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Residential exposure to extremely low-frequency magnetic fields and risk of childhood leukaemia, CNS tumour and lymphoma in Denmark

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Background: We previously reported that children exposed to elevated extremely low-frequency magnetic fields (ELF-MF) had a five to six times higher risk of leukaemia, central nervous system (CNS) tumour and malignant lymphoma. Here we extend the study from 1968 to 1986 through 2003.

Methods: We included 3277 children with leukaemia, CNS tumour or malignant lymphoma during 1968–2003 recorded in the Danish Cancer Registry and 9129 controls randomly selected from the Danish childhood population. ELF-MF from 50 to 400 kV facilities were calculated at the residences.

Results: For recently diagnosed cases (1987–2003), the relative risk (RR) was 0.88 (95% confidence interval (CI): 0.32–2.42), while for the total period (1968–2003) it was 1.63 (95% CI: 0.77–3.46) for leukaemia, CNS tumour and malignant lymphoma combined for exposures $\geq 0.4 \mu\text{T}$ compared with $< 0.1 \mu\text{T}$. These results were based on five cases (recent period) and 11 cases (total period) in the highest exposure group.

Conclusions: We did not confirm the previous finding of a five- to six-fold higher risk for leukaemia, CNS tumour and malignant lymphoma when including data from the more recent time period. For the total time period, the results for childhood leukaemia were in line with large pooled analyses showing RRs between 1.5 and 2.

The International Agency for Research on Cancer has classified extremely low-frequency magnetic fields (ELF-MF) as ‘possibly carcinogenic to humans’ (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2002) based on epidemiological studies showing an association with childhood leukaemia. In 2000, two pooled analyses showed relative risks (RR) for childhood leukaemia of 1.7 and 2.0 in association with exposure to ELF-MF > 0.3 and $\geq 0.4 \mu\text{T}$, respectively, compared with $< 0.1 \mu\text{T}$ (Ahlbom *et al*, 2000; Greenland *et al*, 2000). A pooled analysis of studies

published after 2000 showed an RR of 1.4 in association with exposure to $\geq 0.3 \mu\text{T}$ and of 1.5 with exposures $\geq 0.4 \mu\text{T}$ (Kheifets *et al*, 2010a). Although epidemiological studies have consistently shown associations between ELF-MF and childhood leukaemia, the lack of support from experimental studies and the absence of a biological explanation have questioned whether the association is causal or rather owing to methodological limitations such as selection bias, exposure misclassification, confounding and/or chance (WHO, 2007; Schüz and Ahlbom, 2008). Some studies

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have found an association between exposure to ELF-MF and risk of central nervous system (CNS) tumour and lymphoma (Wertheimer and Leeper, 1979; Savitz *et al*, 1988; Olsen *et al*, 1993a; Verkasalo *et al*, 1993), but no consistent association has been observed (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2002; Kheifets *et al*, 2010b). On the basis of a total of 1707 cases diagnosed before the age of 15 between 1968 and 1986, we previously reported markedly increased RRs for leukaemia, CNS tumour and malignant lymphoma in children in association with residential exposure to ELF-MF from high-voltage facilities above $0.4 \mu\text{T}$ (Olsen *et al*, 1993a), but confidence intervals were wide. Controls were selected at random among the entire Danish childhood population and the exposure assessment was based on calculation of ELF-MF and required no contact with individuals, thus minimizing the potential for selection bias (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2002). However, only six cases were exposed to $\geq 0.4 \mu\text{T}$.

The aim of the present study is to extend the previous study with children diagnosed with leukaemia, CNS tumour and malignant lymphoma between 1987 and 2003.

MATERIALS AND METHODS

Olsen *et al* (1993a) identified cases, selected controls, traced addresses and assessed exposure for cases diagnosed between 1968 and 1986. We used the same cases and controls from the study by Olsen *et al* (1993a) and repeated these procedures for cases diagnosed between 1987 and 2003.

Cases and controls. The study was approved by the Danish Data Protection Agency (2007-41-0239). All children diagnosed with a first primary leukaemia, CNS tumour or malignant lymphoma in Denmark before the age of 15 years during the period 1968–2003 were identified in the nationwide Danish Cancer Registry including information about the date of diagnosis and tumour characteristics (Gjerstorff, 2011). Children with any previous cancer diagnosis were not eligible as case. Two controls for each leukaemia case, three for each CNS tumour and five for each case of malignant lymphoma were selected randomly by incidence density sampling from the entire Danish childhood population. Cases and controls were individually matched by sex and year of birth. All children born in Denmark, who were alive without a previous cancer diagnosis and living in Denmark at the time of diagnosis of their matched case, were eligible to become a control in the study.

Exposure assessment. The addresses of cases and controls were identified in the Danish Civil Registration System using the personal identification number, which is a unique identifier of each Danish citizen allowing accurate linking between Danish registers. The Danish Civil Registration System contains information about vital status and history of migration, including the dates of these events, as well as present and historical addresses (municipality, road, house number and dates of moving) (Pedersen, 2011). Parental addresses during pregnancy were also retrieved from this registry. Addresses located more than 150, 75 or 35 m from an overhead line or transformer substation with 220–400, 132–150 and 50–60 kV, respectively, and more than 20, 5 or 2.5 m from an underground cable with 220–400, 132–150 and 50–60 kV, respectively, were considered exposed to $< 0.1 \mu\text{T}$. Experts at the utility companies calculated the strength of the ELF-MF at addresses within these distance criteria based on distance to the installation, the type of line, type of pylons (height, distance between pylons, distance between phases), ordering of phases, current flow in the line and date(s) of construction and any reconstructions (Olsen *et al*, 1993a; Jensen *et al*, 1994); the experts were blind to the case/control status of the child having lived at the

address. Exposure was calculated for all addresses of the child from 9 months before birth until the diagnosis (and an equivalent date for the controls) and the highest level at any address of each child was considered in the analyses. The ELF-MF was measured at six addresses close to 132–400 kV overhead lines; measured and calculated values correlated well ($r = 0.99$; Olsen *et al*, 1993b). The same approach for the estimation of exposure was applied for cases diagnosed during the period 1987–2003.

For cases diagnosed during 1968–1991 and the matched controls, we had information on some potential confounders, namely domestic radon, traffic related air pollution, maternal age, birth order; and for leukaemia cases and controls, additionally socioeconomic status of the municipality (the average gross income of the municipality) and degree of urbanization. Further description of these potential confounders can be found in our previous papers (Raaschou-Nielsen *et al*, 2000; Raaschou-Nielsen *et al*, 2008; Pedersen *et al*, 2014).

Statistical analysis. The association between ELF-MF and childhood leukaemia, CNS tumour and malignant lymphoma was analysed with conditional logistic regression models (PROC PHREG in SAS 9.3), providing RRs and 95% confidence intervals (CIs). Analyses were conducted separately for each cancer type and for all three cancers combined. RRs were estimated for the period 1968–1986, 1987–2003 and for the total period 1968–2003. Risk was estimated for exposures to 0.1–0.39 and $\geq 0.4 \mu\text{T}$ relative to $< 0.1 \mu\text{T}$, which corresponds to our previous study (Olsen *et al*, 1993a).

In a subset of the data (children diagnosed during 1968–1991), we adjusted for domestic radon, traffic related air pollution, maternal age, birth order; and the analyses for leukaemia were additionally adjusted for socio-economic status of the municipality and degree of urbanization.

RESULTS

Results on the basis of cases diagnosed during the more recent time period, 1987–2003, showed RRs of 0.80 (95% CI: 0.16–4.12), 0.75 (95% CI: 0.16–3.53), 1.67 (95% CI: 0.17–16.02) and 0.88 (95% CI: 0.32–2.42) for leukaemia, CNS tumour, malignant lymphoma and for the three childhood cancers combined in association with exposure to $\geq 0.4 \mu\text{T}$ compared with $< 0.1 \mu\text{T}$. These RRs are markedly lower than those based on cases diagnosed 1968–1986 (Tables 1 and 2).

For the total period, 1968–2003, RRs were 1.67 (95% CI: 0.51–5.46), 1.33 (95% CI: 0.41–4.33), 2.50 (95% CI: 0.46–13.65) and 1.63 (95% CI: 0.77–3.46), for leukaemia, CNS tumour, malignant lymphoma and for the three cancers combined in association with exposure to $\geq 0.4 \mu\text{T}$ compared with $< 0.1 \mu\text{T}$. Even for the total time period, the confidence intervals were wide.

Adjustment for domestic radon, traffic related air pollution, maternal age, birth order and for leukaemia, additionally socioeconomic status of the municipality and urbanization had no substantial effect on the results (data not shown).

DISCUSSION

We found an RR below one for leukaemia, CNS tumour and malignant lymphoma combined in association with exposure to ELF-MF for the most recent time period (1987–2003), based on five exposed cases. An RR above one was observed for leukaemia, CNS tumour and malignant lymphoma combined among children exposed $\geq 0.4 \mu\text{T}$ for the combined time period (1968–2003). Considering the total time period, only 11 cases were exposed to $0.4 \mu\text{T}$ or more, hence, statistical uncertainty of all RRs was high.

Table 1. Exposure to ELF-MF and risk for leukaemia, central nervous system tumour and malignant lymphoma combined

Period of diagnosis	Exposure (μT)	Cases (%)	Controls (%)	Total	RR (CI)
1968–1986 ^a	<0.1	1697 (99.4)	4768 (99.6)	6465	1.00
	0.1–0.39	4 (0.2)	17 (0.4)	21	0.65 (0.22–1.93)
	≥ 0.4	6 (0.4)	3 (0.1)	9	5.72 (1.40–23.36)
	Total	1707 (100)	4788 (100)	6495	
1987–2003	<0.1	1553 (98.9)	4294 (98.9)	5847	1.00
	0.1–0.39	12 (0.8)	31 (0.7)	43	1.18 (0.60–2.33)
	≥ 0.4	5 (0.3)	16 (0.4)	21	0.88 (0.32–2.42)
	Total	1570 (100)	4341 (100)	5911	
1968–2003	<0.1	3250 (99.2)	9062 (99.3)	12312	1.00
	0.1–0.39	16 (0.5)	48 (0.5)	64	0.98 (0.55–1.74)
	≥ 0.4	11 (0.3)	19 (0.2)	30	1.63 (0.77–3.46)
	Total	3277 (100)	9129 (100)	12406	

Abbreviations: ELF-MF = extremely low-frequency magnetic field; CI = confidence interval; RR = relative risk.

^aResults from this time period differ slightly from those reported previously (Olsen et al, 1993a) owing to slight differences in methods applied.

Table 2. Exposure to ELF-MF and risk for leukaemia, central nervous system tumour and malignant lymphoma

Type of cancer	Period of diagnosis	Exposure (μT)	Cases	Controls	Total	RR (CI)
Leukaemia	1968–1986 ^a	<0.1	829	1658	2487	1.00
		0.1–0.39	1	7	8	0.29 (0.04–2.32)
		≥ 0.4	3	1	4	6.00 (0.62–57.68)
		Total	833	1666	2499	
	1987–2003	<0.1	697	1395	2092	1.00
		0.1–0.39	4	6	10	1.33 (0.38–4.73)
		≥ 0.4	2	5	7	0.80 (0.16–4.12)
		Total	703	1406	2109	
	1968–2003	<0.1	1526	3053	4579	1.00
0.1–0.39		5	13	18	0.77 (0.27–2.16)	
≥ 0.4		5	6	11	1.67 (0.51–5.46)	
Total		1536	3072	4608		
Central nervous system tumour	1968–1986 ^a	<0.1	621	1863	2484	1.00
		0.1–0.39	1	8	9	0.38 (0.05–3.00)
		≥ 0.4	2	1	3	6.00 (0.54–66.14)
		Total	624	1872	2496	
	1987–2003	<0.1	691	2077	2768	1.00
		0.1–0.39	7	15	22	1.42 (0.57–3.53)
		≥ 0.4	2	8	10	0.75 (0.16–3.53)
		Total	700	2100	2800	
	1968–2003	<0.1	1312	3940	5252	1.00
0.1–0.39		8	23	31	1.04 (0.46–2.36)	
≥ 0.4		4	9	13	1.33 (0.41–4.33)	
Total		1324	3972	5296		
Malignant lymphomas	1968–1986 ^a	<0.1	247	1247	1494	1.00
		0.1–0.39	2	2	4	5.00 (0.70–35.50)
		≥ 0.4	1	1	2	5.00 (0.31–79.95)
		Total	250	1250	1500	
	1987–2003	<0.1	165	822	987	1.00
		0.1–0.39	1	10	11	0.50 (0.06–3.91)
		≥ 0.4	1	3	4	1.67 (0.17–16.02)
		Total	167	835	1002	
	1968–2003	<0.1	412	2069	2481	1.00
0.1–0.39		3	12	15	1.25 (0.35–4.43)	
≥ 0.4		2	4	6	2.50 (0.46–13.65)	
Total		417	2085	2502		

Abbreviations: ELF-MF = extremely low-frequency magnetic field; CI = confidence interval; RR = relative risk.

^aResults from this time period differ slightly from those reported previously (Olsen et al, 1993a) owing to slight differences in methods applied.

In this population-based case-control study, we included all children diagnosed in Denmark with leukaemia, CNS tumour and malignant lymphoma during a period of 36 years. Cases were drawn from the complete nationwide Danish Cancer Registry (Gjerstorff, 2011), and the controls were sampled at random from the entire Danish childhood population recorded in the Danish Civil Registration System minimizing the potential for selection bias. Exposure to ELF-MF at residences was calculated by experts at the utility companies on the basis of detailed information about distances and characteristics of the high-voltage facilities. The calculations were undertaken without knowledge about the case/control status of the child who had lived at the address, minimizing the risk for differential misclassification of exposure.

Cases and controls were matched by sex and year of birth, and in a subset of data including cases diagnosed 1968–1991 analyses were adjusted for domestic radon, traffic-related air pollution, maternal age, birth order and, for leukaemia cases and controls, additionally socio-economic status of the municipality and urbanization. Adjustment for these potential confounders had no effect. The major limitation of the present study, inherent in the study objective, is the low number of exposed cases owing to the low prevalence of the exposure under study and the low incidence of childhood cancer.

The RR of 0.88 for leukaemia, CNS tumour and malignant lymphoma combined in the most recent time period in the present study contrasts the associations reported previously for the same three cancers in Denmark 1968–1986, where RRs of 5.6 were found for exposures $\geq 0.4 \mu\text{T}$ compared with $< 0.1 \mu\text{T}$. Lower RRs in the more recent period compared with the previous time period were also seen for all three cancers separately, although with a smaller difference in the estimates for lymphoma. Bunch *et al* (2014) found a similar pattern of weaker associations between proximity to power lines and childhood leukaemia in the 1990s–2000s than in the 1960s–1980s in the United Kingdom and suggested that the decrease in risk over time might be due to a change in characteristics of the population living close to power lines. A weakening over time of the association between exposure to ELF-MF and leukaemia, CNS tumour and malignant lymphoma could be seen as an argument against a causal interpretation of the previously observed association; however, the interpretation of the differences over time is not clear. The different results might be explained by a confounding factor, which has changed over time, although – given that hardly any risk factors have been established for those cancers – we do not have a specific suggestion of which factors that might be. Bunch *et al* (2014) suggested changes in the houses that have been built close to power line or changes in the lifestyle or behaviour of people who live close to power lines as possible confounding factors that could have changed over time, but this remains speculative. Another possible explanation is chance as analyses were based on few exposed cases. The proportion of exposed cases was similar for the two periods 1968–1986 and 1987–2003 (0.4% and 0.3%). However, the proportions of exposed controls were 0.1% in the early period and 0.4% in the latter. This may suggest selection bias in the controls. However, as the same approach with the controls drawn randomly from the entire Danish childhood population was applied for both time periods, selection bias is unlikely. The higher proportion of exposed controls in the more recent time period may reflect an increase in high-voltage facilities over time. We cannot, however, explain why such increase should only be seen in controls and not cases.

We assessed exposure from 50 to 400 kV facilities including overhead power lines, transformer substations and underground cables, but other sources of ELF-MF exposure such as exposure from lower voltage lines, electric appliances in the home or indoor wiring were not included, which may result in exposure misclassification. Distribution lines ($< 50 \text{ kV}$), which in Denmark

are either buried or constructed as three-phase symmetrical overhead line, and electrical appliances, which are only used intermittently and short-term, hardly contributes to elevated daily averages of ELF-MF (Jensen *et al*, 1994; Schüz *et al*, 2000). Indoor wiring occasionally leads to exposures similar to those from nearby power lines (Maslanyj *et al*, 2009). However, as the overall exposure prevalence is very low, we would not expect even a low sensitivity of the exposure measure to introduce notable bias in the effect estimate (Schüz, 2007), so that non-differential misclassification of exposure is an unlikely explanation for our finding of attenuated risk over time.

For the total time period, the estimated RRs for leukaemia are consistent with previous pooled analyses suggesting RRs between 1.5 and 2 for $\geq 0.4 \mu\text{T}$ (Ahlbom *et al*, 2000; Greenland *et al*, 2000; Kheifets *et al*, 2010a; Zhao *et al*, 2014).

CONCLUSION

We previously reported that children with residential exposure to ELF-MF above $0.4 \mu\text{T}$ had a five to six times higher risk of leukaemia, CNS tumour and malignant lymphoma in the period 1968–1986. We could not confirm this finding including more recent data of children diagnosed during 1987–2003. For the total time period, the results for childhood leukaemia are in line with previous pooled analyses showing a 1.5- to two-fold increase in risk.

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