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Comments on "Maternal exposure to extremely low frequency magnetic fields: Association with time to pregnancy and foetal growth".

Frank de Vocht[1] and Igor Burstyn[2]

[1] School of Social and Community Medicine, University of Bristol. Bristol, UK

[2] Department of Environmental and Occupational Health and Department of Epidemiology and Biostatistics, Dornsife School of Public Health, Drexel University, Philadelphia, PA, USA

Corresponding author address: Dr Frank de Vocht. School of Social and Community Medicine, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol, UK, BS8 2PS. Email: frank.devocht@bristol.ac.uk

The recent publication in Environment International by Eskelinen and colleagues in which they assess correlations between maternal exposure to extremely low frequency magnetic fields and time-to-pregnancy and foetal growth provides an interesting contribution to the epidemiological evidence on the extent of such an association (Eskelinen *et al.* ,2016).

Eskelinen *et al.* make reference to two studies conducted in England for which distance to power lines, towers, cables and substations served as a proxy for maternal exposure to (electro)magnetic fields (de Vocht *et al.*, 2014; de Vocht and Lee, 2014), and conclude that their results are not in agreement with de Vocht *et al*. (2014). We greatly sympathize with Eskelinen *et al.* in their attempt to replicate earlier findings with improved individual-level exposure assessment, with the aim of reaching a qualitative conclusion as to whether an association exists. In contrast to the stratification based on distance of maternal address to residential EMF sources, Eskelinen *et al.* were able to use questionnaire data, expert assessment of occupational exposures, and quantitative measurements of residential magnetic field, while they further obtained address information before and during pregnancy in an effort aimed at reduction of exposure measurement error.

Eskelinen *et al.* are correct in that the use of distance measure as a proxy for extremely low frequency magnetic field exposure is associated with non-ignorable measurement error at an individual level and that extensive personal and quantitative exposure measurements would have been preferable (but impossible in de Vocht et al, given the sample size and retrospective nature of the study). However, it is not clear which approach produced lesser degree of measurement error, despite an estimate of validity coefficient of 0.77 for one of the exposure metrics used by Eskelinen *et al*., and what measurement error models are in effect for every exposure metric. Without such knowledge, we cannot claim that either approach to exposure assessment is superior *viz-a-viz* reduction in bias in the association of interest. As a result of the aggregation of subjects into groups on the basis of predictors of exposure, de Vocht *et al.* hoped to achieve the measurement error that has the beneficial features of the quasi-Berkson model, which may result in risk estimates that are too precise, but are less biased than either ignoring measurement error or using individual-level estimates subject to classical measurement error (Kim *et al.*, 2011). However, as de Vocht *et al.* did not use group-specific averages of exposure but constructed groups based on the putative predictors of exposure, the actual measurement error structure and its relative merits and weaknesses, despite intuitive appeal, remain to be understood.

Although careful attention to measurement error is important in epidemiology, we contend that a more important source of uncertainty in de Vocht *et al*. studies is due to missing data and unmeasured confounding. de Vocht and Lee tried to address this by combining multiple imputation and propensity score matching, which indeed resulted in a 50% reduction in the effect size (from on average 212 grams difference to 116 grams), and we interpreted this as a more plausible effect size (de Vocht and Lee, 2014). Ideally, one would treat all of these challenges in a single analytical framework, but lacking such tools, we had to, as all epidemiologists do, make a judgement call on the identity of the critical sources of bias.

Unfortunately, as a result of the extensive individual-level exposure assessment, Eskelinen *et al.* had to sacrifice on sample size, while incurring non-ignorable measurement error as well. The error in exposure estimates at the individual level arise from the use of spot measurements: for example, the known spatial variability of EMF exposure combined with movement of the person for whom exposure is estimated can have non-trivial consequences (Savitz, 1995; Miller and Green, 2010), and for this population has been shown to have low to high correlation with 24-hr personal exposure, depending on the location of sampling (Eskilen *et al.* 2002). Similarly, expert assessment of occupational EMF exposure is notoriously difficult (Kheifets et al. 2009; Savitz, 1995; Miller and Green, 2010), while the inference of personal EMF exposure from appliances based on self-reported information is also known to be subject to considerable error (Savitz, 1995). All these may have contributed to the work of Eskelinen *et al.* being underpowered, as evidenced by the very wide confidence intervals of the effect estimates that they report. It would have been impossible to detect differences in birth weight in the order of the 116 grams reduction on average observed after propensity score matching (de Vocht and Lee, 2014) with, for example, the 95% confidence limits on the order of +/- 500 grams for the highest exposure contrast that Eskelinen *et al.* were able to investigate. It must be noted that the qualitative comparison from the two projects is not possible because exposure metrics that were employed had different scales/units, while variations is also expected as a result of the studies being conducted in different populations and settings . However, in both cases the effects were estimated over largest possible contrast in exposure to maximize power. In this sense, the effect estimates are the largest that the authors were able to obtain.

Eskelinen *et al.* in their analyses reported a mean difference in grams of -45 with a 95% confidence interval of -547 grams to 456 grams for all spot measurements and -142 grams

(95%CI -505, 221) for bedroom spot measurements, and as such these point estimates in combination with their precision are in good agreement with the updated de Vocht and Lee finding of -116 grams (95% CI -224, -7). The statement by Eskelinen *et al.* that "The results of the present study do not support the conclusion that ELF MF exposure would be associated with reduction in birth weight" therefore seems too strong. Despite the differences between both studies, both support that the evidence of a 'weak' effect across the full ranges of investigates exposures cannot be ruled out, while the likelihood of a 'strong' effect is remote.

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