Int. J. Epidemiol. Advance Access published February 14, 2008

Published by Oxford University Press on behalf of the International Epidemiological Association
International Journal of Epidemiology 2008;1–3
doi:10.1093/ije/dyn024

Commentary: Epidemiological research on extremely low frequency magnetic fields and Alzheimer's disease—biased or informative?

Martin Röösli

Accepted 14 January 2008

In 2006 the worldwide prevalence of Alzheimer's disease was estimated to be 26.6 million; and by 2050, Alzheimer's disease prevalence is expected to quadruple because of the increasing life expectancy in many countries.[1] Although the years of life lost per Alzheimer's disease case are relatively small, the disease causes considerable distress for afflicted families. Moreover, Alzheimer's disease patients need substantial care resulting in substantial costs for the health care system.

Little is known about the causes of Alzheimer's disease. Several genetic mutations have been identified to be associated with early-onset as well as late-onset disease.[2] In addition, environmental factors are assumed to play an important role, particularly for the development of late-onset Alzheimer's disease.[3] Many environmental, occupational or lifestyle risk factors have been hypothesized to increase the risk for Alzheimer's disease, which include exposure to extremely low frequency magnetic fields (ELF-MF). Given the ubiquity of ELF-MF in our everyday environment, such an association would be of high public health relevance. Therefore, any effort to critically evaluate the research on ELF-MF and Alzheimer's disease is highly welcome.

In this issue of the *IJE*, García and colleagues present a meta-analysis of occupational EMF-MF exposure and the risk for Alzheimer's disease.[4] They calculated a pooled odds ratio of 2.03 (95% CI 1.38–3.00) from nine case–control studies and a pooled relative risk of 1.62 (95% CI 1.16–2.27) from five cohort studies. However, they found indication of publication bias and a large statistical heterogeneity between the study results. This raises the question of whether the heterogeneity was a result of the vast methodological differences between the reviewed studies.

Research on ELF-MF exposure and Alzheimer's disease is challenging for several reasons. First, assessing long-term exposure to ELF-MF in our everyday environment is complex. There are several occupations where ELF-MF exposure is well characterized and considerably higher than in the everyday environment. It is thus not surprising that all studies on ELF-MF exposure and Alzheimer's disease have focused on occupational exposure and no study has been performed in the general population so far. All epidemiological studies included in the meta-analysis of García *et al*. collected exposure data retrospectively. Collecting retrospective exposure data from Alzheimer's disease patients is particularly problematic if one has to rely on recollection only, being unable to retrieve the information from routine data sources, such as census data or occupation records. In seven of the 14 reviewed epidemiological studies exposure information had to be obtained by proxy interviews (e.g. from relatives). Proxies may not be well informed about the exposure-relevant circumstances, or may overestimate the ELF-MF exposure of cases if they are aware of the study hypothesis. This approach is particularly prone to bias if proxy interviews were performed with relatives of cases but controls were directly interviewed, as was done in four of the studies.

A further challenge of Alzheimer's disease research is the case ascertainment. Differentiation between Alzheimer's disease and other forms of dementia needs considerable diagnostic effort and, for this reason, is often inaccurate. Five of the reviewed studies relied on diagnosis data from death certificates. It is well recognized that the Alzheimer's disease diagnosis is substantially underreported on death certificates.[5–7] This is less of a problem if the missed cases are completely randomly distributed in the population. Unfortunately, there are reasons to believe that this is not true. Reliability of the Alzheimer's disease diagnosis on death certificates is related to age, ethnicity, survival time, place of residence and potentially to socio-economic status.[8] Such factors are likely to be correlated to occupational exposure. Thus, case ascertainment by death certificates can introduce bias in occupational studies.

Institute of Social and Preventive Medicine, University of Bern, Switzerland. E-mail: roeoesli@ispm.unibe.ch

García and colleagues calculated pooled effect estimates from all available studies. In view of the large statistical heterogeneity and the observed publication bias, I doubt that these pooled effect estimates are meaningful and they should be considered with caution. On the other hand, I appreciate the approach of García and colleagues in comparing pooled estimates according to different study characteristics. This allows evaluation of whether the heterogeneity between studies is explained by different methodological approaches. Overall, Garcia *et al*. found little evidence that heterogeneity between studies was explained by study type, gender, or differences in the exposure level. Surprisingly, studies based on death certificates reported similar risk estimates like studies based on clinical examinations. This finding contradicts a recent statement from the World Health Organization in the Environmental Health Criteria Monograph 238. The statement concluded that 'the evidence for an association between ELF-MF exposure and Alzheimer's disease is inadequate because the higher quality studies that focused on Alzheimer morbidity rather than mortality do not indicate an association'.[9]

García and colleagues could have compared pooled effect estimates for additional methodological factors. It would be of interest to see whether there are systematic differences between studies that collected exposure information by proxy interviews in contrast to studies that used occupational records. In addition, the age distribution of the cases, the control selection method and the participation rate in case–control studies were likely to have affected the study results. A comparison of effect estimates for different occupations (e.g. welders, electricians) could provide information about the role of confounding from co-exposures, which occur in some occupations but not in others.

Overall, however, it seems unlikely that the heterogeneity of the study results can be fully attributed to methodological differences. Thus, the question of whether ELF-MF causes Alzheimer's disease remains open. On the one hand the majority of studies in the meta-analysis suggested an association. Since completion of García's literature search, three additional studies have reported an association between occupational ELF-MF exposure and Alzheimer's disease,[10–12] whereas only one small case–control study did not.[13] It is hard to believe that these associations are entirely due to bias. On the other hand there are several arguments against an association. I give most credit to studies where exposure assessment is based on occupational records (instead of interviews) and diagnosis is based on clinical examination (instead of death certificates). This was done in only one of the 18 published studies. In this study of 30 000 Danish utility employees no evidence for an association between ELF-MF and Alzheimer's disease was observed.[14] However, the study included only 30 Alzheimer's disease cases. Another argument against an association may be the lack of an observed exposure–response association. But it is not clear whether different exposure levels between studies are real or whether they reflect methodological differences in how the exposure was calculated. Indication of publication bias and lack of an established biological mechanism tend to weigh the evidence against an association between ELF-MF and Alzheimer's disease as well.

Nevertheless, a potential association between ELF-MF and Alzheimer's disease merits our attention. Further critical inspections of the available studies are necessary. But we also need well-designed studies that can overcome previous methodological limitations. An ideal study should make sure that accuracy of diagnosis is not related to exposure and that accuracy of exposure information is not related to the disease. This could be achieved by a cohort study using a systematic disease screening and a prospective collection of exposure information. Such a study should not only focus on occupational exposures but also on exposures in our everyday environment, e.g. from power lines.

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