06	22.8	39.9	2.0 (1.6 – 2.5)*	30.2	1.5 (1.1 – 2.2) ⊤
Nausea	D09	11.2	20.8	1.8 (1.4 – 2.4)*	15.3	1.4 (.9 – 2.3)
Diarrhea or constipation	D11 – D12	20.4	31.5	1.7 (1.3 – 2.1)*	23.0	1.1 (.8 – 1.7)
Eye symptoms	F01 – F02	17.8	31.4	1.8 (1.4 – 2.3)*	23.8	1.3 (.9 – 1.9)
Ear symptoms	H01 – H03, H13	12.7	21.3	1.6 (1.2 – 2.1)*	20.9	1.6 (1.0 – 2.3) ⊤
Heart palpitations/awareness	K04	12.6	21.7	1.5 (1.2 – 1.9) ǂ	26.3	2.3 (1.6 – 3.4)*
Neck or shoulder symptoms	L01, L08	37.0	54.3	1.7 (1.4 – 2.1)*	47.2	1.4 (1.0 – 2.0) ⊤
Back pain	L02 – L03	34.9	49.2	1.6 (1.3 – 2.0)*	42.7	1.3 (.9 – 1.8)
Pain/pressure in chest and heart region	L04, K01 – K03	8.6	16.4	1.9 (1.4 – 2.5)*	20.0	2.5 (1.6 – 3.8)*
Arm/elbow/hand/wrist symptoms	L09 – L12	23.7	37.3	1.5 (1.2 – 1.9)*	27.8	.9 (.6 – 1.4)
Leg/hip/knee/foot symptoms	L13 – L15, L17	31.6	46.3	1.4 (1.2 – 1.8)*	42.4	1.2 (.8 – 1.7)
Pain in muscles	L18	30.3	41.2	1.5 (1.2 – 1.9)*	38.5	1.5 (1.0 – 2.1) ⊤
Headache	N01 – N02	36.8	51.0	1.8 (1.5 – 2.2)*	43.6	1.7 (1.2 – 2.5) ǂ
Tingling of fingers, feet or toes	N05	15.7	27.0	1.6 (1.3 – 2.0)*	25.0	1.6 (1.1 – 2.3) ⊤
Dizziness or feeling light-headed	N17	19.4	37.4	2.0 (1.6 – 2.5)*	36.5	2.3 (1.7 – 3.3)*
Sleep problems	P06	25.6	42.7	1.7 (1.4 – 2.1)*	44.4	2.2 (1.5 – 3.0)*
Memory or concentration problems	P20	19.8	36.2	2.0 (1.6 – 2.4)*	35.0	1.9 (1.4 – 2.8)*
Shortness of breath	R02 – R04, R29	7.8	17.0	2.0 (1.5 – 2.6)*	16.3	1.9 (1.2 – 3.0) ǂ
Cough	R05	21.9	27.2	1.2 (.99 – 1.5)	27.8	1.4 (1.0 – 2.1) ⊤
Nasal symptoms	R07	24.5	37.8	1.8 (1.5 – 2.2)*	26.0	1.1 (.8 – 1.6)
Skin symptoms	S01, S06 – S07	21.8	38.2	2.1 (1.7 – 2.6)*	35.6	1.9 (1.4 – 2.7)*
Weight change	T07 – T08	11.6	16.9	1.3 (.99 – 1.7)**	18.5	1.7 (1.1 – 2.6) ⊤

[a] Between-group differences were adjusted for age, gender, education, ethnic background, medical morbidity, psychiatric morbidity.
[b] Reference group.
[c] No significant differences between GES & IEI-EMF group.
Note: ⊤ $p < .05$; ǂ $p < .01$; *$P < .001$; ** $p = .05$.
Abbreviations: OR, Odds ratio; CI, Confidence interval.

Table 3: Prevalence of self-reported NSPS with duration of ≥4 months in the NS, GES & IEI-EMF group and between-group differences [a]

Self-reported NSPS	NS [b]	GES [c]	OR (95% CI)	IEI-EMF	OR (95% CI)
Fatigue/tiredness	23.3	42.5	2.0 (1.6 – 2.5)*	34.6	1.6 (1.1 – 2.3) ǂ
Abdominal/stomach pain	8.7	20.9	2.4 (1.8 – 3.1)*	14.0	1.5 (.9 – 2.4)
Nausea	2.2	8.2	2.7 (1.8 – 4.1)*	3.4	1.1 (.4 – 2.8)
Diarrhea or constipation	6.2	14.1	2.0 (1.5 – 2.7)*	10.1	1.4 (.8 – 2.5)
Eye symptoms	6.4	14.6	2.0 (1.5 – 2.8)*	10.7	1.3 (.7 – 2.2)
Ear symptoms	6.4	11.6	1.6 (1.1 – 2.2) ǂ	13.2	1.7 (1.0 – 2.8) ⊤
Heart palpitations/awareness	5.6	11.2	1.6 (1.2 – 2.3) ǂ	15.1	2.8 (1.8 – 4.5)*
Neck or shoulder symptoms	19.3	34.0	1.7 (1.4 – 2.2)*	24.0	1.1 (.7 – 1.6)
Back pain	18.3	32.1	1.7 (1.4 – 2.2)*	25.4	1.3 (.9 – 1.9)
Pain/pressure in chest and heart region	3.4	8.8	2.4 (1.6 – 3.5)*	8.3	2.4 (1.3 – 4.5) ǂ
Arm/elbow/hand/wrist symptoms	13.7	25.5	1.6 (1.2 – 2.0)*	17.6	1.0 (.6 – 1.6)
Leg/hip/knee/foot symptoms	19.5	32.8	1.5 (1.2 – 1.8) ǂ	26.6	1.0 (.7 – 1.5)
Pain in muscles	8.5	18.4	1.9 (1.4 – 2.5)*	19.4	2.0 (1.3 – 3.0) ǂ
Headache	10.2	24.5	2.6 (2.0 – 3.3)*	16.6	2.0 (1.3 – 3.0) ǂ
Tingling of fingers, feet or toes	8.6	16.7	1.7 (1.2 – 2.2)*	12.7	1.3 (.8 – 2.1)
Dizziness or feeling light-headed	7.2	19.1	2.4 (1.8 – 3.2)*	16.0	2.2 (1.4 – 3.5)*
Sleep problems	14.6	29.9	1.9 (1.5 – 2.4)*	28.2	2.1 (1.4 – 3.0)*
Memory or concentration problems	11.4	26.3	2.3 (1.8 – 2.9)*	20.7	1.8 (1.2 – 2.8) ǂ
Shortness of breath	4.1	10.1	2.3 (1.6 – 3.2)*	7.5	1.6 (.8 – 3.0)
Cough	5.3	8.0	1.3 (.9 – 2.0)	11.8	2.1 (1.2 – 3.5) ǂ
Nasal symptoms	10.3	19.7	2.0 (1.5 – 2.6)*	12.6	1.1 (.7 – 1.9)
Skin symptoms	11.7	25.7	2.4 (1.9 – 3.0)*	18.0	1.4 (.9 – 2.2)
Weight change	6.4	11.6	1.6 (1.2 – 2.2) ǂ	9.4	1.4 (.8 – 2.5)

[a] Between-group differences were adjusted for age, gender, education, ethnic background, medical morbidity, psychiatric morbidity.
[b] Reference group.
[c] Significant differences between GES & IEI-EMF (ref) group: abdominal/stomach pain (OR 1.7, 95% CI 1.0 – 3.0, p <.05), nausea (OR 2.7, 95% CI 1.0 – 7.4, p <.05), neck or shoulder symptoms (OR 1.6, 95% CI 1.0 – 2.4, p <.05), nasal symptoms (OR 1.8, 95% CI 1.1 – 3.2, p <.05).
Note: ⊤ p <.05; ǂ p <.01; * p <.001; ** p =.05. Abbreviations: OR, Odds ratio; CI, Confidence interval.

Table 4: Unadjusted and adjusted differences between groups on determinants of functional status, illness behavior, symptom perceptions & symptom scores

	GES vs. NS [a]		IEI-EMF vs. NS [a]		GES vs. IEI-EMF [a]	
Regression Coefficient (95% CI)	**Unadjusted**	**Adjusted** [b]	**Unadjusted**	**Adjusted** [b]	**Unadjusted**	**Adjusted** [b]
General health	-9.1 (-11.0 to -7.4)*	-7.4 (-9.0 to -5.7)*	-6.6 (-9.3 to -3.9)*	-3.9 (-6.5 to -1.2)ǂ	-2.5 (-6.1 to 1.0)	-3.1 (-6.7 to .5)
Sleep quality	.9 (.7 to 1.2)*	.6 (.4 to .9)*	1.0 (.6 to 1.4)*	.9 (.5 to 1.3)*	-.07 (-.6 to .4)	-.2 (-.8 to .3)
Psychological distress	1.3 (.8 to 1.8)*	1.0 (.5 to 1.5)*	.9 (.2 to 1.7) ᵀ	1.0 (.2 to 1.8) ǂ	.3 (-.6 to 1.4)	.04 (-1.0 to 1.1)
Perceived impact †	1.2 (.9 to 1.4) ǂ	1.0 (0.7 to 1.2)*	.6 (.2 to 1.1) ǂ	.5 (.09 to 1.0) ǂ	.5 (.02 to 1.0) ᵀ	.4 (-.05 to 1.0)
Emotional response †	1.5 (1.2 to 1.8)*	1.3 (1.0 to 1.6)*	.8 (.3 to 1.3) ǂ	.8 (.3 to 1.4) ǂ	.7 (.1 to 1.2) ᵀ	.6 (-.01 to1.2)**
Number of self-reported NSPS	2.6 (2.3 to 3.0)*	2.1 (1.8 to 2.5)*	1.8 (1.2 to 2.4)*	1.7 (1.1 to 2.3)*	.8 (.03 to 1.6) ᵀ	.5 (-.3 to 1.3)
Duration of self-reported NSPS	9.0 (7.8 to 10.1)*	7.2 (6.1 to 8.4)*	5.7 (3.8 to 7.5)*	5.0 (3.0 to 6.8)*	3.3 (.4 to 6.2) ᵀ	2.7 (-.3 to 5.7)
OR (95% CI)						
Consulting a GP	1.7 (1.3 – 2.2)*	1.2 (.98 – 1.6)	1.2 (.8 – 1.7)	1.0 (.7 – 1.5)	1.4 (.96 – 2.1)	1.2 (.8 – 1.9)
Consulting a psychologist	1.9 (1.5 – 2.4)*	1.9 (1.5– 2.5)*	1.5 (1.0 – 2.3) ᵀ	2.0 (1.3 – 3.1) ǂ	1.2 (.8 – 2.0)	1.0 (.6 – 1.6)
Consulting an alternative therapist	2.1 (1.6 – 2.7)*	1.9 (1.4 – 2.5)*	3.0 (2.0 – 4.4)*	3.8 (2.5 – 5.7)*	.7 (.4 – 1.0)	.5 (.3 - .8) ǂ
Unprescribed medication	1.3 (1.1 – 1.6) ǂ	1.3 (1.1 – 1.6) ǂ	1.0 (.7 – 1.3)	1.1 (.8 – 1.6)	1.3 (.97 – 1.9)	1.2 (.8 – 1.8)
Registered NSPS	1.3 (1.1 – 1.6) ǂ	1.1 (.9 – 1.4)	1.3 (.99 – 1.7)	1.0 (.7 – 1.4)	1.0 (.7 – 1.4)	1.1 (.7 – 1.6)
Prescribed painkillers	1.4 (1.1 – 1.7) ǂ	1.2 (.97 – 1.5)	1.4 (1.0 – 2.0) ᵀ	1.2 (.9 – 1.8)	1.0 (.7 – 1.4)	.9 (.6 – 1.4)
Prescribed benzodiazepines	2.1 (1.6 – 2.7)*	1.4 (1.0 – 1.8) ᵀ	1.9 (1.3 – 2.8) ǂ	1.5 (1.0 – 2.4)**	1.1 (.7 – 1.7)	1.0 (.6 – 1.6)
Prescribed antidepressants	2.2 (1.7 – 2.9)*	1.5 (1.1 – 2.1) ᵀ	1.5 (.95 – 2.4)	1.3 (.7 – 2.3)	1.5 (.9 – 2.4)	1.1 (.6 – 2.0)

[a] Reference group; [b] Between-group differences were adjusted for age, gender, education, ethnic background, medical (co)morbidity, psychiatric (co)morbidity.
Note: ᵀ p <.05; ǂ p <.01; *p <.001; ** p =.05.
Abbreviations: OR, Odds ratio; CI, Confidence interval.
† Referring to the most important symptom among the ones reported.

Table 5: Association between number and duration of self-reported symptoms and determinants of functional status in the NS group and people with GES & IEI-EMF ┼

Functional status		Number of symptoms				Duration of symptoms			
		0 – 1	2 – 9	10 – 14	≥15	<50th percentile	50th – 79th percentile	80th – 94th percentile	95th percentile
General health									
NS [a, b]	(r_{number} =-.47, $r_{dur.}$ =-.52) [c]	74.6 (12.5)	66.0 (15.7)	50.1 (19.1)	39.3 (17.8)	72.0 (13.5)	64.5 (15.4)	54.2 (17.4)	39.8 (17.9)
GES [a, b]	(r_{number} =-.48, $r_{dur.}$ =-.53) [c]	69.7 (14.7)	61.1 (18.9)	46.6 (19.3)	38.9 (16.8)	67.4 (16.2)	62.1 (18.5)	51.6 (17.8)	39.1 (18.6)
IEI-EMF [a, b]	(r_{number} =-.53, $r_{dur.}$ =-.59) [c]	68.8 (15.5)	63.6 (15.1)	47.0 (19.9)	37.7 (24.0)	67.7 (14.6)	62.7 (13.2)	58.2 (13.2)	38.0 (21.4)
Sleep quality									
NS [a, b]	(r_{number} =.45, $r_{dur.}$ =.48) [c]	.89 (1.5)	2.1 (2.4)	4.2 (3.1)	5.9 (2.8)	1.2 (1.8)	2.3 (2.4)	3.9 (2.9)	5.4 (3.0)
GES [a, b]	(r_{number} =.45, $r_{dur.}$ =.49) [c]	.88 (1.7)	2.5 (2.4)	4.6 (2.8)	5.6 (3.2)	1.6 (1.9)	2.6 (2.4)	3.8 (2.8)	5.4 (3.0)
IEI-EMF [a, b]	(r_{number} =.54, $r_{dur.}$ =.59) [c]	1.0 (1.7)	2.8 (2.7)	4.8 (2.6)	6.8 (3.3)	1.6 (1.9)	2.8 (2.7)	4.6 (2.6)	6.0 (2.9)
Psychological distress									
NS [a, b]	(r_{number} =.42, $r_{dur.}$ =.41) [c]	8.0 (3.0)	10.5 (4.9)	14.1 (6.4)	17.7 (7.4)	8.9 (3.9)	10.9 (5.0)	13.4 (6.1)	15.9 (7.5)
GES [a, b]	(r_{number} =.38, $r_{dur.}$ =.4) [c]	8.6 (3.4)	10.8 (5.2)	14.0 (6.9)	16.0 (6.6)	8.6 (3.9)	11.3 (5.1)	13.5 (6.4)	15.2 (6.8)
IEI-EMF [a, b]	(r_{number} =.44, $r_{dur.}$ =.46) [c]	8.1 (2.4)	10.8 (5.1)	15.2 (7.3)	17.9 (8.6)	9.8 (5.3)	10.5 (3.6)	13.1 (6.4)	17.2 (7.8)
Prescribed painkillers									
NS [a, b]	(V_{number} =.13, $V_{dur.}$ =.18) [c]	11.5	19.5	28.2	38.2	13.5	20.6	28.9	38.9
GES [b]	(V_{number} =.08, $V_{dur.}$ =.17) [c]	18.5	23.7	29.6	31.7	16.2	23.7	27.6	38.8
IEI-EMF	(OR_{number} =1.06, $V_{dur.}$ =.12) [c]	26.2ǂ		27.3ǂ		23.8	23.1	35.9	28.0
Prescribed benzodiazepines									
NS [a, b]	(V_{number} =.15, $V_{dur.}$ =.16) [c]	4.7	8.2	14.1	29.8	5.2	9.6	12.2	24.6
GES [a, b]	(V_{number} =.17, $V_{dur.}$ =.21) [c]	14.8	12.7	26.1	26.8	8.5	11.1	23.3	28.2
IEI-EMF	(OR_{number} =1.03, $V_{dur.}$ =.12) [c]	17.7ǂ		18.2ǂ		14.3	17.9	25.6	16.0
Prescribed antidepressants									
NS [a, b]	(V_{number} =.16, $V_{dur.}$ =.18) [c]	2.6	6.3	15.5	20.6	3.2	7.2	13.5	19.3
GES [a, b]	(V_{number} =.16, $V_{dur.}$ =.22) [c]	11.1	10.6	20.9	26.8	6.8	11.1	15.5	29.4
IEI-EMF	(OR_{number} =1.15, $V_{dur.}$ =.95) [c]	10.0ǂ		11.4ǂ		9.8ǂ		9.4ǂ	

┼ Data per symptom category are given as percentage of participants, except for "General Health" "Sleep quality" & "Psychological distress" which are given as mean scores and their standard deviations (SD). Note: Significance level set at $p < .05$.

[a] Significant difference between categories of number of symptoms across rows. [b] Significant difference between categories of symptom duration across rows.

[c] Effect sizes representing the strength of the associations between functional status indicators and symptom number and duration for each group; for the associations with the continuous indicators, the original symptom sum scores were used (abbreviations: r, Pearson r coefficient; V, Cramer's V; OR, Odds ratio). ǂ IEI-EMF group: When the expected count in the chi-squared test was < 5 in more than one cell (symptom category), the symptom number & duration scores were dichotomized (cut-off point: ≥10 symptoms & ≥80th percentile respectively).

Table 6: Association between number and duration of self-reported NSPS and prevalence of illness behavior & symptom perceptions in the three examined groups ‡

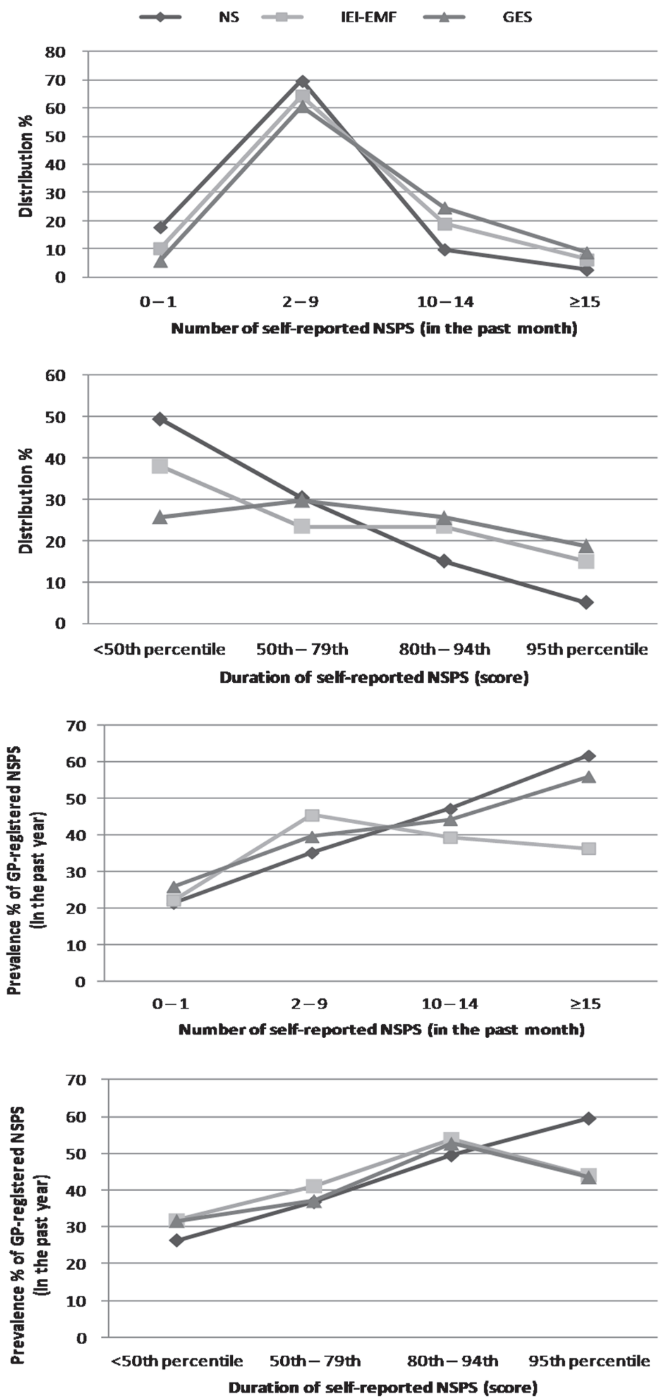
Illness behavior & symptom perceptions		**Number of symptoms**				**Duration of symptoms**			
		0 – 1	**2 – 9**	**10 – 14**	**≥15**	**<50th percentile**	**50th – 79th percentile**	**80th – 94th percentile**	**95th percentile**
Consulting a GP									
NS [a, b]	(V_{number} =.22, $V_{dur.}$ =.23) [c]	55.0	74.7	88.7	91.5	62.8	79.4	86.6	89.3
GES [a, b]	(V_{number} =.15, $V_{dur.}$ =.21) [c]	74.1	78.4	90.4	90.0	71.8	77.6	90.4	90.6
IEI-EMF [b]	(OR_{number} =1.38, $V_{dur.}$ =.23) [c]	76.0‡		81.4‡		64.5	81.6	84.6	88.0
Consulting a psychologist									
NS [a, b]	(V_{number} =.19, $V_{dur.}$ =.18) [c]	4.5	9.1	21.8	33.3	5.6	11.3	16.4	27.0
GES [a, b]	(V_{number} =.18, $V_{dur.}$ =.2) [c]	3.8	14.4	27.8	24.4	7.8	15.8	22.6	29.4
IEI-EMF [a, b]	(OR_{number} =4.2, $V_{dur.}$ =.33)	9.7‡		31.0‡		6.8	5.4	23.1	37.5
Consulting an alternative therapist									
NS [a, b]	(V_{number} =.1, $V_{dur.}$ =.14) [c]	3.7	7.6	12.7	16.5	4.3	9.3	13.0	14.5
GES [a, b]	(V_{number} =.15, $V_{dur.}$ =.15) [c]	3.8	12.9	20.9	26.8	8.7	12.9	23.3	16.5
IEI-EMF	(OR_{number} =1.99, $V_{dur.}$ =.16) [c]	17.9‡		30.2‡		15.5	26.3	17.9	33.3
Unprescribed medication									
NS [a, b]	(V_{number} =.22, $V_{dur.}$ =.16) [c]	27.4	53.7	61.6	66.9	41.9	57.5	58.4	62.4
GES	(V_{number} =.05, $V_{dur.}$ =.08) [c]	50.0	57.6	60.2	60.0	52.3	58.1	62.7	61.2
IEI-EMF [a]	(V_{number} =.23, $V_{dur.}$ =.17) [c]	26.7	50.0	68.8	36.4	41.1	52.8	62.2	58.3
Consequences †									
NS [a, b]	(r_{number} =.36, $r_{dur.}$ =.42) [c]	4.3 (2.7)	5.3 (2.6)	7.1 (2.1)	7.9 (1.7)	4.4 (2.6)	5.6 (2.4)	6.7 (2.2)	8.0 (1.8)
GES [a, b]	(r_{number} =.39, $r_{dur.}$ =.44) [c]	5.0 (3.1)	6.2 (2.5)	7.6 (1.9)	8.0 (2.0)	5.0 (2.6)	6.2 (2.4)	7.1 (2.1)	8.2 (1.6)
IEI-EMF [a, b]	(r_{number} =.36, $r_{dur.}$ =.47) [c]	6.7 (.9)	5.7 (2.6)	7.6 (2.1)	7.5 (2.6)	5.4 (2.5)	4.9 (2.6)	7.2 (1.8)	8.2 (1.7)
Emotional response †									
NS [a, b]	(r_{number} =.36, $r_{dur.}$ =.37) [c]	2.8 (2.9)	4.0 (2.9)	6.0 (2.7)	7.0 (2.4)	3.1 (2.8)	4.2 (2.9)	5.6 (2.8)	6.7 (2.7)
GES [a, b]	(r_{number} =.33, $r_{dur.}$ =.37) [c]	5.5 (2.1)	5.3 (2.8)	6.1 (2.9)	7.8 (2.2)	4.3 (2.8)	5.2 (2.7)	6.2 (2.7)	7.3 (2.6)
IEI-EMF [a, b]	(r_{number} =.32, $r_{dur.}$ =.37) [c]	5.0 (3.8)	4.7 (3.0)	6.2 (2.7)	8.0 (1.8)	4.3 (3.0)	4.6 (3.0)	5.6 (3.1)	7.4 (2.2)

‡ Data per symptom category are given as percentage of participants, except for "Perceived impact" & "Emotional response" which are given as mean scores and their standard deviations (SD). Note: Significance level set at $p < .05$.

[a] Significant difference between symptom number categories across rows. [b] Significant difference between symptom duration categories across rows.

[c] Effect sizes representing the strength of the associations between indicators of illness behavior and symptom perceptions and symptom number and duration for each group; for the associations with the continuous indicators, the original symptom sum scores were used (abbreviations: r, Pearson r coefficient; V, Cramer's V; OR, Odds ratio). ‡ IEI-EMF group: When the expected count in the chi-squared test was < 5 in more than one cell (symptom category), the symptom number & duration scores were dichotomized (cut-off point: ≥10 symptoms & ≥80th percentile respectively). † Referring to the most important symptom among the ones reported.

Figure 1: Illustration of the distribution of the examined self-reported NSPS divided into categories of number and duration, and the associated prevalence of registered NSPS



Discussion

The present study focused on NSPS and potentially clinically relevant characteristics among people with and without self-reported environmental sensitivities. Results showed that the IEI-EMF and GES groups were considerably more symptomatic, with more chronic symptoms, higher levels of functional impairment, negative symptom perceptions and illness behavior that was mainly related to psychological and alternative therapies.

Effect sizes for these differences remained moderate to strong, even after adjustment for medical and psychiatric morbidity. Moreover, there were no distinct differences in the prevalence of GP consultations compared to controls, which is in line with recent evidence [60]. Collectively, increasing number and duration of self-reported NSPS were strongly associated with decrease in functional status and moderately associated with increase in illness behavior, negative symptom perceptions and prevalence of GP-registered NSPS; associations were robust across groups, as indicated by the consistency of the reported effect sizes. Results are in agreement with evidence from studies on disaster survivors and community samples [2,7,14].

Almost half of the respondents in the NS group with a range between 10 and 14 self-reported NSPS in the past month, had at least one NSPS in their medical records; this was over 60% for those who experienced 15 or more NSPS. Similar findings were observed for the categories of longer symptom duration. This pattern was less consistent for the GES and IEI-EMF compared to the NS group: The prevalence of registered NSPS dropped at the highest categories of symptom severity, possibly because of the low (given their functional status) rates of medical consultations, while this was not the case for the prevalence of other types of therapies. This might be explained by the fact that the course of idiopathic environmental sensitivities can be chronic, lasting for years [16,61,62]. It is therefore possible that there was an underestimation of the prevalence rates of registered NSPS and/or medication among environmentally sensitive patients because they already consulted their GP for their symptoms and/or follow other types of consultation/therapy.

This is to our knowledge the largest investigation so far on symptom characteristics of people with GES and IEI-EMF in terms of group sizes and health indicator assessment. It is also the first study addressing a wide range of NSPS in terms of both number and duration in combination with GP-registry data of registered NSPS and medication, based on a large primary care database.

Although the assessment of self-reported NSPS was based on a recently developed scale, we used it in relation to an extended set of (self-reported and registry based) health indicators, showing a number of associations comparable with studies that used different questionnaires [2,7,63], indicating consistency across various measures. Moreover, the prevalence of registered medical morbidity and anxiety and depressive disorder represents real-life practice and was comparable with 12-month rates from epidemiological studies in the Netherlands and other countries [64–69].

In the absence of an established case definition for environmental illnesses [16,21], the IEI-EMF and GES group were defined based on a systematic evaluation of the peer-reviewed literature and use of items on several environmental exposures respectively. We used case-definitions that were independent of attributed symptoms, aiming to a more objective investigation of symptom profiles, without predisposing participants through leading questions. The fact that we adjusted for the presence of common medical and psychiatric disorders makes it unlikely that all the between-group differences and the increased symptomatology in the sensitive groups are the result of an unrecognized medical condition, although there is often some comorbidity between medical and/or psychiatric conditions and NSPS [70–72].

Some limitations of the study should be acknowledged. The first one is related to the sensitivity and specificity of the ICPC codes, which we used to compare GP-registered and self-reported NSPS. It is possible that not all symptoms presented by the patients were registered by the GP or the GP used an ICPC code that we did not consider as corresponding to the self-reported symptom; these could lead to an underestimation of the prevalence of people with registered NSPS in the sample (false negatives). Second, we defined an episode as “non-specific” if it was not related with a medical diagnosis during the year before the completion of data collection for our questionnaire survey. Although this time interval could be considered sufficient for the investigation of such health outcomes, some of the participants might have been diagnosed with a medical condition a few days or months earlier or after the set timeframe. Finally, despite the large sample, some risk for selection bias cannot be ruled out. Since the overall respondents were healthier than the non-respondents, we may have underestimated the prevalence of symptoms to some degree. However, the response rate of the survey is considered satisfactory and comparable to other studies on residential EMF exposure and NSPS [30].

This study aimed to provide insight into clinically relevant characteristics and symptom features of the examined groups. Taking the current findings into account, the notion that IEI-EMF may be part of a broader condition such as GES (or IEI) could be strengthened, considering: 1) the similarities between the sensitive groups in terms of functional impairment and illness behavior 2) the prominence of neurological symptoms, fatigue and muscular pain in both groups and 2) the fact that approximately 40% of participants with IEI-EMF met the criteria for GES and the rest of this group reported high levels of general sensitivity as well (although lower than the threshold that was used for GES). While more than 25% in the GES and IEI-EMF group reported ≥ 10 NSPS in the past month, the one-year prevalence of diagnosed somatization disorder and/or neurasthenia was 2.3% and 1.5% respectively. This might imply that undiagnosed somatoform disorders are more pronounced among people with environmental sensitivities, considering the significant overlap demonstrated in clinical investigations [30,74] and that existing diagnostic criteria have been criticized for their restrictiveness [73]. However, this seems to be only a part of the spectrum and can be influenced by the methodology of identifying patients with self-reported sensitivities.

Symptoms can occur due to different interrelated factors, psychological and environmental [75]. In the case of IEI-EMF for instance, on the one hand, a bioelectromagnetic mechanism cannot be ruled out completely, given the methodological challenges that experimental and observational research in this field are confronted with [76]. On the other hand, a strong body of experimental evidence suggests that patients tend to experience symptoms when they believe they are being exposed regardless of whether these beliefs are accurate [19,77], highlighting the importance of psychological processes [78,79]. We therefore suggest that environmental illnesses should be investigated in line with a psychobiological approach, taking into account the interaction of different potentially causal determinants.

A noteworthy finding was the very high rates of alternative therapy consultations in the sensitive groups, especially IEI-EMF, in agreement with some evidence in the literature [80,81]. Solutions might be sought in better communication between patients and physicians. Dealing with medically unexplained conditions is an important and challenging task for primary care that requires time and serious consideration of patient's concerns and at the same time prevention of unnecessary interventions [82,83]. Medical training does not prepare physicians to deal with symptomatic conditions such as IEI-EMF.

As a result, their advice and recommendations are often not evidence-based, leading patients to further insecurity [84]. There is a need for the development and dissemination of a multidisciplinary case-definition protocol, which will constitute a first step towards the identification of environmental sensitivities in primary care and the development of effective treatment strategies.

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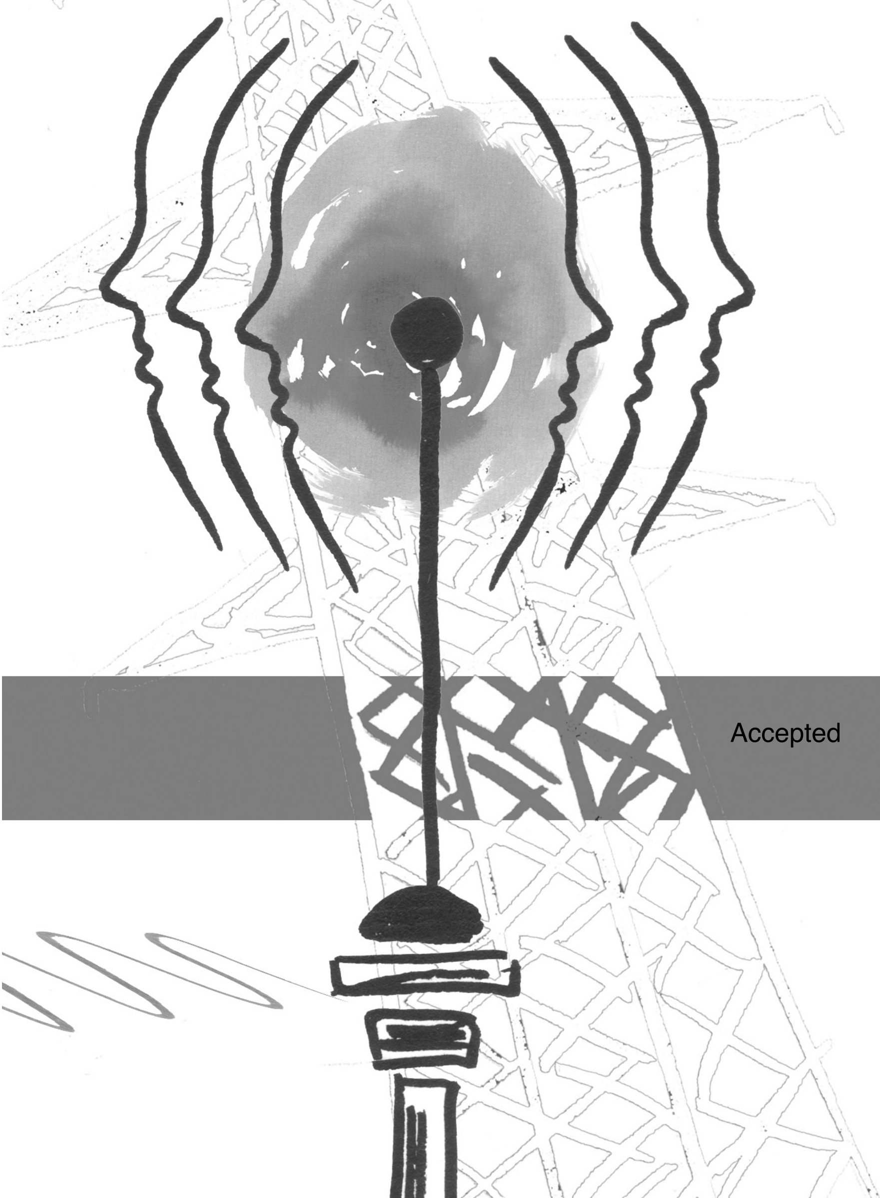
Chapter 6

Actual and perceived exposure to electromagnetic fields and non-specific physical symptoms: An epidemiological study based on self-reported data and electronic medical records

Christos Baliatsas, John Bolte, Joris Yzermans, Gert Kelfkens, Mariette Hooiveld, Erik Lebret, Irene van Kamp



Accepted

Summary

Background: There is continuing scientific debate and increasing public concern regarding the possible effects of electromagnetic fields (EMF) on general population's health. To date, no epidemiological study has investigated the possible association between actual and perceived EMF exposure and non-specific physical symptoms (NSPS) and sleep quality, using both self-reported and general practice (GP)-registered data.

Methods: A health survey of adult (≥18) participants (n=5933) in the Netherlands was combined with the electronic medical records (EMRs) of NSPS as registered by general practitioners. Characterization of actual exposure was based on several proxies, such as prediction models of radiofrequency (RF)-EMF exposure, geo-coded distance to high-voltage overhead power lines and self-reported use/distance of/to indoor electrical appliances. Perceived exposure and the role of psychological variables were also examined.

Results: Perceived exposure had a poor correlation with the actual exposure estimates. No significant association was found between modeled RF-EMF exposure and the investigated outcomes. Associations with NSPS were observed for use of an electric blanket and close distance to an electric charger during sleep. Perceived exposure, perceived control and avoidance behavior were associated with the examined outcomes. The association between perceived exposure was stronger for self-reported than for GP-registered NSPS. There was some indication, but no consistent pattern for an interaction between idiopathic environmental intolerance (IEI-EMF) and the association between actual exposure and NSPS.

Conclusions: In conclusion, there is no convincing evidence for an association between everyday life RF-EMF exposure and NSPS and sleep quality in the population. Better exposure characterization, in particular with respect to sources of extremely low frequency magnetic fields (ELF-MF) is needed to draw more solid conclusions. We argue that perceived exposure is an independent determinant of NSPS.

Introduction

The extensive use of mobile phone devices and associated communication systems and the increasing installation of mobile phone base stations and high-voltage overhead power lines has led to public concern and continuing scientific debate regarding the potential health effects of exposure to electromagnetic fields (EMF) in the general population (Kowall et al., 2012). Recently, the International Agency for Research on Cancer (IARC) classified exposure to radiofrequency (RF) EMF as “possibly carcinogenic” (Baan et al., 2011) and there is evidence that extremely low frequency magnetic field (ELF-MF) may be associated with childhood leukemia (Zhao et al., 2014).

In addition to these diagnosed medical conditions, also a broad range of symptoms has been suspected to be associated with EMF, such as headache, fatigue, dizziness, sleep problems, ear symptoms and skin sensations (Genuis and Lipp, 2011). Self-reported (hyper)sensitivity and/or attribution of such symptoms to EMF sources, has been described by the WHO as idiopathic environmental intolerance attributed to EMF (IEI-EMF) (Baliatsas et al.,2012a; Hillert et al., 2006). Recent evidence from experimental and observational studies consistently suggests that there is no convincing evidence for an association between such symptoms and related physiologic reactions and exposure to EMF (Augner et al., 2012; Baliatsas et al., 2012b; Leitgeb, 2012; Röösli et al., 2010a; Rubin et al., 2010, 2011). Since the cause of these complaints seems to be unclear, they are often referred to as "Medically Unexplained (Physical) Symptoms" (MUPS) (van den Berg, 2007) or alternatively, "Non-specific (Physical) Symptoms" (NSPS) (Baliatsas et al., 2011, 2014).

The current methodological challenges in this research field denote that there is still scope for better research, especially in the epidemiological domain (Baliatsas and Rubin, 2014). While experimental (“provocation”) studies can assess only short-term exposure and effects in small population subgroups, epidemiological studies fill this gap by allowing for the investigation of long-term exposure and outcomes in large samples under normal living conditions. However, exposure characterization remains a major challenge.

Exposure in daily life occurs from far-field sources (e.g fixed transmitters for radio and television and mobile phone base stations) as well as from an array of near-field sources (e.g DECT telephones and wireless networks). All these contribute to an individuals’ personal exposure to a varying degree depending on proximity, source type, source usage and a number of other contextual parameters (Frei et al., 2010). On the one hand, assessment of exposure that relies exclusively on self-report leads to severe misclassification (Frei et al., 2010; Hutter et al., 2012; Inyang et al., 2008; Shum et al., 2011) and should rather be used as an indicator of the individual perception of being exposed (Baliatsas et al., 2012b; Röösli, 2008). On the other hand, only a limited number of epidemiological studies has used methodologically advanced proxies of actual field strength such as spot measurements, personal exposimeters and prediction modeling (Röösli et al., 2010a; Baliatsas et al., 2012b). Still, these approaches are also not free of limitations.

For example, spot measurements provide information only on exposure for specific locations at specific (typically short) times (Frei et al., 2010); personal exposure measurements, although more advanced as a surrogate, are costly, labor-intensive and prone to shortcomings related to e.g. calibration, and body shielding (Bolte et al., 2011; Mann, 2010). It is also unclear whether the use of personal exposure monitors may bias response and systematically alter participants' exposure-related behavior and/or their tendency to perceive exposure. Furthermore, the association between ELF-MF exposure and NSPS in the population has been scarcely investigated (Baliatsas and Rubin, 2014). Bearing these methodological issues in mind and the fact that a biological mechanism for NSPS in relation to EMF is unknown, it is of importance to take into account exposure from all relevant sources (Frei et al., 2012). A prediction model based on modeled exposure from fixed transmitters and exposure-relevant activities may be the best compromise in terms of both adequate characterization and cost-effectiveness (Bolte et al., 2011).

Proper outcome assessment is also a fundamental and still challenging part of research on EMF and NSPS, since the cut-off points for considering a symptom as present or severe vary across studies and it is unknown whether they can be of clinical relevance (Baliatsas et al., 2012b, 2014). The use of data based on symptoms registered in electronic medical records (EMR) of general practices (GP) overcomes such disadvantages and facilitates the comparability of outcome assessment between studies (van den Berg, 2007). Assessment based on symptom scores can be a sound approach, given the possibly large variation of physiological reactions to EMF, if a bioelectromagnetic mechanism exists (Tuengler and von Klitzing, 2013) and considering that scores on symptom number and duration are consistent indicators of severity in environmentally sensitive people and the broader population (Baliatsas et al., 2014; van den Berg et al., 2005).

In addition to research on the possible association between actual EMF exposure levels and NSPS in the population, it is also important to explore the psychological framework through which symptoms may occur, expanding the standard risk-factor approach.

A strong body of evidence from experimental studies suggests that NSPS can occur when people believe they are exposed, irrespective of whether their belief is accurate or not (Röösli 2008; Röösli et al., 2010a; Rubin et al., 2010; Szemerszky et al., 2010). It has been suggested that this could indicate a so-called "nocebo" effect, in which the perception of exposure triggers a self-fulfilling expectation of symptom occurrence (Rubin et al., 2010; Szemerszky et al., 2010).

A number of studies have also emphasized the predictive value of psychological factors in the report of NSPS attributed to EMF, such as environmental worries, dysfunctional cognitions, avoidance of exposure as a strategy to cope with the perceived environmental stressor, anxiety, depression, and increased body awareness and somatosensory amplification (Frick et al., 2002; Johansson et al., 2010; Koteles et al., 2011; Landgrebe et al., 2008; Nordin et al., 2010; Rubin et al., 2008; Witthöft and Rubin, 2013). These seem to be conceptually in line with a generic mechanism of environmental stress (Lazarus and Folkman, 1984; van Kamp, 1990) and more recent cognitive and behavioral models elaborating on medically unexplained symptoms (Rief and Broadbent, 2007; Witthöft and Rubin, 2013). However, the majority of these studies have been focusing on small samples of environmentally sensitive subgroups and in many cases, actual exposure was not considered. In contrast, there is limited knowledge on the role of perceived exposure and potentially relevant psychological variables such as perceived control and coping, in EMF epidemiology (Baliatsas et al., 2011, 2012b). Although a few recent studies (Frei et al., 2012; Heinrich et al., 2011; Mohler et al., 2010, 2012) included variables such as environmental worries, these were solely treated as confounders.

Finally, although people with IEI-EMF experience poorer health, increased illness behavior and more severe NSPS compared to non-sensitive individuals (Baliatsas et al., 2014), very limited evidence exists on the moderating role of IEI-EMF on the association between symptomatology and actual and perceived exposure (Röösli et al., 2010b).

The investigation of the predicting and moderating role of perceived exposure and psychological variables, taking objective exposure estimates into account, could add further to the knowledge about potential determinants of NSPS within the context of environmental health. The current study therefore adopts a multidisciplinary approach on exposure characterization and outcome assessment, investigating proxies of RF-EMF and ELF-MF as well as perceived exposure in relation to both self-reported and GP-registered data.

Furthermore, it makes a first step towards the investigation of the potential role of psychological variables in symptom report.

The main research questions addressed were: 1) What is the association between self-reported and GP-registered NSPS and actual and perceived exposure to EMF in the population and potentially susceptible subgroups? 2) Are psychological factors such as perceived control and coping behavior related to NSPS and 3) Is there a moderating role of psychological variables on the association between perceived exposure and NSPS?

Methods

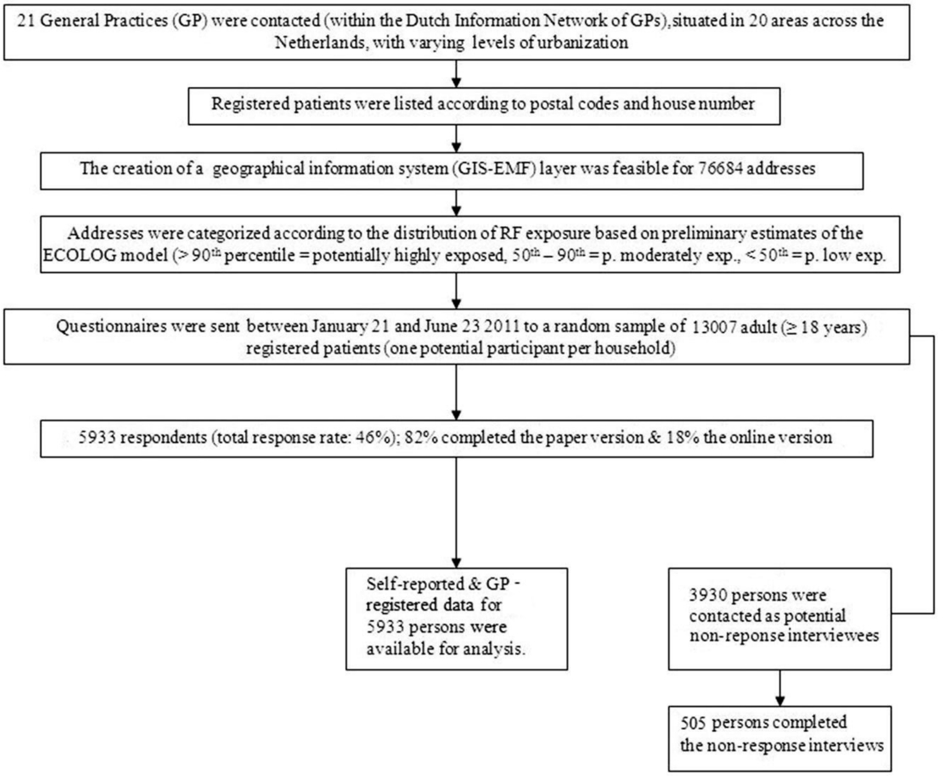
Study design and participants

The present study was performed within the framework of the "EMPHASIS" project ("Non-specific physical symptoms in relation to actual and perceived exposure to EMF and the underlying mechanisms"), which combined two data collection methods: A cross-sectional survey (n=5933, participation rate 46%) using a self-administered questionnaire entitled "Living environment, technology and health" and electronic medical records (EMRs) of health problems and medication prescriptions, as registered by general practitioners. The selection of general practices was made from the primary care database of the Netherlands Institute for Health Services Research (NIVEL).

As shown in Fig. 1, preliminary assessment of residential exposure to mobile phone base stations was an integral part of the study design: During the sampling process, the antenna data and the pool of eligible addresses were imported into the geographic information system (GIS-EMF) operated by the Netherlands National Institute for Public Health and the Environment (RIVM); data reflected the situation at the time of the performance of the study (2011). For every address, all antennas within a radius of 500 m were selected and the power density produced by each base station at the address location was calculated (Kelfkens et al., 2012; Neitzke et al., 2005, 2007). Based on these preliminary estimates, the sample pool was stratified per exposure category (low, medium, high); higher exposure categories were oversampled in order to enhance exposure contrast among participants (Kelfkens et al., 2012). From each household only one adult was randomly sampled. The survey questionnaire consisted of four sections: 1) Residential environment, 2) Health 3) Well-being and 4) Household and demographic information. Potential participants were not informed that the study focused on EMF and the questions on health outcomes preceded questions relevant for exposure assessment. The privacy regulation of the study was approved by the Dutch Data

Protection Authority. Based on the Law on Medical Scientific Research (WMO), the Dutch Medical Ethics Committee decided that an ethical approval was not required.
Additional information on the study sample and survey procedure has been described in more detail elsewhere (Baliatsas et al., 2014).

Figure 1: Schematic Illustration of the study design and sampling process



Characterization of actual EMF exposure

The characterization of actual exposure used a combination of information from different origin, to combine contributions from far-field and near-field sources to personal exposure. As described in the previous section, categorization into exposure percentiles based on preliminary estimates of RF-EMF from mobile phone base stations was one of the criteria used to select the study population.

In the second stage, additional information was obtained from the survey questionnaire in order to calculate the full model of exposure to base stations. This information concerned the orientation of the dwelling and building characteristics such as the properties of the walls and windows (Kelfkens et al., 2012; Neitzke et al., 2007). The exposure model was built based on the approach of the ECOLOG institute (Neitzke et al., 2005, 2007), in which the average RF-EMF exposure at home emitted from mobile phone base stations (GSM900, GSM1800) was estimated. Additional details regarding the calculation of the ECOLOG model in the present study have been described elsewhere (Kelfkens et al., 2012).

Furthermore, a list of questions on exposure-relevant activities was included in the survey. The selection of these activities was based on models from the Activity Exposure Matrix (AEM) (Bolte et al., 2008, 2013); this was developed in an external exposimeter study in the Netherlands. In this study, personal exposure to 12 bands of environmental RF-EMF on the power flux density scale in mW/m^2 was modelled (Bolte and Eikelboom, 2012): FM radio (frequency modulation; 88–108 MHz), TV3 (television; 174–233 MHz), TETRA (terrestrial trunked radio used by emergency services; 380– 400 MHz), TV4&5 (470–830 MHz), GSM uplink (global system for mobile communications; 880–915 MHz), GSM downlink (925–960 MHz), GSM1800 (or DCS) uplink (digital cellular service; 1710–1785 MHz), GSM1800 downlink (1805–1880 MHz), DECT (digital enhanced cordless telecommunication; 1880–1900 MHz), UMTS uplink (universal mobile telecommunication system; 1920–1980 MHz), UMTS downlink (2110–2170 MHz), WiFi (wireless internet; 2400– 2500 MHz). TV3 and TV4&5 were originally the bands for analog TV broadcasts. However, in the Netherlands all broadcasts are Digital Video Broadcasting Terrestrial (DVB-T) in the TV4&5 frequency band. Also part of the radio broadcasts are Terrestrial Digital Audio Broadcasting (T-DAB) at 174–230 MHz in the TV3 band.

Based on the ECOLOG estimation and the models from the AEM study each participant received an exposure predictor based on multivariable non-linear regression models. Six prediction models of individual exposure to RF-EMF were developed, corresponding to different frequency bands. The following exposure-relevant parameters (Bolte and Eikelboom, 2012) were selected for each prediction model:

1) GSM900 base stations (explained variance $R^2 = 0.27$): Hours per week spending at large public transport stations, hours per week traveling with a car, hours per week walking outdoors, white collar occupation indoors and at home exposure from GSM900 computed by the ECOLOG model.

2) GSM1800 base stations ($R^2 = 0.15$): Hours per week spending at large public transport stations, hours per week traveling with a car and at home exposure from GSM1800 base stations, based on the ECOLOG model.

3) DECT (R^2 = 0.26): Type of residency and owning a DECT phone at home.
4) Uplink (exposure from mobile phone use by bystanders, R^2 = 0.27): Outdoor blue collar occupation, hours per week traveling with a car, hours per week spending at a pub/café/disco/snack bar and hours per week relaxing outside.
5) Downlink (cumulative exposure from base stations, R^2 = 0.27): Hours per week spending at large public transport stations, hours per week traveling with a car, hours per week and at home exposure from GSM900 and GSM1800 mobile phone base stations computed by the ECOLOG model.
6) Ratio/TV (RTV) (R^2 = 0.18): Hours per week spending at large public transport stations and indoor blue collar occupation in industry.

The models for ELF exposure yielded less satisfactory results, with lower explained variance than for RF. Therefore, proxies of ELF exposure were not quantified based on modelled personal exposure, but on more qualitative information about ownership, use and proximity of sources. More specifically, the addresses of the n=5,993 final respondents were imported into the geographic information system operated by RIVM, which contains a layer with the location and voltage level of the overhead power lines in the Netherlands. For every respondent, the distance to the closest power line was calculated. The overhead high-voltage power lines have five voltage levels ranging from 50 kilovolts to 380 kilovolts (kV). In the analysis, distance to power lines was treated as dichotomous variable (≤ 200 m vs. > 200 m).

Finally, self-reported use of indoor electrical appliances was assessed. Selection was based on being commonly used in the population, the potential contribution to total magnetic field exposure as documented in technical papers (Leitgeb et al., 2007; Mezei et al., 2001), literature reports on attribution of symptoms by potentially susceptible population subgroups (Baliatsas et al., 2012a; Hagström et al., 2013) and previous epidemiological studies investigating associated health effects (Chen et al., 2013; Kleinerman et al., 2005; Zheng et al., 2000). Questions on the following appliances were included in the survey questionnaire: Electric alarm clock, electric charger, electric oven, induction hob, electric/ceramic hob, personal computer (PC) or laptop, electric blanket and vacuum cleaner. Participants were asked whether they were making use of the examined appliances at home or work.

The questions on the position of electric charger and alarm clock were categorized according to distance from head during sleep (≤ 50 cm vs. > 50 cm).

Assessment of perceived exposure to EMF

This was based on the question *"To what extent do you think you are exposed to electromagnetic fields?"* referring to three situations: *1) at home, 2) at work 3) outdoors.* Items were highly inter-correlated (Spearman's rho=0.7, internal consistency Cronbach's a = 0.87). Responses for each situation were scored on an 11-point scale ranging from "not at all" to "very much". A higher sum score on the three items represents higher (generalized) perceived exposure to EMF.

Assessment of self-reported outcomes

Twenty-three items from the Symptoms and Perceptions (SaP) scale (Baliatsas et al., 2014; Yzermans et al., 2012) were used to assess the number ("in the past month") and duration of NSPS. Selected items correspond to symptoms in different organ systems that frequently labeled as "unexplained"; a higher sum score on the subscales "number of NSPS" and "duration of NSPS" indicates increased symptom report and longer duration.

Sleep quality was measured on a 10-item scale (Visser et al., 1978); a higher score indicates more sleep problems/lower sleep quality.

Assessment of GP-registered outcomes

Non-specific physical symptoms in EMRs were registered by the general practitioners based on the international classification of primary care (ICPC) (Lamberts and Wood, 1987). The assessment of practitioner's clinical evaluation of the symptoms was based on "episodes of care" (WONCA, 1995).

An episode was identified as "non-specific" if there was no registered medical diagnosis as an explanation for the symptoms, during the year before the study.

Registered NSPS which corresponded with the 23 symptoms from the self-reported questionnaire we selected. For instance, the symptom "sleep problems" corresponded to the ICPC code P06 ("sleep disturbance"). More details regarding the assessment of the self-reported and GP-registered outcomes are presented in a previous publication (Baliatsas et al., 2014).

Idiopathic environmental intolerance attributed to EMF (IEI-EMF)

The case definition for IEI-EMF was based on the dominant criteria in the peer-reviewed literature (Baliatsas et al., 2010a). People who reported “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”, were defined as the IEI-EMF group.

Psychological variables

Perceived control was assessed with three items (Baliatsas et al., 2011): “I am always optimistic about my future”, “I hardly ever expect things to go my way” and “If I try I can influence the quality of my living environment”. Answers were scored on a 5-point Likert scale, with a higher sum score indicating less perceived control over a situation.

Avoidance (coping) behavior was assessed using a subscale of the Utrecht Coping List (Schreurs et al., 1993). Items were scored on a 4-point Likert scale; a higher score indicates increased avoidance behavior, representing the effort to avoid dealing with a stressful situation.

Descriptive information and confounders

Information was obtained on socio-demographic and lifestyle characteristics such as age, gender, education, foreign background, home ownership status, degree of urbanization, smoking habits and alcohol and/or substance abuse.

The EMF-related items of the Modern Health Worries (MHW) scale (Kaptein et al., 2005) was used to measure participants’ levels of concern about potentially health effects due to mobile phones, base stations and high-voltage power lines.

Statistical analyses

Descriptive analyses were initially performed to obtain an overview of the distribution of socio-demographic characteristics, lifestyle indicators and EMF exposure in the sample. In the main analyses, the sum scores on symptom number and duration and sleep quality were treated as continuous variables, while the prevalence of GP-registered and single self-reported NSPS as binary. Considering the hierarchical structure of the data, preliminary multilevel analyses yielded no substantial clustering within general practices. Multiple linear and logistic regression models were carried out for the continuous and binary outcomes respectively.

For each examined association, regression coefficients or odds ratios (OR) and 95% confidence intervals (CIs) were computed. A p value of < 0.05 was considered statistically significant.

The association between health outcomes and actual and perceived exposure was examined, adjusted for a core set of a-priori defined potential confounders, such as age, gender, education, foreign background, rented home, degree of urbanization, smoking habits and alcohol and/or substance abuse. Exposure-outcome associations were analyzed separately for each proxy of actual exposure.

Whether IEI-EMF affected the association between actual exposure and each of the primary outcomes was tested for by entering the interaction term (IEI-EMF x each actual exposure proxy; non-IEI-EMF participants comprised the reference group) (Aiken and West, 1991; Baron and Kenny, 1986; Hayes 2013) into the core models. The possible interaction of perceived exposure with IEI-EMF and psychological variables (worries, control, avoidance), was also examined by multiple regression analyses, testing each term separately.

Finally, perceived exposure and the psychological variables were entered in an expanded regression model to be tested as potential independent predictors of NSPS and sleep quality.

In case of significant associations between proxies of actual exposure and primary outcomes in the core exposure-outcome models, the tested interactions between perceived exposure and IEI-EMF and psychological variables were adjusted for these proxies, in order to verify the consistency of the findings. Respondents with > 5 missing items on the self-reported NSPS list and > 2 missing items on the sleep quality scale were excluded from the analyses. Symptoms from the medical records had no missing data. Analyses were carried out using the statistical software packages IBM SPSS Statistics (SPSS Inc version 19, Chicago IL, USA) and R version 3.01.

Sensitivity analysis

In addition to symptom scores, the prevalence ("in the past month") of single self-reported NSPS was assessed in relation to the examined actual exposure proxies, to enhance comparability with previous epidemiological studies that used similar outcome variables (Röösli et al., 2010a).

Selection was based on symptoms frequently investigated in the relevant epidemiological literature and pronounced among IEI-EMF sufferers (Baliatsas et al., 2014; Röösli et al., 2010a):

Headache, dizziness or feeling light-headed, fatigue/tiredness, memory/concentration problems, skin symptoms, heart palpitations and ear symptoms. Interaction analyses between IEI-EMF and actual exposure proxies was repeated for these symptoms.

In addition, the examined RF-EMF and ELF-MF exposure indicators were added in the same model to explore whether any alterations occurred regarding the exposure-outcome associations.

Results

Non-response and descriptive analysis

Results of the non-response analysis, health characteristics and symptomatic profile of the participants (including those with IEI-EMF) have been described in detail elsewhere (Baliatsas et al., 2014). In summary: Participants were somewhat younger, higher educated and reported better general health compared to non-respondents; no difference in gender distribution was observed.

There was a significant difference in the extent to which the two groups considered themselves as sensitive to mobile phone base stations and related communication systems ("quite agree"/"strongly agree" for respondents: 6.5% vs. non-respondents: 14%, $p < 0.001$). Table 1 gives an overview of basic sample characteristics.

The most prevalent self-reported symptoms in the total sample were fatigue (54%), neck or shoulder symptoms (39%), headache (38%), back pain (36%), leg/hip/knee/foot symptoms (33%) and muscular pain (31%).

The predicted RF-EMF exposure levels are reported in Table 2 (all calculations were done in power density and back transformed to electric field). Inter-correlations (Spearman's rho) between different actual exposure proxies ranged between -0.06 and 0.4. The correlation between perceived exposure and the investigated proxies of RF-EMF exposure ranged between 0.1 and 0.2; the correlation with the ELF-MF sources ranged between -0.04 and 0.29. Participants had a mean score of 11.3 (SD=7.32) on the perceived exposure scale (score range: 0–30).

Among the respondents 202 (3.5%) were considered as (hyper)sensitive to EMF, referred to as IEI-EMF, as defined above. Mean RF-EMF exposure levels were similar for both electrosensitive and non-sensitive individuals. Participants with IEI-EMF less often reported use of an electric oven (61% vs. 72%, $p<0.001$) and PC or laptop (74.5% vs. 86.5%, $p<0.001$) but no other differences were observed in relation to other ELF-MF sources.

In addition, they reported higher levels of perceived exposure (mean score: 12.8, SD=8.8 vs. 11.3, SD=7.2, p<0.05) and EMF-related worries (7.0, SD=3.6, vs. 4.4, SD=3.1, p<0.001).

Table 1: Overview of demographic, residential, lifestyle and symptom characteristics of the sample (valid cases) [a].

Characteristic	Analytic sample (n=5933)
Demographic characteristics	
Age (%)	
18 – 24	5.8
25 – 44	30.4
45 – 64	39.5
65 – 74	13.0
75 +	11.1
Mean age (SD)	52.2 (17.3)
Female gender (%)	58.4
Education [b] (%)	
Lower	24.0
Middle	44.3
Higher	31.6
Foreign background (%)	12.6
Residential characteristics	
Home ownership status (%)	
Owned	65.3
Rented	34.7
Degree of urbanization (%)	
Extremely urbanized	22.9
Strongly urbanized	24.6
Moderately urbanized	16.3
Hardly urbanized	18.7
Not urbanized	17.6
Lifestyle characteristics	
Smoking habits (%)	
Never	43.0
In the past	37.0
Yes, currently	20.0
Alcohol and/or substance abuse (> 4 months) (%)	2.4
Symptom characteristics	
Number of symptoms mean score (SD)	5.3 (4.0)
Duration of symptoms mean score (SD)	12.8 (12.5)
(Low) sleep quality (SD)	2.3 (2.6)
Prevalence of GP-registered NSPS (%)	36.5

Table 2: Levels of modeled exposure to RF-EMF (V/m) in the analytic sample.

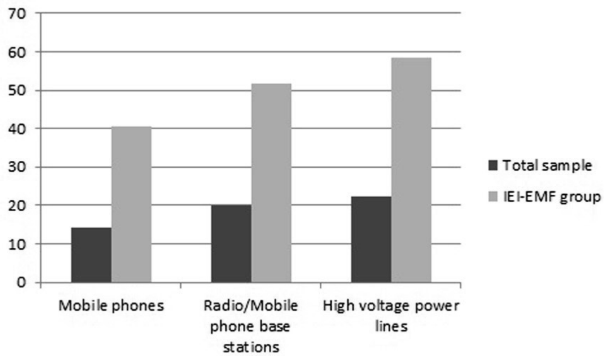
	Exposure levels			
RF band	Sample	Range	Mean (SD)	90^{th} percentile
GSM900	4266	0.02 – 0.29	0.06 (0.06)	0.08
GSM1800	4344	0.04 – 0.46	0.07 (0.08)	0.09
DECT	5447	0.02 – 0.25	0.1 (0.08)	0.13
Uplink	4139	0.09 – 0.37	0.13 (0.12)	0.18
Downlink	4344	0.05 – 0.56	0.09 (0.11)	0.13
Radio/TV	4392	0.04 – 0.49	0.05 (0.07)	0.07

Abbreviations: SD, standard deviation.

Fig. 2 illustrates the prevalence of health worries related to exposure to mobile phones, base stations and power lines. There was no significant difference between sensitive and non-sensitive participants in terms of avoidance behavior and perceived control.

No indication for multicollinearity was observed in the analyzed regression models as indicated by inter-correlations among the independent variables and the variance inflation factor (VIF) and tolerance value.

Figure 2: Percentage (%) of "high" or "extremely high" worry about potential health effects from different EMF sources among participants with IEI-EMF (n=202) and the total study sample (n=5933).



Association between NSPS and modelled RF-EMF

Table 3 summarizes the results of the regression analyses. There was no significant association between modeled RF-EMF exposure and scores on self-reported NSPS, sleep quality or prevalence of NSPS in medical records.

Association between NSPS and sources of ELF-MF

Consistent associations were observed between: 1) close distance to an electric charger (≤ 50 cm from head) during sleep and 2) use of an electric blanket and increased number and duration of self-reported NSPS and higher prevalence of GP-registered NSPS (Table 4).

Furthermore, electric/ceramic hob use was significantly associated with lower sleep quality and induction hob use with GP-registered NSPS (Table 4). People using a pc or laptop tended to experience less sleep problems. No increased risk for NSPS was found in relation to close proximity to power lines.

Association between NSPS and perceived EMF exposure

Perceived exposure was consistently associated with the examined self-reported outcomes, even after adjustment for psychological variables; associations with GP-registered symptoms were mostly borderline significant (Table 3, Table 4, Table 5).

Table 3: Association (regression coefficients and ORs) [a] between modeled RF-EMF (per frequency band) and perceived EMF exposure and NSPS, based on self-reported scores and GP-registered prevalence (significant associations based on *p* values in bold).

	Number of self-reported NSPS	Duration of self-reported NSPS	Sleep quality	GP-registered NSPS
RF-EMF exposure	B coefficient (95% CI) [b]	B coefficient (95% CI) [b]	B coefficient (95% CI) [b]	OR (95% CI)
GSM900	0.07 (-0.05–0.2)	0.22 (-0.17–0.61)	0.01 (-0.08–0.09)	1.00 (0.92–1.07)
Perceived EMF	**0.07 (0.05–0.09)** ǂ	**0.23 (0.17–0.28)** ǂ	**0.02 (0.01–0.03)** †	**1.01 (1.00–1.02) ***
GSM1800	0.06 (-0.01–0.13)	0.21 (-0.004–0.42)	0.01 (-0.04–0.05)	1.01 (0.98–1.05)
Perceived EMF	**0.07 (0.06–0.09)** ǂ	**0.23 (0.18–0.29)** ǂ	**0.02 (0.01–0.03)** ǂ	**1.01 (1.00–1.02)** †
DECT	0.04 (-0.02–0.11)	-0.03 (-0.24–0.17)	-0.003 (-0.05–0.04)	0.99 (0.95–1.03)
Perceived EMF	**0.06 (0.05–0.08)** ǂ	**0.2 (0.15–0.25)** ǂ	**0.02 (0.01–0.03)** †	**1.01 (1.00–1.02) ***
Uplink	-0.001 (-0.04–0.03)	-0.02 (-0.14–0.09)	0.01 (-0.01–0.04)	1.00 (0.98–1.02)
Perceived EMF	**0.06 (0.04–0.08)** ǂ	**0.2 (0.13–0.26)** ǂ	**0.02 (0.002–0.03) ***	1.01 (0.99–1.02)
Downlink	0.02 (-0.01–0.06)	0.07 (-0.05–0.19)	0.002 (-0.02–0.03)	1.00 (0.97–1.02)
Perceived EMF	**0.07 (0.06–0.09)** ǂ	**0.23 (0.18–0.29)** ǂ	**0.02 (0.01–0.03)** ǂ	**1.01 (1.00–1.02)** †
Radio/TV	-0.07 (-0.15–0.01)	-0.21 (-0.46–0.04)	-0.03 (-0.09–0.02)	0.96 (0.9–1.02)
Perceived EMF	**0.06 (0.04–0.08)** ǂ	**0.2 (0.14–0.27)** ǂ	**0.01 (0.002–0.03) ***	1.01 (0.99–1.02)

[a] All models were adjusted for age, gender, education, foreign background, rented home, degree of urbanization, smoking habits, alcohol and/or substance abuse.
[b] Unstandardized regression coefficient.
Abbreviations: OR, Odds ratios; CI, Confidence intervals; NSPS, Non-specific physical symptoms; GP, General practice;
Note: * $p< 0.05$; † $p< 0.01$; ǂ $p< 0.001$.

Interaction between IEI-EMF and the association of actual and perceived exposure with NSPS

The number of regression analyses performed for the different exposures, endpoints and interaction terms precludes the presentation of the data. Therefore, only the few significant interaction terms are mentioned: Analyses showed a trend for increased score on number of symptoms in relation to downlink exposure for participants in the IEI-EMF group (regression coefficient: 0.34, 95% CI=0.04–0.64, p<0.05). This was also the case for the interaction term between sleeping in close distance to an electric alarm clock and sleep problems (regression coefficient: 1.21, 95% CI=0.13–2.3, p<0.05). No significant interaction was observed between IEI-EMF and perceived exposure (p values ranging from 0.1 to 0.4; results not shown).

Table 4: Association (regression coefficients and ORs) [a] between distance to and use of ELF-MF sources and NSPS based on self- reported scores and GP-registered prevalence (significant associations based on *p* values in bold)

	Number of self-reported NSPS	Duration of self-reported NSPS	Sleep quality	GP-registered NSPS
Source/appliance	B coefficient (95% CI) [b]	B coefficient (95% CI) [b]	B coefficient (95% CI) [b]	OR (95% CI)
Distance to power lines				
> 200 m (n=5855)	Ref.	Ref.	Ref.	1
≤ 200 m (n=78)	-0.31 (-1.23–0.61)	0.27 (-2.63–3.17)	-0.26 (-0.89–0.38)	1.25 (0.74–2.1)
Perceived EMF	**0.07 (0.05–0.08)** ‡	**0.21 (0.16–0.26)** ‡	**0.02 (0.01–0.03)** ‡	**1.01 (1.00–1.02) ***
Electric alarm clock				
> 50 cm (n=2960)	Ref.	Ref.	Ref.	1
≤ 50 cm (2833)	-0.08 (-0.29–0.13)	-0.05 (-0.71–0.61)	0.04 (-0.1–0.19)	0.93 (0.82–1.05)
Perceived EMF	**0.07 (0.05–0.08)** ‡	**0.21 (0.16–0.26)** ‡	**0.02 (0.01–0.03)** ‡	**1.01 (1.00–1.02) ***
Electric charger				
> 50 cm (n=4952)	Ref.	Ref.	Ref.	1
≤ 50 cm (n=946)	**0.47 (0.18–0.75)** †	**1.67 (0.79–2.56)** ‡	0.07 (-0.13–0.27)	**1.24 (1.05–1.46)** †
Perceived EMF	**0.06 (0.05–0.08)** ‡	**0.2 (0.15–0.25)** ‡	**0.02 (0.01–0.03)** ‡	**1.01 (1.00–1.02) ***
Electric oven				
No use at all (n=1631)	Ref.	Ref.	Ref.	1
Use (n=4147)	0.13 (-0.11–0.38)	0.08 (-0.68–0.85)	-0.02 (-0.19–0.15)	0.95 (0.82–1.09)
Perceived EMF	**0.07 (0.05–0.08)** ‡	**0.21 (0.16–0.26)** ‡	**0.02 (0.01–0.03)** ‡	**1.01 (1.00–1.02) ***
Induction hob				
No use at all (n=5145)	Ref.	Ref.	Ref.	1
Use (n=547)	-0.1 (-0.45–0.25)	-0.27 (-1.38–0.83)	-0.11 (-0.36–0.13)	**1.34 (1.1–1.63)** †
Perceived EMF	**0.07 (0.05–0.08)** ‡	**0.21 (0.16–0.26)** ‡	**0.02 (0.01–0.03)** ‡	**1.01 (1.00–1.02) ***
Electric/Ceramic hob				
No use at all (n=4532)	Ref.	Ref.	Ref.	1
Use (n=1157)	0.06 (-0.2–0.32)	0.22 (-0.59–1.05)	**0.22 (0.04–0.4) ***	1.11 (0.96–1.29)
Perceived EMF	**0.07 (0.05–0.08)** ‡	**0.21 (0.16–0.27)** ‡	**0.02 (0.01–0.03)** ‡	**1.01 (1.00–1.02)** †
PC or laptop				
No use at all (n=827)	Ref.	Ref.	Ref.	1
Use (n=4894)	-0.33 (-0.71–0.05)	-0.74 (-1.95–0.47)	**-0.34 (-0.61–-0.07) ***	0.99 (0.8–1.23)
Perceived EMF	**0.07 (0.05–0.08)** ‡	**0.21 (0.16–0.26)** ‡	**0.02 (0.01–0.03)** ‡	**1.01 (1.00–1.02) ***
Electric blanket				
No use at all (n=5076)	Ref.	Ref.	Ref.	1
Use (n=654)	**0.58 (0.24–0.91)** †	**1.35 (0.29–2.41) ***	0.02 (-0.21–0.26)	**1.32 (1.09–1.59)** †
Perceived EMF	**0.07 (0.05–0.08)** ‡	**0.21 (0.16–0.27)** ‡	**0.02 (0.01–0.03)** ‡	**1.01 (1.00–1.02) ***
Vacuum cleaner				
No use at all (n=430)	Ref.	Ref.	Ref.	1
Use (n=5291)	0.04 (-0.36–0.44)	-0.06 (-1.32–1.2)	-0.2 (-0.48–0.08)	0.87 (0.69–1.09)
Perceived EMF	**0.07 (0.05–0.08)** ‡	**0.21 (0.16–0.26)** ‡	**0.02 (0.01–0.03)** ‡	**1.01 (1.00–1.02) ***

[a] Adjusted for age, gender, education, foreign background, rented home, degree of urbanization, smoking habits, alcohol and/or substance abuse, perceived EMF exposure.
[b] Unstandardized regression coefficient.
Abbreviations: OR, Odds ratios; CI, Confidence intervals; NSPS, Non-specific physical symptoms; GP, General practice; Ref., Reference category.
Note: * $p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$.

NSPS and perceived control and coping

Analyses showed no significant moderation of perceived control and avoidance on the association between perceived exposure and outcomes. The association between perceived exposure and self-reported outcomes remained consistent after adjustment for psychological factors. Lower perceived control was a consistent predictor of the examined outcomes (Table 5).

Table 5: Expanded regression model showing the association of perceived exposure and psychological variables with the examined health outcomes [a].

Source/appliance	Number of self-reported NSPS	Duration of self-reported NSPS	Sleep quality	GP-registered NSPS
	B coefficient (95% CI) [b]	B coefficient (95% CI) [b]	B coefficient (95% CI) [b]	OR (95% CI)
Perceived exposure	**0.07 (0.05–0.08)** ǂ	**0.21 (0.16–0.26)** ǂ	**0.02 (0.01–0.03)** ǂ	**1.01 (1.00–1.02)** *
Control	**0.42 (0.37–0.48)** ǂ	**1.38 (1.2–1.56)** ǂ	**0.32 (0.27–0.35)** ǂ	**1.06 (1.02–1.1)** †
Avoidance	**0.03 (0.01–0.06)** *	0.01 (-0.08–0.1)	0.01 (-0.01–0.25)	0.98 (0.97–1.00)

[a] Adjusted for age, gender, education, foreign background, rented home, degree of urbanization, smoking habits, alcohol and/or substance abuse, sleeping close to an electric charger, induction hob use, electric/ceramic hob use, electric blanket use. Note: **p*< 0.05; †*p*< 0.01; ǂ*p*< 0.001.
[b] Unstandardized regression coefficient.

Sensitivity analysis

Analyses yielded no association between the investigated RF frequency bands and prevalence of single self-reported NSPS, except for a negative association between uplink exposure and prevalence of headache and dizziness (Appendix, Table 6).

Regarding sources of ELF-MF, sleeping close to a charger was associated with fatigue, while the use of an electric blanket was associated with dizziness, fatigue, palpitations and ear symptoms. There was also a negative association between using a pc or laptop and fatigue (Appendix, Table 7).

When all exposure indicators were included in the same regression model (except for "GSM900" and "GSM1800", which were represented in "downlink"), results on actual and perceived exposure remained consistent (data not shown).

Furthermore, it was found that the association between GSM900 exposure and ear symptoms differed significantly between individuals with IEI-EMF and the remaining sample (OR=1.87, 95% CI=1.01–3.46, p<0.05). A significant higher risk for memory or concentration problems in relation to the use of electric blanket was also observed among participants with IEI-EMF (OR=3.2, 95% CI=1.02–10.1, p<0.05).

Discussion

This is the first epidemiological study into the association between actual and perceived EMF exposure and NSPS and sleep quality combining self-reported and medical record data. A number of theory-based psychological variables were included in the analyses as potential outcome predictors or effect modifiers of the association between perceived exposure and outcomes. The role of perceived exposure in the association between psychological variables and symptoms was also explored. The potential effect modification of IEI-EMF on the (actual and perceived) exposure-outcome association was investigated as well. In the absence of a known biological mechanism related to residential-level EMF and NSPS, a large number of exposure sources and health outcomes were examined as recommended in the literature (Frei et al., 2012; Mohler et al., 2012). The documented levels of RF-EMF exposure were on average far below the current reference levels (ICNIRP, 1998). For this reason our conclusions are limited to low exposure levels.

Exposure-outcome associations

Results, including sensitivity analyses, did not indicate an association between modelled RF-EMF exposure and number and duration of self-reported NSPS and prevalence of GP-registered NSPS. Furthermore, no significant association was observed between RF-EMF bands and self-reported sleep quality. As highlighted by Mohler et al. (2012) if such an association existed, a consistent pattern towards a harmful effect would be expected, even if it was statistically non-significant; this was not the case. These findings confirm those from recent epidemiological studies in Europe on RF-EMF and NSPS and sleep quality (Berg-Beckhoff et al., 2009; Frei et al., 2012; Heinrich et al., 2011; Mohler et al., 2010, 2012; Thomas et al., 2008).

Regarding the examined ELF-MF sources, there is not much evidence in the literature to compare the current results with, except for the lack of an association between NSPS and geo-coded distance to power lines (Baliatsas et al., 2011). Analyses yielded a consistent association between NSPS and use of an electric blanket. A possible explanation is reverse causality, given that people who experience physical symptoms might use such an appliance more often. Nevertheless, an electric blanket is considered to be a source of high exposure (Florig and Hoburg, 1990). Associations were also observed between NSPS and distance to an electric charger (≤ 50 cm from the head) during sleep and use of an induction hob and GP-registered NSPS.

Further research on the association with these sources is required to replicate these observations. Sporadic associations, some of them negative, were found for other sources such as induction hob, electric/ceramic hob and pc or laptop. Considering the large number of regression models carried out, a few statistically significant associations are expected by chance; negative associations have been previously observed in the literature, independently of study design (Augner et al., 2009; Heinrich et al., 2011; Nieto-Hernandez et al., 2011; Thomas et al., 2008).

Perceived exposure was a consistent predictor of the self-reported health indicators across the models, which is in agreement with the limited epidemiological evidence in the peer-reviewed literature (Baliatsas et al., 2011, 2012b). The correlation between perceived and actual exposure (based on the different surrogates) was either low or negligible, which strengthens the notion that perceived exposure should not be considered as a proxy of actual exposure levels (Baliatsas et al., 2012b; Frei et al., 2010; Vrijheid et al., 2009) but rather as an independent predictor of NSPS, as experimental evidence suggests (Röösli et al., 2008, 2010a; Rubin et al., 2010). This low correlation also shows that most of the respondents were not aware of their (most) relevant sources of exposure, which in turn indicates that the risk for information bias was rather low in this study.

IEI-EMF

The actual exposure status of individuals with IEI-EMF in our sample did not differ substantially compared to the rest of the participants. Overall, we found no convincing evidence that individuals who reported to be sensitive to EMF experienced more severe symptoms or lower sleep quality in relation to actual or perceived EMF than the rest of the population, which is in line with recent studies (Frei et al., 2012, Mohler et al., 2012; Röösli et al., 2010b). Nevertheless, we observed a trend for increased score on number of symptoms in relation to downlink exposure and also a significant interaction between sleeping in close distance to an electric alarm clock and sleep problems.

Sensitivity analyses also showed a significant interaction of IEI-EMF with GSM900 and use of an electric blanket, in relation to ear symptoms and memory/concentration problems respectively. The existence of interactions have been mentioned in previous studies (Frei et al., 2012) but no consistent pattern can be discerned. These findings should be interpreted with caution, since false-positives are likely due to the large number of interactions tested, in relation to numerous outcomes (Grobbee and Hoes, 2009).

Epidemiological research on potentially susceptible groups of sufficient sample sizes is still limited and further investigation would help us get a better understanding regarding possible effects of environmental EMF exposure (Bogers et al., 2013).

Implications for psychological mechanisms

Given the limited evidence in the literature for a mechanism for EMF-related NSPS and since our cross-sectional study design cannot establish temporal precedence, the analyses of effect modification in the current study was exploratory; a first attempt to test theoretically relevant determinants of NSPS in a large population sample, taking actual exposure into account. Our results showed that, in addition to perceived exposure, perceived control and avoidance coping were associated with the examined outcomes, with the former being the strongest and most consistent predictor. Perhaps in the case of EMF symptoms, increased avoidance may also have an alleviating effect on symptoms (Hagström et al., 2013) which could potentially mask a more consistent positive association with NSPS.

Although a combination of multiple factors can play a role in the experience and maintenance of NSPS (Engel and Katon 1999; Walker et al., 1998), the present findings highlight the importance of cognitions and behavior within the EMF context: Considering an environmental source as potentially hazardous could increase symptom report or severity when perceiving exposure (Szemerszky et al., 2010, Winters et al., 2003). Since environmental stressors are often outside individual control (Campbell, 1984), lower perceived control over the stressor could be an important factor towards increase in preoccupation with and amplification of bodily reactions (Kroenke and Swindle, 2000). This in turn could increase the likelihood of avoidance coping behavior (Nordin et al., 2010).

The role of perceived exposure in a transactional process needs to be further clarified, together with additional theoretically relevant variables such as environmental worries, negative affectivity and somatosensory amplification (Witthöft and Rubin, 2013). Longitudinal data could allow for the investigation of aspects that are not obtainable in cross-sectional design, such as stability across time and temporal precedence (McKinnon et al., 2007).

Study strengths

To our knowledge, the present study is the largest performed in this field. The inclusion of various exposure surrogates and the large number of examined outcomes allowed the assessment of consistency and biological tenability of the findings, given that no bioelectromagnetic mechanism has been established.

We used a prediction model to characterize RF-EMF levels, based on a number of exposure-related everyday life activities and exposure to mobile phone base stations (Bolte and Eikelboom, 2012; Neitzke et al., 2007).

While the RF-EMF exposure models leave room for improvement, the explained variance of the prediction model was compared reasonably well with the model developed in Switzerland (Frei et al., 2009, 2010). The higher proportion of explained variance in the Swiss study is in part due to the use of the three-dimensional propagation model used, compared to the ECOLOG model. The mean values of exposure levels and per band ranges coincided with those reported in other European surveys (Frei et al., 2010; Viel et al., 2009, 2011). The use of exposure prediction models instead of spot or exposimeter measurements is a time- and cost-effective approach for large epidemiological studies and represent daily life exposure conditions (Bolte et al., 2011; Frei et al., 2010).

In addition, this is amongst the first research efforts to analyze NSPS in relation to sources of ELF-MF. In the absence of a predictive model of personal exposure to ELF-MF, the assessment of exposure to fields from electrical appliances was solely build on geographic and questionnaire information; we used a binary/"use vs. no use" assessment in order to reduce recall bias, which can be introduced by the use of self-reported questionnaires (Mezei et al., 2001).

We tried to minimize sources of bias related to study design as much as possible. The questions regarding indoor electrical appliances and perceived EMF exposure were asked after the questions about health outcomes. Furthermore, the questionnaire items on activity patterns did not explicitly relate EMF to the activities. Self-reported outcomes were previously assessed across environmentally sensitive groups (Baliatsas et al., 2014) and we used medical record data from a registry system with established reliability (Lamberts et al., 2005). In the absence of an internationally recognized case definition for IEI-EMF, inclusion criteria were based on the dominant definitions in the peer-reviewed experimental and observational literature (Baliatsas et al., 2012a). Finally, the response rate of the survey is considered satisfactory and comparable to other studies on residential EMF exposure and NSPS (Baliatsas et al., 2012b).

Study limitations

Besides the cross-sectional nature of the study, some limitations should be acknowledged. Regarding the propagation (ECOLOG) model which was used to estimate residential exposure to mobile phone base stations (Neitzke et al., 2007), only information on the maximum antenna power was available. The antenna dataset did not contain information regarding the tilt of the individual antennas (fixed tilt was used for all antennas). Shielding by vegetation or buildings is not included in the ECOLOG estimation, nor does it account for the further propagation of the signal indoors; it stops after penetration of the signal through the wall or window of the bedroom. Such limitations in the input data reduce the accuracy of exposure prediction (Beekhuizen et al., 2014a). A geospatial model based on detailed three-dimensional data on the neighborhood would have higher accuracy. At the onset of this study, however, such data was not yet available, but much progress has been made recently (Beekhuizen et al., 2014b). Finally, an aspect that could influence specificity of the ECOLOG model was the incomplete questions (23%) in the main epidemiological survey.

In terms of the AEM based models, exposure-related activities might, apart from exposure, also reflect lifestyle characteristics, that in themselves might be associated with health endpoints. Moreover, the explained variance of the prediction model for WiFi exposure was too low to be considered and assessment of mobile phone use was not possible due to the lack of objective operator data. Finally, the explained variance of the prediction models for RF-EMF, was relatively low. This indicates some exposure error and misclassification that may affect the study's statistical power and regression coefficients. Given the size of the study, effects on statistical power may be less important here. Given that a prediction model was not available at the time the present project was running, exposure to ELF-MF was based on geo-coded distance and indoor electric devices on self-reports, which are known to be prone to exposure misclassification (Bonnet-Belfais et al., 2013; Leitgeb et al., 2007).

Another possible limitation is related to the ICPC codes we used to identify GP-registered NSPS. It cannot be ruled out that not all symptoms presented by the patients were registered by the GP or the GP used a code that was not considered as corresponding to the self-reported NSPS. This could lead to an underestimation of the prevalence of registered NSPS in the study sample. In addition, some of the participants might have been diagnosed with a medical condition before or after the time interval we used to define an episode of care as "non-specific". Finally, the respondents were somewhat healthier and reported to be less sensitive to base stations and wireless communication systems than the non-respondents.

This may have led to an underestimation of the examined health outcomes. When only sensitive individuals would experience health problems, an underrepresentation of sensitive individuals would reduce the power to detect such an exposure-outcome associations in a sensitive subgroup.

Conclusions

In conclusion, this study provides no evidence for an association between everyday life RF-EMF exposure and NSPS and sleep quality in the population. This may, in part, be a result of exposure error and misclassification. Better exposure characterization, in particular with respect to ELF-MF is needed to draw more solid conclusions. Perceived exposure, perceived control and avoidance coping were associated with the examined health outcomes. There was some indication, but no consistent pattern, for a potential moderating role of IEI-EMF on the association between actual exposure and symptoms. Longitudinal approaches within a multidisciplinary framework can further elucidate the underlying mechanisms in this research field.

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Appendix

Table 6: Association (ORs)[a] between modeled RF-EMF (per frequency band) and perceived EMF exposure and prevalence of single self-reported NSPS (significant associations based on *p* values in bold)

	Headache	Dizziness or feeling light-headed	Fatigue/tiredness	Memory or concentration problems	Skin symptoms	Heart palpitations	Ear symptoms
RF-EMF exposure	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
GSM900	1.05 (0.97–1.13)	0.95 (0.86–1.04)	1.00 (0.93–1.08)	1.00 (0.92–1.09)	1.07 (0.99–1.15)	0.91 (0.8–1.03)	0.96 (0.86–1.08)
Perceived EMF	**1.02 (1.01–1.03)** ǂ	**1.02 (1.01–1.04)** ǂ	**1.04 (1.03–1.05)** ǂ	**1.02 (1.01–1.04)** ǂ	**1.02 (1.01–1.03)** †	**1.02 (1.01–1.04)** †	**1.02 (1.00–1.03)** *
GSM1800	1.04 (0.99–1.09)	1.00 (0.95–1.04)	1.03 (0.98–1.09)	1.01 (0.97–1.06)	1.02 (0.98–1.06)	0.98 (0.93–1.05)	1.00 (0.94–1.06)
Perceived EMF	**1.02 (1.01–1.03)** ǂ	**1.02 (1.01–1.04)** ǂ	**1.04 (1.03–1.05)** ǂ	**1.03 (1.01–1.04)** ǂ	**1.02 (1.01–1.03)** †	**1.03 (1.01–1.04)** †	**1.02 (1.00–1.03)** *
DECT	0.97 (0.93–1.01)	0.99 (0.95–1.04)	0.99 (0.95–1.03)	0.99 (0.95–1.04)	1.00 (0.96–1.04)	0.98 (0.93–1.04)	1.00 (0.95–1.06)
Perceived EMF	**1.02 (1.01–1.03)** ǂ	**1.02 (1.01–1.03)** ǂ	**1.03 (1.02–1.04)** ǂ	**1.02 (1.01–1.03)** †	**1.01 (1.00–1.02)** *	**1.02 (1.01–1.03)** †	1.01 (1.00–1.03)
Uplink	**0.97 (0.95–0.99)** *	**0.97 (0.95–1.00)** *	0.99 (0.97–1.01)	0.99 (0.97–1.02)	1.00 (0.98 – 1.02)	1.00 (0.97–1.03)	0.99 (0.96–1.02)
Perceived EMF	**1.02 (1.01–1.03)** †	**1.02 (1.01–1.03)** †	**1.03 (1.02–1.05)** ǂ	**1.02 (1.00–1.03)** *	**1.01 (1.00–1.03)** *	**1.02 (1.01–1.04)** †	1.01 (0.99–1.03)
Downlink	1.02 (0.99–1.05)	0.99 (0.97–1.02)	1.01 (0.98–1.04)	1.00 (0.98–1.03)	1.01 (0.99–1.04)	0.99 (0.95–1.02)	0.99 (0.95–1.02)
Perceived EMF	**1.02 (1.01–1.03)** ǂ	**1.02 (1.01–1.04)** ǂ	**1.04 (1.03–1.05)** ǂ	**1.03 (1.01–1.04)** ǂ	**1.02 (1.01–1.03)** †	**1.03 (1.01–1.04)** †	**1.02 (1.00–1.03)** *
Radio/TV	0.98 (0.93–1.02)	1.02 (0.97–1.08)	0.96 (0.92–1.01)	0.99 (0.94–1.04)	1.00 (0.95–1.05)	0.88 (0.77–1.02)	1.01 (0.95–1.07)
Perceived EMF	**1.02 (1.01–1.03)** †	**1.02 (1.01–1.03)** †	**1.03 (1.02–1.05)** ǂ	**1.02 (1.01–1.03)** †	1.01 (1.00–1.02)	**1.02 (1.01–1.04)** †	1.01 (0.99–1.03)

[a] Adjusted for age, gender, education, foreign background, rented home, degree of urbanization, smoking habits, alcohol and/or substance abuse.
Abbreviations: OR, Odds ratios; CI, Confidence intervals.
Note: * $p < 0.05$; † $p < 0.01$; ǂ $p < 0.001$.

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Table 7: Association (ORs)[a] between distance to and use of ELF-MF sources and prevalence of single self-reported NSPS (significant associations based on *p* values in bold)

	Headache	Dizziness or feeling light-headed	Fatigue/tiredness	Memory or concentration problems	Skin symptoms	Heart palpitations	Ear symptoms
Source/appliance	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Distance to power lines							
≤ 200 m	0.62 (0.34–1.14)	0.82 (0.41–1.65)	0.96 (0.57–1.63)	1.08 (0.57–2.03)	0.92 (0.49–1.71)	1.54 (0.79–3.02)	1.07 (0.52–2.2)
Perceived EMF	**1.02 (1.01–1.03)** ‡	**1.02 (1.01–1.03)**‡	**1.03 (1.02–1.04)** ‡	**1.02 (1.01–1.03)** ‡	**1.01 (1.00–1.02)** *	**1.02 (1.01–1.03)** †	**1.01 (1.00–1.03)***
Electric alarm clock							
≤ 50 cm	1.12 (0.99–1.27)	0.95 (0.82–1.09)	1.11 (0.98–1.25)	0.88 (0.76–1.01)	0.9 (0.79–1.03)	0.97 (0.82–1.16)	0.96 (0.81–1.14)
Perceived EMF	**1.02 (1.01–1.03)** ‡	**1.02 (1.01–1.03)** ‡	**1.03 (1.02–1.04)** ‡	**1.02 (1.01–1.03)** ‡	1.01 (0.99–1.02)	**1.02 (1.01–1.03)***	**1.02 (1.00–1.03)** *
Electric charger							
≤ 50 cm	1.02 (0.86–1.2)	1.12 (0.93–1.35)	**1.36 (1.15–1.61)** ‡	1.14 (0.94–1.38)	1.1 (0.92–1.32)	1.03 (0.82–1.3)	0.98 (0.77–1.25)
Perceived EMF	**1.02 (1.01–1.03)** ‡	**1.02 (1.01–1.03)** ‡	**1.03 (1.02–1.04)** ‡	**1.02 (1.01–1.03)** ‡	**1.01 (1.00–1.02)** *	**1.02 (1.01–1.03)** †	**1.01 (1.00–1.03)** *
Electric oven							
Use vs. no use	1.06 (0.92–1.23)	0.93 (0.79–1.1)	1.01 (0.87–1.16)	0.96 (0.81–1.13)	0.99 (0.84–1.16)	1.08 (0.88–1.32)	1.00 (0.82–1.22)
Perceived EMF	**1.02 (1.01–1.03)** ‡	**1.02 (1.01–1.03)** ‡	**1.03 (1.02–1.04)** ‡	**1.02 (1.01–1.03)** ‡	**1.01 (1.00–1.02)** *	**1.02 (1.01–1.03)** †	**1.02 (1.00–1.03)** *
Induction hob							
Use vs. no use	1.06 (0.86–1.3)	0.93 (0.73–1.19)	0.99 (0.81–1.21)	0.92 (0.71–1.18)	0.98 (0.77–1.23)	0.85 (0.62–1.16)	0.91 (0.67–1.23)
Perceived EMF	**1.02 (1.01–1.03)** ‡	**1.02 (1.01–1.03)** ‡	**1.03 (1.02–1.04)** ‡	**1.02 (1.01–1.03)** ‡	**1.01 (1.00–1.02)***	**1.02 (1.01–1.03)** †	**1.02 (1.00–1.03)** *
Electric/Ceramic hob							
Use vs. no use	0.98 (0.84–1.15)	0.95 (0.79–1.14)	1.01 (0.86–1.17)	1.11 (0.93–1.32)	1.09 (0.92–1.29)	1.14 (0.93–1.42)	0.98 (0.79–1.22)
Perceived EMF	**1.02 (1.01–1.03)** ‡	**1.02 (1.01–1.03)** ‡	**1.03 (1.02–1.04)** ‡	**1.02 (1.01–1.03)** ‡	**1.01 (1.00–1.02)** *	**1.02 (1.01–1.03)** †	**1.02 (1.00–1.03)** *
PC or laptop							
Use vs. no use	1.23 (0.96–1.58)	0.99 (0.73–1.33)	**0.76 (0.61–0.94)** *	0.83 (0.65–1.07)	1.00 (0.78–1.28)	0.99 (0.73–1.33)	1.13 (0.85–1.52)
Perceived EMF	**1.02 (1.01–1.03)** ‡	**1.02 (1.01–1.03)** ‡	**1.03 (1.02–1.04)** ‡	**1.02 (1.01–1.03)** ‡	**1.01 (1.00–1.02)** *	**1.02 (1.01–1.03)** †	**1.02 (1.00–1.03)** *
Electric blanket							
Use vs. no use	1.1 (0.9–1.35)	**1.32 (1.06–1.64)** *	**1.39 (1.14–1.69)** †	1.1 (0.88–1.38)	1.19 (0.96–1.17)	**1.31 (1.01–1.69)***	**1.46 (1.14–1.88)**†
Perceived EMF	**1.02 (1.01–1.03)** ‡	**1.02 (1.01–1.03)** ‡	**1.03 (1.02–1.04)** ‡	**1.02 (1.01–1.03)** ‡	**1.01 (1.00–1.02)** *	**1.02 (1.01–1.03)** †	**1.02 (1.00–1.03)** *
Vacuum cleaner							
Use vs. no use	1.14 (0.89–1.47)	1.12 (0.83–1.5)	0.91 (0.72–1.15)	0.92 (0.7–1.21)	0.95 (0.73–1.23)	0.93 (0.66–1.31)	1.26 (0.89–1.79)
Perceived EMF	**1.02 (1.01–1.03)** ‡	**1.02 (1.01–1.03)** ‡	**1.03 (1.02–1.04)** ‡	**1.02 (1.01–1.03)** ‡	1.01 (1.00–1.02)	**1.02 (1.01–1.03)** †	**1.02 (1.00–1.03)** *

[a] Adjusted for age, gender, education, foreign background, rented home, degree of urbanization,, smoking habits, alcohol and/or substance abuse.
Abbreviations: OR, Odds ratios; CI, Confidence intervals.
Note: [*]$p< 0.05$; [†]$p< 0.01$; [‡]$p< 0.001$.

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Chapter 7

General Discussion

The main aims of this thesis were (I) To study the prevalence of NSPS (including sleep quality) in relation to actual and perceived exposure to EMF in the general population, including potentially susceptible people such as those with IEI-EMF and (II) To provide insight into determinants of NSPS and psychological factors that could modify the relationship between perceived exposure to EMF and NSPS.

The thesis comprised two systematic reviews (chapters 2, 4), a pilot epidemiological study (chapter 3) and the central study (chapter 5, 6). The results and lessons learned of the first three studies were used as input to develop the main study. Summarizing the results, no evidence was found for an association between everyday life RF-EMF exposure and NSPS and sleep quality in the general population. A few associations were observed between electric appliances and symptoms. Perceived exposure, perceived control and avoidance coping were associated with the examined health outcomes. There was some indication, but no consistent pattern, for a potential moderating role of IEI-EMF on the association between actual exposure and symptoms, but not for the association of perceived exposure and symptoms.

Discussion of the key findings

Association between NSPS and actual exposure

As a first step, a systematic review with meta-analysis of the epidemiological literature on RF-EMF and NSPS was performed. We decided to focus on RF-EMF since only one epidemiological study was found using magnetic field exposure proxies [1]. Results showed no consistent association between actual RF-EMF exposure levels (based on proxies such as geo-coded distance to base stations, spot measurements, personal dosimetry and prediction models) and prevalence of NSPS in the general population. Measured/modelled exposure levels in all studies were much lower than the limits established by the International Commission on Non-Ionizing Radiation Protection (ICNIRP) [2].

Methodological quality was an important determinant of the strength of the associations, given that studies with a higher risk of bias, primarily regarding exposure assessment and sample selection, demonstrated more significant associations and larger effect sizes. In contrast, more recent studies using more advanced exposure characterization methods did not find a significant effect.

An interesting finding, was that despite the lack of statistical significance, most of the actual exposure studies showed a pattern of positive associations between NSPS and higher exposure levels, independently of study quality, exposure and outcome measures and type of symptoms. This might be explained by factors such as selection bias and/or positive-outcome bias in the literature, low exposure levels and contrast or small prevalence/low participation of susceptible groups which could lower the power for the detection of a hypothetically genuine effect. After rigorous assessment of the information provided in the eligible articles and of the methodological quality of the included studies, we pooled the risk estimates of studies with a smaller risk for bias due to exposure misclassification, sample selection and confounding. Meta-analyses on a few comparable studies yielded no significant risk difference between low and highly exposed individuals in terms of frequency and severity of symptoms. After the publication of the review, only three epidemiological studies (which would have been eligible for inclusion) have been published, to our knowledge [3-5]. Their findings are in line with the conclusions of our systematic review/meta-analysis, therefore we do not expect that inclusion of these studies would have altered the results of the review.

Secondary analyses performed in a large epidemiological survey (Chapter 2) showed no association between NSPS and actual distance to base stations and power lines. Although exposure characterization was based on actual distance, an important comparative advantage of this study was the low risk of information bias. More specifically, sample recruitment was not based on residing in the vicinity of the examined EMF sources nor was the issue of EMF exposure explicitly addressed in the questionnaire. Furthermore, a weak correlation was found between actual distance and perceived proximity. This strengthened our results, since it allowed us to investigate actual and perceived distance/proximity as independent predictors of NSPS.

In the central study (described in Chapter 5 and 6), using more advanced exposure proxies to characterize everyday life exposure to RF-EMF no evidence was found for an association of modelled exposure to RF-EMF with self-reported or GP-registered NSPS nor self-reported sleep quality. These findings confirm those from other recent epidemiological studies on comparable levels of RF-EMF and NSPS and sleep quality [4-7]. Our study is the only one in which GP-registered data on NSPS were combined with self report data. As in previous studies, exposure levels were far below the exposure limits for the general population [2]. Therefore, conclusions in this thesis are restricted to health effects related to low-level RF-EMF exposure.

We also explored the association between the aforementioned outcomes and ELF-MF proxies such as actual/geo-coded distance to high-voltage overhead power lines and use of indoor electric appliances and NSPS. Similar to Chapter 3, no association was observed between symptoms and close proximity to power lines. Associations were found between the examined health outcomes and use/close distance of/to some electric appliances, mainly electric blanket and electric charger. There is not much evidence in previous literature to compare the latter findings with and therefore more research on the effects of these sources is required to corroborate the present findings.

Environmental sensitivity, IEI-EMF and NSPS

In the exploratory study described in Chapter 3, we found that general perceived environmental sensitivity was one of the strongest predictors of NSPS. Based on the data of the main survey (Chapter 5) we performed a more in depth investigation on symptom report in relation to environmental sensitivities, providing insight into health characteristics and symptom features of people with general environmental sensitivity (GES) and IEI-EMF. Similar to other specific subgroups with NSPS [8,9], participants with IEI-EMF (and GES) were, compared to the general population, considerably more symptomatic, with more chronic symptoms, higher levels of functional impairment and illness behavior indicators and more negative symptom perceptions. An interesting finding was the high rate of consultations of alternative therapy among individuals with IEI-EMF, even after adjustment for medical and psychological morbidity.

Despite the experience of more symptoms and poorer health, we found no convincing evidence that individuals with IEI-EMF experience more severe NSPS or lower sleep quality in relation to actual EMF than the rest of the sample (Chapter 6). We observed a trend for increased risk in respondents with IEI-EMF of self-reported symptoms in relation to downlink and GSM900 exposure and use of an electric blanket and close sleeping distance to an electric alarm clock. These findings should be interpreted with caution, since the possibility of false-positives is likely, due to the large number of interactions tested, in relation to numerous outcomes [10]. In addition, residual confounding cannot be entirely ruled out and exposure misclassification is likely to occur, especially regarding the assessment of electric appliances.

Finally, despite the fact that people in the IEI-EMF group reported higher levels of EMF exposure and related worries, the interaction between IEI-EMF and perceived exposure was not significant. This indicates that the association between perceived exposure and the investigated symptoms did not significantly differ between electrosensitive and the other participants.

Association between NSPS and perceived exposure; implications for a generic psychological mechanism

In addition to the risk assessment of physical exposures, it is important to explore the explanatory framework through which symptoms may occur. Based on evidence suggesting that self-estimated exposure to EMF is a poor proxy of actual exposure levels [11-13], we defined perceived exposure as the subjective belief of the magnitude of being exposed to EMF.

Our systematic review (Chapter 2) showed that perceived exposure studies reported consistent significant associations and larger effect sizes than actual exposure studies. However, the vast majority of the reviewed studies used perceived exposure as a proxy for actual exposure; this underlines the lack of a conceptual framework in EMF epidemiology regarding distinction between actual and perceived exposure. In addition most of these studies investigated NSPS in relation to perceived mobile phone call duration. Although people tend to overestimate the duration of calls, which leads to misclassification of exposure [14], one cannot completely rule out that the reported associations are partly explained by actual exposure, since mobile phone devices are near field sources, close to the body.

Both our "pilot" and central study showed that perceived exposure is consistently associated with self-reported health outcomes which is in agreement with the limited, but increasing evidence in the epidemiological literature [4]. It also corroborates experimental evidence suggesting that people can experience/report symptoms when they believe they are exposed to EMF, regardless of the accuracy of this belief [15-18]. The tendency to report ill-health due to the perception of being exposed to a potentially harmful environmental source, is often considered to be indicative of either information bias or a so-called "nocebo" phenomenon [4,5,19].

Our results regarding the association between perceived exposure and NSPS may have implications towards the understanding of the possible pathways that lead to experiencing NSPS. First, the correlation between the three items on perceived exposure was high, although they referred to three different situations (at home, outdoors and at work), which may suggest subjectivity in the estimation. Second, the correlation between perceived and actual exposure (based on the different surrogates) was either low or negligible.

Although this could partly stem from deficiencies in the modelled actual exposure, it rather strengthens the notion that perceived exposure should not be considered as a proxy of actual exposure levels. It also indicates that most of the participants did not seem to be aware of the most relevant sources they were exposed to in everyday life, which lowers the risk for information bias in our study.

Therefore, the association between perceived exposure and the examined outcomes, may indicate the existence of a nocebo phenomenon. Non-specific physical symptoms in our study were also consistently associated with lower perceived control and less consistently with increased avoidance behavior. When individuals perceive an environmental stressor such as EMF, this might trigger or amplify worries about possible health effects. Low perceived control over the stressor could increase preoccupation with and amplification of bodily reactions and the engagement in coping strategies such as avoidance towards the stressor, which might only have a short-term alleviating effect on symptoms. Inversely, people who experience NSPS may have an increased level of awareness and concern about their environment as they look for explanations for their ill health. The consequence may for some people be a vicious circle linking the perception or the fear to be exposed, low control over the stressor, maladaptive coping and symptoms. This is suggestive of a generic mechanism of environmental stress [20,21] and cognitive and behavioral models elaborating on medically unexplained NSPS [22-25]. However, the cross-sectional nature of the study does not allow to explore underlying mechanisms of the observed patterns.

Methodological considerations

Strengths of the study design and methodology

Observational epidemiological studies are particularly useful in assessing long-term and chronic exposure to EMF in relation to health outcomes in the population. Especially in cases where the events are considered to be rare, a sufficiently large sample size is needed for the detection of a “true” effect, if one exists [26]. Additionally, such a design allows for the simultaneous investigation of several other health predictors at population level, without compromising power.

Compared to previous epidemiological studies in this research field, the design and methodology followed in the main study collectively had a number of advantages: 1) Larger sample and a satisfactory response rate, considering the lengthy questionnaire and the general trend towards a decreasing response rate in epidemiological research the recent years [27].

2) Thorough and "state of the art" outcome assessment, based on the combination of self-reported data and electronic medical records on NSPS (GP-registered NSPS), which minimizes the risk of selective response and outcome misclassification. Furthermore, the use of a large primary care database provided insight into the health status of the respondents, such that the prevalence of registered medical morbidity and anxiety and depressive disorder represents real-life practice. 3) A combined approach towards actual exposure based on a variety of surrogates; a relatively limited number of studies have used surrogates of actual exposure to RF-EMF in relation to NSPS. There is also limited research on the association between NSPS and proxies of residential ELF-MF exposure. In addition, estimates of residential exposure to mobile phone base stations were used as a parameter of sample stratification to enhance exposure contrast. 4) Investigation of perceived exposure as a theoretically/conceptually independent predictor of NSPS. 5) The role of psychological factors has been taken into account. 6) Identification of potentially vulnerable subgroups such as people with IEI-EMF (Chapter 4). 7) We tried to minimize well-documented biases related to the observational design and methodology (Chapter 2). The study questionnaire had a general title "Living environment, technology and health" and questions regarding EMF sources and perceived EMF exposure were asked after the questions about health outcomes. In addition, the questionnaire items on activity patterns did not explicitly relate EMF to the activities. Moreover, analyses on the association between symptoms and actual exposure were adjusted for perceived exposure (and vice versa) and several socio-demographic, residential, lifestyle and health characteristics.

Outcome assessment

Only general practitioner's clinical judgement can reliably determine whether the reported symptom(s) is/are associated with a medical disorder [28]. It is unclear to what degree the self-reported symptoms assessed in relation to EMF exposure in the existing epidemiological studies are "truly" unexplained symptoms. The use of medical data from primary care records overcomes this issue [29]. However, persistent/chronic presentation of NSPS in healthcare is not very common [30] and patients who seek help are not always those with poor health [29,31,32]. In the present study we used both self-reported and registry-based data to combine the comparative advantages of both assessments. Aiming to cover the spectrum of NSPS in the main study as well as possible, we used a detailed symptom list that included various symptoms in different bodily areas/organ systems, showing high internal consistency [33].

The scale assessed both number and duration of NSPS and also associated perceptions, providing insight into the potential clinical relevance of symptomatology. Although a lengthy questionnaire can be time-consuming for participants, more than 50% of symptom questionnaires in large-scale studies assess 15 or more symptoms [34]. The SaP scale represents clearly identifiable organ systems, it contains all the symptoms often considered as unexplained [35] and uses a time reference that minimizes recall bias.

In both the "pilot" and main survey, we considered the assessment of self-reported-NSPS based on sum scores highly relevant, given the lack of clear symptom patterns in IEI-EMF [36] and the potential large variation of physiological reactions to EMF (if the existence of a bioelectromagnetic mechanism is assumed) [37]. More importantly, except for knowing whether symptoms are medically unexplained or not, it is even more relevant to identify characteristics of symptoms that make them disabling and potentially influence their clinical course [29]. The number of self-reported symptoms is a consistent indicator of functional impairment and healthcare utilization in primary care patients with NSPS and the broader population [8,9]. The latter was verified in Chapter 5, where we found that both the number and duration of self-reported NSPS were consistently associated with decrease in functional status and increase in illness behavior, negative symptom perceptions and prevalence of GP-registered NSPS. Similarly, we considered the assessment based on a continuous sleep quality scale instead of a single symptom [38-39].

In addition to symptom scores, the prevalence of single self-reported symptoms was examined as well, in order to improve comparability with previous epidemiological studies that used similar outcome variables (Chapter 2); selection was based on symptoms frequently investigated in the relevant epidemiological literature (Chapter 2) and highly reported among IEI-EMF sufferers (Chapter 5).

Corresponding to the SaP list, the prevalence of GP-registered symptoms presented during the past year was also assessed, based on "episodes of care" [40]. An episode was identified as "non-specific" if there was no registered medical diagnosis as an explanation for the symptoms, during the year before the completion of the study. Data from medical records were collected from a classification system with established reliability [41]. Registered NSPS and somatic and psychiatric morbidity were diagnosed and registered by general practitioners according to the International Classification of Primary Care (ICPC-1) [42].

In the Netherlands, general practice is an optimal setting for providing information regarding population's health for research purposes, since every citizen is obliged to be on the list of just one general practice [43]. The general practices that participate in the National Information Network of General Practice (LINH) have been providing annual information on consultation rates, diagnoses and prescribed medication/therapeutic interventions, based on routine information from anonymous electronic medical records.

Actual exposure assessment

While risk identification in epidemiological studies does not necessarily require perfect estimation of individual exposure levels, adequate exposure contrast constitutes a crucial prerequisite for the investigation of health effects [44]. As summarized by Toledano & Smith [45], EMF epidemiology needs integrated approaches towards the assessment of associations of exposure with health effects. Aspects such as the lack of established biological mechanisms, low exposure levels in the population and diversity of EMF sources producing simultaneous and often correlated EMF exposures, dictate that as many relevant sources as possible are taken into account [45]. Cost-efficiency and feasibility of the exposure assessment methods are also important parameters that should be considered [13]. Taking all these aspects into consideration, we assessed various exposure surrogates of RF-EMF and ELF-MF in relation to self-reported and registry-based outcomes).

We used a model combining exposure-related activities and base-station exposure to predict RF-EMF levels. First, a propagation model was built based on the approach of the ECOLOG institute [46,47], in which the average RF-EMF exposure at home emitted from mobile phone base stations was estimated [48]. The advantage of such a model is that it can be applied to large study populations, estimating long-term exposures based on continuously updated data [46-48].

Nevertheless, models of far-field exposure alone, do not provide information on aspects such as indoor EMF sources at home and exposure-related behavior, which are relevant to the total exposure. For this reason, in order to better represent personal daily-life exposure, we combined our ECOLOG model with models that used information on activities associated with the major sources of environmental RF-EMF exposure in the Netherlands [49] extracted from the so-called Activity Exposure Matrix (AEM) [50].

The documented levels of RF-EMF exposure were well below the ICNIRP reference levels (ICNIRP, 2009). Taking the differences into account between the AEM study and the study by Frei and colleagues, the explained variance of the prediction model was compared reasonably well with the model developed in Switzerland [13]. The higher proportion of explained variance in the Swiss study is in part due to the use of the three-dimensional propagation model used, compared to the ECOLOG model. The modelled mean exposure values and ranges per band in our study were in line with those reported in other European studies [13,51,52]. The applied method is considered as cost-efficient and a fair representation of daily life exposure conditions compared to spot or exposimeter measurements [53].

We used geo-coded distance to high-voltage overhead power lines and self-reported use of electric appliances as proxies for ELF-MF exposure. Although actual distance to power lines alone is considered a crude proxy [54], magnetic field levels in residences in the proximity of power lines is considerably higher compared to those farther away [55]. Questions on indoor appliances were based on a clear cut-off point assessment to reduce recall bias.

Perceived exposure assessment

In the exploratory study (Chapter 3), we used two binary items, referring to perceived proximity to base stations and power lines. In the main study presented in Chapter 6, given the inclusion of various actual exposure proxies (RF-EMF frequency bands, power lines, electric appliances) we employed a broader and more comprehensive assessment of perceived exposure. A higher total score on the three items represented higher (generalized) perceived exposure to EMF. Although the items referred to different situations, between-item correlations were high. The correlation between perceived and actual exposure proxies in both studies was either low or negligible regardless the measurement method.

Identification of IEI-EMF

Chapter 4 provided a systematic review that summarized the methodology used in the literature published until 2011 for the identification of individuals with IEI-EMF. After the evaluation of more than 60 peer-reviewed studies of observational and experimental design, we found that IEI-EMF is a self-reported, highly heterogeneous sensitivity without an internationally established, validated case definition.

In the present thesis we have been consistently using the term IEI-EMF which is recommended by the WHO as etiologically neutral [56]. Despite the methodological differences across studies, the most frequently used case definition criteria in the literature (used either alone or combined) were:

1) Self-reported (hyper)sensitivity to a single or (mainly) various EMF source(s), 2) attribution of NSPS to various or specific EMF sources, 3) experience of symptoms during or soon after the perception or actual presence or use of an EMF source and 4) absence of a somatic and/or psychiatric condition that could account for the reported symptoms. Furthermore, the review showed that the demographic profile of subgroups with IEI-EMF was consistent regarding age and gender, since the distribution of female gender and age > 40 years were considerably higher compared to controls.

Based on the findings from the systematic evaluation of the literature, we considered as the IEI-EMF group those respondents who quite or strongly agreed that they were sensitive to both RF-EMF and ELF-MF sources. We chose our case definition to be independent of attributed symptoms, given the lack of clear symptom patterns [36,57]. Additionally, we aimed to an objective investigation of health characteristics and symptom profiles among environmentally sensitive and non-sensitive participants, which was performed in the next stage (described in Chapter 5), without predisposing participants. Especially studies using an experimental design select a patient group with specific thresholds of symptom report, high symptomatic severity and associated health concerns, while the reference/control group usually consists of healthy individuals who are often completely asymptomatic. However, such group selection may compromise the generalizability of the results, because the cases and (especially) the healthy controls do not necessarily reflect typical patients in primary care. Our assessment was performed in close adherence to daily general practice.

Some of the findings reported in Chapter 5 could also contribute to the further characterization of environmentally sensitive groups and add to the notion that different types of sensitivities might share a common (psycho)physiological basis, being part of one, broader environmental sensitivity [58,59]. More specifically, analyses yielded a number of distinct health and behavioral characteristics of people with IEI-EMF. These seem to be common also among participants who reported to be sensitive to various environmental sources (general environmental sensitivity, GES):

1) Higher prevalence and longer duration of NSPS 2) Increased functional impairment and illness behavior (especially regarding alternative therapy consultations) and more negative symptom perceptions, 3) high co-occurrence with other environmental sensitivities; 40% of participants with IEI-EMF met the criteria for GES.

Study limitations

A cross-sectional design, apart from inevitable limitations such as the inability to establish the sequence of events, is susceptible to various methodological biases such as selection, information, recall and confounding bias and exposure misclassification. As reported in earlier sections (*Strengths of the study design and methodology*), we applied a number of strategies to minimize the aforementioned biases. However, not all risks for bias can be ruled out.

Valid actual exposure assessment in EMF epidemiology is still a highly complex issue and even "state of the art" measurement methods come with biases [53,60]. A number of limitations should be acknowledged regarding the calculation of the propagation (ECOLOG) model which was used to estimate residential exposure to mobile phone base stations [48]. First, only information on the maximum antenna power was available. No information was available regarding the tilt of the individual antennas (fixed tilt was used for all antennas). Second, shielding by vegetation or buildings is not included in the ECOLOG estimation, nor does it account for the further propagation of the signal indoors; it stops after penetration of the signal through the wall or window of the bedroom. Such limitations in the input data can reduce the accuracy of exposure prediction [61]. A geospatial model based on detailed three-dimensional data on the neighborhood would be an optimal alternative approach [62]. For this study, however, input data were not available. Recent developments have expanded the possibilities for the application of the model in the Netherlands [63]. Finally, an aspect that could influence specificity of the ECOLOG model was the incomplete questions (23%) in the main epidemiological survey.

Furthermore, the explained variance of the full prediction model for RF-EMF frequencies (combination of the AEM activities and the propagation model), is considered as relatively low. In addition, the explained variance of the prediction model for WiFi exposure was too low to be included and assessment of mobile phone exposure was not possible due to the lack of a more objective surrogate such as operator-recorded data.

These limitations introduce exposure error and misclassification, of largely unknown nature, likely with differential and non-differential components. Apart from lowering the power of the study, this may have resulting in distortion of a “true” exposure–response association.

Regarding assessment of ELF-MF exposure, this was based on geo-coded distance to high-voltage overhead power lines and questionnaire data on use of indoor electric devices, which are both considered crude proxies [54,64].

In terms of the assessment of perceived exposure, we chose a comprehensive approach referring to different daily life situations such as at home, work and indoors. We found quite low correlations between proxies of perceived and actual exposure. However, since our study represents real-life conditions which cannot be manipulated as in the case of controlled experiments, it is inevitable that perceived exposure incorporates some actual exposure (and vice versa).

Another possible limitation is related to the identification of NSPS in the electronic medical records. Although the time interval we used is common for the investigation of non-specific/medically unexplained symptoms [29], some of the participants might have been diagnosed with a medical condition that could account for the presented symptoms somewhat earlier or after the set timeframe. Inaccurate coding would be expected to be unrelated to exposure and would therefore introduce non-differential outcome misclassification.

Since the respondents in the main study were healthier and reported to be less sensitive to base stations and wireless communication systems compared to the non-respondents, this might have led to some underestimation of the examined health outcome rates in the sample. Furthermore, although the employed criteria to select the IEI-EMF group were literature-based, there is no internationally validated case-definition for such environmental sensitivities (Chapter 4). Thus, it is possible that we were not able to identify all relevant subjects with genuine sensitivity to EMF, if such exists.

Finally, epidemiological studies are prone to bias related to the so-called “healthy communicator effect”. This refers to the notion that healthier people make more often use of EMF sources such as wireless communication devices and thus could be more exposed than more susceptible population groups. Generally though, we did not observe substantial differences in terms of RF-EMF exposure levels or use of ELF-MF sources between electrosensitive and non-sensitive respondents in the current investigation.

Recommendations for future research

Valid exposure assessment in EMF research remains a challenge. Given the lack of a bioelectromagnetic mechanism, it is important to follow integrated comprehensive approaches, investigating as many sources as possible. The use of detailed, accurate input data for prediction models is indispensable to reduce measurement errors and misclassification. In addition, assessment of mobile phone use based on self-reports should be improved by more objective measurements, such as operator data.

However, this still does not cover the (uplink) exposures from other people, for instance while in transit or in crowded recreational areas. Longitudinal studies on long-term effects of residential EMF exposure are of particular importance in order to enhance our knowledge.

The combination of self-reported and medical registry data is very useful in gaining insight into the health status of the examined sample and symptomatic effects in relation to environmental exposures. It is also an important element towards minimization of outcome misclassification that often occurs in observational studies.

Investigating the psychosocial framework is crucial for the comprehension of the impact of environmental factors on NSPS. Perceived exposure should be assessed as an independent predictor of NSPS, potentially reflecting processes related to a nocebo phenomenon. In addition to perceived exposure, the role of accompanying worries and theoretically relevant variables such as negative affectivity and somatosensory amplification needs to be further investigated at the population level. Moreover, the reinforcing or alleviating role of avoidant behavior in symptom report should be clarified. The possible impact of external influential factors such as media in the perception of risk and the magnification of related worries can additionally be a dimension of research within the EMF context.

Longitudinal data could allow for the investigation of aspects that are not obtainable in cross-sectional design, such as stability across time and temporal precedence, which are important elements when investigating potential mediators and moderators.

Epidemiological research on potentially susceptible groups of sufficient sample sizes is still very limited and further investigation would help us get a better picture regarding possible effects of everyday life exposure among people with IEI-EMF, which remains a poorly defined condition. The attribution of health outcomes and self-reported sensitivity to EMF inevitably constitute, at the moment, the cornerstone of IEI-EMF case definition in research and clinical practice.

Heterogeneity and ambiguity of the existing definitions and criteria for IEI-EMF show the necessity to develop uniform criteria that will be applicable both in research and clinical practice.

Resolving the issue of the existence or not of causality between everyday life exposure to EMF and NSPS, will allow researchers to proceed to the development of evidence-based interventions for people suffering from associated symptomatic conditions. As long as uncertainty in this field remains, effective risk communication with the general public is necessary, taking into account important aspects such as acknowledgement of citizens' concerns, facilitation of public access to regularly updated scientific knowledge and clear explanation of the methodological shortcomings and challenges of this research field. Collaboration between researchers and journalists would also help the conveyance of objective information to the population.

Bearing these issues in mind, this thesis has prepared the ground for future multidisciplinary studies into the association of actual and perceived exposure to EMF by pinpointing the influence of individual and environmental factors when examining the link between environmental risks and health.

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Summary

The association between non-specific physical symptoms (NSPS) such as headache, fatigue, nausea and sleep problems and exposure to electromagnetic fields (EMF) emitted from sources such as mobile phone base stations, has been a subject of ongoing scientific debate and public concern. A limited number of epidemiological studies has used surrogates of actual field strength, while none of those studies has combined self-reported and general practice (GP)-registered data on NSPS. Evidence from experimental studies suggests that symptoms tend to occur when participants believe they are exposed, irrespective of whether their belief is accurate or not. There is, however, no evidence from epidemiological studies on the role of perceived exposure in symptom report. Evidence on the explanatory role of psychological factors is also scarce at population level. There are no published studies that jointly investigated actual exposure and perceived exposure in combination with psychological factors.

To fill these research gaps, the National Institute for Public Health and the Environment (RIVM), in close collaboration with the Netherlands Institute for Health Services Research (NIVEL) and the Institute for Risk Assessment Sciences (IRAS) of Utrecht University, conducted between 2009 and 2013 the first interdisciplinary epidemiological study on EMF and NSPS in the Netherlands. The study was funded by the Netherlands Organization for Health Research and Development (ZonMw), within the Program "Electromagnetic fields and health research".

This thesis describes the results of this study. The main objectives of this thesis were 1) To study the association between self-reported and general practice (GP)-registered NSPS from electronic medical records (including sleep quality) in relation to actual and perceived exposure to EMF in the general population. Potentially susceptible people such as those with idiopathic environmental intolerance attributed to EMF (IEI-EMF) were also taken into account 2) To provide insight into determinants of NSPS and psychological factors that could modify the relationship between perceived exposure to EMF and NSPS. The thesis comprised two systematic reviews (Chapters 2, 4), a pilot epidemiological study (chapter 3) and the central study carried out in 2011 (Chapters 5, 6), which combined a health survey of adult participants (n=5933) with the electronic medical records of the respondents as registered by general practitioners.

As a first step, a systematic review and meta-analysis of epidemiological studies was conducted (Chapter 2), to gain insight into the quality and strength of evidence for an association between actual and perceived exposure to radio-frequency (RF)-EMF and NSPS in the general population. Results showed no evidence for an association between frequency and severity of NSPS and higher levels of actual measured or modelled EMF exposure, while an association with perceived exposure was more distinct. It was also demonstrated that methodological quality was an important determinant (of the strength) of the exposure-outcome associations. Studies with a higher risk of bias, mainly regarding exposure assessment, sample selection and adjustment for confounders, tend to report more significant symptomatic effects.

In Chapter 3, we report the results of the pilot study, which was based on secondary analyses of epidemiological data collected in 2006. It was found that increased report of NSPS was associated with self-reported environmental sensitivity, perceived proximity to base stations and high-voltage overhead power lines, lower perceived control and increased avoidance (coping) behavior. No significant association was found between symptom report and actual distance to base stations or power lines.

A second systematic review is described in Chapter 4, to determine the case definition criteria and methodology to identify individuals with IEI-EMF in epidemiological research. Despite the high heterogeneity between studies, the review summarized the following prominent criteria: 1) Self-report of being (hyper)sensitive to EMF. 2) Attribution of NSPS to at least one EMF source. 3) Absence of medical or psychiatric/psychological disorder capable of accounting for these symptoms 4) Occurrence of symptoms during or soon after the individual perceives an exposure source or exposed area.

Based on data from the main study, Chapter 5 assessed NSPS and health characteristics in people with general environmental sensitivity (GES) (prevalence: 9%) and IEI-EMF (prevalence: 3,5%) and the broader population. Environmentally sensitive individuals experienced poorer health, increased illness behavior, especially related to alternative therapies, more negative symptom perceptions and more severe NSPS, compared to non-(environmentally) sensitive participants. This was the case also after adjustment for somatic and psychiatric morbidity. It was also concluded that the number and duration of self-reported NSPS were important components of symptom severity in the investigated groups. The observed overlap between the two sensitive groups (GES and IEI-EMF) strengthens the notion that different types of sensitivities might have common underlying components.

In Chapter 6 the primary results of the main study are presented. Characterization of actual exposure was based on several proxies, such as prediction models of radiofrequency (RF)-EMF exposure, geo-coded distance to high-voltage overhead power lines and self-reported use/distance of/to indoor electrical appliances. Perceived exposure and the role of psychological variables were also examined. In line with other European countries, the mean RF exposure levels were far below the thresholds established by the International Commission on Non-Ionizing Radiation Protection (ICNIRP). Perceived exposure had a poor correlation with the actual exposure estimates. Findings showed no convincing evidence for an association between everyday life RF-EMF exposure and NSPS and sleep quality in the general population. A few associations were observed between electric appliances and symptoms. Perceived exposure, perceived control and avoidance coping were independently associated with the examined health outcomes.

Several methodological issues are discussed in the General Discussion (Chapter 7). Compared to previous research efforts, the design and methodology followed in the main study had a number of advantages: 1) Larger sample and a satisfactory response rate, 2) Thorough outcome assessment, based on the combination of self-reported data and electronic medical records 3) A combined approach towards actual exposure based on a variety of surrogates 4) Investigation of perceived exposure as a theoretically/conceptually independent predictor of NSPS. 5) Investigation of the potential role of psychological factors 6) Identification of potentially vulnerable subgroups such as people with IEI-EMF. 7) Careful consideration of confounders. In addition to the cross-sectional design of the study, a number of limitations were also acknowledged, primarily related to the characterization of actual EMF exposure; a highly complex issue that remains a challenge for epidemiological studies internationally.

Finally, conclusions are drawn and recommendations are given. The findings indicate that perceived exposure is an independent determinant of NSPS and should be taken into account in future epidemiological studies on EMF and NSPS.

The combination of self-reported and medical registry data is very useful in gaining insight into the health status of the examined sample and symptomatic effects in relation to environmental exposures. It is also an important asset for the minimization of outcome misclassification that often occurs in observational studies. Despite the lack of evidence between EMF and NSPS in the population, the need for better exposure characterization remains in order to draw more solid conclusions.

Samenvatting

De samenhang tussen niet-specifieke lichamelijke klachten (NSLK) als hoofdpijn, vermoeidheid, misselijkheid en slaapproblemen en blootstelling aan elektromagnetische velden (EMV) vanuit verschillende bronnen is onderwerp van doorlopende wetenschappelijke discussie en maatschappelijk debat. Tot zover heeft slechts een beperkt aantal studies de werkelijke veldsterktes van EMV in kaart gebracht hierbij gebruikmakend van metingen of van modellering. Geen van de tot dusver gepubliceerde onderzoeken heeft zelfgerapporteerde klachten gepresenteerd in combinatie met door huisartsen geregistreerde klachten. Bovendien is er nog nooit gekeken naar de invloed van waargenomen/gepercipieerde blootstelling, ondanks het feit dat experimenteel onderzoek er op wijst dat het ervaren van symptomen het gevolg kan zijn van het idee blootgesteld te worden ook als dat niet het geval is. Ook is er nog weinig bekend over de wijze waarop psychische kenmerken de relatie beïnvloeden tussen werkelijke en gepercipieerde blootstelling aan EMV en niet-specifieke lichamelijke klachten.

Om deze hiaten in de kennis op te vullen heeft het Rijksinstituut voor Volksgezondheid & Milieu (RIVM) in de periode 2009-2013 in Nederland de eerste multidisciplinaire epidemiologische studie uitgevoerd naar werkelijke en gepercipieerde blootstelling aan EMV in relatie tot NSLK. Het onderzoek was gefinancierd door de Nederlandse organisatie voor gezondheidsonderzoek en zorginnovatie (ZonMw), programma “Elektromagnetische velden en Gezondheid”. Het onderzoek is uitgevoerd in nauwe samenwerking met het Nederlands Instituut voor Onderzoek van de Gezondheidszorg (NIVEL) en het Institute for Risk Assessment Sciences (IRAS) van de Universiteit Utrecht. Dit proefschrift presenteert de resultaten van dit onderzoek. De hoofddoelstellingen waren: 1) De relatie in de algemene bevolking tussen werkelijke en gepercipieerde blootstelling aan EMV enerzijds met zelfgerapporteerde en door de huisarts in elektronisch patiëntendossiers (EPD) geregistreerde NSLK anderzijds. Er is ook rekening gehouden met potentieel kwetsbare populatiegroepen zoals mensen met idiopathische milieu-intolerantie toegeschreven aan elektromagnetische velden (IMI-EMV). 2) Inzicht in determinanten van NSLK en psychologische factoren die de relatie zou kunnen modificeren tussen gepercipieerde blootstelling en NSLK.

Deze dissertatie bestaat uit twee systematische studies van de (internationale) literatuur (Hoofdstukken 2, 4), een verkennend observationeel onderzoek (Hoofdstuk 3) en het hoofdonderzoek uitgevoerd in 2011 (Hoofstukken 5, 6), waarin twee informatiebronnen werden gecombineerd: NSLK uit elektronische patiëntendossiers (EPD) en zelfgerapporteerde NSLK uit vragenlijsten (n=5933 volwassenen).

Op basis van het literatuuronderzoek (met meta-analyse) in Hoofdstuk 2 bleek dat bij onderzoek in de algemene bevolking geen verband is gevonden tussen blootstelling aan radiofrequente (RF)-EMV bronnen en niet-specifieke lichamelijke klachten. Wel bleken de klachten samen te hangen met de gepercipieerde blootstelling aan EMV. De methodologische kwaliteit van de onderzoeken bleek in belangrijke mate de sterkte van het verband te bepalen: Hoe beter de studie, hoe zwakker de gevonden samenhang tussen EMV en NSLK.

De (secundaire) analyse van de resultaten van een observationele studie uit 2006 in Hoofdstuk 3 liet zien dat werkelijke (geo-gecodeerde) afstand tot basisstations en hoogspanningslijnen niet samenhing met het aantal zelfgerapporteerde lichamelijke klachten. Factoren als gepercipieerde afstand, algemene milieugevoeligheid, het gevoel geen controle te hebben en vermijdingsgedrag kwamen naar voren als belangrijke voorspellers voor NSLK.

In een tweede literatuurstudie (Hoofdstuk 4) werd, ondanks de diversiteit van de onderzoeken, een aantal belangrijke criteria gevonden op basis waarvan elektrogevoelige mensen geïdentificeerd kunnen worden voor onderzoek: 1) Zelfgerapporteerde elektrogevoeligheid of IMI-EMV en/of 2) De attributie van niet-specifieke lichamelijke klachten aan verschillende EMV bronnen en/of 3) Afwezigheid van een medische of psychiatrische/psychologische conditie die de symptomen volledig kan verklaren en/of 4) De ervaring van symptomen tijdens of vlak na de blootstelling na de gepercipieerde of werkelijke bloostelling aan een EMV bron.

Hoofdstuk 5 is gebaseerd op zowel zelfgerapporteerde klachten als door huisartsen in het EPD vastgelegde klachten, zoals verzameld in het hoofdonderzoek. Het doel was om gezondheidskenmerken en niet-specifieke lichamelijke symptomen (NSLS) te vergelijken bij mensen met IMI-EMV (prevalentie: 3,5%), met algemene milieugevoeligheid (AMG) (prevalentie: 9%) en de algemene bevolking/niet-gevoeligen.

Hieruit bleek dat ook na controle voor vastgestelde somatische en psychische morbiditeit, milieugevoelige mensen een slechtere gezondheid en negatievere symptoomperceptie rapporteerden en een toename in ziektegedag vertoonden (zich uitend in het zoeken van psychologische en/of alternatieve behandelingen). Ook bleken het aantal en de duur van zelfgerapporteerde NSLK belangrijke indicatoren voor de ernst van de symptomen. De overlap tussen de twee verschillende milieugevoelige groepen (IMI-EMV en AMG) versterkt de notie dat verschillende soorten milieugevoeligheid gemeenschappelijke onderliggende factoren hebben.

Resultaten die beschreven worden in Hoofdstuk 6 vormen de primaire bevindingen van de hoofdstudie. Het bepalen van werkelijke blootstelling was gebaseerd op verscheidene benaderingen zoals predictiemodellen van blootstelling aan RF-EMV, geo-gecodeerde afstand tot hoogspanningslijnen en zelfgerapporteerd gebruik van/afstand tot elektrische apparatuur. Ook de rol van waargenomen blootstelling en psychologische variabelen was onderzocht. In overeenstemming met andere Europese landen bleken de gemodelleerde blootstellingniveaus van RF-EMV in dit onderzoek beneden de drempelwaarden te liggen, zoals gesteld door de International Commission on Non-Ionizing Radiation Protection (ICNIRP). De samenhang tussen werkelijke en gepercipieerde blootstelling bleek erg zwak te zijn. Op grond van de bevindingen was er geen overtuigend bewijs voor een blootstelling-respons verband tussen blootstellingen aan RF-EMV en NSLK. Wel werden enkele associaties gevonden tussen gebruik van elektrische apparatuur in huis en gerapporteerde klachten. Gepercipieerde blootstelling, het gevoel geen controle te hebben en vermijdingsgedrag hingen samen met de onderzochte gezondheidsuitkomsten.

De Algemene Discussie (Hoofdstuk 7) gaat in op diverse methodologische aspecten van het onderzoek. In vergelijking met eerder onderzoek heeft het ontwerp van onze studie en de gehanteerde methodologie een aantal voordelen: 1) Grote steekproef en een aantal deelnemers dat redelijk groot is voor dit type onderzoek, 2) Gedetailleerde symptoomevaluatie gebaseerd op de combinatie tussen zelfgerapporteerde en de door de huisarts geregistreerde klachten, 3) Een gecombineerde benadering om de werkelijke blootstelling van verschillende EMV bronnen te karakteriseren, 4) Opname van gepercipieerde blootstelling als conceptueel onafhankelijke voorspeller van NSLK, 5) Aandacht voor de potentiele rol van psychische factoren, 6) Het identificeren van potentieel kwetsbare groepen zoals personen met IMI-EMV op basis van een systematische evaluatie van de gepubliceerde wetenschappelijk literatuur en het gebruik van vragen over diverse milieublootstellingen en 7) Het grondig controleren van de mogelijke invloed van verstorende variabelen (confounders). Het onderzoek heeft, naast de dwarsdoorsnede opzet, een belangrijke beperking; het schatten van de werkelijke blootstelling blijft een grote uitdaging voor epidemiologisch onderzoek.

Tot slot worden er een aantal conclusies getrokken en worden aanbevelingen gedaan. Uit de bevindingen blijkt dat gepercipieerde blootstelling een onafhankelijke determinant van NSLK is waar rekening mee moet worden gehouden bij toekomstig epidemiologische onderzoek naar EMV en NSLK. De combinatie van zelfgerapporteerde- en huisartsendata verschaft inzicht in de gezondheidsstatus van de studiepopulatie en symptomatische effecten in relatie tot milieublootstellingen. Deze combinatie van methoden draagt ook bij aan de vermindering van misclassificatie die zich bij observationele studies vaak voordoet. Ondanks het feit dat er geen overtuigend bewijs is voor een verband tussen EMV en NSLK in de algemene bevolking, is er nog steeds behoefte aan een betere karakterisering van blootstelling om meer gedegen conclusies te kunnen trekken over een mogelijke samenhang.

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Chris

About the Author

Christos Baliatsas was born on May 20th 1984, in Chalkida, Greece. After completing his secondary education he studied Psychology at the University of Crete. In 2009 he graduated from Leiden University with a master degree in Health Psychology. From February 2009 to February 2013 he was appointed as PhD candidate at the Institute for Risk Assessment Sciences (IRAS) of Utrecht University and the National Institute for Public Health and the Environment (RIVM). Within the framework of his PhD program he followed the post-graduate master program in Epidemiology at the University Medical Center Utrecht. Apart from his PhD research, he was also involved in other projects related to the topic of non-specific physical symptoms and environmental sensitivities. Currently he is working as a researcher at the Centre of Sustainability, Environment and Health (DMG) at the RIVM.

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