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Occupational exposure to extremely low frequency electric and magnetic fields and Alzheimer disease: a meta-analysis

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Background Among potential environmental risk factors for Alzheimer disease (AD), occupational exposures have received some attention, including extremely low frequency electromagnetic fields (ELF-EMF). A systematic review and meta-analysis of published epidemiological studies on this subject was carried out.

Methods The search was concluded in April 2006. Bibliographic databases consulted included PubMed, EMBASE, Cochrane Library and NIOSHTIC2. Pooled estimates were obtained using random-effects meta-analysis. Sources of heterogeneity between studies were explored, as was publication bias.

Results Fourteen different studies (nine case-control and five cohort studies) accomplished inclusion criteria. All these studies followed standardized criteria for AD diagnosis and most of them obtained quantitative estimates of exposure. Pooled estimates suggest an increased risk of AD from case-control studies (OR_{pooled} 2.03; 95% CI 1.38–3.00) and from cohort studies (RR_{pooled} 1.62; 95% CI 1.16–2.27), with moderate to high statistical heterogeneity in both cases (respectively, $I^2 = 58\%$ and $I^2 = 54\%$). Cohort studies showed consistently increased risks for exposed men (RR_{pooled} 2.05; 95% CI 1.51–2.80, $I^2 = 0\%$). Evidence of dose–response relationship was not present. Test for publication bias suggests small study effects, mostly for case-control studies.

Conclusions Available epidemiological evidence suggests an association between occupational exposure to ELF-EMF and AD. However, some limitations affecting the results from this meta-analysis should be considered. More information on relevant duration and time windows of exposure, on biological mechanisms for this potential association and on interactions between electromagnetic fields exposure and established risk factors for AD is needed.

Keywords Alzheimer disease, electromagnetic fields, occupational exposure, review literature, meta-analysis

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Introduction

Alzheimer disease (AD) is the predominant type of dementia and a major cause of disability in elderly people. Despite the high frequency of AD and its major impact on patients, their families and the society, treatment is highly limited and preventable causes of AD are mostly unknown. The best established risk factors identified so far are age, familial aggregation, isoform $\varepsilon 4$ of apolipoprotein E gene (APOE*4), autosomal-dominant mutations in hereditary AD and Down syndrome. Substantial controversy remains regarding other genetic and environmental factors.[1–4] As a consequence, opportunities for AD prevention remain highly limited.[5,6]

Among potential environmental risk factors of AD, occupational exposures have received some attention. The most widely studied occupational agents have been aluminium, solvents, pesticides, lead and electromagnetic fields (EMF). Again, available evidence about the association of occupational exposures with AD is in general inconsistent. In a review on this subject including epidemiological studies published up to June 2003,[7] pesticides were the agents for which there was more consistent evidence of association, but neither conclusive.

Occupational exposure to EMF has received in the previous years increased attention as a potential risk factor for different long-term health effects, including dementia and AD. Forms of electromagnetic energy, ordered in decreasing frequency measured in hertz (Hz), include gamma rays, X-rays, ultraviolet radiation, visible light, infrared radiation, microwaves, radiofrequencies, very low frequencies and extremely low frequencies fields. Most of the epidemiological research on occupational exposure to non-ionizing electromagnetic fields and long-term effects on health has focused on workers exposed to extremely low frequency electric and magnetic fields (ELF-EMF), with frequencies ranging between 3 and 3000 Hz, and primarily on workers with occupational exposure to power-frequency fields (50–60 Hz). Occupations with typical exposures to ELF-EMF include electric power installers and repairers, power plant operators, electricians, electrical and electronic equipment repairers, telephone line technicians, installers and repairers and workers operating electrical equipments such as welders, carpenters or machinists. Exposure levels for these different occupations are usually measured according to the level of the magnetic field created in units of Gauss (mG; 1 Gauss = 1000 mG) or Tesla (μT; 0.1 μT = 1 mG). Even though sources of ELF-EMF produce both electric (measured in volts per meter, V/m) and magnetic fields, research has mostly focused on potential health effects of magnetic field exposure, because some seminal epidemiological studies reported increased cancer risk associated with estimates of magnetic field exposure and because many of the studies examining biological effects of electric fields were essentially negative.[8]

Research on long-term effects of ELF-EMF has mostly focused on childhood and adult cancer.[9] For other non-cancer endpoints, epidemiological research has been much scarcer. For neurodegenerative diseases, a pioneer study in 1995[10] reported an association between working in occupations with probable medium or high exposure to ELF-EMF and sporadic AD. Since then, some epidemiological research has focused on this association and a number of studies with additional evidence have been produced.

In this report published epidemiological studies on the association between occupational exposure to ELF-EMF and AD are systematically and critically reviewed.

Methods

The aim was to locate published epidemiological studies on the association between occupational exposure to ELF-EMF and AD. The search was concluded in April 2006, and no limits for publication year were introduced. *In vivo* or *in vitro* experimental studies were excluded. Studies published in languages other than English and Spanish were excluded. Studies not specifically evaluating the risk for occupational exposure to ELF-EMF (e.g. studies assessing the risk of AD for the whole range of different occupations or job titles in a series) were also excluded, as were studies focusing on the risk for dementia as a whole, without specific results for AD.

International bibliographic databases consulted were PubMed, EMBASE, The Cochrane Library and NIOSHTIC2. Spanish databases IME, Teseo, CIS, CSIC and the Spanish Virtual Library in Health Sciences were also reviewed. Key words used for the search were 'Alzheimer's disease' and 'electromagnetic fields'. Web searcher *Google* was also used with the same key words. Institutional information sources (the National Institute of Environmental Health Sciences, the National Academy of Sciences, the World Health Organization, the International Agency for Research on Cancer and the International Commission on Non-Ionizing Radiation Protection) were also consulted. Bibliographic references in all these sources were reviewed, as were the references in the relevant papers located in the search. No attempt was undertaken to retrieve unpublished studies.

Summary risk estimates were obtained using random-effects meta-analysis. Statistical heterogeneity was assessed through Cochran's Q-test and I^2 statistic, which describes the percentage of total variation across studies that is attributable to statistical heterogeneity rather than to chance.[11] I^2 values of 25, 50 and 75% correspond to low, moderate and high between-study statistical heterogeneity. A priori established study characteristics that might account for between-studies heterogeneity were study design (case-control vs cohort), sex of participants, criteria for AD diagnosis and cut-off points for exposure levels, and subgroup analyses were performed

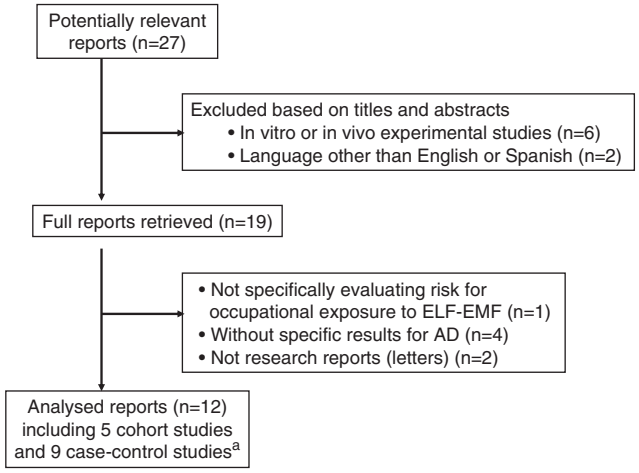

Figure 1 Identification of eligible epidemiological studies on occupational exposure to extremely low frequency electric and magnetic fields (ELF-EMF) and Alzheimer disease (AD), last updated in April 2006. [a]One of the reports includes results from three different series of cases and controls

stratifying by these characteristics. Univariable random-effects meta-regression models were also used to examine whether these characteristics statistically affected effect sizes. Publication bias was assessed using Egger's regression asymmetry test.[12] All analyses were conducted with Stata v.9 using the meta, metareg and metabias series of commands.

Results

Figure 1 summarizes the process of identifying eligible epidemiological studies. Finally, 14 different studies (published in 12 different papers,[10,13–23] as the first paper by Sobel *et al*.[10] includes three different series of cases and controls) met inclusion criteria.

Table 1 shows the characteristics of the studies included for review. The papers were published between 1995 and 2004, although time periods for the ascertainment of the cases included in the studies range from 1977 to 1978 in a case-control series in Finland[10] up to 1996 for three of the more recent studies.[19,20,23] Six of the studies were carried out in USA, seven studies were carried out in Northern Europe countries (Sweden, Finland and Denmark) and one was carried out in Turkey. The number of AD cases included in these studies ranges from 30 in a Danish cohort study[18] up to 2000 in a large Swedish cohort.[22] Seven of the studies include less than 100 cases of AD. All the studies but three have data for both sexes, but in the papers results are not always presented differentially for males and females. Nine case-control studies and five cohort studies are included. For AD diagnosis, five of the studies (two case-control and three cohort studies) used information collected in death certificates and nine studies used data from clinical examination of subjects as registered in routine medical records or *ad hoc* registries. Most of the studies applied NINCDS-ADRDA criteria or ICD-8 or ICD-9 criteria for AD diagnosis (respectively, $n=5$ and $n=6$). Exposure assessment was based on occupational history collected through personal interviews ($n=7$) or in routine registries (including death certificates, occupational records and clinical records, $n=7$). Exposure categories are established according to job titles alone ($n=1$), job titles combined with expert's assessment of level of exposure ($n=6$) or job exposure matrices ($n=6$), and sample workplace measurements ($n=1$). All the studies but one[15] use quantitative estimates of exposure, always presented in μT (intensity of magnetic fields). All the estimates in the table are adjusted by several confounding variables, with the only exceptions of the odds ratio for men in the first series of case-control studies reported by Sobel *et al*.[10] and the relative risk for women in the Danish cohort study.[18] In general, unadjusted estimates reported in the revised papers did not differ substantially from these adjusted estimates (data not shown), suggesting a weak effect of confounding from variables considered for adjustment.

Meta-analysis of all the estimates included in Table 1 showed substantial statistical heterogeneity between studies ($P=0.001$, I^2 100%), and statistical pooling of all these individual estimates was not felt justified. Moderate heterogeneity was still present when all case-control ($p=0.004$, $I^2=58\%$) and cohort studies ($p=0.016$, $I^2=54\%$) were differentially analysed (Figure 2). Sources of heterogeneity were further explored through subgroup analysis according to previously established characteristics of the studies (Table 2). Pooled estimates for case-control studies according to selected study characteristics suggest increased risks, mostly with low to moderate heterogeneity. Analyses restricted to women, studies based on death certificates and studies establishing cut off point for exposure at $\geqslant 0.2$ μT did not show evidence of heterogeneity ($I^2=0\%$), but most of these estimates are based on a relatively low number of studies. As regards cohort studies, pooled estimates generally show increased risks too. Evidence of moderate to high heterogeneity is still present, except for estimates for men and in the two higher levels of exposure ($I^2=0\%$), although risk is only clearly increased for the medium cut off point for level of exposure ($\geqslant 0.5$ μT) and no evidence of dose–response relationship is observed. When we undertook meta-regression to explore the impact of our a priori sources of heterogeneity (Table 2), we found no effect of study design (case-control vs cohort studies, $P=0.330$). Meta-regression analysis for type of examination for AD diagnosis (clinical vs based on death certificates) showed a consistent interaction effect on reported associations, while exposure level had no effect. Sex only showed an interaction effect on reported associations in cohort studies.

Table 1 Characteristics of epidemiological studies on occupational exposure to ELF-EMF and AD

First author, year of publication [reference] (country)	Time period	Design	Number of cases	Disease[a]: source, assessment, criteria	Exposure: source, assessment, criteria	Confounding variables[b]	Main results[c]	
							Males	Females
Sobel, 1995[10] Series #1 (Finland)	1982–85	Case-control	53	• Medical records • Clinical examination • NINCDS-ADRDA	• Occupational history (interview) • Industrial hygienist assessment • Job titles + environmental measurements • Magnetic field levels ($\geqslant 0.2\,\mu T$)	Age at onset Age at diagnosis (Sex) Education	0.7 (0.1–8.9)[e]	10.2 (1.1–95.3)
Sobel, 1995[10] Series #2 (Finland)	1977–78	Case-control	198	• Medical records • Clinical examination • NINCDS-ADRDA	• Occupational history (interview) • Industrial hygienist assessment • Job titles + environmental measurements • Magnetic field levels ($\geqslant 0.2\,\mu T$)	Age at diagnosis (Sex) Social class	2.7 (0.7–9.8)	3.5 (1.3–9.6)
Sobel, 1995[10] Series #3 (USA)	1982–83	Case-control	136	• Medical records • Clinical examination • Criteria of Roth	• Occupational history (interview) • Industrial hygienist assessment • Job titles + environmental measurements • Magnetic field levels ($\geqslant 0.2\,\mu T$)	(Sex) Education Age at diagnosis	1.7 (0.3–10.3)	3.7 (0.4–33.6)
Sobel, 1996[13] (USA)	Not reported	Case-control	326	• Medical records • Clinical examination • NINCDS-ADRDA (excluding possible AD)	• Clinical records • Industrial hygienist assessment • Job titles + environmental measurements • Magnetic field levels ($\geqslant 0.2\,\mu T$)	Age at onset Age at diagnosis Sex Education	4.9 (1.3–7.9)	3.4 (0.8–16.0)
Feychting, 1998[14] (Sweden)	1989–91	Case-control	77	• Follow-up registries • Clinical examination • NINCDS-ADRDA (probable and possible AD)	• Occupational history (interview) • Job exposure matrix • Magnetic field levels ($\geqslant 0.2\,\mu T$) • Magnetic field levels ($\geqslant 0.5\,\mu T$)	Age at onset/ examination Sex Education	**Both** 2.7 (0.9–7.8)[f] 8.3 (1.1–62.7)[f]	

Savitz, 1998[15] (USA)	1985–91	Case-control	256	• Death certificates • Underlying cause of death • ICD-9	• Death certificates • Electrical occupations	Age at death Calendar period at death Social class	1.2 (1.0–1.4)	
Savitz, 1998[16] (USA)	1950–86	Cohort	80	• Death certificates • Underlying cause of death • ICD-9	• Occupational records • Sample workplace measurements • Magnetic field levels ($\geqslant 2.06\,\mu T$)	Age at death Calendar period at death Social class Work status at death PCB exposure Solvent exposure	2.0 (0.6–7.0)	
Graves, 1999[17] (USA)	1987-not reported	Case-control	89	• Medical records • Clinical examination • NINCDS-ADRDA (probable and possible AD)	• Occupational history (interview) • Industrial hygienists assessment • Magnetic field levels ($\geqslant 0.3\,\mu T$)	Age Education	**Both** 0.7 (0.3–1.9)[g]	
Johansen, 2000[18] (Denmark)	1978–93	Cohort	30	• Hospital records • Clinical examination ICD-8 (presenility, including AD)	• Occupational records Job exposure matrix Magnetic field levels ($\geqslant 1.0\,\mu T$)	Age Calendar period Duration of employment	0.9 (0.3–3.4)	1.3 (0.4–3.4)[e]
Noonan, 2002[19] (USA)	1987–96	Case-control	1556	• Death certificates • Any mention of AD • ICD-9	• Death certificates • Job exposure matrix • Magnetic field levels ($\geqslant 0.3\,\mu T$)	Age at death Social class Race	1.0 (0.7–1.5)	
Hakanson, 2003[20] (Sweden)	1985–96	Cohort	40	• Death certificates • Any mention of AD • ICD-8 and ICD-9	• Occupational records • Job Exposure Matrix • Magnetic field levels ($\geqslant 0.5\,\mu T$)	Age at year of entry Sex Social class	2.7 (0.9–8.3)	22.7 (1.3–390.8)
Harmanci, 2003[21] (Turkey)	Not reported	Case-control	57	• Cross-sectional study • Clinical examination • MMSE followed by DSMMD (probable AD)	• Occupational history (interview) • Industrial hygienist assessment • Job titles + environmental measurements • Magnetic field levels ($\geqslant 0.2\,\mu T$)	(Age) (Sex) Education Rural or urban residence Electrical appliances Water heating Medical history Drugs use (NSAIDs[d]) Alcohol	**Both** 4.0 (1.0–15.8)	

(continued)

Table 1 Continued

First author, year of publication [reference] (country)	Time period	Design	Number of cases	Disease[a]: source, assessment, criteria	Exposure: source, assessment, criteria	Confounding variables[b]	Main results[c]	
							Males	Females
Feychting, 2003[22] (Sweden)	1981–95	Cohort	2000	• Death certificates • Any mention of AD • ICD-8 and ICD-9	• Census • Job exposure matrix • Magnetic field levels ($\geqslant 0.3\,\mu T$) • Magnetic field levels ($\geqslant 0.5\,\mu T$)	Age at death Socioeconomic status	2.0 (1.2–3.3)[h] 2.2 (1.2–3.8)[h]	1.1 (0.7–1.6) [h] 2.3 (1.0–5.2) [h]
Qiu, 2004[23] (Sweden)	1987–96	Cohort	202	• Medical records • Clinical examination • DSMMD	• Occupational history (interview) • Job exposure matrix Magnetic field levels ($\geqslant 0.2\,\mu T$)	Age at baseline interview Education Vascular disease Alcohol Smoking Mental activity Social activity ApoE genotype	2.3 (1.0–5.1)	0.8 (0.5–1.1)

[a]NINCDS-ADRDA, criteria from the National Institute of Neurologic and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association; ICD, criteria for the International Classification of Diseases; MMSE, Mini Mental State Examination; DSMMD, criteria from the Diagnostic and Statistical Manual of Mental Disorders.
[b]In brackets variables for which the researchers had information but which are not specifically mentioned as included in the multivariate analysis.
[c]Adjusted estimates of risk (odds ratios for case-control studies, rate ratios for cohort studies) and 95% CI. When results from different analyses are reported, estimates are selected with higher precision and according to criteria presented in previous columns and/or in footnotes.
[d]NSAIDs, nonsteroidal anti inflammatory drugs.
[e]Unadjusted (adjusted not available).
[f]Results for last occupation, reference group 2.
[g]Results for industrial hygienist 1.
[h]Results for occupation held in 1970, follow-up to 1990.

Table 2 Pooled estimates of risk from epidemiological studies on occupational exposure to ELF-EMF (extremely low frequency electric and magnetic fields) and Alzheimer disease

Subgroup analysis	References (No. of observations)[a]	Pooled estimate [95%CI]	Heterogeneity I^2[b]	Heterogeneity P-value[c]	P for interaction[d]
Case-control studies					
All	10–13,15,17,19 ($n=14$)	2.03 [1.38–3.00]	58%	0.004	0.330[e]
Sex					
Men	10,11,13,17 ($n=6$)	1.50 [0.97–2.30]	58%	0.038	
Women	10,11 ($n=4$)	3.93 [1.88–8.19]	0%	0.851	0.516
Type of examination					
Clinical examination	10–12,15,19 ($n=12$)	2.76 [1.73–4.30]	20%	0.242	
Death certificates	13,17 ($n=2$)	1.17 [1.00–1.36]	0%	0.429	<0.001
Exposure level					
$\geqslant 0.2\,\mu T$	10–12,19 ($n=10$)	3.36 [2.20–5.14]	0%	0.882	
$\geqslant 0.3\,\mu T$	15,17 ($n=3$)	1.20 [0.53–2.71]	56%	0.102	0.300
Cohort studies					
All	14,16,18,20,21 ($n=11$)	1.62 [1.16–2.27]	54%	0.016	0.330[e]
Sex					
Men	14,16,18,20,21 ($n=6$)	2.05 [1.51–2.80]	0%	0.874	
Women	16,18,20,21 ($n=5$)	1.29 [0.77–2.14]	60%	0.040	0.002
Type of examination					
Clinical examination	16,21 ($n=4$)	1.17 [0.67–2.04]	46%	0.137	
Death certificates	14,18,20 ($n=7$)	1.89 [1.31–2.71]	39%	0.131	0.094
Exposure level					
$\geqslant 0.2\,\mu T$ or $\geqslant 0.3\,\mu T$	20,21 ($n=4$)	1.33 [0.83–2.13]	72%	0.014	
$\geqslant 0.5\,\mu T$	18,20 ($n=4$)	2.42 [1.58–3.72]	0%	0.469	
$\geqslant 1.0\,\mu T$	14,16 ($n=3$)	1.37 [0.68–2.76]	0%	0.697	0.485

[a]Some studies provide only one risk estimate and some provide two risk estimates (for men and women and/or for two levels of exposure). First report by Sobel *et al.*[10] includes results from three different studies. See Table 1.
[b]Percentage of total variation across studies attributable to statistical heterogeneity rather than to chance (25%, low; 50%, moderate; 75%, high).
[c]P-value for heterogeneity test (Cochran's Q test).
[d]P-value for interaction from meta-regression models.
[e]All case-control studies vs all cohort studies.

Testing for publication bias including all the studies ($n=25$ observations) resulted in substantial asymmetry (Figure 3), with larger studies showing a smaller degree of association than smaller studies (intercept = 3.11; 90% CI 1.92–4.30, $P<0.001$). This effect was still present when restricting this analysis to case-control studies (14 observations, intercept = 4.03; 90% CI 2.25–5.82, $P=0.002$), but it was less evident for the same analysis limited to cohort studies (11 observations, intercept = 2.85; 90% CI −0.18 to 5.88, $P=0.119$).

Discussion

Results from this meta-analysis of available epidemiological evidence suggest increased risks for occupational exposure to ELF-ELF and AD. However, some of the pooled estimates obtained show moderate to high statistical heterogeneity. Also, there was some statistical suggestion of publication bias affecting small studies with smaller degrees of association, mostly for case-control studies. Several points are worthy of further discussion.

Limitations and strengths of searching strategy

For this review a wide variety of sources and databases were explored, using quite ample search terms ('Alzheimer's disease' and 'electromagnetic fields'), with no limits except for publication language. Bibliographic references in all retrieved papers and reports were reviewed, and, as far as we can

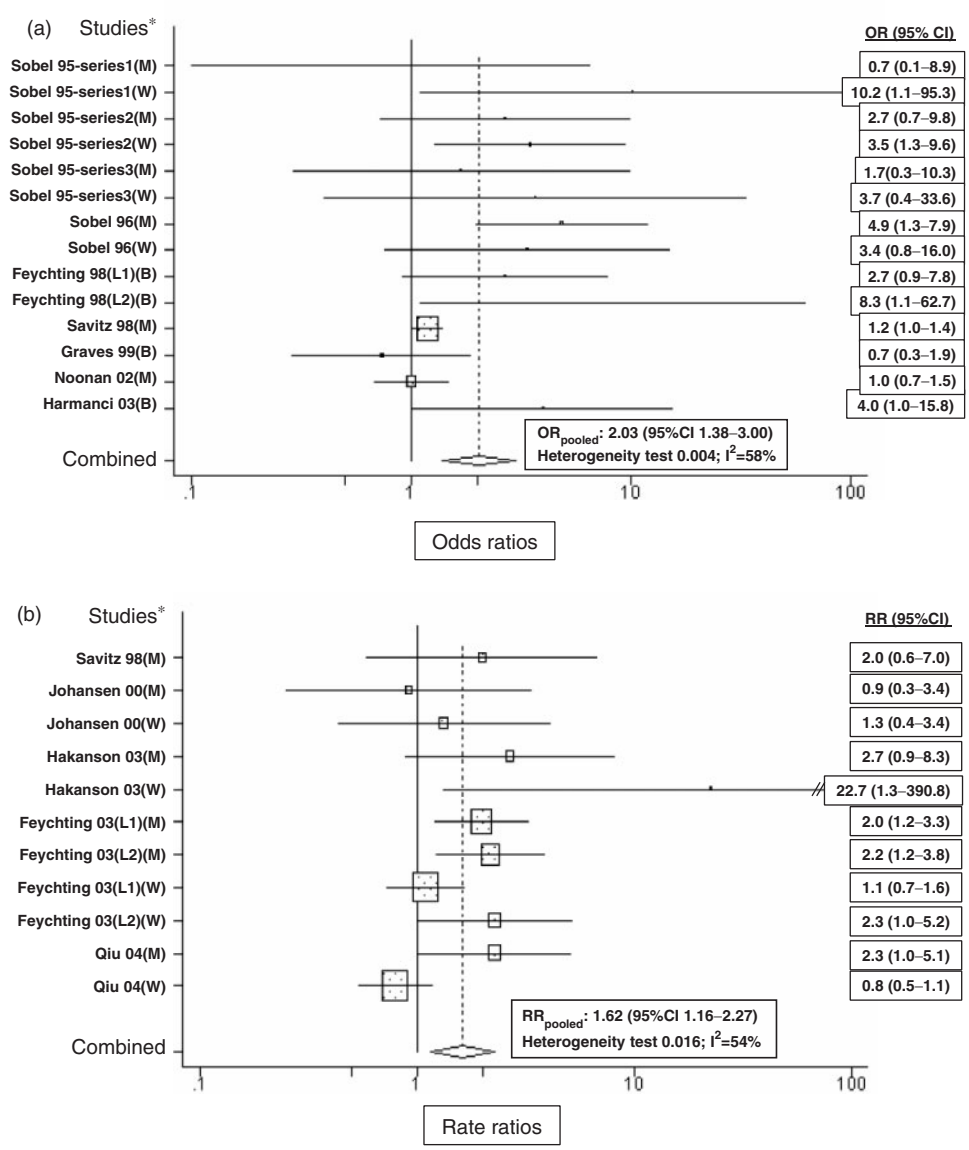

Figure 2 Individual and pooled estimates from case-control studies (a) and cohort studies (b) on occupational exposure to extremely low frequency electric and magnetic fields (ELF-EMF) and Alzheimer disease (see Table 1).
*Estimates for individual studies as reported in Table 1. (M): estimates for men; (W) estimates for women; (B): estimates for both sexes; (L1) estimates for lower level of exposure reported; (L2): estimates for higher level of exposure reported

assess this point, we are quite confident on the exhaustivity of our searching strategy of published research. Only two papers were excluded because of language of publication (Figure 1). According to the abstract, the results of one of them (a cohort study published in Danish[24]) are based in the same sample of workers as the English report included in our review.[18] The other one, published in Chinese,[25] is a case-control study showing an increased risk of AD (adjusted OR 2.49; 95% CI 0.96–6.45) for men early exposed to EMF. Only the English abstracts were accessed for both papers and both were excluded from our analysis.

Publication bias, more accurately small study effects, represent a particular threat to the validity of meta-analysis of observational studies.[26,27] In our review, there was evidence of larger studies showing a smaller degree of association than smaller studies, mostly affecting case-control studies (Figure 3). It should also be noticed that sensitivity of the methods applied for assessing this bias, including Egger's regression asymmetry test,[12] is generally low.[27] Hence, an effect of publication bias in our results, yielding overestimation of reported associations, cannot be discarded.

Limitations and strengths in the original studies

Epidemiological research of AD and occupational exposure to ELF-EMF has to face several threats to

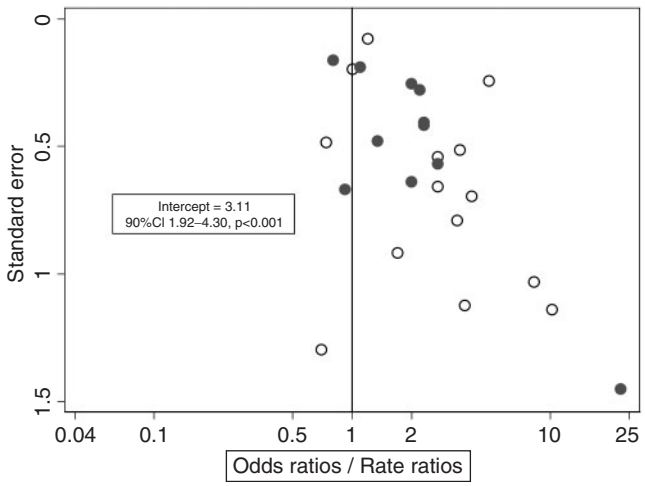

Figure 3 Funnel plot and Egger's regression asymmetry test for all individual studies (cohort studies: solid circles; case-control studies: open circles)

validity, mostly in relation to case ascertainment, control selection in case-control studies, surrogated information, exposure assessment and control of confounding.[1–4] These points are next briefly discussed in relation to included studies in this review.

Cases ascertainment

Diagnosis of AD is not easy. Differential diagnosis with other dementias, which may represent different pathologies but also may accompany AD, is not easy either. In particular, the distinction between AD and vascular dementia is complicated, mostly when vascular components have been involved in AD development.[28,29] Evidence obtained from a biopsy or autopsy is required for a definite diagnosis of AD.[30] All the epidemiological studies included in this review followed standardized criteria (Table 1). The more widely accepted criteria for AD diagnosis are the NINCDS-ADRDA criteria, yielding relatively good agreement with pathological diagnosis.[31] Reviewed mortality studies.[15,16,19,20,22] ascertained AD through ICD-8 and/or ICD-9 codes as primary or contributing cause of death in mortality registries. Death certificates are limited sources for AD assessment.[32,33] Inclusion in the case series of false diagnosis of AD will generally produce non-differential misclassification bias if an association with exposure exists for AD, hence decreasing observed associations. Incomplete ascertainment of cases will also contribute to decreased statistical power in the studies. For the case-control studies, higher pooled risks were observed in the results of studies based on clinical examination as compared to studies based on death certificates, and substantial heterogeneity was observed when the results from both approaches were compared (Table 2, $P < 0.001$). In cohort studies this effect was still evident ($P = 0.094$). Also, it has been pointed out that long latency and survival periods might bias results based on mortality data, particularly if a diagnosis of a long premorbid phase has an effect on exposure (e.g. leads to a change from high to low exposed occupations).[20] As most of AD cases are diagnosed after retirement age of 65 (with the exception of presenile and familial types), we do not think this effect could be of concern for the potential association between ELF-EMF and sporadic AD. The healthy worker effect is also unlikely for studies on AD, as first symptoms of the disease will usually appear after age of retirement. Age at death (<75 years, ⩾75 years) was not consistently related to the risk of disease for ELF-EMF exposed in the large Swedish mortality cohort.[22]

Selection of controls

Different strategies where applied for the selection of controls in the nine case-control studies revised, including controls selected from hospitals, neighbourhood, mortality statistics and population. In general, potential for selection bias (i.e. selection of controls somehow related with their potential for exposure) arriving from these different sources for controls selection could be low. Criteria for inclusion and exclusion of controls also substantially differ between studies. These sources of variation could explain observed heterogeneity affecting pooled analysis of case-control studies.

Surrogated information

In retrospective etiological studies of AD using interviews for gathering relevant information (on past exposures of interest and control variables), surrogate informants (next-of-kin, other relatives or acquaintances of the case subjects) are commonly used, whose responses depend on their knowledge of the index subjects previous history. Hence, there is an added risk for incomplete or biased information for cases. Six studies in the review used interviews and surrogate informants only for demented subjects[10,14,17,23] and three studies included analyses with surrogated information for controls too.[17,21,23] Both approaches gave negative results in the study by Graves *et al*.[17] A study aimed to investigate usefulness of information obtained from proxy respondents in retrospective studies of AD by comparing the information obtained with a questionnaire from controls and from their proxy respondents reported acceptable indices for validity and reliability of information regarding occupational history and exposures, without neither major loss of information nor systematic biases.[34]

Assessment of exposure

All the revised studies put an effort in the assessment of exposure to ELF-EMF, obtaining quantitative estimates (Table 1). However, criteria for definition of exposure to occupational ELF-EMF vary between the reviewed studies, as do cut-off points of exposure.

The only study assessing the risk according exclusively to job title ('electrical occupations') did not find increased risks for exposed workers.[15] As observed by Noonan *et al.*,[19] electrical occupations traditionally considered to have high magnetic-field exposure are not always ranked in the highest categories of exposure when using quantitative methods for exposure assessment: according to the job exposure matrix used by these researchers, textile sewing machine operators and welders exhibited higher estimates of exposure (respectively, geometric mean 2.99 and 0.95 μT) than any of the electrical occupations (for the highest exposed, 'electric power installers and repairers', geometric mean 0.94 μT). Besides, although most of the studies on human health effects of ELF-EMF have concentrated on magnetic field exposures, there are some studies indicating that electric field exposures may enhance cancer risks with evidence of dose–response relationship.[35]

On the other hand, concerns have also been raised about the relevant estimator of exposure to be measured in relation to potential biological effects of ELF-EMF. More attention to transient exposures, besides averaged and/or cumulative levels, has been claimed. In this review, most of the studies assessed exposure according to primary lifetime occupation. Primary lifetime occupation is expected to be related to a large time of exposure. According to their analysis and results, some researchers suggested that exposures later in life could have a greater effect on the development of the disease,[14] while other studies do not find evidence for this.[23] Also, while a late-acting influence of exposure in the disease process and lesser importance of accumulated exposure throughout the lifetime has been proposed,[14] increased risks (and dose–response relationships) only for time lags of exposure $\geqslant$20 years in the past were reported in a different study.[16] Data about relevant time periods of exposure and about duration of exposure are in general scarce and poor, and more analyses considering both factors seem to be needed.

Control of confounding

The comparison of crude and adjusted estimates in the revised studies (data not shown) is not suggestive of strong confounding effects derived from variables controlled for analysis as potential confounders. Confounding effects derived from unknown and unmeasured variables are still possible, but it is not likely that strong risk factors for AD remain unnoticed. More importantly, the study of interaction effects between ELF-EMF exposure and established risk factors is almost unexplored. This should be a mostly interesting focus for future research in this area.

Exposure to ELF-EMF from non-occupational sources could be suspected as a potential confounding factor. ELF-EMF are generalized exposures through environmental external (e.g. high-voltage power lines, electric transportation systems) and home sources (e.g. internal wiring, electrical appliances). Most of the studies (from North America and Europe) measuring typical non-occupational levels of exposure, included in a recent exhaustive review, reported average levels <0.1 μT.[35] Average magnetic field exposure for 86% of the US population is estimated to be <0.2 μT.[8] Although some electric appliances used at home can cause transient exposures to relatively high magnetic fields,[8,35] electrical appliances used in occupational settings usually are associated to higher magnetic fields and longer exposure periods.

Educational level could be a reasonable potential confounding factor, because its strong relationship to occupation and its reported relationship with AD. However, although it has been suggested that highly educated subjects have a lower risk of AD, results are not always consistent.[3] In this review education or social class were included in adjusted analyses in all the studies but one.[18]

Other occupational exposures related to ELF-EMF exposure are also frequently discussed as a potential source of confounding. Conclusive evidence is not available for an association between several occupational exposures and AD, although only a limited number of exposures have received some attention (including aluminium, solvents, pesticides and lead).[7] Only one study in our review included other occupational exposures (solvents, PCBs) for control in the analyses.[16] Because of their known potential for neurological damage, solvents have been repeatedly suspected and assessed as potential risk factors for AD, but results are mostly contradictory.[6,7] On the other hand, in a recent study increased risk was observed for dementia in women with high occupationally exposure to PCBs (RR 2.04, 95% CI 1.12–3.43), but not in men.[36] As PCBs exposure could be associated to some ELF-EMF exposed occupations, this result merits further research.

Biological mechanisms

Several mechanisms have been proposed and studied in order to explain ELF-EMF potential actions on biological systems,[35] involving melatonin and biosynthetic enzymes in the pineal gland[23,37] (melatonin hypothesis), oxidative stress[38,39] or Ca^{2+} efflux (release of calcium ions from a sample into a surrounding solution) in immune system cells and neurons.[40,41] Other potential pathways, which may be involved in the relationship between ELF-EMF and AD include apoptosis and necrosis in brain cells, effects on biomagnetic particles reported in the human brain or differential levels of electrosensibility among the general population,[35] but their potential nexus with AD remain unknown. In so far, considering available evidence, it seems that biologic pathways by which exposure to ELF-EMF might precipitate pathological changes for AD have not been identified.

Conclusions

This review includes 12 papers—with results from 14 different epidemiological studies, nine case-control studies and five cohort studies—published between 1995 and 2004 on the association between AD and occupational ELF-EMF exposure. Most of the studies put marked efforts into disease and exposure measurements. Pooled estimates for all case-control studies (OR_{pooled} 2.03, 95% CI 1.38–3.00) and for all cohort studies (RR_{pooled} 1.62, 95% CI 1.16–2.27) suggest increased risk of AD for occupational exposure to ELF-EMF. However, there was evidence of statistical heterogeneity in a number of subgroup analyses, and an effect of publication bias could not be excluded. Results were also uncertain regarding different risk for exposed men and women and there was not evidence of a linear dose–response relationship. In these respects, it should be noticed that, frequently, tools used for assessing occupational exposures (such as job exposure matrices) are commonly based in typical male workers exposures. On the other hand, if an association between exposure and disease would really exist, the lack of dose–response relationship could be produced by missclasification in the quantitative assessment of exposure levels or to presence of non-lineal relationships. Our knowledge about the biophysical interaction mechanisms that may explain how ELF-EMF could affect biological systems is still too insufficient to uncritically expect a linear dose–response relationship between exposure and disease.

For future research, results for exposed men and women merit to be evaluated and reported separately. Also, additional efforts should be directed to better characterize ELF-EMF exposure situations for female workers and housewives, as to include sufficient numbers of exposed cases from both sexes. It would be useful to investigate common cut-off points of exposure, particularly $\geqslant 0.2$ and $\geqslant 0.5\,\mu T$. Some focus on potential non-linear relationships is needed too. Also, information on relevant duration and time windows of exposure is mostly absent. And more evidence is needed on interactions between ELF-EMF exposure and established risk factors for AD, such as age at onset, familial aggregation and isoforms of ApoE lipoprotein gene. Confounding by unmeasured and/or unknown causes of AD seems not to cause large bias, but some occupational exposures, such as PCBs, may deserve some attention. Additional research on AD pathogenesis and potentially related ELF-EMF exposure biological actions is highly needed. Last, all the reviewed epidemiological studies focus exclusively on magnetic fields exposure, while experimental research has observed that electric fields could also be a biologically relevant metric.

At present, safety limits for ELF-EMF exposure recommended by institutions and organizations throughout the world are well over levels with observed effects in this review, ranging between 2.75 μT for general public (6.15 μT for exposed workers) at the Canadian Safety Code 6 of 1999, up to 1600 μT at 50 Hz at the National Radiological Protection Board of the United Kingdom.[35] This wide range of variability between different guidelines surely reflects uncertainties regarding ELF-EMF health effects. But most of these exposure guidelines are based on recognized and reproducible acute effects.

Conflict of interest: None declared.

KEY MESSAGES

- A number of epidemiological studies have focused on the relationship between occupational exposure to ELF-EMF and AD.
- A systematic review and meta-analysis of published research on this topic (five cohort studies and nine case-control studies) suggest increased risks of AD, although an effect of publication bias (small studies effect) could not be discarded.
- Increased risk is mostly seen for men occupationally exposed to averaged ELF-EMF levels $\geqslant 0.5\,\mu T$.
- Further research is needed on relevant duration and time windows of exposure, on potential interactions between EMF exposure and other risk factors for AD, and on the biological mechanisms potentially relating ELF-EMF exposure to neurodegenerative changes involved in the development of AD.

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