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Commentary: Magnetic field exposure and childhood leukaemia—moving the research agenda forward

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An association between childhood leukaemia and exposure to extremely low-frequency magnetic fields (ELF-MF) has been consistently documented in reviews of this field of research.[1–3] Nevertheless, the relationship remains questionable because the risks were observed at exposure levels where biological effects are not assumed to occur.[4] Animal data have mostly been negative and a plausible and reproducible biological mechanism is still lacking.[5] Studies on adult leukaemia in populations with much higher occupational ELF-MF exposures are inconclusive, though a trend towards an increased risk among highly exposed workers has been noted by the International Commission on Non-Ionizing Radiation Protection.[3] Thus, there is ongoing debate among scientists as to whether the observed statistical association between incidence of childhood leukaemia and exposure to residential ELF-MF is primarily due to bias.

Three main sources of bias have been identified as being potentially important to this field of inquiry: confounding, exposure misclassification, and selection bias. It has previously been shown that confounding due to an unknown, aetiologically relevant correlate of ELF-MF levels (e.g. traffic density) is unlikely to be important in this context.[6,7] Exposure misclassification is likely to be non-differential and is expected to result in an underestimation of the true exposure–response association.[7] In this issue of the journal, Mezei and Kheifets focus on the role of selection bias.[8] Their tutorial presentation of hypothetical examples of selection bias is relevant for the interpretation of case–control studies in general, and in particular for studies dealing with environmental exposures or other factors related to socioeconomic status (SES). The review is also timely given the accumulating evidence on declining participation rates in epidemiological studies, in general, and among controls, in particular.[9] Mezei and Kheifets found some evidence for the presence of control selection resulting in a bias away from the null. However, in view of their hypothetical examples this appears unlikely to be the sole explanation for the observed association.[7,10]

The authors do not discuss the possibility that in the residential ELF-MF studies, controls who live close to power lines may be more willing to participate in such a study and allow measurements in their home. There is some evidence that in case–control studies of brain tumour risk and mobile phone use, controls were more likely to participate if they used a mobile phone.[11] Such selection bias would result in an underestimation of the true exposure–response association and could occur independently of selection biases related to SES. In our view Mezei and Kheifets' work supports the hypothesis that the observed association between childhood leukaemia and exposure to magnetic fields from power lines is unlikely to be explained by selection bias.

We should now move the research agenda on this issue forward: Why are associations between childhood leukaemia and residential ELF-MF so consistently observed? How can we learn more about the nature of the observed associations? What are the biological underpinnings of this relationship? We agree with Mezei and Kheifets that future studies should provide more detail about the recruitment and selection of research participants. Likewise, innovative approaches to reduce bias are welcome. However, we doubt that additional studies of the same type will advance the state of knowledge. Rather, we propose two key areas that should be addressed in future research: (i) better exposure assessment and (ii) the use of susceptibility factors, in particular studying gene–environment interactions. It is essential to identify the biologically relevant exposures. It seems likely that measures of ELF-MF levels (e.g. >0.3 μT) are not a relevant exposure metric. Contact currents or contact voltages have been proposed because they are related to residential EMF levels and biologically relevant doses are likely to occur close to power lines.[12] Another potentially relevant exposure metric is high-frequency transients from power lines.[13]

Developing markers of biological susceptibility might help separating spurious from true associations. As with other 'small' environmental risks, it is unlikely that all children are equally susceptible to EMF, and interactions between genetic factors and EMF could be relevant. Stratification by polymorphisms relevant along the biological pathways have been successfully used in observational epidemiology, including other areas of environmental epidemiology.[14,15] For example, polymorphisms in genes determining the cellular response to xenobiotics or modifying DNA repair mechanisms may be relevant and may identify subjects of increased susceptibility.[16,17] Selection of study

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participants is unlikely to occur by these genetic factors, and taking advantage of such Mendelian randomization[14] could thus strengthen inferences drawn from observational studies and advance our understanding of the biological underpinnings of epidemiological observations. Moving the research agenda forward using biologically relevant exposure metrics and innovative study designs is crucial to clarify the potential risks from ELF-MF to the health of the public.

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