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Pooled analysis of recent studies of magnetic fields and childhood leukemia

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ABSTRACT

Background: Over forty epidemiologic studies have addressed an association between measured or calculated extremely-low-frequency magnetic fields (MF) and childhood leukemia. These studies have been aggregated in a series of pooled analyses, but it has been 10 years since the last such.

Methods: We present a pooled analysis combining individual-level data (24,994 cases, 30,769 controls) from four recent studies on MF and childhood leukemia.

Results: Unlike previous pooled analyses, we found no increased risk of leukemia among children exposed to greater MF: odds ratio (OR) = 1.01, for exposure ≥0.4 μT (μT) compared with exposures <0.1 μT. Similarly, no association was observed in the subset of acute lymphoblastic leukemia, birth homes, studies using calculated fields, or when geocoding accuracy was ignored. In these studies, there is a decline in risk over time, also evident when we compare three pooled analyses. A meta-analysis of the three pooled analyses overall presents an OR of 1.45 (95% CI: 0.95–2.20) for exposures ≥0.4 μT.

Conclusions: Our results are **not** in line with previous pooled analysis and show a decrease in effect to no association between MF and childhood leukemia. This could be due to methodological issues, random chance, or a true finding of disappearing effect.

1. Background

Over forty epidemiologic studies have addressed an association between measured, calculated, or imputed extremely low frequency (ELF) magnetic fields (MF) and childhood leukemia (Kheifets and Swanson, 2014; Swanson et al., 2019). Exposure assessment in these studies was based on a variety of proxy measures for historical exposure, which included: wire codes, where exposure is categorized on the basis of the type of electric utility wiring adjacent to the residence and the distance from that wiring to the residence; measured fields, spot or longer-term measurements, usually if subjects still lived in the residence of interest; and calculated magnetic fields, where exposure is based on distance, power-line load data, and other information for power lines specific to the time period of interest. As an estimate of magnetic fields, wire codes introduce considerable misclassification (Kheifets et al., 1997) and, as more direct measurement or calculation methods have been developed, their use in epidemiologic studies has largely been superseded.

The association between exposure to extremely-low-frequency magnetic fields (ELF-MF) and childhood leukemia reported in these studies has led to the classification of ELF-MF as "possibly carcinogenic to humans" by the International Agency for Research on Cancer and WHO Environmental Health Criteria (IARC, 2002; World Health Organization, 2007). Epidemiological studies, and in particular pooled analyses, have played a pivotal role in these assessments.

There have been several pooled analyses to date, conducted at different points in time and using different inclusion criteria.

Greenland et al. (Greenland et al., 2000) identified nineteen studies eligible for inclusion in their pooled analysis (i.e. studies with any quantitative magnetic field measures or enough information to approximate wire codes), published by 1999. Pooling twelve studies with measured or calculated fields, with a total of 2656 cases and 7084 controls, they found a combined estimated odds ratio (OR) of 1.68 (95%

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confidence interval (CI), 1.23–2.31) for exposures >0.3 μT (μT) compared with exposures <0.1 μT, controlling for age, sex, and study (Greenland et al., 2000).

Conducted at about the same time, but with tighter inclusion criteria, focusing on population-based studies with fields measured over at least a day or calculated, Ahlbom et al. (2000) included nine studies with a total of 3203 cases and 10,338 controls. There, the combined estimated OR was 2.00 (95% CI, 1.27–3.13) for exposures ≥0.4 μT compared with exposures <0.1 μT, controlling for age, sex, socioeconomic status (SES) (in measurement studies only), and East/West (in the German study only). The measurement studies alone reported an OR of 1.87 (95% CI: 1.10–3.18), with the calculated fields studies reporting an OR of 2.13 (95% CI: 0.93–11.37) (Ahlbom et al., 2000).

Of fourteen additional studies published after 2000, Kheifets et al. (2010), using similar inclusion criteria to Ahlbom et al. identified seven eligible studies (i.e. those that provided data separately for childhood leukemia, were population-based, and provided measured or calculated residential magnetic fields inside a home) with a total of 10,865 cases and 12,853 controls. The OR (95%CI) for exposures ≥0.4 μT compared with <0.1 μT was 1.46 (0.80–2.68). Without the most influential study, from Brazil, which is suspected to have a particular source of potential bias in addition to biases that may be present in all studies, the ORs increased (for≥0.4 μT compared with <0.1 μT OR: 2.02 (0.87–4.69)) and became similar to previous pooled analysis (Kheifets et al., 2010). Similar estimates were obtained for measurement (OR: 1.41, 95% CI: 0.73–2.71) and calculated fields studies (OR: 1.68, 95% CI: 0.24–8.38).

A fourth pooled analysis was designed principally to specifically test the hypothesis that the childhood leukemia association is stronger for night-time exposure than for total exposure (Schuz et al., 2007). The findings did not support the night–time association with childhood leukemia. However, all four pooled analyses, while focusing on overlapping, but distinct sets of studies, came to similar conclusions.

It has been 10 years since the last pooled analysis of childhood leukemia and magnetic fields (Kheifets et al., 2010). Since then, several large studies have been published with either new results (California (Kheifets et al., 2017), Italy (Salvan et al., 2015)) or major updates to existing studies (United Kingdom (UK) (Bunch et al., 2016) and Denmark (Pedersen et al., 2015)).

In California, the California Power Line Study (CAPS) is a large records-based case-control study of childhood leukemia risk and calculated exposure to magnetic fields from power lines (Kheifets et al., 2015). Strengths of CAPS include its population-based design, a relatively large sample size of 5788 childhood leukemia cases and 5788 matched controls, and an improved exposure assessment. CAPS did not provide clear evidence of risk associated with exposure to magnetic fields from power lines (Kheifets et al., 2017); the OR was 1.5 (95% CI: 0.7–3.2) for the highest exposure group (≥0.4 μT).

In Italy, SETIL is a population-based case-control study of fourteen Italian regions. This was an interview-based study, followed by a 48-h measurements if the child was still living in the home inhabited one year before the date of diagnosis (or reference date for controls). The main analysis was based on 409 cases and 569 controls, with few subjects in the highest exposure category (which was only >0.2 μT given the low number of subjects in the higher exposure categories). There was no exposure-outcome relationship, with an OR of 1.72 (95% CI: 0.95–3.13) for an intermediate exposure group and an OR of 0.42 (95% CI 0.13–1.37) for the high exposure group, based on only four cases.

In the United Kingdom, a study initially found an association between childhood leukemia and the distance between home address at birth and the nearest high-voltage overhead line (Draper et al., 2005), and, although very imprecisely, the resulting calculated magnetic field (Kroll et al., 2010). However, the apparent risk was found to extend out to some 600 m (m), a distance greater than would be expected if magnetic fields from the high-voltage lines were a causal agent, since the fields, which typically fall at least inversely with distance, are very small beyond 100 m. This study was extended to cover more recent time periods and lower line voltages. The updated study found higher risks in the earlier decades declining in the latest decades, with no overall elevated risks (Bunch et al., 2016).

Similarly, in Denmark, an initial study (covering the years 1968–1986) reported an OR of 6.0 (95% CI: 0.8 to 44) for calculated fields ≥0.4 μT and childhood leukemia, albeit based on only 3 cases and 1 control (Olsen et al., 1993). This study was then extended through 2003, and the updated OR reduced to 1.67 (95% CI: 0.51–5.46), and the increased risk was limited to an earlier time period (Pedersen et al., 2015).

Based on a recent meta-analysis of 41 studies (Swanson et al., 2019), it appears that there is a decline in reported risk from the mid-1990s to now. Pooled analysis would be a preferred approach to confirm this. Pooled analysis, considered the gold standard for synthesizing results from multiple studies, allows for comparison across different metrics and studies for derivation of statistically more stable results, free of artifacts introduced by analytic differences (Kheifets et al., 2006). Pooled analysis uses raw data from the component studies and thus can apply identical analyses to all included studies. The choices of, for example, cut points, reference groups, and metrics in a pooled analysis may differ from the choices made in the original studies and may result in changes in the study-specific effect estimates.

In this paper, we present a pooled analysis based on primary data from four recent studies on magnetic fields and childhood leukemia, to provide a more recent update to previously conducted pooled analyses assessing whether there is an association between EMF exposure and childhood leukemia and whether, indeed, there has been a decline in risk over time. We use similar approaches and inclusion criteria to Ahlbom et al. (2000) and the first update, Kheifets et al. (2010).

2. Methods

The present study is a pooled analysis combining raw individual-level data from multiple studies (Debray et al., 2015; Stewart et al., 2012). We searched the published literature through PubMed and EMF database, as well as references of papers, to identify relevant recent studies on residential magnetic field exposure and childhood leukemia published since the previous pooled analyses in 2010 (Kheifets et al., 2010). Following the previous criteria, to be included, studies had to: provide data for children, provide data separately for childhood leukemia, be population based, and provide measured or calculated residential magnetic fields inside a home. We identified nine studies (Table 1), four of which met our inclusion criteria. The following five studies did not; the reasons are detailed in Table 1:

One study (Auger et al., 2019) was a retrospective cohort study of childhood cancer, which enrolled 784,944 children born 2006–2016 in Quebec, Canada who were followed for a decade. Of 1114 incident cases of cancer, 248 were acute lymphoblastic leukemia (ALL). Exposure was assessed as the distance between centroids of six-digit postal codes of the residence and the nearest transformer station or transmission line. Residential proximity to transmission lines was not associated with childhood cancer overall or with childhood leukemia during earlier years (details for childhood leukemia are not given). At exactly 10 years of age, a distance of <100 m was associated with a hazard ratio of 1.30 (95% CI: 0.99–1.70) for ALL.

A small study from the Czech Republic (Jirik et al., 2012) did not report any associations with measured magnetic fields (OR: 0.9, 95% CI: 0.37–2.22). It used hospital controls, and also lacked crucial methodologic details, such as time period and how cases and controls were selected.

Two Iranian studies (Sohrabi et al., 2010; Tabrizi and Bidgoli, 2015) reported high risks but used hospital controls and did not have measured or calculated fields, as well as lacking crucial methodologic details.

Finally, a case-control study in Mexico (Nunez-Enriquez et al., 2020) of 290 cases of childhood leukemia, reported a relative risk of 1.87 (1.04–3.35) for measured fields of ≥0.4 μT. Higher risks were also

Table 1
Characteristics of studies in new pooled analysis of childhood leukemia and MF exposure.

Study	1st Author/Year	Ca/Co	Years of Diagnosis	Age	Measured Fields	Calculated Fields from	Highest MF Category	Published OR (95% CI)	
Included									
California	Kheifets (2017)	5788/5788	1988–2008	0-<16		60–500 kV	≥0.4 μT	1.52 (0.71–3.25)	
Denmark	Pedersen (2015)	1536/3072	1968–2003	0-<16		132–400 kV	≥0.4 μT	1.67 (0.51–5.46)	
Italy	Salvan (2015)	601/893	1998–2001	0–10	24–48 h		>0.2 μT	0.88 (0.38–2.00)	
UK	Bunch (2016)	16,604/20,976	1962–2010	0–16		132–400 kV	≥0.4 μT	0.50 (0.15–1.62)	
Not Included									**Reason for Exclusion**
Canada	Auger (2019)	248/–	2006–2016	0-<12		<100 m		1.30 (0.99–1.70)	Distance Only
Czech Republic	Jirik (2012)	82/81		0-<15			>0.4 μT	0.90 (0.37–2.22)	Hospital Controls
Iran	Tabrizi (2015)	22/100	2013–2014	0-<12				3.65 (1.69–7.87)	Hospital Controls; No Field Data
	Sohrabi (2010)	300/300		0–18		<600 m		2.61 (1.73–3.94)	Hospital Controls
Mexico	Núnez-Enríquez (2020)	290/407	2010–2011	0-<16			≥0.4 μT	1.87 (1.04–3.35)	Hospital Controls

Ca cases, *Co* controls, *MF* magnetic fields, *OR* odds ratio, *CI* confidence interval, *μT* microtesla, *UK* United Kingdom, *m* meter.

reported for higher cut points. A relatively high cut point of <0.2 μT was used to define the reference category. This study also used hospital controls.

Four studies were therefore included in this current analysis: one each from California, Denmark, Italy, and the UK. We had planned on including results on magnetic fields from a large French study (Sermage-Faure et al., 2013) which are anticipated, but they were not available in time for this pooling effort.

2.1. Material

All studies were case-control studies matched on at least age and sex (California, Denmark) and additionally, local geographic location (Italy, UK). The age of diagnosis was 0–16 years, except for Italy, which included children only through age 10. All studies provided information on age, sex, and SES. The study periods ranged from 1962 to 2010.

California, Denmark, and the UK all utilized calculated magnetic fields, based on proximity to overhead power lines (Table 1). Calculated fields were modeled based on distance between the subject's home and relevant lines, taking into account historical load conditions and other line characteristics. California and UK provided calculated fields for birth homes. In Denmark, exposure was calculated for all addresses the child lived in from 9 months before birth until diagnosis (or an equivalent date for the controls), and the highest exposure level at any address of each child was used in the main analysis. In Italy, the study focus was on the home occupied one year prior to diagnosis, which often was the home occupied through diagnosis, and sometimes, since birth. Magnetic fields available for a few additional non-diagnosis homes were also used in our analysis. Italy used measurements in the childhood bedroom longer than 24 h (for 80% of study subjects the measurements were 48 h long). Long-term measurements can be affected by short duration exposure to high fields, e.g., from domestic electrical appliances, which are not part of the background field at home. We followed previous pooled analysis and used geometric means of the long-term measurements in our analyses to reduce such effects.

All variables were recoded to make them as compatible as possible.

2.2. Statistical analysis

The primary analyses used a traditional pooled analysis design, where data from all studies were entered simultaneously into a single logistic regression model. Three different models were assessed for model-fit: a random effects model with random intercepts for both study and exposure; a mixed-effects model with random intercepts for study; and a fixed-effects model which included study as a categorical variable.

The main analysis estimated risk of childhood leukemia associated with MF and was restricted to participants who had study-defined accurate geocoding. All cases of leukemia and primary controls were included; a mixture of birth and diagnosis homes was used, based on available data, with the home used in prior publications given preference. To use as many cases and controls as possible to increase the flexibility of the analysis (and for other methodological reasons as described in Greenland et al. (2000)), we ignored matching and instead used unconditional logistic regression with adjustments for age, sex, and study. For comparison, the analysis was repeated several ways: 1) adjusting for age at diagnosis, sex, and study only; 2) adjusting for age, sex, study, and SES; 3) conditional logistic regression adjusted for study only; and 4) conditional logistic regression with adjustment for study and SES.

Subgroup analyses were performed as well, including a subset of just birth homes; a subset of just calculated fields; a subset of only ALL cases and controls; and by time period based on the distribution of controls' birth years (1953–1983, 1984–1994, 1995–2010). Sensitivity analyses included: assessing different category breakdowns for MF and including all observations, regardless of geocoding quality. Finally, estimates were compared and combined, using a random-effects meta-analysis model,

Table 2
Odds ratios for childhood leukemia by category of magnetic field and model used.

Model[a]	MF (μT)	Study									
		California		Denmark		Italy		UK		Total	
		Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)	Ca/Cos	OR (95% CI)	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)
ULR, adjusted for age and sex	<0.1	4824/4782	1.00 (ref)	1405/2848	1.00 (ref)	552/829	1.00 (ref)	15060/18642	1.00 (ref)	21841/27101	1.00 (ref)
	0.1-<0.4	38/42	0.90 (0.58–1.40)	5/13	0.79 (0.28–2.22)	47/56	1.26 (0.84–1.89)	8/16	0.62 (0.26–1.44)	98/127	0.99 (0.76–1.30)
	≥0.4	17/11	1.52 (0.71–3.25)	5/6	1.67 (0.51–5.49)	2/8	N/A[b]	2/9	N/A[b]	26/34	0.95 (0.57–1.60)
ULR, adjusted for age, sex, SES	<0.1	46944655/	1.00 (ref)	1405/2848	1.00 (ref)	552/829	1.00 (ref)	15060/18642	1.00 (ref)	21711/26974	1.00 (ref)
	0.1-<0.4	38/41	0.93 (0.60–1.44)	5/13	0.77 (0.28–2.18)	47/56	1.28 (0.85–1.91)	8/16	0.61 (0.26–1.43)	98/126	1.00 (0.77–1.31)
	≥0.4	17/11	1.50 (0.70–3.20)	5/6	1.65 (0.50–5.41)	2/8	N/A[b]	2/9	N/A[b]	26/34	0.95 (0.57–1.60)
CLR	<0.1	5733/5735	1.00 (ref)	1526/3053	1.00 (ref)	459/678	1.00 (ref)	16592/20946	1.00 (ref)	24310/30412	1.00 (ref)
	0.1-<0.4	38/42	0.91 (0.58–1.41)	5/13	0.77 (0.27–2.16)	40/41	1.55 (0.95–2.53)	8/20	0.55 (0.24–1.26)	91/116	1.01 (0.76–1.34)
	≥0.4	17/11	1.55 (0.72–3.30)	5/6	1.67 (0.51–5.46)	2/6	N/A[b]	4/10	0.53 (0.16–1.70)	28/33	1.08 (0.65–1.80)
CLR, adjusted for SES	<0.1	54665468/	1.00 (ref)	1506/2983	1.00 (ref)	459/678	1.00 (ref)	16592/20946	1.00 (ref)	24023/30075	1.00 (ref)
	0.1-<0.4	36/40	0.90 (0.57–1.41)	5/12	0.82 (0.29–2.32)	40/41	1.52 (0.92–2.50)	8/20	0.55 (0.24–1.26)	89/113	1.02 (0.76–1.36)
	≥0.4	17/11	1.54 (0.72–3.29)	5/6	1.56 (0.47–5.13)	2/6	N/A[b]	4/10	0.50 (0.16–1.63)	28/33	1.07 (0.64–1.78)

MF magnetic fields, μT microtesla, UK United Kindom, OR odds ratio, CI confidence interval, ULR unconditional logistic regression, CLR conditional logistic regression, SES socioeconomic status.
Unconditional (unmatched) analyses are restricted to subjects with good geocode accuracy. Conditional (matched) analyses are not restricted by geocode accuracy.

[a] All models are also adjusted for study.

[b] OR not calculated due to cells with n < 4.

with previous pooled analyses' estimates (Ahlbom et al., 2000; Kheifets et al., 2010). We also stratified by age: 0–4 years, 5–9 years, and those 10 and older. Additionally, the Italian study included only children under ten, we ran one more analysis restricting to all children under the age of ten.

In most analyses, MF was categorized based on previous literature into three categories: <0.1 μT, 0.1-<0.4 μT, and ≥0.4 μT. We also obtained odds ratios using a moving window of exposure. These analyses used open-ended exposure categories in increasing increments of 0.05 (i.e. ≥0.1, ≥0.15, ≥0.2, …, ≥0.75) compared to a reference category of <0.1 μT, and were adjusted for age, sex, SES, and study. For comparison with results in previous pooled analysis, we also analyzed magnetic field exposure using four categories: <0.1 μT, 0.1-<0.2 μT, 0.2-<0.4 μT, and ≥0.4 μT.

Analyses were conducted using SAS 9.3 and Stata 14.2.

3. Results

Our pooled dataset included 24,994 childhood leukemia cases and 30,769 controls. After restriction to participants with study-defined accurate geocoding of homes, we were left with 49,715 participants (22,128 cases, 27,587 controls). Two of the included studies previously reported risks above 1.0 and two below 1.0, but all the estimates were imprecise (Table 1).

Upon assessment, the three models (random effects, mixed effects, fixed effects) yielded similar results; the fixed-effects model was shown to be the best fit for the data and was used for the presented analyses. Table 2 presents the results of the primary analyses, both unmatched and matched, as well as with minimal adjustments or additional adjustment for SES. Unmatched analyses are restricted to subjects with measured fields or study-defined good geocoding. Matched analyses are not restricted by geocode accuracy to avoid loss of pairs for whom matching accuracy differed. Although individual study numbers were small in the highest category, results of all analyses were remarkably consistent, with no association for the highest exposure level (ORs: 0.95–1.08). Adjustment for SES made no difference. All results were imprecise and not statistically significant (Table 2).

When using all available data, including observations with less accurate geocoding, the unconditional logistic regression OR for the highest exposure category of ≥0.4 μT, adjusted for age, sex, and SES, increased slightly overall from 0.95 to 1.01, although remained imprecise (results not shown). Additionally, we assessed a moving window of exposure for MF categories (Fig. 1). While the OR did increase slightly with a higher risk category, reaching an OR of 1.45 for exposure of 0.65+ μT, results were even more imprecise.

Table 3 provides subgroup analyses for the different subsets. There was no increased risk in childhood leukemia in the highest MF category in the ALL subset, birth homes subset, nor calculated fields subset. There did appear to be a time period trend, with the earliest period (1953–1983) showing a higher OR (1.54) compared to the most recent period (0.71). However, the earliest period suffered from small numbers and all results were imprecise (Table 3). Age subgroups did not exhibit association between high MF exposures and childhood leukemia. Age did not modify the effect: stratifying on age did not materially change the effect of exposure on childhood leukemia.

Similarly, in Table 4, showing the results of the current pooled analysis compared to those from Ahlbom et al. (2000) and Kheifets et al. (2010), an apparent decrease with each subsequent update appears, in both calculated field subset and overall. Measured fields do not show the same trend, but as mentioned previously, this could be due to the Brazil study and its bias. Likewise, in the current update, only Italy utilized measured fields and the OR for exposure of ≥0.4 μT is based on only two cases. A meta-analysis of the three pooled analyses overall presents an OR of 1.45 (95% CI: 0.95–2.20) for the highest exposure category (Table 4). As in the previous analyses, pooled results are similar for both measured and calculated fields studies only.

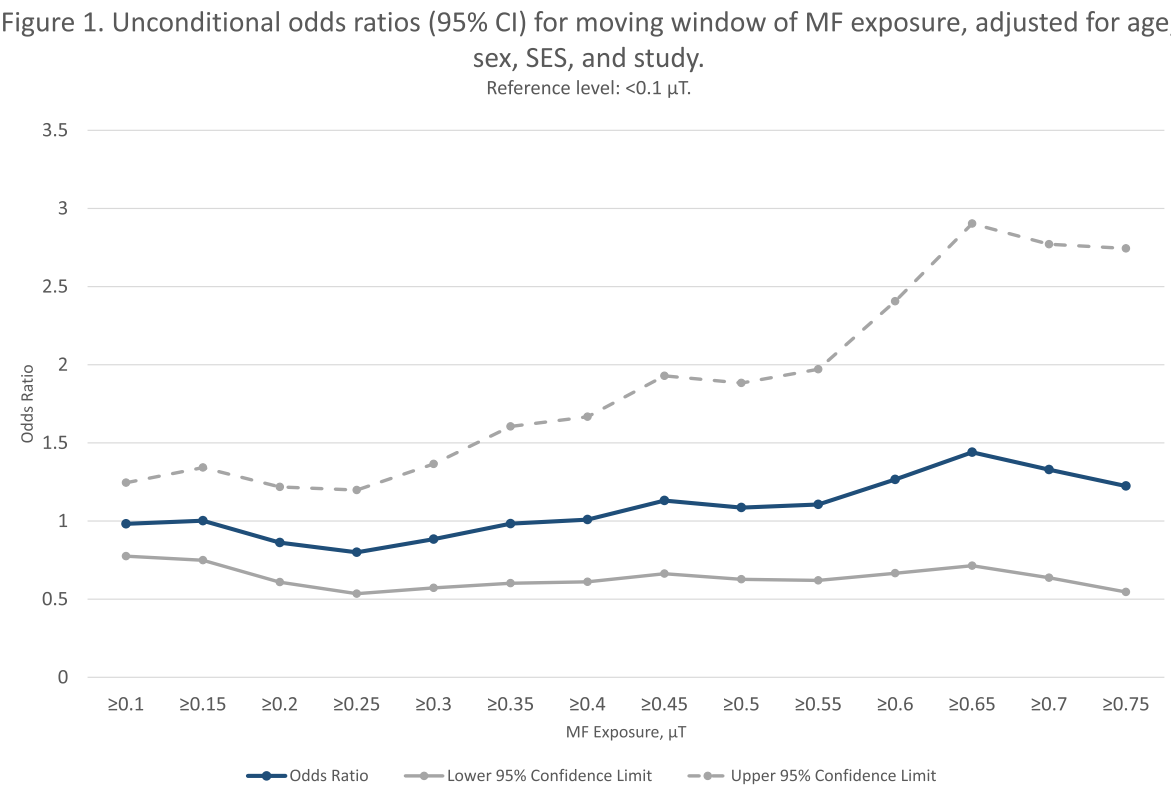

Fig. 1. Unconditional odds ratios (95% CI) for moving window of MF exposure, adjusted for age, sex, SES, and study.

Table 3
Odds ratios for childhood leukemia by MF category within subgroups.

Subgroup	MF (μT)	Cases	Controls	OR (95% CI)
ALL	<0.1	17118	21223	1.00 (ref)
	0.1-<0.4	75	104	0.93 (0.69–1.26)
	≥0.4	22	27	1.05 (0.59–1.85)
Birth Homes	<0.1	21745	27133	1.00 (ref)
	0.1-<0.4	81	105	0.96 (0.72–1.30)
	≥0.4	22	30	0.87 (0.50–1.51)
Calculated MF	<0.1	21159	26145	1.00 (ref)
	0.1-<0.4	51	70	0.83 (0.58–1.19)
	≥0.4	24	26	1.12 (0.64–1.96)
Time Period				
1953–1983	<0.1	8207	9061	1.00 (ref)
	0.1-<0.4	4	10	0.58 (0.18–1.89)
	≥0.4	4	4	1.54 (0.38–6.28)
1984–1994	<0.1	7458	8819	1.00 (ref)
	0.1-<0.4	45	53	1.09 (0.72–1.64)
	≥0.4	12	12	1.20 (0.53–2.71)
1995–2010	<0.1	6046	9094	1.00 (ref)
	0.1-<0.4	49	63	1.01 (0.69–1.48)
	≥0.4	10	18	0.71 (0.32–1.55)
Age Group[a]				
<5 years	<0.1	12433	15163	1.00 (ref)
	0.1-<0.4	59	78	0.94 (0.67–1.33)
	≥0.4	20	22	1.13 (0.61–2.09)
5-<10 years	<0.1	5940	7431	1.00 (ref)
	0.1-<0.4	29	35	1.13 (0.68–1.88)
	≥0.4	5	8	0.82 (0.27–2.54)

MF magnetic fields, μT microtesla, OR odds ratio, CI confidence interval.
All analyses were conducted with unconditional logistic regression, adjusting for age, sex, SES, and study, restricted to only subjects with good geocode accuracy.
[a] There was only 1 case and 4 controls in the 10+ age group.

4. Discussion

We conducted an updated pooled analysis of four recently published epidemiological studies, either newly created, or recently updated, on the association between residential magnetic field exposure and childhood leukemia. Unlike previous pooled analyses, we found no increased risk of leukemia among children exposed to greater magnetic fields in this sample. In fact, a small, albeit imprecise, reduction in risk appeared instead. Similarly, no association was observed in the subset of ALL, birth home dwellers, or studies using calculated fields. Disregarding geocode accuracy had no effect either. Neither did sub-setting to children less than 10 years of age to account for potential differences in behavior based on subjects age, nor for the 0–4 years age group, where peak incidence occurs.

Historically, higher and higher cut points were used: initially studies defined their highest category as above 0.2 μT; later pooled analyses defined the highest category as 0.3 or 0.4 μT. In this analysis, even a small increase in risk was not seen until a much higher cut point (0.65 μT). Notably, the risk was smaller than in the previous analyses, even for such high exposure, indicating that the results are not compatible with a single progressive exposure-response relationship.

As mentioned previously, pooled analyses can provide some benefits over individual studies, results of which often vary, in particular increasing statistical power, which is especially important if the possible effect estimate is small, as with the association between MF and childhood leukemia. While a pooled analysis is considered a gold standard for synthesizing results from multiple studies, it is still prone to biases. A pooled dataset is only as good as the underlying studies. We attempted to address this by including only studies meeting our criteria, which were set a priori.

With only four component studies, our results could be particularly influenced by features of any single study. Individually, the studies suffered from small numbers in the highest exposure category, except for the California study. Additionally, California and Denmark were the only two studies to present a consistently greater risk of leukemia, suggesting that the picture may be different if more subjects with high exposures were available. Despite an overall sample size of 49,715 subjects, there were only 60 children who were exposed to magnetic fields ≥0.4 μT, mostly from California, which diminishes our ability to detect weaker associations, should there be any.

Table 4
Comparison of summary odds ratios in current pooled analysis to previous pooled analyses.

Exposure Category	Study			
	Ahlbom et al.	Kheifets et al.	Current update	Combined Estimate[a]
Measurement Studies				
0.1 - <0.2 μT	1.05 (0.86–1.28)	1.05 (0.73–1.50)	1.45 (0.92–2.28)	
0.2 - <0.4 μT	1.15 (0.85–1.54)	1.36 (0.75–2.48)	0.81 (0.34–1.94)	
≥0.4 μT	1.87 (1.10–3.18)	2.23 (0.83–5.99)	N/A[b]	1.46 (0.65–3.25)
Calculated Studies				
0.1 - <0.2 μT	1.58 (0.77–3.25)	2.02 (0.75–5.41)	0.84 (0.53–1.34)	
0.2 - <0.4 μT	0.79 (0.27–2.28)	N/A[b]	0.72 (0.41–1.29)	
≥0.4 μT	2.13 (0.93–4.88)	1.68 (0.34–8.38)	1.18 (0.68–2.03)	1.43 (0.92–2.22)
All Studies				
0.1 - <0.2 μT	1.08 (0.89–1.31)	1.07 (0.81–1.41)	1.10 (0.80–1.53)	
0.2 - <0.4 μT	1.11 (0.84–1.47)	1.22 (0.78–1.89)	0.75 (0.46–1.21)	
≥0.4 μT	2.00 (1.27–3.13)	1.46 (0.80–2.68)	1.01 (0.61–1.66)	1.45 (0.95–2.20)

[a] Meta-analysis of all three pooled estimates.
[b] OR not calculated due to cells with n < 4.

Although three of the four studies were records-based, Italy involved 48 h in-home measurements and extensive subject interviewing about homes occupied, which could lead to lower participation rates and potential selection bias (Mezei and Kheifets, 2006). Conversely, calculated fields neglect sources of MF other than overhead power lines and could lead to potential exposure misclassification. Additional exposure misclassification due to poor geocode accuracy is unlikely and/or minimal as inclusion of all subjects did not change the risk estimates. Whilst pooled analysis allows for making many common analytical choices across studies, some differing analytical choices in the component studies remain: for example, the Danish study considered the highest exposure over the child's lifetime rather than either at the birth or diagnosis home. Additionally, results could have been influenced by different exposure distribution in different studies: the UK, is the largest in terms of total numbers, but with few exposed at the highest levels; in Italy, while the prevalence of high exposure was higher among controls, it was similar to other studies for cases.

Similarly, our results could have changed with the inclusion of further studies that were not available: especially, the French study, which reported an elevated risk (OR: 1.7) for residences within 50 m of the highest voltage lines, but has not yet published results for the corresponding magnetic fields. Additionally, while one of the excluded studies reported a risk below one, all other studies reported relatively high risks. These studies were hospital based and thus particularly prone to bias (the reason why they were excluded).

This is the third of three pooled analyses using broadly comparable inclusion criteria and methods. Ahlbom et al. (2000) included studies published up to 2000, Kheifets et al. (2010) included studies published between 2000 and 2010, and this analysis included studies published from 2010 to 2020. Comparing the results (Table 4) reveals a decline in the apparent risk in successive pooled analyses. Although the present analysis comprises studies published in the most recent decade, some of those studies covered a longer period, and just within the studies included here, there appears to be a similar decline in risk over the period (Table 3).

An apparent decline in risk over time was also noted by a recent meta-analysis (Swanson et al., 2019), which, compared to the present analysis, included more studies, but lacked the date information for individual subjects that we have used. The internal evidence from the present analysis, the comparison to the two previous pooled analyses, and the meta-analysis all seem to confirm that there has been a decline in observed risk over time.

We have no obvious explanation for such a decline. If earlier elevated risks were a consequence of poor study design, and study quality has improved over time, that would produce a declining risk. We see no good evidence to support this explanation. Study design may have improved from the earliest studies in the 1980s, but we see no evidence of further methodological improvements from the 1990s onwards. Further, the decline is apparently also seen within some single studies that span a longer period, where a common methodology is applied to the whole period.

Data available for present analyses did not include some possible factors for childhood leukemia, such as infections (Rudant et al., 2015), or road traffic, and related benzene exposure (Carlos-Wallace et al., 2016; Houot et al., 2015). While these factors have not been found to strongly confound the association (Kheifets et al., 2010), the change over time in the prevalence of these exposures could contribute to the decline in observed MF associated risk. Further, decline in MF exposure is an unlikely explanation. First, it is unclear that exposure in fact has declined: while better design of appliances and use of low field transmission lines have been implemented in some countries, increased use of electricity in general and in number of appliances used would countervail and likely result in higher average exposures to the population. Second, even if there was a reduction of persons highly exposed, such a reduction is unlikely to differ for cases and controls and thus should not result in decline in risk over time. Other explanations include chance, and a genuinely declining risk.

In conclusion, our results do not show the risk increase observed in previous pooled analysis and, over time, show a decrease in effect to no association between MF and childhood leukemia. This could be due to methodological issues, random chance, or a true finding of disappearing effect. The public-health implications of this finding are, of course, very different depending on whether the best estimate of the true risk is regarded as the most recent evidence (essentially no evidence of elevated risk) or as the aggregate evidence over the whole period (a small elevated risk).

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Declaration of competing interest

The authors declare that they have no other known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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