Review Article

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Review of the scientific evidence on the individual sensitivity to electromagnetic fields (EHS)

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Abstract: Part of the population considers themselves as sensitive to the man-made electromagnetic radiation (EMF) emitted by powerlines, electric wiring, electric home appliance and the wireless communication devices and networks. Sensitivity is characterized by a broad variety of non-specific symptoms that the sensitive people claim to experience when exposed to EMF. While the experienced symptoms are currently considered as a real life impairment, the factor causing these symptoms remains unclear. So far, scientists were unable to find causality link between symptoms experienced by sensitive persons and the exposures to EMF. However, as presented in this review, the executed to-date scientific studies, examining sensitivity to EMF, are of poor quality to find the link between EMF exposures and sensitivity symptoms of some people. It is logical to consider that the sensitivity to EMF exists but the scientific methodology used to find it is of insufficient quality. It is time to drop out psychology driven provocation studies that ask about feelings-based non-specific symptoms experienced by volunteers under EMF exposure. Such research approach produces only subjective and therefore highly unreliable data that is insufficient to prove, or to disprove, causality link between EHS and EMF. There is a need for a new direction in studying sensitivity to EMF. The basis for it is the notion of a commonly known phenomenon of individual sensitivity, where individuals' responses to EMF depend on the genetic and epigenetic properties of the individual. It is proposed here that new studies, combining provocation approach, where volunteers are exposed to EMF, and high-throughput technologies of transcriptomics and proteomics are used to generate objective data, detecting molecular level biochemical responses of human body to EMF.

Keywords: electromagnetic hyper-sensitivity; ELF-EMF; RF-EMF; survey studies; provocation studies.

Introduction

Phenomenon of sensitivity to electromagnetic radiation, like radiation emitted by e.g. electric wiring, electric appliances, power lines, wireless communication devices and networks, is commonly, and historically, known as electromagnetic (hyper)-sensitivity (EHS) or, with its newer scientific term, idiopathic environmental intolerance attributed to electromagnetic fields (IEI-EMF) [1]. Persons claiming to be EHS are commonly more concerned with the exposures to radiation emitted by base stations and Wi-Fi devices because the radiation exposure is involuntary, not possible to regulate by the unwillingly exposed person and it is continuous in the environment, lasting 24/7. Exposures of the EHS persons to cell phone handsets are often, mistakenly, of lesser concern to EHS persons because the user can decide how and when the radiation-emitting phone handset is used. The scientifically correct argument that the majority of radiation exposure received by the people comes from the phone handset [2] is often mistakenly overlooked. Scientific research of EHS consists of three types of studies:

– Survey studies, where examined persons are not exposed experimentally to EMF. Surveys examine the prevalence of the self-diagnosed EHS persons in the whole population and attempts to determine whether there is any link between EHS symptoms and the environmental or personal exposures to various sources of EMF.
– Provocation studies, where the self-diagnosed EHS or control volunteers are experimentally exposed to a single particular type of EMF, at well-known and monitored quantity. During or soon after the end of exposure the study subjects are being asked whether they feel any of the EHS symptoms to be induced

Article note: The numbering of references within the text citations includes all references in tables of supplementary materials.

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during experimental exposure or sham exposure and whether they are able to recognize when the radiation source is emitting EMF and when it is not.
– Biochemical and physiological studies, are looking for biochemical markers of EHS that are expressed in self-diagnosed EHS persons. The markers, selected for examination, are known to be likely associated with the symptoms in self-diagnosed EHS persons. Currently, in the biochemical studies, the examined self-diagnosed EHS persons are not exposed experimentally to EMF but they provide scientists with detailed information on what kind of EMF sources they believe cause their symptoms and what kind of physiological symptoms. Researchers in such studies attempt to determine whether any particular biochemical marker is expressed more or less prominently in the self-diagnosed EHS persons.

The above listed three types of studies have one overarching problem that is not addressed at all in EHS research. It is that the researchers analyze solely effects of exposures to EMF and do not address simultaneously occurring in real life exposures to other environmental pollutants, e.g. chemicals, particulate matter, radiations other than EMF. These environmental pollutants might act in concert with the EMF exposures what might lead in some cases to additive or even synergistic effects.

This review summarizes results of the to-date performed research on EHS, critically analyzes the obtained data and suggests the future directions for research.

Literature search

The following science databases were searched: PubMed (www.ncbi.nlm.nih.gov/pubmed), EMF-Portal (https://www.emf-portal.org/) and ORSAA (https://www.orsaa.org/orsaa-database.html).

The following terms used in searches: electromagnetic (hyper)-sensitivity (EHS), idiopathic environmental intolerance attributed to electromagnetic fields (IEI-EMF), provocation studies, ELF-EMF, RF-EMF.

Only peer-reviewed original experimental studies published in the English language until March, 2021 were considered.

Survey studies

The first approach, to find the prevalence of EHS, was to perform questionnaire surveys of the population. This approach has some major problems. The first one is that not all persons approached by scientists with questionnaire about health and EMF exposures, respond and return the questionnaire. Thus, even if scientists selected the most representative subset of population the results will be skewed because only the persons most interested in the research topic will respond to scientists' inquiries. Those with less interest or those not affected personally by EMF exposures might not respond, simply because of the lack of interest or lack of time. This, in turn skews results as the final population sample may significantly differ from the originally selected representative group, and EHS persons might be overrepresented in the examined population. Any estimates of EHS prevalence or potential impact of EMF on the prevalence of EHS become less representative of the population.

Another problem of surveys is that this approach was doable in the past. Currently it is more difficult to perform because of the omnipresence of devices emitting man-made ELF-EMF and RF-EMF in the living environment. The omnipresence of the EMF-emitting devices causes the difficulty to find a suitable control populations that could be compared with the exposed populations and with the self-diagnosed EHS sub-populations.

When reviewing survey studies, it is necessary to keep in mind that all survey studies claiming to examine prevalence of EHS in response to a certain type of EMF exposure are misleading because of the ubiquity of ELF and RF exposures in living environment. All persons examined in surveys are exposed to the particular EMF examined in survey but, also, exposed to a multitude of other EMF sources that might, or might not, have synergistic or additive effect on EHS symptoms.

ELF-EMF survey studies on general population and on EHS persons

Table 1 (see supplementary materials) presents ELF-EMF survey studies [3–35] published from 1985 till the present. Studies published in 1980s examined the effects of exposures to visual display terminals (VDT) and complaints of the VDT operators of e.g. headache, vision problems muscular discomfort or skin rashes. Several of the VDT studies found no excess of symptoms in VDT operators group vs. controls [26, 30, 32, 33], but other VDT studies found some correlation between the occupational-time spent in front of VDT and number of health complaints [29, 34]. There were also studies that have found differences in the occurrence of skin symptoms in VDT operators but, according to the study authors, these differences were related not to VDT-emitted radiation but rather to psychological differences between persons [24, 25, 27]. Overall, it remained unclear whether any of the health complaints of the VDT operators were due to the

VDT-emitted radiation or whether the health problems were caused by the long work hours in ergonomically inconvenient positions.

One of the VDT studies has examined a hypothesis that antioxidants (vitamins C and E and selenium) could alleviate symptoms of EHS in persons occupationally exposed to VDT [21]. Study has examined not only subjective self-reported symptoms but also objective, serum levels of uric acid and diphenylpycrylhydrazyl. Serum levels of these two biochemical markers did not show correlation with the self-reported EHS symptoms. The study concluded that the antioxidant therapy had no alleviating impact on the EHS symptoms.

Several studies examined, cancer-unrelated, effects of exposures to residential powerlines [28, 31] as well as occupational exposures of persons working at electrical power plants and transmission stations [3, 7, 8, 23, 28].

The study of 120 households in close proximity to powerlines and 120 control households were examined with questionnaire on symptoms like headache, migraine, depression and number of sick leave days and the distance from the powerline. The authors found that the health problems were more frequent in those living close to powerlines. However, the authors did not have any other objective measure except for the number of sick leave days [31].

Study of 152 women living in close proximity to electric transmission lines examined impact of the proximity to electric transmission line on the general health problems and on the worry associated with the proximity. It appears that the split between worried and not worried persons was 45–55%, respectively. Among the persons living farther from the electric transmission lines the prevalence of health problems was lower than in persons living in close proximity. However, as authors stated, there were several limiting factors that lessen the value of this study, such as recall bias, social desirability or the not examined at all hypochondriasis [28].

Studies of the occupational exposures of persons working in power plants or power transmission facilities used questionnaires asking for the number of the subjective self-reported symptoms like sleep problems, stress, depression, anxiety and general health. Study of 287 workers of electrical power transmission and distribution stations demonstrated no significant correlation between ELF exposures and health [35]. A small study of 40 workers of power substation in Iran has shown that, compared with control workers not exposed to ELF, the exposed workers had more problems with sleep and with general health [12]. The study of 854 workers of power plant in China has shown that occupational exposure to EMF was correlated with poor sleep quality and duration. However, there was no association with the overall duration of the occupational exposure or with the use of mobile phone [7]. Another study of 275 power plant workers has suggested that long-term occupational exposure to ELF MF may lead to depression, anxiety and poor sleep quality [3].

A French study has examined effects of occupational exposure to EMF generated by transformers [23] on the blood and blood cells' properties. The study found that occupational exposure for 8 h daily for 1–5 years to 50 Hz radiation has led to a decline in blood lymphocytes in general and to a specific decline of subsets of lymphocytes CD4, CD3 and CD2 with the concomitant increase in the number of NK cells. It also appeared that physiological changes were reversed when the exposure was terminated and re-appeared after the re-exposure. Unfortunately, the size of this study (13 exposed + 13 controls) is too small to draw any more generalized conclusions.

A number of studies used questionnaires to examine residential and personal exposures to multitude types of EMF (ELF and RF) that are present in nowadays human environment [4, 5, 9–11, 13–17]. Overall, as expected, the self-diagnosed EHS persons had significantly more health and quality of life complaints than the non-EHS persons. There was a tendency that women had more frequently the self-diagnosed EHS and more of the EHS associated non-specific health symptoms. The lack of objective metrics for EHS and relying solely on the subjective self-diagnosis of EHS made it problematic to correlate EHS symptoms with EMF exposures.

Two potentially meaningful, EHS survey studies were performed in Taiwan. Data collection for both of the studies was separated by the 5 years' time period. The first Taiwanese study, published in 2011 [14], has determined the prevalence of EHS in Taiwan to be 13.3%. The study performed 5 years later and published in 2018 [4] has shown a decline in EHS prevalence to 4.6% of the examined population. The study subjects of the research published in 2011 were only men whereas the study subjects of the research published in 2018 were both, men and women. Therefore, because the populations examined in both Taiwanese studies were this much different, the final result of the decline of EHS in Taiwan population from 13.3 to 4.6% is uncertain as it might have been caused by the differences between examined populations.

Overall, EHS surveys had relatively small sample size what diminished their scientific value. The exceptionally large group of examined subjects consisted of 10,605 persons [20]. Only few surveys had several thousands of participants [4, 5, 9, 14, 16, 19, 30], and the majority of studies had only few tens to few hundreds of participants.

The majority of the studied endpoints were non-specific and subjective symptoms, in some studies the list of symptoms was long, listing 43 [13] or even 68 [11] symptoms examined by a questionnaire. However, no matter how long was the list of non-specific symptoms, the problem was that these symptoms were subject to personal feelings and thinking of the study subjects. Thus, results of such EHS survey studies are difficult to judge and compare because the data in every study comes from different population and is subjective, not objective. The data might be subject to the particular set of participants, especially in the small studies, what might affect the conclusions of the study. Reliability of such studies is difficult to assess when the data, provided either directly by the study subjects or collected by the trained interviewing personnel, however, remains subjective and depending on the personal feelings and attitudes of the examined person at the time of examination.

Only two of the studies, listed in Table 1, have collected, besides the list of subjective non-specific symptoms, also physiological samples for biochemical evaluation [21, 23]. This is real problem because the vast majority of research on ELF effects on human physiology is not using objective measures of effects but is based nearly exclusively on subjective self-reported of health problems.

Unfortunately, there are also published studies that had a very small number of subjects what prevented reliable statistical analysis, even when there appeared to be some likelihood of correlation between ELF MF exposures and the non-specific symptoms [6, 8].

RF-EMF survey studies on general population

Table 2 (see supplementary materials) presents survey-type studies [4, 5, 9, 14, 16, 17, 36–50, 51–70, 71–97, 102–117], published from 1996 till the present, examining the possibility of causality link between RF-EMF exposures and the non-specific health symptoms experienced by the members of the general public. These survey studies have examined persons of different age, from 0 to over 80 years, but designations of children, adolescents and adults varied. In this review is used United Nations definition of age: children 0–10 years, adolescents 10–19 years and adults over 19 years.

One of the problems in evaluation of the data obtained in RF-EMF surveys is the long list of examined non-specific symptoms. These symptoms might be caused by a variety of stimuli and not solely the RF-EMF. The list of some over 70 symptoms, examined to a varying extent in the majority of the RF-EMF survey studies (alphabetical order):

> allergy, arrhythmia, back pain, bloated feeling in abdomen, blurred vision, bodily pain, chest pain, compulsive/obsessive behaviour, concentration capacity, concentration difficulties, conduct problems, dementia, depressive symptoms, discomfort during calls, dizziness, dryness of the throat, ear symptoms, emotional disorders, emotional problems, emotional role functioning, fainting, fatigue, flushing, forgetfulness, general health perceptions, headaches, hearing difficulties, heart palpitations, hostility, hyperactivity, hypertension, inattention, interpersonal sensitivity, irritability, lack of energy, loss of appetite, memory problems, mental health, migraine, muscular pain, nausea, neck or shoulder symptoms, neck pain, nervousness, numbness in the heed or face, pain abdomen, palpitations, paranoid ideation, peer relationship problems, phobic anxiety, physical functioning, physical ill-being, prickling in the ear, pro-social behavior, psychosocial well-being, psychoticism, salivary problems, sensitivity towards sounds, shortness of breath, skin symptoms, sleep – insomnia, sleep adequacy, sleep disturbance, sleep latency, social role functioning, sweating, tight feeling in chest, tingling fingers, tinnitus, tiredness, tremor, visual disturbances, vitality, warming of the ear.

All the symptoms lack precise definitions and are prone to individual interpretation by the study subjects. This long list of symptoms, examined in different combinations in different studies, shows how unspecific the survey inquiries were and how very subjective is the data collected in the to-date executed research on the RF-EMF effects on healthy or self-diagnosed EHS persons.

Several cohort studies examined effects of RF-EMF exposures on health. Possibly the largest cohort study that examined risk of nervous disease among Danish mobile phone subscribers, was based on the data from the Danish Cohort [97]. The study found small but significant increase in hospitalizations for migraine and vertigo and concluded that this finding should be further studied. The problem with the Danish Cohort studies on mobile phones is not only the lack of radiation exposure data but the use as a substitute the mobile phone subscription records. The RF-EMF exposure substitute data of Danish Cohort is of lesser quality than in the studies that used minutes of calling as a surrogate of radiation exposure [98, 99]. The COSMOS Cohort, has published to-date two studies based on the parts of the total cohort from Sweden and Finland. The Swedish/Finnish part of the COSMOS Cohort consisted of total 24,169 participants where 21,049 were from Sweden and 3,120 from Finland. The first study has examined headache, hearing problems and tinnitus [37] and the second study has examined sleep and sleep problems [36]. Both studies reported lack of correlation between operator-recorded mobile phone use and end-points examined in the study. However, there might be some concerns about the reliability of the results of these published already COSMOS Cohort studies [36, 37] as well as the future publications from the COSMOS Cohort. The reason is the fact that of paramount importance for the correct evaluation of data is the correct data on exposure to RF-EMF. Unfortunately, while there is some progress in the quality of the exposure data in COSMOS cohort study, as compared with e.g. Danish cohort study [100] or INRERPHONE case-control study [101], this progress is still insufficient to assure the reliability of the final conclusions because none of the used surrogates of radiation exposure is of satisfactory quality. INTERPHONE study used as surrogate of RF-EMF exposure minutes of calling, provided by the cases and controls from their own memory. This of course caused possible recall bias and especially the persons who developed brain cancer might have been recalling higher phone use than it was in reality. To avoid the recall bias, COSMOS cohort relies on the calling information from the network operators who provide the minutes of phone use by cohort participants. This removes some of the recall bias present in the INTREPHONE study [102]. However, it does not improve much the reliability of data analysis. In both, INTERPHONE and COSMOS, the surrogate of radiation exposure are minutes of calling by the participants. This information is insufficient to estimate the real radiation exposure of person. Mobile phones are designed to emit radiation depending on how far or how close the phone is to the nearest base station. Mobile phone being in close proximity to base station emits less radiation than the mobile phone being far away from base station (Figure 1). This means that two persons using mobile phone for the same length of time will be exposed to different doses of radiation, depending on their proximity to the base station. This means that in both, INTERPHONE and COSMOS studies, persons exposed to different levels of radiation are placed in the same exposure group for the statistical analysis because they used mobile phone for the same number of minutes. This likely leads to an underestimation of the effects (dilution of the effects) of radiation exposure in INTERPHONE and COSMOS studies. A relatively in small size, prospective cohort study on 3,396 adult students from China has examined the effects of using mobile phone, for over 4 h per day, on sleep parameters [39]. Conclusion of the study was that use of mobile phone for over 4 h per day caused sleep disturbance and that lessening the use of the mobile phone ameliorated the sleep problem. Another cohort study, the Dutch AMIGO cohort, was used to analyze whether perceived exposures to mobile phone RF-EMF, noise and air pollution have impact on appearance of non-specific symptoms. The cohort was sizable, 14,829 persons, and has shown that the perceived exposures were associated with higher scores on non-specific symptoms [43]. A South Korean study examined the correlation between the length of mobile phone calls (in minutes, self-reported) and occurrence of non-specific symptoms [48]. Increase/decline in the average length of phone call correlated directly with an increase/decline in headaches in women. The length of the call had no impact on e.g. stress, sleep, cognition or depression. A very similar results were obtained in earlier study from the same research team in South Korea [52]. Headache and related back pain was examined in small group (1,270) of persons that were part of the Dutch AMIGO cohort. It appeared that persons with perceived exposure to mobile phone base station, the perceived risk and health problems scored higher on the analysis of the non-specific symptoms caused by the base stations. It also appeared that female sex, young age and high education led to more concerns over the safety of base stations [41]. The Dutch AMIGO cohort was also used to examine effects of mobile phone base station on variety of non-specific health symptoms. Interestingly, analysis of 222 follow-up participants has determined that an increase in exposure did not correlate with ill health. However, perceived higher exposure was associated with higher symptoms reporting, what suggests that the radiation emitted by the base station was not the cause of the symptoms [47].

Several studies examined distance-dependency, from the nearest mobile phone base station, on the non-specific health symptoms [55, 58, 63]. These studies have examined only a very small number of persons living in close proximity to mobile phone base stations. The obtained results suggested that the distance from the base station might correlate with the frequency of the non-specific health symptoms. However, there were significant differences in the distance from base station to the dwelling that appeared to correlate with lesser impact on health symptoms: over 50 m [63], over 300 m [58], over 1 km [55].

An interesting, but small, study of the impact of mobile phone use and exposure to mobile phone base stations was published from Poland [40]. The obtained data suggested that exposures to base stations contributed to the occurrence of depression and that the conversations, using mobile phone, decreased the feeling of depression. This curious finding may suggest that the problem of depression and amelioration of it by talking on mobile phone is likely not caused by the radiation exposure.

Numbers of adult participants, in many survey studies examining effects of mobile phones and mobile phone base stations on induction of non-specific symptoms in healthy persons, were relatively small (below 1,000 persons) or very small (below 500 persons). These small group sizes, in combination with the broad array of non-specific symptoms, and the complete lack of real radiation exposure data

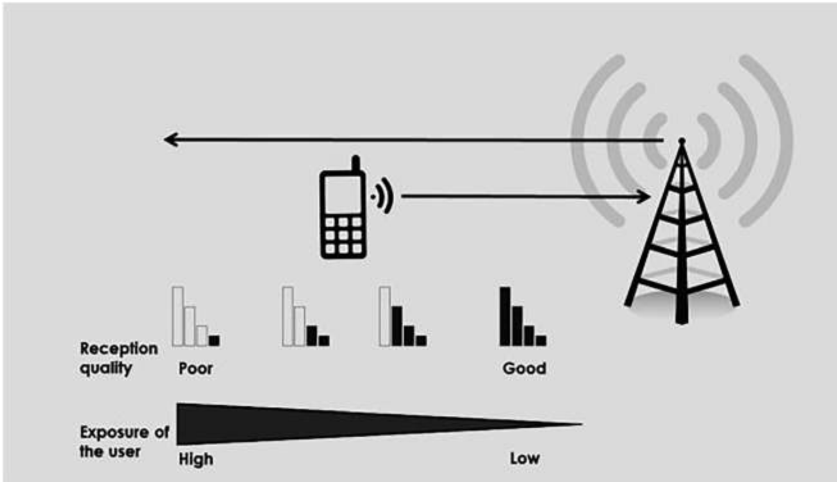

Figure 1: Correlation between the distance of the mobile phone user from the base station and the quality of reception and the level of radiation emitted by the mobile phone. The farther user is from the base station, the more radiation is emitted by mobile phone and exposure of the user to RF-EMF increases. Users in close proximity to base station are less exposed than the users located far from the base station.

makes it very difficult to draw reliable conclusions for the broader population [17, 40, 42, 44, 48, 52, 56, 58, 62–64, 66–68, 73, 75, 78, 79, 84, 85, 89, 95, 96, 102–113, 116].

The insufficient number of the participants in the survey studies becomes apparent in the meta-analysis study where results of 17 research studies were pooled together [74]. Combining survey participants from the 17 various studies led to analysis of total 1,174 cases, what means an average of only 69 cases per study [118–134]. Such a small size of the studies practically precludes drawing reliable population-related conclusions of effects or lack of these. It is also uncertain whether combining statistically non-significant data from 17 studies into one meta-analysis, will achieve statistically more reliable outcome.

An interesting study was performed in India but, unfortunately because of the very small sample size (178 adult persons) it is difficult to assess the significance of the results [50]. What is different from other studies is that usually persons that are selected for the studies are of good health. However, the study in India has selected persons with epilepsy and examined whether use of mobile phone will have effect on the frequency of seizures. Results indicated that over the one year of follow-up there was no significant impact of mobile phone use on the frequency of seizures. However, the usage of mobile phone by the persons with epilepsy was very low and this, not radiation exposures per se, might have contributed to the final result of no effect on seizure frequency. However, it is advisable that studies would use not only healthy volunteers but also persons with significant health problems. Such studies would provide evidence on whether the current safety limits protect users with health problems.

Children and adolescents were examined in several survey studies examining the effects of mobile phone and base stations emitted radiation [38, 46, 49, 53–55, 59–61, 65, 70–72, 77, 81, 83, 88, 94]. In general, these studies concluded that the various problems with sleep, behavior and learning correlate well with the years of use of mobile phone and with the daily length of mobile phone use but not necessarily with the exposure to RF-EMF radiation emitted by these devices.

There are also studies with unfulfilled expectations, possibly due to design or execution problems. Large study of 18,935 children, examined potential loss of hearing in small children, age up to 7 years, had inconclusive outcome due to, as stated by the authors, a variety of biases that were not accounted for [70]. A South Korean study that examined correlation between the attention deficit-hyperactivity disorder (ADHD), mobile phone use and lead exposure was also inconclusive as it was not possible to determine whether the ADHD occurred due to mobile phone use or due to the concurrently happening lead exposure [71]. Another inconclusive study in children came from Denmark, examined was correlation between mobile phone use and headache/migraine. Unfortunately, list of unexamined confounders, like watching TV, playing video games and use of computers, prevented scientists from making any reliable conclusions [72]. A series of studies from Germany, has specifically pointed out that the RF-EMF exposures in their studies were below the ICNIRP guidelines and that the observed symptoms, like fatigue, rather occurred by chance and were not caused by the radiation exposures [81, 83, 88]. Study from Sweden [95] has found out that girls use much more DECT phones than boys and that the most frequent symptoms correlated with mobile phone use are asthmatic symptoms, difficulties in concentration and headaches. However, the results are of little use as this study was solely explorative in nature and, as stated by the authors, unaccounted for many bias and confounding. An important opinion was expressed in an Iranian study in children. The results indicated a correlation between mobile phone use and several non-specific symptoms like: headache, myalgia, palpitation, fatigue, tinnitus, concentration problems, attention problems and nervousness. However the authors wrote: "*Imprecise definitions of the symptoms might have affected responses*" [77]. This lack of precise definitions for a number of non-specific symptoms is a larger problem because not only study subjects but also scientists might have collected data that is very subjective and prone to varying misinterpretations when there is lack of precise and commonly accepted definitions of what given symptom means and how it should be recognized. Of course, on top of the lack of precise definitions come problems with the measurments of the strength of the symptom. E.g. pain, that is a common part of the non-specific symptoms, has no method to measure it strength objectively. Every person is likely to have subjective and differing threshold for what they consider a strong or a weak pain.

RF-EMF survey studies of EHS persons

Table 3 (see supplementary materials) briefly presents survey studies [10, 11, 13, 15, 74, 135–146] examining causality link between RF-EMF exposures and non-specific symptoms in EHS persons. These studies attempted to find out what sources of RF-EMF (mobile phone, mobile phone base station, Wi-Fi), in what order of causality-importance and what type of symptoms, induce in persons claiming to be EHS. One of the problems with relating the symptoms with particular exposures is the fact that all study-participants lived in environments full of exposures to variety of man-made EMF sources. Singling out a particular radiation source, without detailed measurement of radiation from this and other sources, prevents making reliable conclusions on how the particular source of RF-EMF affects given EHS person. Another problem of exposures is that even when the radiation from a particular source is measured, still it is unknown how other concurrent EMF exposures affect, or not, the symptoms experienced by the study subjects, especially in subjects that are very EMF sensitive by own admission.

It has been known, and recently it has been confirmed by a research study [2] that the majority of RF-EMF exposure comes from the own mobile phone. Exposures from the mobile phone base stations and Wi-Fi are, in comparison, very small. Therefore, any studies on the effects of mobile phone base stations performed on study-subjects are likely to be biased or misinterpreted because of the concurrent exposures to mobile phones. While the scientists try to estimate levels of mobile phone base station's radiation output, they collect data where mobile phone radiation has, to various degree in different persons, affected the occurrence of non-specific symptoms.

One of the problems experienced by EHS persons is not only lack of tools to diagnose EHS but also lack of understanding, from health professionals, of what EHS is. A Dutch study attempted to examine how many EHS persons end up looking for advice from health professionals [51]. Study has shown that the majority of health professionals complain of being inadequately informed about EHS and, in general, on health effects of EMF. This might be one of the reasons why only a third of the occupational health professionals has ever been contacted by EHS sufferers.

Recently, has been published a new methodological approach to study responses of self-diagnosed EHS persons to RF-EMF exposures in regular daily life [137, 138]. EHS volunteers were equipped with exposimeter and electronic diaries. Exposimeters recorded, continuously, exposures to a broad spectrum of EMF in city environment and the occurrence of symptoms was recorded by EHS persons in electronic diary at the time of occurrence. This permitted to look for any time-correlation between exposure and symptoms. In the first very small study with 7 participants were found some correlations between perceived and occurred exposure and some correlations in respect of strength of the symptoms [138]. In the second study with 57 participants there was no correlation, on the group level, between exposures and symptoms. Only in one particular participant the correlation between exposure and symptoms was found [137]. This pilot approach might be the best way to proceed with evaluating correlation between symptoms and exposures. However, currently, the use of this method is limited by the size of the exposimeter (backpack-size) and by the cost of it. It would be very helpful if the rapid progress in miniaturization of the equipment could lead to speeding up of future studies where symptoms and exposures would be recorded concurrently and each EHS persons would be evaluated individually for his/her responses to specific exposures.

An interesting observation was made on differences between the self-diagnosed EHS persons recruited to experiments from the general population via Internet and recruited via Non-Governmental Organization [10]. It appeared that the persons recruited by the NGO had much stronger EHS symptoms than persons recruited as sensitive through the Internet call. This difference might cause bias affecting results in studies where researchers used different ways to recruit EHS volunteers.

Study executed in Finland, with a long list of 68 examined symptoms, and population sample of 194 EHS volunteers, has found that before the onset of EHS the most common health complaint were allergies [11]. However, after the onset of EHS the dominant health problems were nervous system related. The most of complaints were recorded for mobile phones and VDT. Avoidance of these devices provided the best help in alleviation of EHS symptoms. The other ways to alleviate symptoms were dietary change, nutritional supplements and exercise. Psychotherapy and medications were not helpful in alleviation of health symptoms. The possible bias towards the stronger health complaints was potentially caused by the sex composition of the participants, 37 men and 157 women, since women are known to more readily admit health problems than men.

Another study of self-diagnosed EHS persons came to the conclusion that in order to perform good quality study it is necessary to have a versatile interdisciplinary team of researchers [146]. Scientists measured the exposures of volunteers in their homes and found that while the radiation levels were within the current safety standards, in some participants (8 of 25) some of the reported health symptoms correlated with EMF exposure. In order to perform EHS studies correctly, team of psychology and psychiatry experts supplemented with experts in dosimetry was required. Such composition of research teams is, unfortunately, not the case in the majority of the published EHS research.

Another problem, besides the often lack of interdisciplinary approach, is the small number of EHS persons examined in surveys. Studies listed in Table 3 had at most less than 100 self-diagnosed EHS volunteers what caused problems in achieving statistical significance admitted by many authors. The proposed recently approach of examining individual cases seems to be the best way to resolve the problem of the low number of volunteers willing to participate in research studies.

Provocation studies of EHS persons

Research using provocation studies is dominated by the psychology-related approach and psychology methods. In such studies volunteers, either healthy controls or persons with self-diagnosed EHS, are exposed in a controlled setting to a particular type of EMF and asked what kind of symptoms of EHS they felt during and shortly after the exposure and whether they can recognize when the EMF exposure is on and when it is off.

The majority of to-date research on EHS that forms the basis for the WHO and ICNIRP opinions on sensitivity to EMF, are the provocation studies. Reliability of these studies, similarly to survey studies, is hampered by the subjectivity of the data. Both, the surveys and the provocations, rely on what the study subjects/volunteers said to feel when exposed to EMF or to sham exposures. Preformed personal opinions on EHS and subjective feelings of study subjects about the EHS and about the research team performing the study might have a direct influence on the subjective responses given to the scientists. This is a serious subjective-data-reliability problem that is not sufficiently addressed when determining the existence and the prevalence of EHS.

For tens of years people were complaining about health symptoms they experience in response to EMF. First there were powerlines and electric wiring at home and at work, then came computer screens (VDU) and most recently came mobile phones, mobile phone base stations and Wi-Fi. As shown elegantly by Dieudonne [140], the symptoms of EHS appear before the subjects start questioning effects of EMF on their health. Dieudonne has listed 7 stages how persons, experiencing non-specific symptoms which source clinicians are unable to determine and are unable to treat, are arriving at self-diagnosis of EHS: (1) onset of symptoms; (2) failure to find a solution; (3) discovery of EHS; (4) gathering of information about EHS; (5) implicit appearance of conviction; (6) self-experimentation; (7) conscious acceptance of conviction that the experienced symptoms are EHS caused by EMF exposures [140].

ELF-EMF provocation studies

Table 4 (see supplementary materials) presents ELF-EMF provocation studies [147–171]. The problem of this evidence are too small, for reliable statistics, groups of self-diagnosed EHS persons or healthy volunteers used as stand-alone experimental group or as controls for the EHS volunteers. The size of studies ranges from a single case study to studies of groups of slightly over 100 persons. Data obtained in studies with such small numbers of cases are insufficient for reliable statistical analysis. In some cases scientists themselves admitted that the low numbers affected sensitivity of the experiments [159].

As seen in Table 4, exposure conditions in all studies are very different in respect of devices providing exposure, the quality and quantity of exposure and the time-frame of exposure (length, continuous or on/off) as well as time-frame of post-exposure inquiries about symptoms and perceiving of the exposure. This large variability of experimental conditions makes direct comparisons between the studies as well as meta-analyses very difficult if not impossible statistically.

Examined endpoints were mostly subjective feelings and health symptoms self-described by the volunteers. Only very few studies included in their evaluations also objective measures of the effects as, e.g. EKG or EEG, histopathology or biochemical markers. Both, objective and subjective endpoints appeared to have mostly no correlation with ELF exposures. Also, one result appears to be common for all studies. The subjects, no matter whether self-diagnosed EHS or healthy controls, were not able to recognize when the exposure was on and when it was off.

However, even though the ELF provocation studies showed largely no correlation between the examined battery of symptoms and ELF exposures, it might be that the studies were in some ways insufficiently sensitive and accurate to detect effects of ELF exposure. It is possible that when examining group of cases the statistical analysis shows overall no effect but some of the individual cases might in fact respond to ELF. Some of the case-studies have shown a possibility that some persons might respond to ELF exposure.

A single case study executed in USA by the team of Andrew A. Marino [155] observed effect of 60 Hz electric field on self-diagnosed female physician. In a double-blind study, subject experienced temporal pain, headache, muscles' twitching and skipped heartbeats. The symptoms were caused not by continuous exposure but by the field transitions (off–on, on–off). However, like in other provocation studies, the subject was not able to feel the ELF field consciously but only through the experienced symptoms.

However, not always the single cases, claiming to be affected by ELF exposures, are indeed affected in blinded experiment. In a single-case study in Sweden, a plumber complaining of severe EHS was examined in blinded provocation studies [169]. The whole-body exposures to electromagnetic coil using random mix of sham, 34 μT or 100 μT did not cause any EHS symptoms or were not recognized when field was on or off. Interestingly and importantly, after the plumber was informed about the outcome of the experiment, he was able to return to his work. The author suggested that this kind of examinations might help some EHS persons to understand that sometimes EMF exposures might not be the cause of their particular health problem.

In a case study, performed on two persons complaining of skin-related effects from occupational exposures to video terminal unit (VDU), scientists examined the presence of the mast cells in skin biopsies [170]. It was possible to correlate the disappearance of the somatostatin positive mast cells with the end of exposure to VDU. The authors concluded that it is likely that the decline in the number of mast cells in skin biopsies is due to the disappearance of the somatostatin positive mast cells. This might explain the lessening of the clinical skin symptoms such as itch, pain, edema and erythema upon termination of exposure to VDU. It appears that in these particular two EHS cases it was possible to correlate the VDU exposure with the objective data from the histological and physiological examination of the skin.

However, a double blind provocation VDU study on 12 EHS persons and 12 matching controls has shown lack of effect on mast cells and inflammatory mediators [163]. Blood samples were analyzed for number of stress biomarkers like melatonin, prolactin, adrenocorticotrophic hormone, neuropeptide Y, and growth hormone, and the expression of different peptides, cellular markers, and cytokines (somatostatin, CD1, factor XIIIa, and tumor necrosis factor-alpha). Skin biopsies were also analyzed for the occurrence of mast cells. The outcome of the study was negative. Study subjects were not able to recognize when the exposure was on and when it was off. Also, there was no significant differences in examined biomarkers of stress. Similar lack of effect of ELF exposure on blood stress markers was observed in double blind provocation study on 17 EHS persons [168]. Blood analysis for the presence of prolactin, cortisol, dehydro-epiandrosterone, and cholesterol levels has shown lack of any effect from the ELF exposure.

The opposing results obtained by the studies that examined the same marker of the stress – presence of mast cells in skin biopsies following exposure to VDU – suggest that the single case evaluations might be a better way to find sensitive persons. Analyses of larger groups of EHS persons might mask the presence of a single sensitive person within the group [163, 168, 170].

Some of the old and some of the newer studies that examined biochemical markers of stress have come to no-effect conclusions. A study of effects of VDT on stress markers in group of 36 women and one man (students) has observed lack of the effect of exposure on the levels of biochemical markers, 8-hydroxy-2-deoxyguanosine and chromogranin A. The study concluded that while the work with VDT leads to mental fatigue, it is not a health effect per se [158]. The study on men working on powerlines lines has examined series of blood hormones, thyroid stimulating hormone, luteinizing hormone, follicle stimulating hormone, prolactin, cortisol, neopterin, testosterone, and found no effect of exposure [171].

One of the ELF provocation studies has examined impact of nocebo on the appearance and experiencing of EHS. Experiments performed on 40 university students have indicated that the psycho-social factors may play a dominant role in becoming an EHS person, through an enhanced risk perception and expectations, self-monitoring, somatization and somatosensory amplification [156].

Taken together, the majority of the ELF-EMF provocation studies have not found correlation between effects of exposures and the examined subjective endpoints. Examination of the objective endpoints, like various biomarkers of stress in blood samples, provided mixed evidence of the effects. It might be reasonable to continue research looking for single cases that clearly respond with subjective and objective endpoints. Analyses of groups of EHS, no matter how well set up, might miss the single cases in the "crowd" of non-responders.

RF-EMF provocation studies

Table 5 (see supplementary materials) presents a number of provocation studies where volunteers were exposed to RF-EMF at the levels of mobile phone or mobile phone base station, Wi-Fi or TETRA radio [122, 124–129, 131, 132, 134, 150, 170, 172–190, 191–210, 211–231]. Additionally, in recent years, a number of studies have examined whether nocebo effect might be responsible for the onset of EHS symptoms.

Provocation studies examined causality link between RF-EMF exposure and symptoms of EHS by exposing volunteers to RF-EMF in controlled conditions. Radiation exposures lasted from few seconds or minutes to few hours and were, with a few exceptions, of the power level that was in compliance with the international safety guidelines. Study subjects were asked of their feelings and symptoms and whether they are able to determine when the radiation is on and when it is off. The majority of such provocation studies have not found causality link between symptoms of EHS and exposures to RF-EMF. Also, commonly, the study subjects were unable to correctly recognize when the radiation exposure is on and when it is off.

The majority of the provocation studies were performed in research laboratory. However, some of the studies attempted to improve radiation exposure conditions by performing experiments in subjects' home setting. Only a few studies have measured biochemical endpoints to provide objective experimental data.

Studies performed at home of the volunteers attempted to mimic as closely as possible real everyday exposures of the volunteers. Leitgeb and co-workers [209] performed study on 43 subjects, who were deeply convinced that RF-EMF exposures cause their sleep problems. Experiments were performed at homes of the study subjects under a real environmental conditions. The study did not found any EMF-dependent sleep disturbances and volunteer-specific analysis of data did not show any significant effects of exposure. Similar approach of exposing volunteers at home was used in recent Australian study, co-authored by an international team of EHS experts [179]. The study was performed using only three subjects because of the recruitment problems. Severity of symptoms experienced by the study subjects was assessed with a visual analog scale. Additionally, study subjects were asked about the RF-EMF field perception. Obtained data did not show significant difference between exposure and sham conditions. Volunteers were also unable to correctly recognize when the exposure was on and when it was off. Furthermore, the belief that exposure was on has correlated with the severity of symptom scoring on analog scale.

The same Australian team attempted to elucidate the mechanism regulating alpha EEG activity in persons exposed to RF-EMF [176]. Besides the measurement of EEG, researchers measured skin temperature in 8 different sites. Exposures were performed at SAR of 1 and 2 W/kg. In both exposure conditions there was a small increase in temperature of the finger's skin. This made the researchers to propose that the RF-EMF exposure-induced change in EEG is a thermal effect. It also was suggested that this small thermal effect is ameliorated by the radiation safety guidelines that should protect against thermal effects of exposures. Unfortunately, this explanation might be premature. First of all, SAR levels that were used in experiments might cause small temperature increases of 0.1–0.3 °C. Thus, the small increase in temperature of the finger's skin is not surprising. Safety guidelines protect from the thermal effects but it relates to much stronger increases of temperature by more than 1 °C. Australian team observed the increase of the temperature in the range of 0.1 °C, what means that this kind of small increase is not being alleviated by the current international safety guidelines.

On the other hand, the lack of effect of RF-EMF exposure on EEG was observed in study of healthy volunteers treated by a variety of exposure protocols at 1,800 MHz [221]. The authors did not observe any effects on EEG and subjects did not report any remarkable sensations during the exposure. It was also concluded that there was no evidence for athermic (non-thermal) effects of the exposure.

Another study has examined changes in the skin temperature in response to EMF exposure to TETRA field [188]. In this blinded study, using healthy volunteers, exposures at SAR of 1.5 W/kg had no effect on skin temperature. Exposures at high SAR of 6 W/kg have increased skin temperature by 0.8 °C, but this increase of the skin temperature was not recognized, felt, by the study subjects.

Only few studies had examined objective endpoints, of the response to RF-EMF, by measuring biochemical markers. Hillert and co-workers [125] have performed biochemical blood analysis and determined the values of erythrocyte sedimentation rate, white blood cell count, electrolytes, glucose, liver function enzymes, thyroid stimulating hormone, creatinine, cortisol, prolactin, and hemoglobin. There was no significant difference between exposed and non-exposed groups in examined biochemical markers. It was also observed that the belief that RF-EMF exposure was active led study subjects to experience skin symptoms. In another study [213], has been found difference, between the unexposed cases and controls, in the presence of such biochemical markers as substance P, TNF R1 and brain derived neurotrophic factor BDNF. However, exposure to RF-EMF had no effect on the examined biomarkers.

A case-study from Australia [228] has demonstrated that, if determined correctly, analysis of a single person-case might provide reliable evidence to support the existence of EHS. In this single case study, has been examined a 34 years old female journalist complaining of dysaesthesiae, an abnormal unpleasant sensation felt when touched skin, caused by damage to peripheral nerves. During experiment, the subject spoke on the phone wrapped in a thin layer of polystyrene, to avoid heating effects. The symptoms of dysaesthesiae appeared after ca. 7 min of the mobile phone use. The authors concluded that there might be neurological basis for some cases of the dysaesthesiae, and that dysaesthesiae in some of the cases might be associated with the use of mobile phone. The cause of the dysaesthesiae appeared to be non-thermal. The study by Hocking and Westerman [228] suggests that evaluation of groups of healthy or EHS volunteers might hide effects experienced by single cases within the group. Finding and examining such single cases, consistently responding to EMF exposures, might help in search for the proof of EHS existence and for the causality link between EHS and EMF exposures.

As the provocation studies were unable to find causality link between symptoms of EHS and exposures to EMF, scientists begun to look for other, radiation unrelated, explanations for the symptoms experienced by self-diagnosed EHS persons. A number of studies have examined possibility of a link between a nocebo and EHS symptoms [172, 174, 175, 178, 181, 192]. In such studies, healthy volunteers were shown either movies presenting dangers of EMF exposures or neutral films. Afterwards, when exposed to sham EMF, persons that saw film on dangers of EMF exposures have experienced more frequently non-specific symptoms, like these experienced by the self-diagnosed EHS persons. This outcome has been used as an argument that there is no link between EMF exposures and EHS symptoms but that the alarmist presentations in the news media may cause some people to develop non-specific symptoms of EHS.

Biochemical and physiological approach studies of EHS persons

With very few exceptions, the majority of research on EHS has examined a diverse variety of subjective endpoints, based on the feelings experienced by study subjects during or after exposure. Experimental data collected in such studies is likely biased because of the strong individual-dependent subjectivity of responses provided by each study subject. Relying solely on such subjective database of effects might lead to bias in evaluation of the results of the studies and cause dismissal of the EHS because the feelings-based data is too diverse and has too much of internal variability to provide statistically significant results.

In order to acquire objective data from the examination of the EHS subjects it is necessary to complement the feelings-based non-specific and subjective data with the objective data from examining biochemical changes in response to EMF exposures.

As shown in Tables 1–5, only a very few studies of EHS have examined biochemical markers [21, 23, 125, 163, 168, 170, 204, 213]. This data lacks systematic approach and, because of its scarcity, is still insufficient to provide scientifically reliable data on the biochemistry and physiology of EHS.

A study from Sweden has examined whether RF-EMF affects human blood-brain barrier and blood-cerebrospinal fluid barrier. As markers of leakage were measured blood levels of transthyretin and S100B protein [232]. The obtained results were not statistically significant with the exception of the transthyretin sample analyzed 1 h after end of exposure. Overall, scientists were unable to explain whether the observation had any clinical or diagnostic significance.

Levels of salivary and urinary markers in 30 EHS and 25 controls were analyzed by Andrianome and co-workers [233]. Quantified were cortisol in saliva and urine, alpha-amylase (sAA), immunoglobulin A and C Reactive Protein levels in saliva and neopterin in urine (uNeopterin). Only saliva alpha-amylase was found to be significantly higher ($p<0.005$) in the EHS group, what suggests that the sympathetic adrenal medullar system might be activated. Balakrishnan and co-workers [234] examined blood samples of heavy users of mobile phones and determined that the serum levels of C-reactive protein and Hsp70 as well as the gene expression of hsp70 were significantly increased as compared with controls. Dahmen and co-workers analyzed blood samples of EHS patients and found significantly lower TSH and higher alanine transaminase – and aspartate aminotransferase. Some EHS had also elevated levels of C-reactive protein. Authors concluded that EHS might not be a single disorder but rather a complex mixture of different etiology [235]. Markova and co-workers have examined effects of mobile phone radiation, *in vitro*, on lymphocytes from EHS persons. RF-EMF appeared to affect chromatin conformation and 53BP1/gamma-H2AX foci in way similar to thermal shock. However, there was no difference in responses of leukocytes from control and EHS patients [236]. The clinical and/or diagnostic significance of these biochemical observations remains still unknown.

The largest effort to determine biochemical changes in EHS persons was performed by the team of Belpomme and co-workers [237–239]. However, the French team did not examine effects of EMF exposures per se because the study subjects were not exposed experimentally to EMF. Assumption that EMF, was the cause of the non-specific EHS symptoms, was based entirely on the self-diagnosis stories of the EHS persons, provided to the research team. The French team, using biochemistry/physiology approach, has claimed that not only EHS is proven to be caused by EMF exposures but they claimed to identify biochemical markers of EHS, that could be used in clinical diagnosis of the EHS.

The first experimental study by the French team was published in 2015 [237]. The authors indicated that the collection of physiological samples and interviews with the self-diagnosed EHS persons begun in 2009. The cohort consisted of 1,216 persons of whom, for not explained reasons, only 727 were analyzed in this study. Remaining, the unanalyzed persons, were excluded by some not precisely described criteria, including unspecified pathologies discovered after their enrollment in the study. According to the authors, the cohort consisted of persons from different European countries (not specified in detail) as well as from the USA, Canada, Australia, Russia, China, Middle East and Africa. Selection of EHS persons for the study was claimed to be done in face-to-face interview, using a validated pre-established questionnaire. However, the questionnaire as well as its validation method were not presented in the article. French team has used several criteria to exclude/include cases for the research shown in Table 6, with some critical comments. Considering large geographical dispersion of the cohort, the authors did not explain how the biological samples were collected, stored and analyzed while preventing the potential degradation of the sensitive biological material. There is also lack of explanation whether the cohort members themselves approached scientists or whether they were, in a balanced way, pre-selected by the research team using some, unspecified in the article, criteria. The way of collecting the cohort is of importance. The authors claim that the females are more susceptible to develop EHS. As proof of this claim they stated that for this reason the cohort has more females than males (495 women vs. 232 men). The claim of the higher susceptibility of women, in this particular study, might be questionable because the higher number of participating women might be just a selection bias. It might be caused by the higher number of self-enrolling women to the cohort.

The working hypothesis of the French team was that environmental factors, such as EMFs and/or chemicals, induce neuro-inflammation and oxidative stress in the brain, leading to disruption of the blood-brain barrier (BBB). While there are experimental studies in animals [240–242] and *in vitro* [243] suggesting that BBB might be affected by the EMF exposures, none of the studies has shown it to occur in humans. In agreement with the working hypothesis the health status of the participants was analyzed with battery of physiological tests for which there is lack of information to assure reliable quality of sample collection and analysis, especially in the context of the geographical spread of the cohort. Biochemical tests analyzed the following endpoints, thought to fit well the working hypothesis presented above: high-sensitivity C reactive protein (hs-CRP), Vitamin D2-D3, histamine, IgE, protein S100B, nitrotyrosine (NTT), heat shock protein 70 (HSP70), heat shock protein 27 (HSP27), Aati-O-myelin autoantibodies, hydroxy-melatonin sulfate (6-Ω), and 6-Ω/creatinine. In addition to the biochemical tests, the authors analyzed blood flow in the temporal lobes and determined the pulsometric index (PI) using a non-invasive method of ultrasonic tomosphygmography.

The changes in expression of the examined biochemical markers did not occur in the majority of the patients but only in a relatively small proportion of persons with self-diagnosed EHS, multiple chemical sensitivity (MCS), or persons with both ailments (EHS + MCS). The proportion of examined persons with the increased expression of the biochemical marker has been used by the authors to claim that the statistical significance of the change in examined

Table 6: Criteria used by French team [237] and comments [author of this review] concerning the validity and applicability of the criteria for the selection of EHS persons for the study.

French team's criteria	Comment
Absence of known pathology accounting for the observed clinical symptoms	Potential cause of selection bias. Some diseases and ailments might predispose patients to be more, or less, sensitive to EMF exposures
Reproducibility of symptom occurrence under the influence of EMFs and/or multiple chemicals whatever their incriminated source	Claim of reproducibility of the symptoms, whenever the exposure happens, is based solely on the opinion of the volunteer. Subjective claim, not confirmed by the scientists
Regression or disappearance of symptoms in the case of EMF and/or multiple chemical avoidance	Claim of regression and of disappearance of symptoms is based solely on the opinion of the volunteer. Subjective claim, not confirmed by the scientists
Chronic evolution	Claim of the chronic evolution of symptoms in the presence of exposure is based solely on the opinion of volunteer. Subjective claim, not confirmed by the scientists
Symptoms such as headache, superficial and/or deep sensibility abnormalities, skin lesions, sympathetic nerve dysfunction, reduced cognitive ability including loss of immediate memory and attention and/or concentration deficiencies, insomnia, chronic fatigue and depressive tendency, all main clinical symptoms reported as non-specific symptoms in the scientific literature, but which when grouped together may evoke clinically the diagnosis of EHS (data not shown)	Variety of symptoms listed but without any data support. The scientists specifically mentioned that "data not shown"
No serious pre-existing pathology such as atherosclerosis, diabetes, cancer; and/or neurodegenerative or psychiatric diseases which have been associated with EHS and/or MCS in the past or at the inclusion time but would render difficult the interpretation of clinical symptoms and biomarker data (see Section "EHS/MCS as a possible sentinel pathological disorder")	Potential selection bias. Some pathologies might predispose person for EHS. Such volunteers should be used in studies but analyzed separately from other EHS volunteers
For each patient written informed consent. Study of this large cohort of patients was not a case-control study neither a randomized study so there was no specific control group	Lack of controls leads to lack of baseline of the effects observed in EHS persons and makes the size of the observed effects unverifiable

markers is a possible clinical detection of EHS. For example, the authors presented claim that histamine is the key molecular marker of EHS. However, only 40% of self-diagnosed EHS persons had an increase of histamine level. None of the remaining stress factors was highly prevalent in EHS persons: hs-CRP increased in 15% of EHS, vitamin D2–D3 declined in 23.2% of EHS, histamine increased in 40% of EHS, IgE increased in 22% of EHS, protein S100B increased in 15.5% of EHS, nitrotyrosin (NTT) increased in 29% of EHS, Hsp27, Hsp70 detected in 7–19% of EHS, antibody to O-myelin detected in 17–29% of EHS, melatonin to creatinine ratio declined in EHS but the variation was too large to provide a specific number for the ratio, pulsatility declined in 50.5% of EHS, but data for the pulsatility were not shown by the authors in the published study. Furthermore, the authors did not specify whether there was any overlap in the changes of the expression of different markers and whether there was any EHS person that expressed majority or even all of the examined biochemical markers. Most importantly, there was not presented evidence that any of the markers was induced by EMF exposure or affected by EMF exposure

The French team concluded that EHS and MCS were both associated with the same abnormalities, based on the analyses of biochemical factors. Furthermore, the French team suggested that both pathologies, EHS and MCS, share a common pathophysiological mechanism. It might be so, but it remains unproven based on the provided evidence. It also might be that the groups of self-diagnosed EHS patients and self-diagnosed MCS patients are cross-contaminated because of the possible incorrect self-diagnoses. Thus the claim of common pathophysiological mechanism is uncertain, at the best, and it requires a better supportive evidence.

The French team has proposed pathophysiological model for the development of EHS (Table 7; with critical comments). However, without the evidence linking EMF exposures with the occurrence of non-specific symptoms and biochemical markers, claimed to be manifestations of EHS, this proposed model of mechanism remains unproven.

Table 7: The proposed pathophysiological model for the development of EHS [237] with comments [author of the review].

Steps of the proposed mechanism of EHS	Comment
Under the influence of EMF, a cerebral hypoperfusion/hypoxia-related neuro-inflammation may occur	The authors did not demonstrate that EMF exposures lead to cerebral hypoperfusion or neuro-inflammation. This link is claimed only because of the self-diagnosis of EHS persons. If self-diagnosis is incorrect the whole mechanism collapses
Due to the release of histamine and other mediators the blood-brain barrier stability is disrupted and an increase in permeability may result from the oxidative and/or nitrosative stress	The authors did not examine impact on BBB. Only 40% of the self-diagnosed EHS had an increased blood level of histamine. The other 60% did not have increased histamine levels. Possibility that they might have local release of histamine is only speculation, not supported by the data
Circulating inflammatory cells could pass through BBB and enter the brain to initiate a vicious circle which may considerably amplify the neuro-inflammation process	No evidence presented
Because of oxidative and nitrosative stress and subsequent decreased melatonin bioavailability and autoimmune response, physiological defense mechanisms are weakened making EHS and/or MCS patients to be potentially at risk of developing chronic neurodegenerative diseases and cancer	No evidence presented

The second experimental study from the French team was published in 2018 [238]. In this study has been presented evidence to support the establishment of the diagnostic criteria for distinguishing the EHS persons from the non-EHS persons. The French team has examined the list of 23 symptoms that might distinguish an EHS from a non-EHS person. The data was presented solely as a percentage of persons having the examined EHS symptoms. For the majority of symptoms in non-EHS persons (14 out of 23) the percentage equaled 0%. For each symptom, the authors claimed the p-value was calculated. Unfortunately, from the presented data it was not possible to determine the reliability of the presented p-values, because the occurrence of symptoms was presented only as a single percentage number. For example, for the symptom of headache, the value for EHS persons was 88% but for non-EHS controls it was 0%, as if non-EHS persons would not suffer of headache at all. But, puzzlingly, the p-value presented for the headache is shown as highly statistically significant of $p<0.0001$, which claim is not verifiable due to the lack of data. The same goes for the claim that the pulsatility index of brain's front lobes declines in EHS persons. French team did not present any evidence linking changes of pulsatility with past EMF exposures. The claim that anyone having a decline in pulsatility index suffers of EHS has not been proven.

In the diagnosis of EHS, French team has relied solely on the self-statements of the self-diagnosed EHS persons [238]. Interestingly, the patients claimed to get symptoms of EHS during exposures to EMF and the symptoms subsided when avoiding exposures. Acceptance of this claim as such, without any objective evidence, would mean that the French team has found several hundreds of persons that are able to feel EMF exposures. However, French team did not present any experimental evidence that would validate this claim. Furthermore, this claim is in clear contradiction with the results of the majority of the psychologic provocation studies where EHS persons were unable to recognize active EMF exposure.

The third experimental study from the French team was published in 2018 [239]. In this study, as the inclusion criteria for study subjects were the self-diagnosed EHS combined with the pulsatility index and with the four markers of the oxidative stress: plasma histamine, serum protein S100B, serum Hsp70 and serum Hsp27. The study subjects were not exposed to EMF but the causality link of EHS with EMF was based solely on the self-diagnosis of EHS. The study presented a very long speculation of how the oxidative stress may influence normal physiology. However, there was not presented any evidence that would demonstrate that the oxidative stress is caused in the self-diagnosed EHS persons by the past EMF exposures, or that the oxidative stress induced by exposures affects overall physiology of EHS persons. The same applies to the pulsatility index – it has not been shown that pulsatility index is in any way affected/connected to EMF exposures. It remains unknown what has caused the decline in the pulsatility index observed in the self-diagnosed EHS persons.

Recently published review article on use of the ultrasonic tomosphygmography in detection of EHS does not produce any evidence to back up claim that EHS is detectable by ultrasonic tomosphygmography detected changes in pulsatility of the brain's front lobes [244]. The author, of this review, solely refers to the opinions presented in articles of the French team [237–239], claiming that pulsatility and oxidative stress were proven to be markers of EHS. They were not.

In summary, research studies examining different biomarkers in EHS persons have the problem of the lack of evidence showing correlation between the EMF exposures and the biomarkers considered as the biomarkers of EHS. The selection of the study subjects has relied solely on the opinion presented by the self-diagnosed EHS person. The scientists do not have knowledge whether the self-diagnoses of EHS are correct or not. The scientists do not know whether the EHS group is contaminated by the incorrectly self-diagnosed EHS persons, and, if so, to what degree. As proposed by Dahmen and co-workers, EHS might not be a single disorder but rather a complex mixture of different etiology [235]. Because of that, it is important to determine whether any of the examined biomarkers is in any way correlating with past or present EMF exposures. Without this knowledge, it might be very difficult to study EHS biomarkers when scientists examine simultaneously several different etiologies.

Does EHS exist?

Collectively, the to-date executed studies were unable to prove causal link between EHS and EMF exposures. However, there are several indicators suggesting that individual sensitivity to EMF might exist. There is a well-known, and scientifically well-established, phenomenon of the individual sensitivity [245]. Individual sensitivity means that, because of the genetic and the epigenetic differences between people, different persons may have different sensitivity to the same agent, whether it is natural or man-made, radiation or chemical. The phenomenon of the individual sensitivity to radiation is well known for ionizing radiation [246, 247], for non-ionizing ultraviolet radiation [248, 249] and for ultrasound [250].

In respect of the EMF exposures, several studies have shown that individual differences might led to individual sensitivity to EMF. Epidemiological case-control study, Interphone, has shown that only some of the persons in the highest exposed to mobile phone radiation group have developed brain cancer. The recent study from the National Toxicology Program (NTP) in USA has shown that in the highest exposure group, where radiation dose received by animals (rats) was very high only few rats from this highly exposed group have developed cancer. There are also laboratory studies on *in vitro* exposed cells showing that different cell types may have different sensitivity to EMF exposures [251–253]. Therefore, it is scientifically justified to suspect (assume) that the individual sensitivity maight also exist for the EMF exposures. However, the essential, but still unanswered questions are:

- what are the levels of EMF that are tolerated without adverse health effects by the majority of the population and,
- what are the physiological pre-conditions (e.g. health status) for the occurrence of the higher sensitivity to EMF and,
- what counter-measures need to be considered to protect those more sensitive and vulnerable to EMF exposures.

Therefore, there is discrepancy between the probability of EHS existence and the outcomes of the EHS research studies. If the logical argument supporting existence of EHS is correct then there might be problems with the quality of the design of the EHS research studies.

Quality of the EHS research

As presented above, there are several common problems with the to-date executed EHS studies. These problems are:

- the majority of research data is subjective and describes non-specific symptoms
- lack of objective markers of EMF effects
- low numbers of EHS volunteers participating in the studies what might cause selection bias
- very large diversity of EMF exposure protocols
- acquiring data, either during the exposure or soon afterwards, precludes look at the late or chronic effects.

In 2019 a review study analyzed methodological limitations of the to-date performed psychological provocation studies [254]. It has presented an extensive list of 13 possible biases and errors in psychological provocation studies. However, some important potential biases were not considered by the authors of the review.

The list of bias presented in Schmiedchen and co-workers [254] was as follows:

(1) Was the level of EMF exposure and method of blinding appropriate?
(2) Were individuals excluded whose symptoms may be explained by somatic diseases or mental disorders?
(3) Was the contrast in the severity of symptoms between situations with/without exposure verified?

(4) Were EMF exposures (type of exposure source, frequency range and exposure level) applied that individuals associate with their symptoms?
(5) Were exposure durations and assessment times applied that matched the time scales for the symptoms to appear?
(6) Were the symptoms registered in the trials matched with those experienced in everyday exposure situations?
(7) Was the background exposure level controlled and minimized?
(8) Was the exposure level controlled?
(9) Were the intervals between exposure sessions sufficiently long to allow for recovery and to avoid carry-over effects?
(10) Were biases related to sequence and period of the exposure conditions minimized (for studies with cross-over design)?
(11) Were biases related to confounders and cofactors minimized (for studies comparing parallel groups of IEI-EMF participants with different exposure conditions)?
(12) Were biases minimized that are related to attrition and to incomplete data included in the analysis?
(13) Was bias related to selective outcome reporting minimized?

Only 28 of the to-date published EHS psychological provocation studies was considered by the review authors to be of sufficient quality for the inclusion in the review. These 28 studies were considered to be methodically sound. As stated by the authors, these methodically sound studies indicated that an effect of exposure is unlikely. The authors speculated that, even if the physical effect exists, it must be either very weak or affects only small number of individuals.

This review [254] shows how very imperfect is the research on EHS because of the identified 845 studies only 28 were selected as of eligible quality, after fulfilling the 13 criteria. However, after all, these 28 studies that passed the 13 quality criteria were not of good quality as judged by the authors of the review:

> Seven (25%) studies included in this review reported elevated or reduced symptom levels upon exposure to EMF, while the majority of the studies (n=21, 75%) did not find evidence for exposure-related effects in IEI-EMF individuals. Study outcomes, i.e., positive or negative results, were not restricted to specific types or frequency ranges of exposure.

It means that only 7 studies have shown either positive or negative effect. Such extremely limited evidence is insufficient to claim that EHS exists or that EHS does not exist. It is also far too little of the data to speculate about lack of restrictions towards any specific frequency ranges of exposure. The final recommendation of this review was that further experimental studies should be performed preferably at the individual level and not like it was mostly done till now, on group level where small effects might have remind hidden when examining larger group of EHS individuals together. This recommendations strengthens the notion that it is very likely that the groups of self-diagnosed EHS volunteers are contaminated, to the unknown degree, by the falsely self-diagnosed EHS persons that suffer of the non-specific symptoms that are caused by other than EMF exposures.

The major quality and reliability problems of the to-date performed EHS studies (surveys, provocations and biochemical studies) that were not included in the review by Schmiedchen and co-workers [254] is that the obtained experimental data is mostly subjective and not objective information.

Recent review of the hypotheses explaining occurrence of EHS has examined three types of hypotheses examined in studies of EHS [255]:
(1) The electromagnetic hypothesis – EMF exposures cause EHS, in particular, the non-thermal effects induced by EMF
(2) The cognitive hypothesis – false assumption that EMF causes symptoms of EHS that assumption is potentiated by the nocebo effect
(3) The attributive hypothesis – symptoms are being explained by EHS to cope with the symptoms of unknown and unexplainable origin

It was suggested that all three hypotheses might be correct and that several sub-groups of EHS sufferers might exist:
- those that respond to EMF exposures from some of the EMF-emitting devices and have EMF-induced health problems
- those that believe in harm caused by EMF devices and this belief causes their health symptoms
- those that have health problem that medical doctors fail to identify its source and persons attribute it to EMF exposures to cope with the problem (avoidance of EMF).

However, no hypothesis could be considered satisfactory. All of the hypotheses and research studies performed to examine these hypotheses, rely solely on the self-diagnosis of EHS by the study subjects. Many, or even majority, of self-diagnoses might be false. This leads to contamination of the experimental group and to the dilution of the observed, if any, EHS effects.

Ledent and co-workers [255] have stated that the best suited for isolating effects of EMF are provocation studies but number of innovations should be included in protocols, such as: the involvement of people with EHS in the development of the protocol, the attenuation of the anxiogenic nature of the tests, the individualization of the protocol, the validation of the neutral or normal reactivity state before the test, and the use of a cocktail of real, rather than artificially generated, sources.

Unfortunately, the unlimited trust in provocation studies, as the best suited to find out an explanation for the cause(s) of EHS, is worrisome as it might lead to further delays in finding answers about the causes of EHS. The involvement of EHS persons in the process of developing improved exposure protocol, the co-development, is laudable but similar approach was tried in the past and with no advance in research outcomes.

However, no matter how the experiments were prepared, several major problems remain:

(1) Did co-designing experiments, where researchers and EHS volunteers collaborated closely, in any meaningful way alleviated distrust of the volunteers?
(2) Are the self-diagnoses of EHS correct when done in collaboration with research team?
(3) Are the exposures sufficient enough to cause symptoms?
(4) Are the lag-times after exposure long enough to allow development of delayed symptoms?
(5) Responses provided by the volunteers remain subjective.
(6) No objective way to assure that exposure protocol and symptoms have causality link.

There is a number of drawbacks in the design of all of the to-date executed EHS studies that were not mentioned but that will prevent making any far reaching conclusions on the existence and on the causes of the EHS. The drawbacks [as proposed by D. Leszczynski] are as follows:

– Drawback #1: It is not known whether the volunteers are indeed suffering of EHS. This means that the experimental groups of self-diagnosed EHS persons might be contaminated by the misdiagnosed EHS persons. In extreme cases it might happen that none of the self-diagnosed EHS volunteers is indeed and EHS sufferer. They might experience non-specific symptoms caused by non-EMF environmental exposures.
– Drawback #2: There are two types of selection bias in the to-date executed EHS studies. The first one is introduced by the scientists who exclude persons with any pre-existing health problems. Scientists do not know whether pre-existing health problems might predispose a person to develop EHS. Exclusion of persons with pre-existing health problems is incorrect at this discovery stage. Persons with pre-existing health problems should be included, though they could/should be analyzed separately. The second selection bias is introduced by the volunteers who either fail to volunteer or who initially agree to participate in a study but later withdraw their consent because of either becoming afraid of potential health risk from exposures or because of the distrust in the scientific team.
– Drawback #3: Psychological methods of inquiry, used in psychological provocation studies, were not examined and not proven for their suitability to detect EHS. Assuming that the EHS exists, none of the experimental methods of psychology, used in the to-date executed psychological provocation studies, has been demonstrated to be able to detect physiological outcomes of the EHS stemming from the exposures to EMF. Furthermore, all psychological provocation studies were designed to examine acute occurrences of EHS symptoms and might be unsuitable to detect delayed or chronic EHS symptoms.
– Drawback #4: Conclusions of the provocation studies performed using psychology methods might be affected and/or even invalidated because of the existence of the *placebo* and *nocebo* phenomena. *Placebo* and *nocebo* indicate the ability of the human mind to affect physiology of human body [256, 257]. There is a well-known phenomenon among medical students of the “medical students’ disease”. It is a condition frequently reported in medical students, who perceive themselves to be experiencing the symptoms of a disease that they are currently studying. The condition is associated with the fear of contracting the disease in question. The same is likely happening when researchers show to study subjects’ films presenting dangers of EMF exposures. It is obvious and expected that some persons will afterwards “experience” some of the symptoms presented in the film. Furthermore, volunteers participating in such studies have preconceived opinions on EMF and health. Thus, claims that news media reports cause rise in the occurrence of EHS is incorrect. Also, the responses of the self-diagnosed EHS persons given during the provocation experiments are likely influenced by their pre-existing opinions about EHS. Thus, the data collected in the psychological provocation studies is not only unobjective but it is affected by the pre-existing opinions.

The way how EHS persons arrive at own self-diagnosis of EHS was elegantly presented by Dieudonné [140] and it is in agreement with the drawback #4 by D. Leszczynski. Claiming that the subjective data of the to-date executed provocation studies is scientifically reliable to diagnose EHS is incorrect. Subjective data from the psychological provocation studies does not prove, as some claim, that EHS is caused solely by a worry and not by EMF exposures. The above-listed drawbacks suggest/indicate that the scientific data obtained in the to-date executed survey studies, the psychological provocation studies and the biochemical EHS studies is unreliable and insufficient to prove, or to disprove, the existence of EHS.

The future of the research on EHS

The psychological approach of surveys and provocation studies has to be supplemented with physiological and biochemical measurements, examining the individual's molecular level responses to EMF exposures [258]. The future studies should have part of provocation study where individuals, not groups of individuals, would be examined with questions about what and when they feel in response to exposure. The other part of the same research should be the collection of samples for biochemical analysis of whether the exposure causes changes in expression of biochemical markers and whether it will be possible to find biochemical markers that will be universally altered by the exposures. The studies should have double-blind set up and both healthy and EHS persons should be analyzed together and only after the analysis is completed, the health status of volunteers should be revealed. Furthermore, the problem of the lag between the exposure and the appearance of symptoms is an important one but not easy to resolve. The supplementation of the subjective psychology data with the objective biochemistry data will help to establish whether the acute EHS responses take place. Once the acute EHS is established, a remedy to the lag problem might be considered. It will be likely very costly as it might require sequestering volunteers, for some period of time (days–weeks) in environmental isolation from environmental EMF exposures, to perform psychological inquiries and biochemical samplings at different times after exposure to examined EMF exposure.

The current diminished interest in studying EHS is fueled by the misconception that the provocation studies alone, using psychology approach and asking about feelings, were enough to prove that EHS is not caused by EMF exposures. This is absolutely incorrect. Only combination of provocation study with biochemical examination will resolve the EHS enigma. However, the idea of examining biochemistry of EMF exposed persons is being opposed by many researchers of bioelectromagnetics. Thus, for comparison, it is good to look elsewhere, where transcriptomics and proteomics approaches are being used to resolve and explain health problems.

Pain is one of the non-specific symptoms experienced, among others, by the EHS sufferers. Feeling of pain is very individual and there is no objective scale to measure pain. Pain is considered to be multidimensional and adaptive. Individual expectations, moods or attention affect how the pain is handled by the brain and how it is, in the end, felt by the individual. In some cases to relieve pain is necessary surgical or chemical intervention. However, many cases of pain is possible to relieve without surgery or drugs, just by psychological intervention [259, 260]. In understanding the pain, and in research towards controlling it, is important to know where from the pain comes. Chronic pain is classified into three categories, nociceptive pain caused by tissue damage, neuropathic pain caused by nerve damage and pain of unknown source, the idiopathic pain. For example stress and sleep problems disturb mechanisms that regulate feeling of pain. The positive expectation that a drug will help in relieving pain were shown to increase efficacy of the drug [261]. Furthermore, MRI images have shown that different areas of the brain differently respond to the same drug when it is associated with positive or with negative expectations. If the source of the pain is unknown then the methods to alleviate this pain might fail. Chronic pain develops in some 20% of people experiencing pain. Women are more susceptible to develop chronic pain. Other factors that help to develop chronic pain are age, stressful experiences and prone to catastrophic-thinking nature of the patient.

Scientists are now looking for objective measurements of pain because all current methods of relieving pain are based on subjective information received from the patient. This is insufficient. The problem is that currently there are no methods to detect pain and strength of it from e.g. blood test. However, methods using biomarkers, genetics and epigenetics are considered to be of paramount importance in the future of developing objective tests for pain [262].

Patients' subjective description of symptoms combined with the biomarker objective information is considered the future for developing pain control. The same approach should be taken to resolve the problem of sensitivity to exposures from EMF. Physiological studies of responses to EMF exposures will generate data useful for developing diagnostic tools for the detection of EMF sensitive persons and to, potentially, develop methods to mitigate the physiological effects of EMF exposures without the necessity of avoidance of EMF exposures. This biochemical approach has been shown to be able to

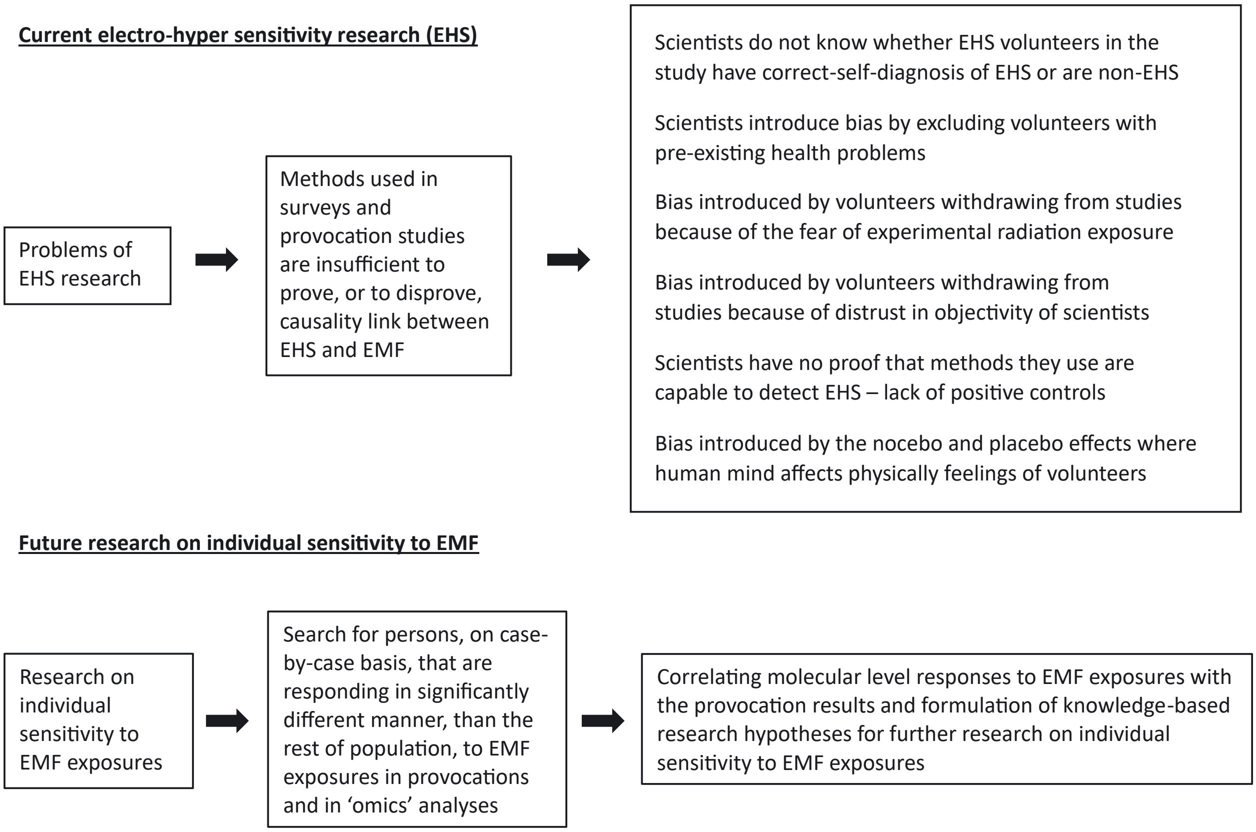

Figure 2: Problems of the current EHS studies and need for introduction of combination of provocation approach and 'omics' techniques approach to research on EHS.

experimentally generate data on EMF-exposure affected proteins or genes [263]. In the coming era of 5G technology and the already being developed 6G technology, avoidance of EMF exposures will become virtually impossible for any person wishing to remain function and prosper in the society.

Final conclusions

- Problems and solutions for EHS research are summarized in Figure 2.
- Over the last 30 years, a sizable number of research studies has examined causality link between EMF exposures and EHS symptoms.
- The majority of the studies did not find any link between EMF and EHS.
- The EHS studies have examined acute effects but did not have capability to examine delayed EMF responses.
- The major problem is that scientists do not know whether EHS volunteers have indeed correct self-diagnosis of EHS or whether the diagnosis is incorrect and experimental groups are contaminated, to unknown degree, by non-EHS persons. In extreme situation, the small group of volunteers used in research study might have no EHS persons at all.
- Recently, research on EHS has drifted into direction of *nocebo* as the cause of EHS, what is incorrect.
- Instead of studying obvious impact of *nocebo*, or likes of *medical students' disease*, research should focus on finding suitable biochemical and biophysical markers that could be used, in combination with single-individual-focused provocation studies, to determine the sources of the EHS symptoms.
- The opinion that there is no causality link between EHS and EMF is unproven. This opinion, expressed by the World Health Organization EMF Project, the International Commission on Non-Ionizing Radiation Protection, International Committee on Electromagnetic Safety and numerous governmental organizations, should be revised because the scientific research data is of insufficient quality to be used as a proof of the lack of causality.

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