

A Pooled Analysis of Magnetic Fields, Wire Codes, and Childhood Leukemia

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We obtained original individual data from 15 studies of magnetic fields or wire codes and childhood leukemia, and we estimated magnetic field exposure for subjects with sufficient data to do so. Summary estimates from 12 studies that supplied magnetic field measures exhibited little or no association of magnetic fields with leukemia when comparing 0.1–0.2 and 0.2–0.3 microtesla (μT) categories with the 0–0.1 μT category, but the Mantel-Haenszel summary odds ratio comparing $>0.3 \mu\text{T}$ to 0–0.1 μT was 1.7 (95% confidence limits = 1.2, 2.3). Similar results were obtained using covariate adjustment and spline regression. The study-specific relations appeared consistent despite the numerous methodologic differences among the studies. The association of wire codes with leukemia varied considerably across studies, with odds ratio estimates for very high current vs low current configurations ranging from

0.7 to 3.0 (homogeneity $P = 0.005$). Based on a survey of household magnetic fields, an estimate of the U.S. population attributable fraction of childhood leukemia associated with residential exposure is 3% (95% confidence limits = –2%, 8%). Our results contradict the idea that the magnetic field association with leukemia is less consistent than the wire code association with leukemia, although analysis of the four studies with both measures indicates that the wire code association is not explained by measured fields. The results also suggest that appreciable magnetic field effects, if any, may be concentrated among relatively high and uncommon exposures, and that studies of highly exposed populations would be needed to clarify the relation of magnetic fields to childhood leukemia. (Epidemiology 2000;11:624–634)

Keywords: childhood neoplasms, electromagnetic fields, environmental exposure, leukemia, magnetic fields, wire codes.

The question of health effects of extremely low-frequency electromagnetic fields (EMFs) remains an unset-

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tled topic.¹ The National Institute of Environmental Health Sciences funded our research team to conduct a pooled analysis of those studies of EMF and childhood leukemia for which original data could be obtained. We felt that a direct analysis of individual study data would allow a more reliable evaluation of interstudy differences in results (heterogeneity). It also could allow more reliable evaluation of dose-response relations and effects on public health than could a combination of summaries from studies, especially in light of the very different analyses presented in the published reports. The present paper reports our analyses.

Subjects and Methods

STUDIES

From literature searches, we identified 24 studies^{2–25} that presented data on household EMF or power-supply wiring information and childhood leukemia. To be eligible for inclusion in our pooled analysis, the study had to have obtained quantitative magnetic field measures for individual subjects or enough information to approximate Wertheimer-Leeper wire codes.¹ Nineteen studies^{2–16,22–25} had eligible data. Five articles reporting four studies^{22–26} appeared after our initial search in 1998; investigators in two of those studies^{22,23} supplied data in time for inclusion here. One study group¹⁶ refused our data request. Two studies^{8,15} were conducted using identical methods within the same

TABLE 1. Description of Studies in Pooled Analyses [All Are Case-Control Studies (Verkasalo Nested in Cohort)]

First Author	Location	Measurements*	Matching Factors†
Coghill ²	England	Direct	Age, sex
Dockerty ²³	New Zealand	Direct	Birth quarter, sex
Fajardo-Gutiérrez ²	Mexico	WC	Age, sex
Feychting ⁴	Sweden	Calc; some direct	Birth year, sex, diagnosis year, parish, transmission-line corridor
Fulton ⁵	Rhode Island	WC	Birth year
Green ²⁴	Ontario	WC†	Birth year, sex
Linnet ⁶	Eastern U.S.	Direct; some WC	Age, race, RDD
London ⁷	Los Angeles	Direct; WC	Age, sex, race; some friend, RDD
McBride ²²	Canada	Direct; WC	Age, sex, area
Michaelis ⁸	Germany	Direct	Birth date, sex; some by locale
Olsen ⁹	Denmark	Calc	Birth year, sex, diagnosis date
Savitz ¹⁰	Denver	WC; some direct	Age, sex, RDD
Tomenius ¹¹	Sweden	Direct	Age, sex, birth district
Tynes ¹²	Norway	Calc	Birth year, sex, municipality
Verkasalo ¹³	Finland	Calc	Age, sex
Wertheimer ¹⁴	Denver	WC	Birth date; some by county

* Calc = magnetic field exposure calculated from configuration and electric load data; direct = direct magnetic field measurements; WC = wire code.

† RDD = random-digit dialing.

‡ Only wire code data from published report used here. Green *et al.*^{24,25} also obtained magnetic field data.

rooms,^{6,10} and averaged personal and house measures²²).

Some studies^{4,6-8,10,22} supplied more than one type of magnetic field measurement. For example, there were normal- or low-power measurements, spot and 24-hour measurements, mean and median values, data from the residence at diagnosis, and data from other residences. There is as yet no measure of magnetic field exposure that is known to be biologically the most relevant. In the absence of such knowledge, it would be best to examine a number of different measures. This was indeed done in several studies, but it raises multiplicity problems that are difficult to deal with statistically in even a single study. For a pooled analysis of the studies here, there would be more than 100 combinations of measures (although we did not have all measures for all of the

country and treated as one study.⁸ Fulton *et al.*⁵ and Tomenius¹¹ published analyses that used residence as the analysis unit, but we used individual-level exposures from their data. We thus had anonymous records on individual subjects from 15 distinct studies.

Table 1 summarizes the studies included here. All are case-control studies. Verkasalo *et al.*¹³ initially conducted and reported a person-time cohort study. They supplied data from an unpublished case-control study nested within their cohort, based on all cases observed in the cohort plus ten controls for each case, and which obtained additional covariate data; the controls were age-sex matched but otherwise randomly sampled from the cohort. The two Swedish studies^{4,11} had a small overlap in source populations and so share a few cases, but this overlap could not be identified from the available data. Most studies had geographic restrictions on their source populations beyond those shown in Table 1; some had restrictions to areas near or crossed by high-voltage lines.^{4,12,13}

PRIMARY MEASURES

Twelve studies supplied magnetic field exposure estimates for some or all individuals. For four Nordic studies,^{4,9,12,13} we used estimates calculated by the original investigators from measured proximity to power lines and historical current-supply data. For eight studies,^{2,6-8,10,11,22,23} we used estimates based on direct measurements (measured magnetic fields at the front door of the residence,¹¹ measured fields in the child's bedroom,^{2,7,8,23} averaged fields in several

studies).

To avoid multiplicity issues and to keep our task manageable, we defined our target measure to be a child's time-weighted average exposure up to 3 months before diagnosis. When we had several measures from a study, we used a measure that, based on earlier work,²⁷⁻²⁹ seemed likely to provide the best approximation to this target. In particular, we preferred calculated historical fields or averages of multiple measurements rather than spot measurements when there was a choice. Table 2 summarizes the measurements used from each study. We also conducted analyses of each supplied measure and a

TABLE 2. Magnetic-Field Measures Used in Primary Analyses

First Author	Summary Measure Description*
Coghill ²	Nighttime (8:00 pm to 8:00 am) recordings in child's bedroom
Dockerty ²³	Arithmetic mean of 24-hour recordings in child's bedroom
Feychting ⁴	Average of calculations based on distances, phases, and loads of above-ground lines
Linnet ⁶	Time-weighted household mean based on typical child activity patterns and 24-hour child bedroom measurements and spot measurements in kitchen and family room; front door measurement when these data were not available; includes multiple homes covering 70% or more of the reference period (up to 5 years before diagnosis date)
London ⁷	Arithmetic mean of 24-hour recordings in child's bedroom
McBride ²²	Time-weighted mean based on 48-hour personal monitoring plus predictions from perimeter measurements
Michaelis ⁸	Arithmetic mean of 24-hour recordings in child's bedroom
Olsen ⁹	Average of calculations based on distances; phases; and loads of 50-400-kV transmission lines, cables, and substations within areas calculated as potentially having $\geq 0.1 \mu\text{T}$ exposure
Savitz ¹⁰	Arithmetic mean of low-power spot measurement in three or more locations (child's bedroom, parent's bedroom, other room occupied by child ≥ 1 hour/day, front door)
Tomenius ¹¹	Maximum uniaxial value outside front door of single-family homes and apartments
Tynes ¹²	Average of calculations based on distances, phases, and loads of above-ground lines ≥ 11 kV
Verkasalo ¹³	Average of calculations based on distances, typical line configuration, and loads of overhead 110-400-kV lines

* For details see original reports.

limited sensitivity analysis of summaries based on revisions of initial choices.

All North American studies^{3,5-7,10,14,22,24} obtained wire code data. Wire codes from two studies^{5,14} were recalculated from original data on distances to type of distribution line. Wire codes from one study³ were in a unique three-level form.

OTHER INFORMATION

Studies varied considerably in the covariates available for control and in their completeness of exposure and covariate information. One study¹¹ supplied no covariate data and so was excluded from covariate-adjusted analyses. Several studies^{4-9,12,22,23} supplied at least one socioeconomic variable on some or all subjects. One important ecologic covariate available for all studies was location; studies in North America involved 60-Hz fields with 110-125-V home supply, whereas all other studies involved 50-Hz fields with 220-240-V power. Thus, all comparisons of 60-Hz vs 50-Hz fields are also comparisons of 110-125-V vs 220-240-V systems and of North America vs other locations.

There are several discrepancies between the data we report and those in some published reports.^{6,7,10,14,22,23} Some differences arose because we did not impose exclusion criteria used by certain authors. For example, we included ten Down-syndrome subjects excluded by Linet et al⁶ because we could not identify such subjects in other studies and we could not identify any bias that would justify such an exclusion. Other differences arose from postpublication corrections or additions to the study data by the original investigators and from our use of exposure measures and cutpoints different from those used in the original publications; these differences led to especially large upward changes for the Tomenius¹¹ and McBride et al²² estimates. A few small discrepancies were unresolved; no such discrepancy appeared capable of producing more than negligible differences in summary results.

Coghill et al² and Linet et al⁶ restricted their cases to acute lymphoblastic leukemia (ALL). Because about 80% of childhood leukemias are ALL, and because not all datasets distinguished leukemia subtypes, we conducted no analysis restricted to ALL.

STATISTICAL METHODS

Data were analyzed using inverse-variance weighted (Woolf), Mantel-Haenszel, and maximum-likelihood (ML) tabular methods, and using ML logistic regression.^{30,31} (Inverse variance methods were included because they are common in meta-analysis.) All *P*-values were derived from score statistics or deviance (log likelihood-ratio) statistics.³⁰ For magnetic field exposures, dose response was examined using category indicators and splines in logistic models.³¹⁻³³ All results were adjusted for study: tabular analyses were always stratified on study, and all regressions included indicators for study.

All magnetic field measurements were converted into units of microtesla (μT). Only two studies^{6,7} had more than four cases above 0.4 μT ; therefore, for categorical magnetic field analyses, values above 0.3 μT were combined in a single category to ensure cell counts large enough for all statistical procedures. To avoid the trend distortions and power loss associated with percentile-category boundaries,^{33,34} we used equally spaced boundaries below the 0.3- μT cutpoint. We combined low-exposure wire codes (UG = underground, VLCC = very low current code, and OLCC = ordinary low current code) into a single "LCC" low-current reference category for comparison with the two high-exposure wire codes (OHCC = ordinary high current, and VHCC = very high current). Previous results indicate that the three low-current categories do not correspond to meaningful differences in EMF exposure or childhood leukemia risk.^{3,5-7,10,22,24,35} Furthermore, in three studies,^{5,6,14} the proportions of subjects with a UG or VLCC code were too small to yield efficient estimates using those codes as reference category; in another,⁶ UG and VLCC were combined in the supplied data; and in another,³ low-current codes had been combined in data collection.

Complications arose in accounting for the variety of matching protocols used. Most studies matched on certain covariates (typically sex, age or birth date, and some sort of geographic unit). Many studies experienced some failures to match, leading to fewer subjects available for matched analyses than unmatched analyses. Several considerations led us to focus on unmatched analyses with analytic control for matched covariates. First, this choice provided the most subjects for analysis. Second, this choice avoided further efficiency loss due to the type of analysis overmatching documented by Brookmeyer et al.³⁶ Third, this choice also helped avoid small-sample bias away from the null due to sparse matched-set counts in study-specific analyses³⁷; although we would expect the unmatched analyses to suffer some small bias toward the null, we thought this possibility preferable to a potentially large bias away from the null due to sparse data. Fourth, results from matched analyses were less stable but exhibited the same patterns seen in the unmatched analyses.

Results for Magnetic Fields

CATEGORICAL ANALYSES

Table 3 displays the distribution of magnetic field measurements among the studies supplying such measurements. There are extensive differences among the studies, ranging from Olsen et al⁸ (which has only 0.5% of cases and controls above 0.1 μT) to Linet et al⁶ (which has more than one-third of measured subjects above 0.1 μT). Values above 0.3 μT are relatively infrequent in all studies. The differences appear associated chiefly with location rather than with measurement method (direct vs calculated). Distributions in North American studies tend to be much higher than those in European studies, probably reflecting differences in power systems (for example, more overhead wires and lower household

TABLE 3. Study-Specific Distributions of Magnetic-Field Data

First Author	Magnetic-Field Category (μT)						Total	No Measure*
	≤ 0.1	$>0.1-\leq 0.2$	$>0.2-\leq 0.3$	$>0.3-\leq 0.4$	$>0.4-\leq 0.5$	>0.5		
Cases								
Coghill ²	48	5	2	0	1	0	56	0
Dockerty ²³	72	9	3	1	1	1	87	34
Feychting ⁴	30	1	1	2	1	4	38	0
Linet ⁶	403	152	41	20	13	9	638	46
London ⁷	110	30	5	9	4	4	162	68
McBride ²²	174	77	32	11	1	2	297	102
Michaelis ⁸	150	17	3	3	3	0	176	0
Olsen ⁹	829	1	0	0	0	3	833	0
Savitz ¹⁰	24	7	2	3	0	0	36	62
Tomenius ¹¹	129	16	5	0	0	3	153	0
Tynes ¹²	146	2	0	0	0	0	148	0
Verkasalo ¹³	30	1	0	0	1	0	32	3
Controls								
Coghill ²	47	9	0	0	0	0	56	0
Dockerty ²³	68	13	1	0	0	0	82	39
Feychting ⁴	488	26	18	10	2	10	554	0
Linet ⁶	407	144	41	17	5	6	620	69
London ⁷	99	28	6	2	2	6	143	89
McBride ²²	194	96	28	5	3	3	329	70
Michaelis ⁸	372	29	7	4	0	2	414	0
Olsen ⁹	1,658	3	2	2	0	1	1,666	0
Savitz ¹⁰	155	28	10	3	2	0	198	67
Tomenius ¹¹	546	119	24	4	2	3	698	21
Tynes ¹²	1,941	25	7	5	4	22	2,004	0
Verkasalo ¹³	300	9	6	4	0	1	320	30

* No measure for a residence at or before time of diagnosis (cases) or corresponding index date (for controls).

voltage in North America), per capita electricity consumption,³⁸ and grounding practices. The higher distribution in Feychting and Ahlbom⁴ compared with the other Nordic studies reflects the fact that the source population was restricted to children dwelling within 300 meters of high-voltage lines⁴ (although Verkasalo et

al¹³ imposed a 500-meter limit and Tomenius¹¹ restricted subjects to census wards with transmission lines).

Table 4 displays odds ratio estimates computed directly from the raw counts underlying Table 3 and summary estimates assuming common odds ratios for each analysis category. The study-specific and summary esti-

TABLE 4. Study-Specific Odds Ratio Estimates and Study-Adjusted Summary Estimates, Magnetic Field Data (Reference Category, $\leq 0.1 \mu\text{T}$)

First Author	Magnetic Field Category (μT)					
	$>0.1-\leq 0.2$		$>0.2-\leq 0.3$		>0.3	
	Estimate	95% CL	Estimate	95% CL	Estimate	95% CL
Coghill ²	0.54	0.17, 1.74				
Dockerty ²³	0.65	0.26, 1.63	2.83	No controls		No controls
Feychting ⁴	0.63	0.08, 4.77	0.90	0.29, 27.9	4.44	No controls
Linet ⁶	1.07	0.82, 1.39	1.01	0.12, 7.00	1.51	1.67, 11.7
London ⁷	0.96	0.54, 1.73	0.75	0.64, 1.59	1.53	0.92, 2.49
McBride ²²	0.89	0.62, 1.29	1.27	0.22, 2.53	1.42	0.67, 3.50
Michaelis ⁸	1.45	0.78, 2.72	1.06	0.74, 2.20	1.42	0.63, 3.21
Olsen ⁹	0.67	0.07, 6.42		0.27, 4.16	2.48	0.79, 7.81
Savitz ¹⁰	1.61	0.64, 4.11	1.29	No cases	2.00	0.40, 9.93
Tomenius ¹¹	0.57	0.33, 0.99	0.88	0.27, 6.26	3.87	0.87, 17.3
Tynes ¹²	1.06	0.25, 4.53		0.33, 2.36	1.41	0.38, 5.29
Verkasalo ¹³	1.11	0.14, 9.07		No cases	2.00	No cases
Study-adjusted summaries*						
Woolf	0.96	0.81, 1.14	1.08	0.80, 1.45	1.83	1.34, 2.49
MH	0.95	0.80, 1.12	1.06	0.79, 1.42	1.69	1.25, 2.29
Study + age + sex adjusted†						
MH	1.01	0.84, 1.21	1.06	0.78, 1.44	1.68	1.23, 2.31
Spline‡	1.00	0.81, 1.22	1.13	0.92, 1.39	1.65	1.15, 2.36

95% CL = 95% confidence limits.

* MH = Mantel-Haenszel; maximum-likelihood summaries differed by less than 1% from these summaries; based on 2,656 cases and 7,084 controls. Summary tests: 3-degree-of-freedom (df) MH categorical $P = 0.01$; 1 df Mantel trend $P = 0.06$ (from continuous data).

† Excludes Tomenius et al¹¹ (no covariate data); based on 2,484 cases and 6,335 controls with age and sex data; 3-df MH categorical $P = 0.01$; 1 df Mantel trend $P = 0.04$ (from continuous data).

‡ Estimates comparing odds at category means (0.14, 0.25, and 0.58 vs 0.02 μT) from a quadratic logistic spline with one knot at 0.2 μT , plus age and sex terms.

mates tend to show little or no association of fields below $0.3 \mu\text{T}$ with leukemia, but all studies with cases and controls in the $>0.3 \mu\text{T}$ category exhibit positive associations for that category. The differences across studies were within chance variation (deviance $P = 0.42$ using exposure categories in Table 4), as were differences between studies with different measures [ML odds ratios for $>0.3 \mu\text{T} = 1.70$ from studies with calculated fields and 1.68 from studies with direct measurement; 95% confidence limits (95% CL) for ratio of odds ratios = 0.46, 2.22] or different field frequencies (ML odds ratios for $>0.3 \mu\text{T} = 1.97$ from studies with 50-Hz fields and 1.58 from studies with 60-Hz fields; 95% CL for ratio of odds ratios = 0.66, 2.36).

The Tomenius data¹¹ included no covariate and so were excluded from covariate-adjusted analyses. The penultimate line of Table 4 shows the age-sex-study-adjusted Mantel-Haenszel estimates. The exclusions and adjustments had negligible effect, and odds ratio differences across age and sex categories (not shown) were within chance variation. Table 5 summarizes categorical analyses upon restriction to subjects with no missing data. Neither restriction nor adjustment for available covariates changed the qualitative result that there was little or no association evident below $0.2 \mu\text{T}$, but some positive association was evident above $0.3 \mu\text{T}$.

TREND ANALYSIS

The final line of Table 4 displays estimated odds ratios from a logistic model fit to individual-level magnetic field data using a quadratic spline for field along with age, squared age, and sex terms. The spline has a single knot at $0.2 \mu\text{T}$ (the middle category boundary) and so has one linear and two quadratic magnetic field terms; the model thus uses 3 degrees of freedom for field, the same number of degrees of freedom as in the four-category analysis. The spline estimate under each category is the leukemia odds ratio comparing the mean field measure in that category with the mean field measure in the $\leq 0.1 \mu\text{T}$ category and is thus a continuous-data analogue of the categorical summary estimate. Unlike the categorical analysis, the spline analysis imposes a smooth dose-response relation between field level and leukemia. Nonetheless, the spline results are similar to the categorical results: there appears to be little or no association below $0.2 \mu\text{T}$ but some association comparing high with low exposures; furthermore, differences among covariate-specific curves (not shown) were within chance variation.

Figure 1 displays a graph of the "floated" case-control ratios³⁹ fit by the spline model, along with pointwise confidence limits. This figure is a plot of the fitted odds of being a case *vs* being a control in our studies. Assuming these odds are proportional to the underlying childhood leukemia rates, this plot is an estimate of the shape of the curve relating leukemia rates to magnetic fields under the spline model.³⁹ The vertical axis corresponds to geometric mean case-control ratios rather than to odds ratios, but ratios of different points on the curve

equal the model-fitted odds ratios³⁹; for example, the ratio of the curve heights at 0.58 and $0.02 \mu\text{T}$ (the means of the >0.3 and $\leq 0.1 \mu\text{T}$ categories) is 1.65, equal to the final odds ratio in Table 4. We caution against focusing on the central curve, however, because the data are compatible with a wide range of trends, including nonmonotonic, linear, and exponentially increasing shapes. For example, the strictly increasing trend above $0.1 \mu\text{T}$ is *not* a statistically stable feature, in that curves that plateau or even decline above $0.6 \mu\text{T}$ also fit the data well.

INFLUENCE AND SENSITIVITY ANALYSES

As with covariate adjustment, neither single-study deletions nor alternative choices for the exposure measure altered results qualitatively, nor did deletion of large field values (for example, the five subjects above $2.0 \mu\text{T}$, all controls from Tynes and Haldorsen¹²). Although the highest-category estimates and the fitted curve varied considerably with category-boundary and model choices, these choices also did not alter the basic qualitative results.

Use of alternatives among the supplied exposure measures produced only small differences in the summaries; we did not have all measures from all studies, however. Missing data varied with choice of measure, and this variation sometimes had more influence on estimates than the choice of measure. Two studies^{4,13} supplied calculated yearly exposure of children; we used these data to construct alternative-exposure measures that might arguably approximate more closely our target than the measures used in the original reports and in our analysis above. Use of these alternatives had little effect on the study-specific odds ratios below $0.3 \mu\text{T}$ but raised the >0.3 -*vs*- ≤ 0.1 odds ratio to 5.9 (95% CL = 2.0, 17) for Feychting and Ahlbom⁴ and to 10 (95% CL = 1.4, 74) for Verkasalo *et al.*¹³ Some of this increase may only be increased small-sample bias³⁷ due to reduction in numbers above $0.3 \mu\text{T}$. In any event, use of these alternatives changed the summaries by only a few percent.

The calculated-field measures from the Nordic studies were based on high-voltage lines and did not include contributions from sources such as in-home wiring and appliances.^{4,9,12,13} The effect of the latter omissions is not straightforward to assess, because fields are vector additive and so may even destructively interfere with one another, depending on the relative orientation and phase of the contributions from different sources. One study⁴ supplied spot measurements as well as calculated fields on 24 of 38 cases and 344 of 554 controls. These dual measurements permitted instrumental-variable corrections⁴⁰ for estimates from the calculated fields in the Nordic studies. Because these corrections involve strict assumptions and require extensive technical description,⁴⁰ they were not used in Tables 3 and 5, and we omit details. The main result was that odds ratio estimates from the Nordic studies^{4,9,12,13} were corrected toward the null. Nonetheless, because these studies contributed so few cases at the higher exposure levels, the corrections had only a small effect on the overall summary estimates.

TABLE 5. Study-Specific Odds Ratio Estimates and Study-Adjusted Summary Magnetic Field Estimates from Data Restricted to the 2,078 Cases and 5,516 Controls with Complete Covariate Data, without and with Covariate Adjustment* (Reference Category, $\leq 0.1 \mu\text{T}$)

First Author	Magnetic Field Category (μT)					
	>0.1- \leq 0.2		>0.2- \leq 0.3		>0.3	
	Estimate	95% CL	Estimate	95% CL	Estimate	95% CL
Restricted, no covariate adjustment						
Coghill ²	0.30	0.06, 1.52				
Dockerry ²³	0.65	0.24, 1.78	3.05	0.31, 30.1		
Feychting ⁴	0.63	0.08, 4.77	0.90	0.12, 7.00	4.44	1.67, 11.7
Linnet ⁶	1.06	0.81, 1.40	0.99	0.63, 1.58	1.70	1.01, 2.87
London ⁷	1.08	0.58, 2.01	1.07	0.28, 4.12	1.82	0.75, 4.43
McBride ²²	0.88	0.61, 1.28	1.30	0.75, 2.25	1.45	0.64, 3.27
Michaelis ⁸	1.45	0.78, 2.72	1.06	0.27, 4.16	2.48	0.79, 7.81
Olsen ⁹	1.03	0.09, 11.4			4.13	0.37, 45.7
Savitz ¹⁰	1.68	0.66, 4.30	1.30	0.27, 6.29	3.89	0.87, 17.4
Tynes ¹²	1.11	0.26, 4.74				
Verkasalo ¹³	1.13	0.14, 9.25				
MH*	1.02	0.85, 1.23	1.10	0.81, 1.51	2.04	0.23, 18.0
Restricted and covariate adjusted						
Coghill ²	0.28	0.06, 1.44				
Dockerry ²³	0.66	0.24, 1.81	2.83	0.29, 27.9		
Feychting ⁴	0.60	0.08, 4.54	0.80	0.10, 6.22	4.57	1.72, 12.1
Linnet ⁶	1.07	0.81, 1.42	0.96	0.61, 1.52	1.67	0.99, 2.82
London ⁷	1.02	0.55, 1.89	0.98	0.25, 3.75	1.82	0.75, 4.44
McBride ²²	0.85	0.59, 1.23	1.24	0.72, 2.14	1.40	0.62, 3.18
Michaelis ⁸	1.24	0.66, 2.33	0.93	0.24, 3.64	2.02	0.64, 6.37
Olsen ⁹	1.03	0.09, 11.4			3.74	0.34, 41.4
Savitz ¹⁰	1.78	0.70, 4.57	1.27	0.26, 6.17	4.08	0.91, 18.2
Tynes ¹²	1.12	0.26, 4.78				
Verkasalo ¹³	1.13	0.14, 9.25				
MH*	1.01	0.82, 1.25	0.94	0.65, 1.37	2.05	0.23, 18.1
					2.06	1.40, 3.01

95% CL = 95% confidence limits; MH = Mantel-Haenszel.

* Excludes Tomenius *et al*¹¹ (no covariate data). Covariate adjustment is for age and sex, plus social and economic variables in nine studies.^{4,6-9,12,13,22,23} Covariate-adjusted summary: 3-degrees-of-freedom Mantel-Haenszel categorical $P = 0.01$.

The dip in the curve in Figure 1 below 0.1 μT is mostly attributable to the Danish data,⁹ in which exposures below 0.1 μT were effectively set to 0 when calculating averages, and which contributed about one-quarter of the subjects in the $\leq 0.1 \mu\text{T}$ category. When this study was deleted, the dip disappeared, but the curve remained mildly sigmoidal.

NONCONTRIBUTING STUDIES

Myers *et al*¹⁶ reported only one case and two controls for "non-solid tumors" above 0.1 μT ; exclusion of this study could not have influenced our results to an important degree. Most of the data from the much larger study by Green *et al*²⁴ were neither presented in categories that could be combined directly with our categories nor broken into analysis categories above 0.15 μT ; the estimates in this study varied considerably with the measure and adjustment used, but all had wide confidence intervals and were statistically compatible with our results. Crude data from a personal-monitoring substudy by Green *et al*²⁵ produced odds ratios of 1.20 (95% CL = 0.59, 2.41), 1.76 (95% CL = 0.82, 3.80), and 0.71 (95% CL = 0.18, 2.88) comparing 0.1-0.2, 0.2-0.3, and >0.3 μT with $\leq 0.1 \mu\text{T}$, reflecting the small numbers in this substudy. The U.K. Childhood Cancer Study group²⁶ reported birthdate-sex-socioeconomic status-adjusted odds ratios for total leukemia of 0.78 (95% CL = 0.55, 1.12), 0.78 (95% CL = 0.40, 1.52), and 1.68 (95%

CL = 0.40, 7.10) comparing categories of 0.1-0.2, 0.2-0.4, and >0.4 μT with $\leq 0.1 \mu\text{T}$; our pooled data yielded age-sex-study-adjusted ML estimates of 1.01 (95% CL =

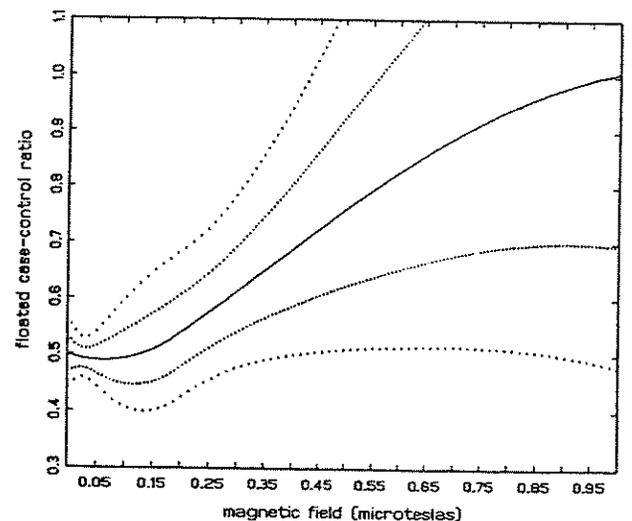


FIGURE 1. Floated case-control ratios³⁹ from 3-degree-of-freedom quadratic-logistic spline model fit to pooled magnetic field data, with adjustment for study, age, and sex. Inner dotted lines are pointwise 80% confidence limits; outer dotted lines are pointwise 99% confidence limits.

TABLE 6. Distribution of Residential Magnetic Field Measurements in Electric Power Research Institute Survey of U.S. Homes⁴¹ (N = 987) (Categories Exclude Lower Boundary)

Category (μ T)	No. of Homes in Category	%
≤ 0.05	437	44.2
0.05-0.1	277	28.1
0.1-0.2	173	17.5
0.2-0.3	55	5.6
0.3-0.4	20	2.0
0.4-0.5	8	0.8
0.5-0.6	7	0.7
0.6-0.75	6	0.6
over 0.75	4	0.4

Median = 0.06 μ T, mean = 0.09 μ T, and maximum = 1.01 μ T.

0.84, 1.21), 1.25 (95% CL = 0.96, 1.61), and 1.60 (95% CL = 1.03, 2.48) using the same categories.

ATTRIBUTABLE-FRACTION ANALYSIS

We estimated the excess fraction of U.S. childhood leukemia incidence that would be attributable to magnetic field exposures above 0.05 μ T, under the assumption that the dose-response estimate in Figure 1 represents the causal effects of fields. To estimate the U.S. population distribution of field exposure, we used data from a utility-based cluster-sampled survey conducted by the Electric Power Research Institute (EPRI).⁴¹ The data we obtained (Table 6) comprised spot field measurements averaged across rooms within each of 987 homes sampled from residences served by 301 EPRI utilities, which together served about 67% of U.S. homes.⁴¹

When these data were combined with the spline function in Figure 1 using a model-based attributable-fraction formula,⁴² we obtained a population attributable-fraction estimate of 3% for the effect of magnetic fields greater than 0.05 μ T (95% CL = -2%, 8%). The estimate is nearly the same if one uses any reference level up to 0.15 μ T (rather than 0.05 μ T), reflecting the fact that 90% of surveyed homes are in the 0-0.2 μ T range, in which the fitted ratios exhibit little variation. The wide confidence interval reflects the uncertainty about the distribution of exposure, as well as the considerable uncertainty about dose response. We further caution that our estimate refers only to effects of ambient residential fields and excludes effects of unmeasured personal field sources such as electric blankets.

We did not have survey data for Europe, but given the low Northern European exposures seen in Table 3, we would expect a correspondingly lower attributable-fraction estimate for Northern Europe.

RESULTS FOR WIRE CODES

Table 7 displays the distribution of wire codes among the studies supplying such codes, as well as data from Table V of Green et al.²⁴ As with fields, there are extensive differences among the studies, ranging within the U.S. from 15% with OHCC or VHCC codes in Linet et al.⁶ to nearly 50% with those codes in London et al.⁷ These differences reflect well-documented differences in power-grid architecture within the United States.^{1,41}

Table 8 displays odds ratio estimates computed directly from the raw counts underlying Table 7, and the corresponding covariate-adjusted estimates. Summary estimates are omitted because of the extensive unexplained heterogeneity among the study-specific results; for example, the VHCC odds ratios are less than 1 in three studies and more than 2 in three others (homogeneity $P = 0.005$). We found no covariate that accounted for the large variation in results, but deletion of Wertheimer and Leeper¹⁴ increased the homogeneity P -value to 0.11; no other single-study deletion increased the homogeneity P -value above 0.04. Eliminating Wertheimer and Leeper¹⁴ and Fulton et al.⁵ (the two earliest studies) yielded summary ML odds ratios of 1.02 (95% CL = 0.87, 1.22) for OHCC and 1.50 (95% CL = 1.17, 1.92) for VHCC based on 1,457 cases and 1,962 controls from six studies^{3,6,7,10,22,24} (deviance $P = 0.005$ for wire code; homogeneity $P = 0.15$).

As with fields, confounder adjustment had little effect on the wire code results beyond reducing the number of subjects, resulting in less stable estimates and more pronounced heterogeneity. For example, adjustment changed the Savitz et al.¹⁰ estimate of the VHCC odds ratio from 2.6 (95% CL = 0.92, 7.5) to 3.8 (95% CL = 1.2, 12); this change was entirely due to the deletion of

TABLE 7. Study-Specific Distributions of Wire-Code Data

First Author	Wire Code				No Measure
	VLCC*	OLCC	OHCC	VHCC	
Cases					
Fajardo-Gutiérrez ³		13†	92	82	0
Fulton ⁵	7		33	10	0
Green ²⁴ §	82	41	26	6	46
Linet ⁶	180	120	91	25	268‡
London ⁷	34	66	71	43	16
McBride ²²	152	77	83	39	48
Savitz ¹⁰	32	38	21	7	0
Wertheimer ¹⁴	4	86	53	13	7
Controls					
Fajardo-Gutiérrez ³		20†	102	65	0
Fulton ⁵	8	126	65	26	0
Green ²⁴ §	172	81	65	14	74
Linet ⁶	179	117	93	27	273‡
London ⁷	37	87	54	24	30
McBride ²²	157	77	105	23	37
Savitz ¹⁰	108	103	46	8	0
Wertheimer ¹⁴	17	107	26	6	7

VLCC = very low current code; OLCC = ordinary low current code; OHCC = ordinary high current code; VHCC = very high current code.

* VLCC includes underground (UG).

† Low-current categories not distinguished; translated as "baja" = LOC (low current code), "mediana" = OHCC, "alta" = VHCC.

‡ Subjects in Linet et al.⁶ had to meet a "residential stability" criterion to be wire coded.

§ Taken from Table V of Green et al.²⁴

TABLE 8. Study-Specific Odds Ratio Estimates and Study-Adjusted Summary Estimates without and with Restriction and Covariate Adjustment, Wire-Code Data [Reference Category: LCC (OLCC + VLCC + UG)]

First Author	Wire Code			
	OHCC		VHCC	
	Estimate	95% CL	Estimate	95% CL
Without restriction or adjustment				
Fajardo-Gutiérrez ³	1.39	0.65, 2.95	1.94	0.90, 4.19
Fulton ⁵	0.92	0.55, 1.52	0.70	0.32, 1.52
Green ^{24*}	0.82	0.50, 1.36	0.88	0.33, 2.35
Linet ⁶	0.97	0.69, 1.34	0.91	0.52, 1.61
London ⁷	1.63	1.05, 2.53	2.22	1.26, 3.91
McBride ²²	0.81	0.57, 1.14	1.73	1.00, 2.99
Savitz ¹⁰	1.38	0.77, 2.46	2.64	0.92, 7.54
Wertheimer ¹⁴	2.81	1.63, 4.83	2.99	1.09, 8.15
With restriction and adjustment†				
Fajardo-Gutiérrez ³	1.41	0.66, 2.99	2.05	0.95, 4.43
Fulton ⁵	0.79	0.40, 1.53	0.54	0.21, 1.41
Linet ⁶	0.99	0.70, 1.41	0.92	0.51, 1.66
London ⁷	1.46	0.91, 2.35	2.25	1.21, 4.20
McBride ²²	0.79	0.56, 1.12	1.55	0.89, 2.68
Savitz ¹⁰	1.52	0.82, 2.83	3.77	1.22, 11.7
Wertheimer ¹⁴	2.84	1.65, 4.89	3.10	1.14, 8.47

OLCC = ordinary low current code; VLCC = very low current code; UG = underground (LCC combines these three categories); OHCC = ordinary high current code; VHCC = very high current code.
* Computed from Table V of Green *et al.*²⁴
† Excludes Green *et al.*²⁴ (which was not in our database); restricted to subjects with covariate data; covariate adjustment is for age and sex, plus social or economic variables in four studies.^{6,7,10,22}

15 cases and 23 controls without covariate data. Adjusted results in our three-level format could not be computed from Green *et al.*²⁴ but their own adjustment produced little change in their estimates.²⁴ Table V Fajardo-Gutiérrez supplied additional data on wiring configurations that allowed one of us (W. T. K.) to construct an alternative approximation to the Wertheimer-Leeper wire code in this study.³ This alternative coding produced OHCC and VHCC (vs LCC) odds ratios of 1.5 (95% CL = 0.80, 2.9) and 1.2 (95% CL = 0.80, 1.9), which appear less consistent with other studies than the odds ratios from the original coding (Table 8).

Four studies^{6,7,10,22} recorded both magnetic fields and wire codes, allowing us to examine these exposures together (Table 9). Because these analyses involve only a

fraction of all subjects and because fields and codes are strongly associated (mean fields of 0.09 for LCC, 0.13 for OHCC, and 0.19 for VHCC), the results are even more unstable. Nonetheless, the associations seen with fields and codes entered into the same model were similar to the associations seen with separate models for the measures.

Discussion

For brevity and on scientific grounds, we restricted this report to analyses specified as *a priori* relevant to the main study question: Are magnetic fields or wire codes consistently associated with childhood leukemia? Our prior restrictions were meant to avoid analyses that "capitalize on chance" (small numbers and unstable estimates) either to reinforce or refute a particular hypothesis. Such restrictions are especially important in dose-response analyses of magnetic fields because of suggestions that the entire topic of EMF research is a product of unconstrained data dredging.⁴³

Purely categorical dose-response analyses (that is, those conducted without regard to ordering, spacing, or smoothness constraints) can almost always be made to yield nonmonotone patterns by using categories small enough so that category-specific estimates become unstable. To avoid such problems, we supplemented our initial categorical analyses with smooth regression analyses (splines) rather than with smaller categories. We believe that dose-response modeling is important in the present context because, even upon pooling, there are still too few data to reject any plausible dose-response shape, especially above 0.2 μ T. In particular, the data appear to be statistically consistent with anything from

TABLE 9. Summary Odds Ratio Estimates Based on 850 Cases and 1,004 Controls from Four Studies with Both Magnetic Field Measurements and Wire Codes^{6,7,10,22} (Reference Categories: $\leq 0.1 \mu$ T and LCC)

	Estimates from Logistic Regression* with					
	Magnetic Field Alone		Wire Code Alone		Field and Wire Code	
	Estimate	95% CL	Estimate	95% CL	Estimate	95% CL
Field (μ T)						
0.1-0.2	1.08	0.86, 1.35			1.02	0.81, 1.29
0.2-0.3	1.10	0.76, 1.60			1.01	0.69, 1.48
>0.3	1.52	0.99, 2.33			1.38	0.89, 2.13
P value†		0.27				0.55
Wire code						
OHCC			1.15	0.92, 1.44	1.13	0.90, 1.42
VHCC			1.65	1.15, 2.35	1.58	1.18, 2.28
P value†				0.02		0.04

LCC = low current code; OHCC = ordinary high current code; VHCC = very high current code.
* Includes study indicators.
† From deviance tests of all categories.

curves that are nearly flat to curves that rise and then fall at high exposures to curves that rise faster than exponentially.

We had planned to use available information to impute magnetic field values for subjects having only wire codes, on the basis of information relating codes to field measurements.^{10,35} Nonetheless, because of the heterogeneity among wire code results and doubts about the accuracy of the imputation, we decided to forego those analyses.

One interesting result from our analysis is resolution of an apparent "wire code paradox." It has been remarked that wire codes show more consistent associations with childhood cancers across studies than do magnetic fields. The paradoxical element arose in part from the presumption that wire codes were a proxy for fields and thus should show less consistent associations if fields have an effect. An examination of our tables suggests that, after allowing for statistical variability, wire codes in fact show less consistent associations with childhood leukemia than do magnetic fields. Nonetheless, adjustment for measured fields does not reduce the association of wire codes with childhood leukemia (Table 9). Perhaps only fields are biologically relevant, but errors in the field measures are so large that wire codes pick up much of the field effect; another possibility is that both measures only reflect effects of some biologically relevant exposure that is missing from our data.

One can of course raise many criticisms of the individual studies, which would increase the already large uncertainty in our results. For example, confounding effects of socioeconomic status, residential mobility, residence type, viral contacts, and traffic density have been raised as possible explanations for the observed associations.⁴⁴⁻⁵¹ These confounding hypotheses are themselves problematic. First, a confounding explanation requires the confounder to have an effect considerably larger than the observed association, as well as a strong association with exposure.^{30,Ch. 2} These attributes have not yet been demonstrated for the hypothesized confounders across the different populations that display positive associations. Adjustment for recorded socioeconomic and housing factors produced only small changes in the field-leukemia association, but our data on such factors are incomplete and we have only limited data on other potential confounders. Some results suggest that traffic-density effects may be large enough to partly explain the associations seen here.⁴⁴⁻⁴⁷ We thus recommend that future studies obtain data on traffic density and ambient pollution levels, as well as details of socioeconomic status and residence history.

Biases due to measurement errors are undoubtedly present in and vary across all of the studies, but their assessment is not wholly straightforward. One problem is that there is no agreed-upon definition of the target exposure, although it is often thought of as some sort of average or cumulative exposure during some biologically relevant time before leukemia diagnosis. Only under fairly restrictive conditions^{40,52} can one be certain that the net bias due to such error will be toward the null.

Unfortunately, there is little or no evidence to establish such detailed attributes of the errors, and there is no basis for assuming such attributes are the same across studies and measures. For example, although some U.S. studies have found clear associations between fields measured at the front door, average magnetic fields in the home, and personal exposure to children^{27,53} and another U.S. study found some repeatability of spot measures over extended time periods,⁵⁴ these associations are not large enough to ensure that the measures would tend to exhibit similar associations with childhood leukemia. Furthermore, the associations are imperfect enough to indicate that probably all of the measures suffer considerable error as proxies for any biologically relevant exposure measure (if one exists). One study suggested that electric rather than magnetic fields may be the relevant exposure.² Other studies conflict with this suggestion, however, insofar as the electric-field associations with childhood leukemia reported in those studies tended to be null or smaller than the reported magnetic-field associations.^{7,10,23,25}

Selection biases may be present in the studies, but for most there is little evidence that would establish their magnitude or even their direction with any certainty. Some studies reported low response rates (for example, field measurements were obtained on only half the identified potential controls in McBride *et al*²²), and accurate response rates cannot be determined for all studies. Whether such problems have led to serious bias remains a matter of speculation; the limited evidence from U.S. studies appears conflicting (for example, contrast Savitz *et al*^{10,35} with Hatch *et al*⁵¹ and Savitz and Kaune⁵⁵).

Given the preceding considerations, it seems reasonable to suppose that measurement and validity differences are responsible for some of the variation in study-specific results. Those considerations also raise a serious criticism of our analysis, in that we pooled different magnetic field measures without demonstrating that all of the measures are comparable or combinable. Indeed, it is highly implausible that the measures we used (or any other choices among available measures) reflect common underlying exposure and error distributions. Furthermore, our criteria for choosing measures when we had a choice are not compelling (for example, minimize missing data), and one could reasonably argue in favor of other choices⁵⁶ (although not without dispute^{57,58}). We expected that measure heterogeneity would lead to extra variation among the study-specific results, so we are all the more surprised that the observed variation was limited. We caution, however, that other choices could lead to very different degrees of variation; our results may not even be typical of what would be seen upon trying all defensible choices (although exploring the full range of choices would not indicate which choice is most valid). These problems should further expand the considerable uncertainty apparent in our results.

Another meta-analytic issue is that of publication bias. Because of the publicity surrounding the topic, we speculate that the data in small unpublished studies (if any exist) would have little influence on the results, and

that all large studies of this topic get published. Unfortunately, there are as yet too few published studies of fields or wire codes and childhood leukemia to support a reliable analysis of this bias,^{59,60} and current methods for analyzing the bias are not well suited for relations that require several degrees of freedom to summarize.

Our attributable-fraction estimate is subject to further criticism through its dependence on the EPRI survey.⁴¹ The survey measurements are of residential fields and therefore exclude sources such as school exposures and electric blankets; this exclusion error probably increases with age, especially upon school entry. Furthermore, selection bias could have been introduced because the survey homes were not limited to homes with children. Nonetheless, we think our estimate shows that any population effect of fields is probably much too small to detect via ecologic or time-trend studies; large ecologic variation or trends in leukemia rates would more likely be due to ecologic or temporal confounding than to real EMF effects.

In light of the above problems, the inconclusiveness of our results seems inescapable; resolution will have to await considerably more data on high electric and magnetic-field exposures, childhood leukemia, and possible bias sources. It also appears to us that, if an effect exists below 0.2 μT , it is probably too small to reach consensus about it via epidemiologic investigation alone. In contrast, both our categorical and trend analyses indicate that there is some association comparing fields above 0.3 μT to lower exposures, although there are as yet insufficient data to provide more than a vague sense of its form and its possible sources. We believe individual-level studies that focus on highly exposed populations would be needed to clarify this association. Such populations might be found in densely settled areas of some industrialized countries, such as Japan.⁶¹ Even in these countries, efficiency might be improved by restricting the source population to locales containing transmission lines, as was done in some Scandinavian studies.

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