Review Article

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Exposure to magnetic fields and childhood leukemia: a systematic review and meta-analysis of case-control and cohort studies

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Abstract: The association between childhood leukemia and extremely low frequency magnetic fields (ELF-MF) generated by power lines and various electric appliances has been studied extensively during the past 40 years. However, the conditions under which ELF-MF represent a risk factor for leukemia are still unclear. Therefore, we have performed a systematic review and meta-analysis to clarify the relation between ELF-MF from several sources and childhood leukemia. We have systematically searched Medline, Scopus, Cochrane Database of Systematic Review and DARE to identify each article that has examined the relationship between ELF-MF and childhood leukemia. We have performed a global meta-analysis that takes into account the different measures used to assess magnetic field exposure: magnetic flux density measurements (<0.2 μT vs. >0.2 μT), distances between the child's home and power lines (>200 m vs. <200 m) and wire codings (low current configuration vs. high current configuration). Moreover, meta-analyses either based on magnetic flux densities, on proximity to power lines or on wire codings have been performed. The association between electric appliances and childhood leukemia has also been examined. Of the 863 references identified, 38 studies have been included in our systematic review. Our global meta-analysis indicated an association between childhood leukemia and ELF-MF (21 studies, pooled OR=1.26; 95% CI 1.06–1.49), an association mainly explained by the studies conducted before 2000 (earlier studies: pooled OR=1.51; 95% CI 1.26–1.80 vs. later studies: pooled OR=1.04; 95% CI 0.84–1.29). Our meta-analyses based only on magnetic field measurements indicated that the magnetic flux density threshold associated with childhood leukemia is higher than 0.4 μT (12 studies, >0.4 μT: pooled OR=1.37; 95% CI 1.05–1.80; acute lymphoblastic leukemia alone: seven studies, >0.4 μT: pooled OR=1.88; 95% CI 1.31–2.70). Lower magnetic fields were not associated with leukemia (12 studies, 0.1–0.2 μT: pooled OR=1.04; 95% CI 0.88–1.24; 0.2–0.4 μT: pooled OR=1.07; 95% CI 0.87–1.30). Our meta-analyses based only on distances (five studies) showed that the pooled ORs for living within 50 m and 200 m of power lines were 1.11 (95% CI 0.81–1.52) and 0.98 (95% CI 0.85–1.12), respectively. The pooled OR for living within 50 m of power lines and acute lymphoblastic leukemia analyzed separately was 1.44 (95% CI 0.72–2.88). Our meta-analyses based only on wire codings (five studies) indicated that the pooled OR for the very high current configuration (VHCC) was 1.23 (95% CI 0.72–2.10). Finally, the risk of childhood leukemia was increased after exposure to electric blankets (four studies, pooled OR=2.75; 95% CI 1.71–4.42) and, to a lesser extent, electric clocks (four studies, pooled OR=1.27; 95% CI 1.01–1.60). Our results suggest that ELF-MF higher than 0.4 μT can increase the risk of developing leukemia in children, probably acute lymphoblastic leukemia. Prolonged exposure to electric appliances that generate magnetic fields higher than 0.4 μT like electric blankets is associated with a greater risk of childhood leukemia.

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Introduction

Leukemia is the most common cancer in childhood. It is a blood cancer that generally starts in the bone marrow and is characterized by an uncontrolled growth of blood cells, usually white blood cells. These blood cells are not fully developed and are called leukemia cells. The most common subtypes of leukemia are acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphoblastic leukemia and chronic myeloid leukemia. Symptoms depend on the subtype of leukemia but typically include bleeding and bruising, fatigue, fever and an increased risk of infections. Acute lymphoblastic leukemia is the most common subtype of leukemia among children and represents about 75% of all childhood leukemia cases [1]. The factors that cause childhood leukemia are still poorly understood but the role of residential magnetic fields has been proposed in 1979 by Wertheimer and Leeper [2]. During the past decades, an abundant scientific literature has examined the relation between magnetic fields and childhood leukemia but with conflicting results [3–6].

Extremely low frequency magnetic fields (ELF-MF) typically refer to electromagnetic waves with frequencies from 3 to 30 Hz but higher frequencies up to 300 Hz are also often defined as ELF-MF in the medical literature [7]. In the context of the present work, ELF-MF will refer to magnetic fields lower than 100 Hz, mostly 50 Hz (utility frequency used in Europe) and 60 Hz (utility frequency used in North America). Residential magnetic fields like those emitted by overhead power lines and magnetic fields generated by household electric appliances are in the range of ELF-MF [5, 8, 9]. Three measurements have been used in the studies that have examined the relation between residential magnetic fields and childhood leukemia: the wire coding classification system defined by Wertheimer and Leeper [2], magnetic flux density measurements [5] and the distance between the child's home and the power lines [10]. The magnetic flux density is measured in tesla (T) or in gauss (G) and the studies interested in the relation between ELF-MF and childhood leukemia typically use microteslas (μT) and sometimes milligauss (mG) (1 μT = 10 mG). Two approaches have been used to assess residential magnetic fields: direct magnetic field measurements in residences (using for example an Emdex-C meter like in Linet et al. [5]) and calculated magnetic fields based on the distance from the power line and the characteristics of the power line (like in Kroll et al. [11]). Since the pioneer study published by Wertheimer and Leeper [2], several epidemiological studies have been conducted to examine the long-term effects of ELF-MF on health [12]. In 2002, the International Agency for Research on Cancer classified residential magnetic fields as possibly carcinogenic to humans (Group 2B) [13]. All residential areas are affected by ELF-MF at least to some degree, which involves that virtually all children are exposed to these electromagnetic waves in high income countries. Nevertheless, the risk of childhood leukemia has not been supported by all empirical data and the safe distance from overhead power lines has not clearly been defined.

In 2014, Zhao and colleagues [14] published a meta-analysis that synthetizes the scientific literature on ELF-MF and childhood leukemia but they were exclusively interested in residential magnetic fields and not in distances to power lines. Seomun and colleagues [15] have recently performed a meta-analysis about the association between ELF-MF and different childhood cancers. However, their work does not focus on childhood leukemia, the different subtypes of leukemia have not been analyzed separately and distances to power lines have not been examined. Pooled analyses have also been published but they cover only a limited number of studies [3, 16–20]. Finally, none of these studies have performed a meta-analysis on ELF-MF from household electric appliances. Therefore, we have performed a meta-analysis to assess the relation between ELF-MF and childhood leukemia based on the most recent data and using residential magnetic fields, wire codings, proximity to power lines and household electric appliances. Residential magnetic fields, wire codings and proximity to power lines have been analyzed in separate meta-analyses and also in the same global meta-analysis. In order to define the magnetic field levels and the safe distance from power lines that are not linked to childhood leukemia, all the magnetic field exposure categories and distance categories available in the scientific literature have been taken into account in our meta-analyses. Moreover, we have investigated the relation between ELF-MF generated by household electric appliances and childhood leukemia. Finally, acute lymphoblastic leukemia has been analyzed separately after each meta-analysis.

Methods

Search strategy and selection criteria

We have performed a systematic review and meta-analysis to examine whether exposure to ELF-MF can increase the risk of childhood leukemia. The population of our study was limited to children under the age of 21. The intervention was defined as exposure to ELF-MF lower than 100 Hz. Since all children from high income countries are exposed to residential magnetic fields at least to some degree, there is no control group with children that have never been exposed to ELF-MF. However, a reference category is typically defined in the scientific literature as ELF-MF lower than 0.1 μT [11, 14]. The outcome of our study is the occurrence of leukemia. All leukemia subtypes have been taken into account but only acute lymphoblastic leukemia could be analyzed separately in secondary meta-analyses. We have followed the PRISMA guidelines [21] to report this meta-analysis and our protocol has been pre-registered in Prospero in May 2018 (Registration number: CRD42018087863; Web address: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=87863).

We have used Medline, Scopus, Cochrane Database of Systematic Review and DARE (Database of Abstracts of Reviews of Effects) to find all the studies that have examined the relation between ELF-MF and childhood leukemia. Supplementary Table 1 describes the search strategy and search terms used for Medline (via Ovid). Moreover, we have performed a manual search of the bibliographic references of relevant studies and reviews. Finally, we have interacted with experts in the field of ELF-MF and childhood leukemia to guarantee that we have not missed relevant studies.

Study selection, data extraction and assessment of methodological quality have been performed by two reviewers independently (CBr and AG). Any differences of opinion between reviewers in these different steps have been resolved through discussion and consensus.

Study selection has been done in two steps: title/abstract screening and then, full-text screening. Inclusion and exclusion criteria are defined in Table 1.

Data have been extracted in a standardized Excel sheet pretested on a sample of studies. The data extraction involved the following data: authors, journal name, year of publication, country, objective of the study, socio-demographic data (type of population, sex ratio and average age), sample size, design, outcomes, type of electromagnetic field (frequency and magnetic flux density), moment of magnetic field exposure (date, time of the day, season), method used to assess the magnetic field exposure, distance between the child's home and overhead power lines, characteristics of the power lines, leukemia subtype, moving house history, conclusion, presence of conflicts of interest and funding. We have contacted Dr Jirik and Dr Núñez-Enríquez to have all the information necessary for the extraction of the data of their studies [26, 27].

The assessment of methodological quality has been performed using the Newcastle-Ottawa Scale (NOS) [28].

Data analysis and statistics

We have performed a global meta-analysis and secondary meta-analyses based on the three measurements that have been used to examine the relation between residential magnetic fields and childhood leukemia: (1) magnetic flux density measurements in μT (or in mG like in London et al. [29]), (2) distances between the child's home and power lines and (3) the wire coding classification system of Wertheimer and Leeper [2]. This wire coding system comprised four current configurations: the very low current configuration (VLCC), the ordinary low current configuration (OLCC), the ordinary high current configuration (OHCC) and the very high current configuration (VHCC). Nevertheless, it is noteworthy that Wertheimer and Leeper only used a low current configuration (LCC) and a high current configuration (HCC) in their pioneer article published in 1979 [2].

Table 1: Inclusion criteria.

Study design	Case-control and cohort studies. Only case-control and cohort studies have examined the relation between ELF-MF and childhood leukemia; there are no randomized controlled trials in this research field.
Participants	Children under the age of 21. Our systematic review covers all the studies that have examined the relation between ELF-MF and childhood leukemia. The oldest children in the studies covered by our systematic review were 21 years old. Note: Our protocol published in Prospero (2018) mentioned that we have planned to restrict our meta-analysis to children under the age of 15. As a result, we have performed a sensitivity analysis that restricts our analysis to children under the age of 15 in the global meta-analysis of the present systematic review. The age limit used in our protocol published in Prospero was based on the NRCT, a high-quality population-based specialist childhood cancer registry [22].
Interventions	Exposure to magnetic fields between 0 and 100 Hz.
Magnetic field categories, distance categories and type of studies	To perform our meta-analysis, we have selected the studies that have used the magnetic field categories (0.1–0.2 μT, 0.2–0.3 μT, 0.3–0.4 μT, 0.2–0.4 μT, >0.2 μT, >0.3 μT and >0.4 μT) or distance categories (0–50 m, 0–200 m, 200–600 m) that have most often been defined in previous studies [10, 14]. Studies that have used atypical magnetic or distance categories are only included in the qualitative synthesis and their results are shown in Table 3. We have also selected the studies based on the current configurations defined by Wertheimer and Leeper [2] and on household electric appliances.
Outcomes	Occurrence of childhood leukemia (all leukemia subtypes). Leukemias have typically been defined according to international classifications of childhood cancer ([23, 24] like in Kroll et al. [11]) or according to the International Classification of Diseases (like in Verkasalo et al. [25]).

Table 1: (continued)

Language	English, French, Italian (because authors are fluent in English and in French and one author [ET] is fluent in Italian).
Date	Studies published until April 2021 (from 1979 to April 15, 2021).

NRCT, National Registry of Childhood Tumors.

To include as many studies as possible in the same meta-analysis and take into account the method used to assess magnetic field exposure, we have performed a global meta-analysis based on the exposure levels (cutoffs) of the three measurements that have most often been used to examine the relation between residential magnetic fields and childhood leukemia: <0.2 μT vs. >0.2 μT for magnetic flux densities, >200 m vs. <200 m for distances and the LCC (or underground/extremely low + VLCC + OLCC) vs. the HCC (or OHCC + VHCC) for wire codings. In our global meta-analysis, <0.2 μT served as the reference category for magnetic flux densities. Living more than 200 m away from power lines (>200 m) served as the reference category for distances to power lines whereas the low current configuration (LCC or underground/extremely low + VLCC + OLCC) served as the reference category for wire codings. It is noteworthy that magnetic fields higher than 0.2 μT have not been found in residences located between 200 m and 600 m away from power lines in the studies of Kroll et al. [11] and Crespi et al. [30]. However, magnetic fields can reach more than 0.4 μT in residences located within 200 m of power lines [11, 30]. Moreover, mean measured magnetic flux densities were always lower than 0.2 μT for the OLCC and the VLCC in the studies conducted by Green et al. [31] and McBride et al. [6]. Therefore, it is rationale to assume that the reference categories for magnetic fields, distances to power lines and wire codings used in our global meta-analysis corresponded to magnetic fields lower than 0.2 μT. When the studies included in our global meta-analysis performed several measurements to estimate magnetic fields (like magnetic flux density measurements and wire codings) using the same subjects, only magnetic flux density measurements have been taken into account in the global meta-analysis.

We have performed three separate secondary meta-analyses based either on magnetic flux densities, proximity to overhead power lines or wire codings. To be consistent with previous studies, we have used the following reference categories: <0.1 μT for magnetic flux densities [11, 14]; living more than 600 m away from power lines for distances [32] and the underground/extremely low current configuration for the wire coding system of Wertheimer and Leeper [2]. We have used the magnetic field (0.1–0.2 μT, 0.2–0.3 μT, 0.3–0.4 μT, 0.2–0.4 μT, >0.3 μT and >0.4 μT) and distance categories (0–50 m, 0–200 m, 200–600 m) that have most often been defined in previous studies [6, 10, 14, 32] and the four current configurations defined by Wertheimer and Leeper [2]: VLCC, OLCC, OHCC and VHCC.

Additional secondary meta-analyses that have examined the relationship between ELF-MF generated by household electric appliances and childhood leukemia have also been performed. Moreover, the different subtypes of leukemia (like acute lymphoblastic leukemia) have been analyzed separately when possible.

We have performed a meta-analysis based on the outcomes reported by the different studies we have selected. Study results were expressed as odds ratios (OR) with 95% confidence intervals (CI). When available, adjusted ORs have been reported. Otherwise, crude ORs have been computed from the results that were available in the article. Since participant demographics differed a lot among studies, we have assumed the presence of heterogeneity *a priori* and used a random-effects model to analyze the results. We have assessed heterogeneity using the χ^2-based Q-Cochrane test and the I^2 measure of inconsistency.

To evaluate the impact of individual studies on the overall results, we have performed sensitivity analyses. If the necessary data were available, we have performed subgroup analyses based on the methodological quality, the method to estimate the magnetic field exposure, the frequency (50 Hz vs. 60 Hz) and the period of magnetic field exposure. Very few studies included in the subgroup analyses had a NOS score higher than seven and none of them had a NOS score of nine. Therefore, we have defined the subgroups with a lower threshold (<7 points vs. ≥7 points) than in our previous work (≤7 points vs. >7 points [33]). Studies with a NOS score lower than seven points were defined as "low quality studies". Studies with a NOS score ≥7 points were defined as "high-quality studies". The subgroup analyses based on the period of magnetic field exposure compared the earlier studies whose magnetic field exposure ended before January 1, 2000 with more recent studies whose magnetic field exposure ended after January 1, 2000. A test of interaction using a mixed-effects model has been performed for all subgroups to determine whether the difference in effect size among subgroups was statistically significant.

The publication bias has been evaluated using a funnel plot and the Egger's regression asymmetry test when there were at least 10 studies per meta-analysis [34]. Significance was always set at $p<0.05$ except when assessing heterogeneity with the Cochran's Q test ($p<0.10$). We have performed our analyses using Review Manager (version 5.3) and R (metafor package [35]).

Results

Selected studies and study characteristics

A total of 38 articles have been included in our systematic review (see flowchart on Figure 1 and Appendix for the studies excluded from our systematic review and reasons of exclusion). The characteristics of the studies included in our systematic review are presented in Table 2. Most studies were retrospective case-control studies and two studies were cohort studies. One cohort study was based on magnetic fields [25] and the other one was based on distances [60] (Table 3). Thus, we could not perform a meta-analysis based only on these two cohort studies. Eight studies have used distance and/or magnetic field categories incompatible with those defined in our systematic review. These studies could thus not be included in any of our meta-analyses. The results of these studies are shown in Table 3.

All the studies included in our systematic review were mixed-gender studies, with the percentage of girls suffering from leukemia varying between 40.6% [49] and 54.2% [25]. The number of leukemia cases ranged from 22 [57] to 16 457 [10]. Most studies have been performed in

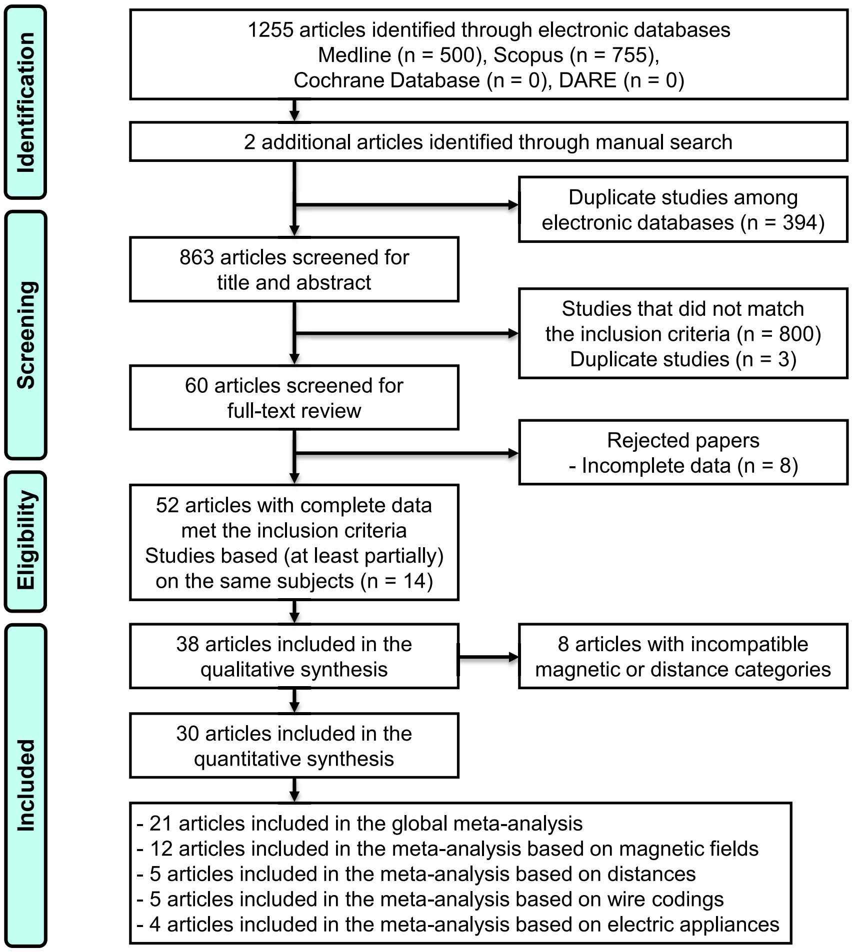

Figure 1: Flowchart of selection of studies for inclusion in the meta-analysis. See Appendix for the studies excluded from our systematic review and the reasons of exclusion.

Europe (16 articles referring to 13 studies) and in North America (13 articles referring to nine studies). Six studies have been conducted in Asia [4, 47, 49, 51, 57, 60], one in South America (Brazil [32]) and one in Oceania (New Zealand study referring to the articles by Dockerty and colleagues [41, 42]). No study has been performed in Africa.

Most studies included in our systematic review have been conducted in high income countries. Based on the World Bank Income classification [61], all the European studies and the studies conducted in the USA, Canada, Japan and New Zealand come from high income countries. Some studies have been conducted in upper middle income countries: the studies performed in Mexico [27, 48], Brazil [32] and Malaysia [49]. Finally, the studies by Feizi and Arabi [47], Sohrabi et al. [51] and Tabrizi and Hosseini [57] have been conducted in Iran, a lower middle income country. None of the studies included in our review belong to low income countries. Our systematic review indicates that less children from high income countries have been exposed to residential magnetic fields above 0.4 µT than children from lower income countries. Only 0.3% of children from high income countries have been exposed to ELF-MF higher than 0.4 µT [4–6, 26, 31, 46, 50, 54, 55, 59] whereas 11.6% of children from lower income countries [27, 47, 48] have been exposed to ELF-MF above 0.4 µT.

The quality of the studies included in our systematic review was generally below seven points on the NOS (Supplementary Table 2). Given the limited number of studies that have analyzed the association between ELF-MF and specific subtypes of leukemia, acute lymphoblastic leukemia was the only subtype of leukemia that could be analyzed separately in our meta-analyses.

Global meta-analysis based on magnetic fields, distances to power lines and wire codings

The global meta-analysis based on the exposure levels (cutoff points) that have most often been used in the studies included in our review (0.2 µT for magnetic fields, 200 m for distances to power lines and the LCC vs. HCC for wire codings) included 21 studies and indicated a significant association between ELF-MF and childhood leukemia

Table 2: Characteristics of the studies included in the systematic review.

First author	Cases	Controls	Geographic area, age, sex ratio	Source of cases, participation level of cases, percentage of cases in the highest exposure category	Source of controls, participation level of controls, percentage of controls in the highest exposure category	Year of diagnosis	Measurement	Main results (OR or RR with 95% CI)	Funding
Case-control studies									
Wertheimer, 1979 [2]	136	136	USA, Colorado, <19 y, 43% of cases are girls, 51% of controls are girls	Birth and death certificate files, NR, HCC (birth addresses): 38.2%	Birth and death certificate files, NR, HCC (birth addresses): 21.3%	1950–1973	Wire coding	This study supports an association between wiring configuration and childhood leukemia (LCC vs. HCC for birth addresses: OR=2.28; 1.33–3.91)	Not reported
Savitz, 1988 [36]	36	207	USA, Colorado, <15 y, NR	Colorado Cancer Registry, 35%, >0.2 μT: 13.8%	RDD, 74%, >0.2 μT: 7.7%	1976–1983	Direct MF measure, wire coding	This study supports an association between low power use conditions and childhood leukemia (>0.2 μT, OR=1.93; 0.67–5.56)	Not explicitly reported
Savitz, 1990 [9]	73	73	USA, Colorado, <15 y, NR	Colorado Cancer Registry, 71% (for cancer cases, NR for leukemia cases), percentage exposed to electric blankets: 5.4%	RDD, 80%, percentage exposed to electric blankets: 3.7%	1976–1983	Exposure to electric appliances	This study supports a relation between exposure to electric blankets and childhood acute lymphoblastic leukemia (OR=1.9; 0.6–6.5)	Not explicitly reported
London, 1991 [29]	232	232	USA, California, <11 y, 44% of cases are girls, 44.4% of controls are girls	Los Angeles County Cancer Surveillance Program, 70%, percentage exposed to electric blankets: 3.0%	RDD, 90%, percentage exposed to electric blankets: 0.4%	1980–1987	Direct MF measure, wire coding and exposure to electric appliances	This study shows that childhood leukemia is associated with wiring codings (VHCC: OR=1.75; 0.66–4.64) but not with direct MF measures. Moreover, this study supports an association between childhood leukemia and exposure to electric blankets (OR=7.19; 0.88–58.91)	Supported by the Electric Power Research Institute

Table 2: (continued)

Case-control studies									
First author	**Cases**	**Controls**	**Geographic area, age, sex ratio**	**Source of cases, participation level of cases, percentage of cases in the highest exposure category**	**Source of controls, participation level of controls, percentage of controls in the highest exposure category**	**Year of diagnosis**	**Measurement**	**Main results (OR or RR with 95% CI)**	**Funding**
Feychting, 1993 [37]	38	554	Sweden, <16 y, 47.8% of cases are girls, 46.4% of controls are girls	Swedish Cancer Registry, 97%, >0.3 µT: 18.4%	CSR, 99%, >0.3 µT: 5.7%	1960–1985	Calculated MF, direct MF measure	This study supports an association between childhood leukemia and magnetic fields (>0.3 µT: RR=3.8; 1.4–9.3)	Study funded in part by the National Board for Industrial and Technical Development (NUTEK)
Linet, 1997 [5]	624	615	USA, Midwest and Northeast, <15 y, 47.7% of cases are girls and 47.8% of controls are girls	Children's Cancer Group [a], 78%, >0.5 µT: 1.4%	RDD, 63%, >0.5 µT: 0.9%	1989–1994	Direct MF measure, wire coding	This study provides some evidence for an association between ELF-MF and childhood acute lymphoblastic leukemia (>0.4 µT: OR=2.16; 1.04–4.48)	Supported by the National Cancer Institute and the University of Minnesota Children's Cancer Research Fund
Michaelis, 1997 [38]	129	328	Germany, Lower Saxony, <15 y, 42.6% of cases are girls and 52.4% of controls are girls	German Childhood Cancer Registry, 59%, >0.2 µT: 3.1%	CSR, 54%, >0.2 µT: 1.8%	1988–1993	Direct MF measure	This study provides some evidence for an association between ELF-MF and childhood leukemia (>0.2 µT: OR=1.5; 0.4–5.5)	Funded partially by the Ministry of Health of Lower Saxony
Petridou, 1997 [39]	117	202	Greece, <15 y, NR	Greek hospitals, 76%, highest wire code adapted to Greek conditions: 3.4%	Hospital controls, 66%, highest wire code adapted to Greek conditions: 3.9%	1993–1994	Wire coding adapted to Greek conditions	This study provides no strong support for a relation between ELF-MF and childhood leukemia	Supported by Europe Against Cancer Program (DGV) of the European Union
Tynes, 1997 [40]	148	579	Norway, <15 y, NR	Cancer Registry of Norway, 94% (for cancer cases, NR for leukemia cases), >0.14 µT: 0.7%	CSR, 95%, >0.14 µT: 2.4%	1965–1989	Calculated MF, distances	This study does not support an association between ELF-MF and childhood leukemia	Supported by the Norwegian Research Council, the Norwegian Electricity Federation and the Ministry of Energy

Table 2: (continued)

Case-control studies

First author	Cases	Controls	Geographic area, age, sex ratio	Source of cases, participation level of cases, percentage of cases in the highest exposure category	Source of controls, participation level of controls, percentage of controls in the highest exposure category	Year of diagnosis	Measurement	Main results (OR or RR with 95% CI)	Funding
Dockerty, 1998 [41]	121	121	New Zealand, <15 y, 45.5% of cases are girls and 45.5% of controls are girls	New Zealand Cancer Registry, public hospital admission/discharge computer system and Children's Cancer Registry, 92%, percentage exposed to electric blankets: 14.0%	CSR, 69%, percentage exposed to electric blankets: 8.2%	1990–1993	Direct MF measure, exposure to electric appliances	This study provides some support for the relation between ELF-MF and childhood leukemia (electric blanket: OR=2.2; 0.7–6.4)	Study funded by The Health Research Council of New Zealand and by several other organizations
Hatch, 1998 [8]	640	640	USA, Midwest and Northeast, <15 y, 48% of cases are girls and 47.3% of controls are girls	Children's Cancer Group, 88%, percentage exposed to electric blankets: 7.0%	RDD, 64%, percentage exposed to electric blankets: 2.9%	1989–1993	Exposure to electric appliances	This study provides some support for the relation between ELF-MF from electric appliances and childhood acute lymphoblastic leukemia (electric blanket: OR=2.75; 1.52–4.98)	Study funded in part by the National Cancer Institute and the University of Minnesota Children's Cancer Research Fund
Dockerty, 1999 [42]	40	40	New Zealand, <15 y, 45.5% of cases are girls and 45.5% of controls are girls	New Zealand Cancer Registry, public hospital admission/discharge computer system and Children's Cancer Registry, NR, >0.2 μT: 12.5%	CSR, NR, >0.2 μT: 5.0%	1990–1993	Direct MF measure	No significant association between childhood leukemia and the time-weighted average of the magnetic field in the bedroom and living room combined	Study funded by the Health Research Council of New Zealand and by several other organizations
Green, 1999 [31]	88	131	Canada, Ontario, <15 y, 45.4% of cases are girls and 48.1% of controls are girls	Pediatric Oncology Group Registry, NR, >0.8 μT: 0%	RDD, NR, >0.8 μT: 1.5%	1985–1993	Direct MF measure, wire coding	The results support an association between childhood leukemia and magnetic fields (>0.14 μT: OR=4.5; 1.3–15.9)	Not explicitly reported
McBride, 1999 [6]	351	362	Canada, British Columbia, Alberta, Saskatchewan, Manitoba and Quebec [b], <15 y, 49% of cases are girls and 49% of controls are girls	Pediatric oncology treatment centers and population-based cancer registries, 90%, >0.5 μT: 2.7%	CSR, 76%, >0.5 μT: 1.7%	1990–1995	Direct MF measure, wire coding	This study provides little support for a relation between ELF-MF and childhood leukemia	Funded by the National Health Research and Development Programme of Health Canada and by the Canadian Electricity Association

Table 2: (continued)

Case-control studies

First author	Cases	Controls	Geographic area, age, sex ratio	Source of cases, participation level of cases, percentage of cases in the highest exposure category	Source of controls, participation level of controls, percentage of controls in the highest exposure category	Year of diagnosis	Measurement	Main results (OR or RR with 95% CI)	Funding
UK Childhood Cancer Study, 1999 [43]	1,073	1,073	UK, <15 y, 43.6% of cases are girls and 43.6% of controls are girls	Family Health Service Authorities or Health Boards, 87%, >0.4 µT: 0.4%	CSR, 64%, >0.4 µT: 0.2%	1991–1996	Direct MF measure	This study provides no strong support for a relation between ELF-MF and childhood leukemia	Funded by the Cancer Research Campaign and several other organizations
Bianchi, 2000 [44]	101	412	Italy, Lombardy, <15 y, NR	Lombardy Cancer Registry, 98%, >0.1 µT: 2.9%	CSR, 99%, >0.1 µT: 0.7%	1976–1992	Direct MF measure	This study supports an association between ELF-MF and childhood leukemia (>0.1 µT: RR=4.51; 0.88–23.17)	Supported by the Associazione Bianca Garavaglia and the Bramantesco Lion's club of Busto Arsizio
Kleinerman, 2000 [45]	405	405	USA, Midwest and Northeast, <15 y, NR	Children's Cancer Group, 90%, 0–14 m: 7.1%	RDD, 64%, 0–14 m: 8.3%	1989–1993	Calculated MF, distances (selected only for distances)	This study does not support an association between living near power lines and childhood acute lymphoblastic leukemia	Not reported
Schüz, 2001 [46]	514	1,301	Germany (Lower Saxony excluded), <16 y, 40.9% of cases are girls and 40.1% of controls are girls	German Childhood Cancer Registry, 61%, >0.4 µT: 0.5%	CSR, 62%, >0.4 µT: 0.2%	1980–1994	Direct MF measure	This study supports an association between ELF-MF and childhood leukemia (>0.4 µT: OR=5.94; 0.80–44.1)	Supported by the German Federal Ministry for the Environment, Nuclear Safety and Nature Preservation
Kabuto, 2006 [4]	312	603	Japan, <16 y, 41.8% of cases are girls and 42% of controls are girls	Five major children's cancer study groups [c], 49%, >0.4 µT: 1.9%	CSR, 29%, >0.4 µT: 0.8%	NR (before 2006)	Direct MF measure, distances	This study supports an association between ELF-MF and childhood leukemia (>0.4 µT: OR=2.36; 0.72–7.79)	Supported by the Ministry of Education, Culture, Sports, Science and Technology
Feizi, 2007 [47]	60	59	Iran, East Azerbaijan Province, <15 y, 42% of cases are girls and 36% of controls are girls	Hematology/oncology clinic of Children's Hospital of Tabriz Medical Sciences University, 84%, >0.45 µT: 25%	Hospital controls, 79%, >0.45 µT: 8.4%	1998–2004	Calculated MF, distances	This study supports an association between ELF-MF and childhood leukemia (>0.45 µT: OR=3.60; 1.11–12.39)	Not reported

Table 2: (continued)

Case-control studies

First author	Cases	Controls	Geographic area, age, sex ratio	Source of cases, participation level of cases, percentage of cases in the highest exposure category	Source of controls, participation level of controls, percentage of controls in the highest exposure category	Year of diagnosis	Measurement	Main results (OR or RR with 95% CI)	Funding
Mejia-Arangure, 2007 [48]	42	124	Mexico, Mexico city, <16 y, 52% of cases are girls and 41% of controls are girls	Mexican hospitals, 100%, >0.6 µT: 23.8%	Instituto John Langdon Down and Centro de Atencion Integral del Nino con Sindrome de Down, 56%, >0.6 µT: 10.4%	1995–2003	Direct magnetic field measure	This study supports an association between ELF-MF and acute leukemia in children with Down syndrome (>0.4 µT: OR=1.42; 0.57–3.53)	Supported by the “Instituto Mexicano del Seguro Social grant 2003/162”, the CONACYT and the “Fondos Sectoriales Salud-2003-C01-102”
Abdul Rahman, 2008 [49]	128	128	Malaysia, Klang Valley, <15 y, 40.6% of the cases are girls and 49.2% of controls are girls	National University of Malaysia Hospital and Kuala Lumpur General Hospital, NR, 0–200 m: 40.6%	Hospital controls, NR, 0–200 m: 24.2%	2001–2007	Distances	This study supports an association between living in proximity to power lines and childhood leukemia (0–200 m: OR=2.30; 1.18–4.49)	Not reported
Malagoli, 2010 [50]	46	184	Italy, Emilia-Romagna, Modena and Reggio Emilia, <14 y, 47.8% of cases are girls and 47.8% of controls are girls	AIEOP Registry [d], NR, >0.4%: 2.1%	CSR, NR, >0.4%: 1.0%	1986–2007	Calculated MF	This study supports an association between childhood leukemia and ELF-MF (>0.4 µT: OR=2.06; 0.18–23.19)	Funded by Associazione Sostegno Ematologia Oncologia Pediatrica and Department of the Environment of Reggio Emilia Municipality
Sohrabi, 2010 [51]	300	300	Iran, Tehran province, <19 y, 44% of the cases are girls and 44% of controls are girls	Children’s medical center, Ali-Asghar teaching center, Children’s Mofid teaching center, Mahak Hospital, NR, 0–600 m: 29.6%	Hospital controls, NR, 0–600 m: 14.0%	NR (before 2010)	Distances	This study supports an association between living in proximity to power lines and childhood acute lymphoblastic leukemia (0–600 m: OR=2.61; 1.73–3.94)	Not reported

Table 2: (continued)

Case-control studies

First author	Cases	Controls	Geographic area, age, sex ratio	Source of cases, participation level of cases, percentage of cases in the highest exposure category	Source of controls, participation level of controls, percentage of controls in the highest exposure category	Year of diagnosis	Measurement	Main results (OR or RR with 95% CI)	Funding
Wünsch-Filho, 2011 [32]	162	565	Brazil, São Paulo, <10 y, 46.9% of cases are girls and 47.4% of controls are girls	Brazilian hospitals, 65%, >0.3 µT: 6.7%	São Paulo Birth Registry, CSR, 23%, >0.3 µT: 6.0%	2003–2009	Direct MF measure, distances	This study provides some support for an association between childhood acute lymphoblastic leukemia and proximity to power lines (0–50 m: OR=3.57; 0.41–31.44)	Funded by the Brazilian Electricity Regulatory Agency
Jirik, 2012 [26]	82	81	Czech Republic, <15 y, NR	University hospitals, NR, >0.4 µT: 17.0%	Hospital controls, NR, >0.4 µT: 18.5%	2003–2007	Direct MF measure	This study does not support an association between ELF-MF and childhood leukemia	Not reported
Sermage-Faure, 2013 [52]	2,779	30,000	France, <15 y, 45% of cases are girls	French National Registry of Childhood Hematopoietic Malignancies, 98%, 0–50 m: 0.8%	CSR, 99%, 0–50 m: 0.7%	2002–2007	Distances	This study provides some support for an association between childhood leukemia and proximity to power lines (<50 m from 225–400 kV power lines: OR=1.7; 0.9–3.6)	Funded by the Institut de Veille Sanitaire and several other organizations
Bunch, 2014 [10]	16,457	20,241	UK, <15 y, NR	National Registry of Childhood Tumors, NR, 0–50 m: 0.1%	Birth registers, CSR, NR, 0–50 m: 0.1%	1962–2008	Distances	This study provides little support for a relation between proximity to power lines and childhood leukemia	Funded by a Programme Grant awarded from Children with Cancer UK
Pedersen, 2014 [53]	1,577	3,191	Denmark, <15 y, NR	Danish Cancer Registry, 93%, 0–200 m: 0.8%	CSR, 94%, 0–200 m: 1.0%	1968–2006	Distances	This study provides little support for a relation between proximity to power lines and childhood leukemia	Funded by the foundation Children with Cancer UK and by other organizations
Pedersen, 2015 [55]	1,536	3,072	Denmark, <15 y, NR	Danish Cancer Registry, NR, >0.4 µT: 0.3%	CSR, NR, >0.4 µT: 0.1%	1968–2003	Calculated MF	This study provides some support for an association between childhood leukemia and ELF-MF (>0.4 µT: OR=1.67; 0.51–5.47)	Funded by the foundation Children with Cancer UK and by other organizations

Table 2: (continued)

Case-control studies									
First author	**Cases**	**Controls**	**Geographic area, age, sex ratio**	**Source of cases, participation level of cases, percentage of cases in the highest exposure category**	**Source of controls, participation level of controls, percentage of controls in the highest exposure category**	**Year of diagnosis**	**Measurement**	**Main results (OR or RR with 95% CI)**	**Funding**
Salvan, 2015 [56]	409	569	Italy, SETIL study covering 14 Italian regions [e], <11 y, 45.6% of cases are girls and 46.5% of controls are girls	AIEOP [d] and pediatric hospital in Rome, 82%, >0.2 μT: 2.4%	CSR, 61%, >0.2 μT: 2.9%	1998–2001	Direct MF measure	This study provides no support for a relation between ELF-MF and childhood leukemia	Funded by Italian Association on Research on Cancer and other organizations
Tabrizi, 2015 [57]	22	100	Iran, Tehran Province, <12 y, NR	The children were born in Tehran and lived in Tehran [f], NR, 0–20 m: 18.1%	NR, NR, 0–20 m: 3.0%	NR (before 2015)	Distances	This study supports an association between living in proximity to power lines and childhood acute lymphoblastic leukemia (0–20 m: OR=3.65; 1.69–7.87)	Not reported
Bunch, 2016 [54]	15,920	19,608	UK, <15 y, NR	National Registry of Childhood Tumors, NR, >0.4 μT: 0.02%	Birth registers, CSR, NR, >0.4 μT: 0.05%	1962–2008	Calculated MF, distances	This study provides no support for a relation between childhood leukemia and ELF-MF	Funded by the UK Department of Health Radiation Protection Research Programme and by other organizations
Crespi, 2016 [58]	4,659	4,585	USA, California, <16 y, NR	California Cancer Registry, 70%, 0–50 m: 0.4%	California Birth Registry, CSR, 69%, 0–50 m: 0.3%	1988–2008	Distances	This study provides some support for a relation between living in proximity to power lines and childhood leukemia (0–50 m: OR=1.40; 0.7–2.7)	Funded by the Electric Power Research Institute
Kheifets, 2017 [59]	5,788	5,788	USA, California, <16 y, NR	California Cancer Registry, 87%, >0.4 μT: 0.2%	California Birth Registry, CSR, NR, >0.4 μT: 0.1%	1988–2008	Calculated MF	This study provides some support for a relation between ELF-MF and childhood leukemia (>0.4 μT: OR=1.48; 0.69–3.19)	Funded by the Electric Power Research Institute

Table 2: (continued)

Case-control studies

First author	Cases	Controls	Geographic area, age, sex ratio	Source of cases, participation level of cases, percentage of cases in the highest exposure category	Source of controls, participation level of controls, percentage of controls in the highest exposure category	Year of diagnosis	Measurement	Main results (OR or RR with 95% CI)	Funding
Núñez-Enríquez, 2020 [27]	290	407	Mexico, Mexico city, <16 y, 49.2% of the cases are girls and 45.6% of controls are girls	Public hospitals, 81%, >0.6 μT: 6.5%	Hospital controls, 81%, >0.6 μT: 3.6%	2010–2011	Direct MF measure	This study supports an association between ELF-MF and childhood acute lymphoblastic leukemia (≥0.6 μT: OR=2.32; 1.10–4.93)	Supported by the "Consejo Nacional de Ciencia y Tecnología"

Cohort studies

First author	Cases	Controls	Geographic area, age, sex ratio	Source of cases, percentage of cases in the highest exposure category	Source of controls, percentage of controls in the highest exposure category	Year of diagnosis	Measurement	Main results (OR or RR with 95% CI)	Funding
Verkasalo, 1993 [25]	35	134,660	Finland, <20 y, 54.2% of the cases are girls	Finish Cancer Registry, >0.2 μT: 8.5%	Central population register, >0.2 μT: 5.4%	1970–1989	Calculated MF	This study provides little support for a relation between ELF-MF and childhood leukemia	Funded by Imatran Voima Oy
Li, 1998 [60]	28	120,668	Taiwan, <15 y, NR	National Cancer Registration Center of Taiwan, 0–100 m: 25.0%	Taipei Metropolitan area, 0–100 m: 7.5%	1987–1992	Distances	This study supports an association between living in proximity to power lines and childhood leukemia (0–100 m: SIR=2.69; 1.08–5.55)	Not reported

CSR, controls were selected at random from the study population; MF, magnetic field; NR, not reported; OR, odds ratio; RDD, controls were selected through random-digit dialing; RR, relative risk; SIR, standardized incidence ratio; y, year. Two approaches have been used to assess residential magnetic fields: direct magnetic field measurements in residences (using for example an Emdex-C meter like in Linet et al.[5]) and calculated magnetic fields based on the distance from the power line and the characteristics of the power line (like in Kheifets et al. [59]). "Distance" refers to the distance between the child's home and power lines unless otherwise stated. "Wire coding" refers to the wire coding classification system of Wertheimer and Leeper [2]. The number of cases and controls refers to the number of leukemia cases and controls. [a]The Children's Cancer Group studies by Linet and colleagues [5, 8, 45] include subjects from nine Midwestern and Northeastern US states: Illinois, Indiana, Iowa, Michigan, Minnesota, New Jersey, Ohio, Pennsylvania and Wisconsin. [b]The study by McBride et al. [6] is based on subjects from the following Canadian provinces: British Columbia (BC), Alberta (AB), Saskatchewan (SK), Manitoba (MB) and Quebec (QC). [c]The leukemia cases in the Japanese study by Kabuto et al. [4] have been identified through five major children's cancer study groups in Japan: Tokyo Children's Cancer Study Group, Children's Cancer and Leukemia Study Group, Tohoku Children's Leukemia Study Group, Japan Association of Childhood Leukemia Study and Kyushu/Yamaguchi Children's Cancer Study Group. [d]AIEOP, Associazione Italiana Ematologia Oncologia Pediatrica (nation-wide hospital-based registry of childhood malignancies). [e]The SETIL case-control study is a collaborative project conducted in 14 Italian regions (Piedmont, Liguria, Lombardy, Veneto, Friuli-Venezia-Giulia, Emilia-Romagna, Tuscany, Umbria, Marche, Latium, Campania, Puglia, East Sicily, West Sicily, Sardinia). It is noteworthy that there is no overlap between the subjects of the three Italian studies [44, 50, 56] included in our systematic review according to the authors of these studies. [f]The study by Tabrizi and Hosseini [57] lacks important methodological details about the source of cases and controls. As a result, we cannot completely rule out that there is an overlap between the subjects from the studies by Tabrizi and Hosseini [57] and Sohrabi et al. [51] both conducted in Tehran province.

Table 3: Studies with atypical exposure categories.

First author	Exposure categories	Cases	Controls	OR or RR or SIR with 95% CI
Magnetic fields				
Tynes, 1997 [40]	<0.05 μT:	139	546	OR=1 (Ref.)
	0.05–0.14 μT:	8	19	OR=1.8 (0.7–4.2)
	>0.14 μT:	1	14	OR=0.3 (0.0–2.1)
	Total:	148	579	
Bianchi, 2000 [44]	<0.001 μT:	92	401	RR=1 (Ref.)
	0.001–0.1 μT:	6	8	RR=3.29 (1.1–9.7)
	>0.1 μT:	3	3	RR=4.51 (0.8–23.1)
	Total:	101	412	
Feizi, 2007 [47]	<0.45 μT:	45	54	OR=3.60 (1.1–12.3)
	>0.45 μT:	15	5	
	Total:	60	59	
Distances from power lines (case-control studies)				
Tynes, 1997 [40]	≥101 m:	121	475	OR=1 (Ref.)
	51–101 m:	18	49	OR=1.4 (0.8–2.6)
	0–51 m:	9	55	OR=0.6 (0.3–1.3)
	Total:	148	579	
Kleinerman, 2000 [45][a]	>40 m:	297	300	OR=1 (Ref.)
	24–40 m:	43	37	OR=1.23 (0.7–2.0)
	15–23 m:	36	34	OR=1.01 (0.6–1.7)
	0–14 m:	29	34	OR=0.79 (0.4–1.3)
	Total:	405	405	
Feizi, 2007 [47]	>500 m:	46	57	OR=8.76 (1.7–58.4)
	0–500 m:	14	2	
	Total:	60	59	
Sohrabi, 2010 [51]	>600 m:	211	258	OR=2.61 (1.7–3.9)
	0–600 m:	89	42	
	Total:	300	300	
Tabrizi, 2015 [57][b]	>20 m:	18	97	OR=3.65 (1.6–7.8)
	0–20 m:	4	3	
	Total:	22	100	
Wire codings				
Petridou, 1997 [39][c]	Wire code 1 (low):	30	57	baseline
	Wire code 2:	72	128	OR=0.99 (0.5–1.8)
	Wire code 3:	4	3	OR=1.84 (0.2–12.8)
	Wire code 4:	7	6	OR=4.26 (0.9–19.4)
	Wire code 5 (High):	4	8	OR=1.56 (0.2–9.3)
	Total:	117	202	
Cohort study using distances from power lines				
Li, 1998 [60]	>100 m:	21	111,575	SIR=1.05 (0.6–1.5)
	0–100 m:	7	9,093	SIR=2.69 (1.0–5.5)
	Total:	28	120,668	

Ref., reference category; OR, odds ratio; RR, relative risk; SIR, standardized incidence ratio. [a]The studies by Kleinerman et al. [45] and by Linet et al. [5] are at least partly based on the same subjects from the Children's Cancer Group. The study by Kleinerman et al. [45] has only been selected for the data on distances to power lines. [b]An overlap between the subjects from the Iranian studies conducted in Tehran province by Sohrabi et al. [51] and Tabrizi and Hosseini [57] cannot completely be ruled out. However, this potential overlap cannot be identified from the available data. [c]Adaptation of the wire coding classification system of Wertheimer and Leeper [2] to Greek conditions.

(pooled OR=1.26; 95% CI 1.06–1.49; p=0.007; Figure 2). Heterogeneity between studies was moderate (Q (20)=34.70; p=0.02; I^2=42%). The publication bias was unlikely (Supplementary Figure 1; Egger's test: p=0.082).

We have performed subgroup analyses based on the NOS score, the method to measure magnetic fields, the frequency and the magnetic field exposure period (Table 4). The subgroup analysis based on the period of magnetic field exposure detected a significant subgroup difference (Q (1)=6.64; p=0.01; I^2=84.9%). There was a significant relation between ELF-MF and childhood leukemia in the earlier studies conducted with subjects

Study or Subgroup	log[Odds Ratio]	SE	Leukemia cases Total	Controls Total	Weight	Odds Ratio IV, Random, 95% CI
5.1.1 Direct magnetic field measurement: <0.2 μT vs >0.2 μT						
Dockerty et al (1999) New Zealand	0.997	0.87	40	40	0.9%	2.71 [0.49, 14.91]
Green et al (1999) Canada (Ontario)	0.322	0.342	88	131	4.3%	1.38 [0.71, 2.70]
Jirik et al (2012) Czech Republic	-0.073	0.32	82	81	4.7%	0.93 [0.50, 1.74]
Kabuto et al (2006) Japan	0.351	0.316	312	603	4.8%	1.42 [0.76, 2.64]
Linet et al (1997) USA (Midwest and Northeast)	0.174	0.176	624	615	8.6%	1.19 [0.84, 1.68]
McBride et al (1999) Canada (BC, AB, SK, MB, QC)	0.113	0.242	293	339	6.5%	1.12 [0.70, 1.80]
Michaelis et al (1997) Germany (Lower Saxony)	0.405	0.663	129	328	1.5%	1.50 [0.41, 5.50]
Núñez-Enríquez et al (2020) Mexico	0.231	0.207	290	407	7.6%	1.26 [0.84, 1.89]
Salvan et al (2015) Italy (SETIL)	-0.211	0.407	409	569	3.4%	0.81 [0.36, 1.80]
Savitz et al (1988) USA (Colorado 1976-83)	0.658	0.546	36	207	2.1%	1.93 [0.66, 5.63]
Schüz et al (2001) Germany (without Lower Saxony)	0.525	0.366	514	1301	3.9%	1.69 [0.83, 3.46]
Subtotal (95% CI)			**2817**	**4621**	**48.4%**	**1.23 [1.03, 1.47]**
Heterogeneity: Tau² = 0.00; Chi² = 4.69, df = 10 (P = 0.91); I² = 0%						
Test for overall effect: Z = 2.32 (P = 0.02)						
5.1.2 Calculated magnetic field: <0.2 μT vs >0.2 μT						
Bunch et al (2016) UK	-0.734	0.446	15920	19608	2.9%	0.48 [0.20, 1.15]
Feychting and Ahlbom (1993) Sweden	0.912	0.447	38	554	2.9%	2.49 [1.04, 5.98]
Kheifets et al (2017) USA (California 1988-2008)	0.174	0.267	5788	5788	5.9%	1.19 [0.71, 2.01]
Verkasalo et al (1993) Finland	0.495	0.603	35	134660	1.8%	1.64 [0.50, 5.35]
Subtotal (95% CI)			**21781**	**160610**	**13.5%**	**1.21 [0.64, 2.29]**
Heterogeneity: Tau² = 0.24; Chi² = 7.15, df = 3 (P = 0.07); I² = 58%						
Test for overall effect: Z = 0.58 (P = 0.56)						
5.1.3 Distance between the child's home and power lines: >200 m vs <200 m						
Abdul Rahman et al (2008) Malaysia	0.833	0.341	128	128	4.3%	2.30 [1.18, 4.49]
Pedersen et al (2014) Denmark	-0.261	0.33	1577	3191	4.5%	0.77 [0.40, 1.47]
Sermage-Faure et al (2013) France	-0.151	0.111	2712	29797	10.9%	0.86 [0.69, 1.07]
Wünsch-Filho et al (2011) Brazil	0.068	0.314	121	418	4.8%	1.07 [0.58, 1.98]
Subtotal (95% CI)			**4538**	**33534**	**24.6%**	**1.07 [0.71, 1.63]**
Heterogeneity: Tau² = 0.11; Chi² = 8.07, df = 3 (P = 0.04); I² = 63%						
Test for overall effect: Z = 0.34 (P = 0.74)						
5.1.4 Wire coding: low current configuration vs high current configuration						
London et al (1991) USA (California 1980-87)	0.519	0.199	211	205	7.8%	1.68 [1.14, 2.48]
Wertheimer & Leeper (1979) USA (Colorado 1950-73)	0.824	0.275	136	136	5.7%	2.28 [1.33, 3.91]
Subtotal (95% CI)			**347**	**341**	**13.5%**	**1.87 [1.36, 2.56]**
Heterogeneity: Tau² = 0.00; Chi² = 0.81, df = 1 (P = 0.37); I² = 0%						
Test for overall effect: Z = 3.87 (P = 0.0001)						
Total (95% CI)			**29483**	**199106**	**100.0%**	**1.26 [1.06, 1.49]**
Heterogeneity: Tau² = 0.06; Chi² = 34.70, df = 20 (P = 0.02); I² = 42%						
Test for overall effect: Z = 2.69 (P = 0.007)						
Test for subgroup differences: Chi² = 6.16, df = 3 (P = 0.10), I² = 51.3%						

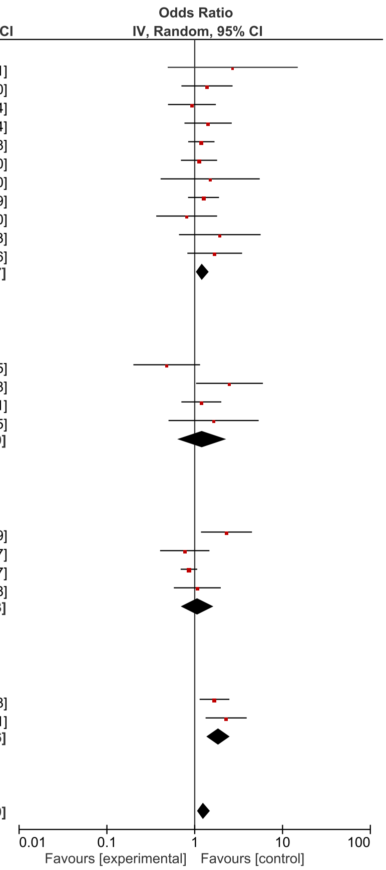

Figure 2: Global meta-analysis based on the exposure levels (cutoff points) that have most often been used in the studies included in the present systematic review (<0.2 μT vs. >0.2 μT for magnetic fields, >200 m vs. <200 m for distances to power lines and the low current configuration vs. the high current configuration for wire codings). The study by Verkasalo et al. [25] is a cohort study and the exclusion of this study did not substantially affect the association between ELF-MF and childhood leukemia (pooled OR=1.26; 95% CI 1.06–1.49; p=0.01). The studies of Savitz et al. [36], Linet et al. [5], Green et al. [31] and McBride et al. [6] were only selected for their magnetic flux density measurements but not for the wire codings to avoid that the same subjects were counted twice in the global meta-analysis. Bunch et al. [54] have calculated magnetic fields with the same subjects as Bunch et al. [10], a study based on distances. Thus, we have only selected Bunch et al. [54] in the global meta-analysis to avoid that the same subjects were counted twice in the global meta-analysis. Similarly, Kheifets et al. [59] have calculated magnetic fields with the same subjects as Crespi et al. [58], a study based on distances. Thus, we have only selected Kheifets et al. [59] in the global meta-analysis. The OR of the study performed by Wertheimer and Leeper [2] has been calculated using birth addresses. Note that Wünsch-Filho et al. [32] used distances to power lines and also performed magnetic flux density measurements but they did not use the 0.2 μT exposure level in their article. Moreover, London et al. [29] used wire codings and also performed magnetic flux density measurements but they did not use the 0.2 μT exposure level in their article. The study by Green et al. [31] is based on subjects from Canada, Ontario whereas the study by McBride et al. [6] is based subjects from other Canadian provinces: British Columbia (BC), Alberta (AB), Saskatchewan (SK), Manitoba (MB) and Quebec (QC).

exposed to magnetic fields before 2000 (pooled OR=1.51; 95% CI 1.26–1.80) but not in the more recent studies.

After a sensitivity analysis that restricted the global meta-analysis to children under the age of 15 by removing seven studies [2, 4, 25, 27, 37, 46, 59], the estimated pooled OR for the relation between ELF-MF and childhood leukemia was 1.13 (95% CI 0.92–1.39; p=0.23). The study by Verkasalo et al. [25] is a cohort study and the exclusion of this study did not substantially affect the association between ELF-MF and childhood leukemia (pooled OR=1.26; 95% CI 1.06–1.49; p=0.01). Although the Californian studies by London et al. [29] and Kheifets et al. [59] included in the global meta-analysis refer to different periods, a small overlap between the subjects of these Californian studies cannot be ruled out completely. This potential small overlap cannot be identified from the available data. The exclusion of the study by London et al. [29] very slightly decreased the association between ELF-MF and childhood leukemia (pooled OR=1.23; 95% CI 1.03–1.46; p=0.02). The studies by Michaelis et al. [38] and Schüz et al. [46] have both been conducted in

Table 4: Subgroup analyses (global meta-analysis).

	Number of studies	OR (95% CI) and heterogeneity	P-value
Overall effect	21	OR=1.26 [1.06, 1.49]; p=0.007 Q (20)=34.70; p=0.02; I^2=42%	Test for overall effect: p=0.007
NOS score			
<7 points	11	OR=1.35 [1.07, 1.71]; p=0.01 Q (10)=23.12; p=0.01; I^2=57%	Test for subgroup differences: Q (1)=0.87;
≥7 points	10	OR=1.15 [0.89, 1.48]; p=0.29 Q (9)=11.54; p=0.39; I^2=22%	p=0.35; I^2=0%
Method to estimate magnetic field exposure			
Direct MF measure	11	OR=1.23 [1.03, 1.47]; p=0.02 Q (10)=4.69; p=0.91; I^2=0%	Test for subgroup differences: Q (3)=6.16;
Calculated MF	4	OR=1.21 [0.64, 2.29]; p=0.56 Q (3)=7.15; p=0.07; I^2=58%	p=0.10; I^2=51.3%
Distances	4	OR=1.07 [0.71, 1.63]; p=0.74 Q (3)=8.07; p=0.04; I^2=63%	
Wire codings	2	OR=1.87 [1.36, 2.56]; p=0.0001 Q (1)=0.81; p=0.37; I^2=0%	
Frequency			
50 Hz	11	OR=1.15 [0.85, 1.57]; p=0.37 Q (10)=20.04; p=0.03; I^2=50%	Test for subgroup differences Q (1)=0.85;
60 Hz	9	OR=1.36 [1.16, 1.60]; p=0.0002 Q (8)=7.26; p=0.51; I^2=0%	p=0.36; I^2=0%
End of period of magnetic field exposure			
Before 2000	11	OR=1.51 [1.26, 1.80]; p<0.0001 Q (10)=7.98; p=0.63; I^2=0%	Test for subgroup differences Q (1)=6.64;
After 2000	10	OR=1.04 [0.84, 1.29]; p=0.71 Q (9)=14.42; p=0.11; I^2=38%	p=0.01; I^2=84.9%

The subgroup analysis based on the frequency comprises only 20 studies, because the study of Kabuto et al. [4] performed in Japan has been removed (the catchment area used in this study comprises 50 Hz and 60 Hz).

Germany and are based on subjects from the German Childhood Cancer Registry. The study by Michaelis et al. [38] has been performed in Lower Saxony whereas Schüz and colleagues [46] had excluded subjects from Lower Saxony. However, a small overlap remains possible between these two German studies. The exclusion of the study by Michaelis et al. [38] did not substantially affect the relation between ELF-MF and childhood leukemia (pooled OR=1.26; 95% CI 1.06–1.50; p=0.009). The exclusion of the pioneer study by Wertheimer and Leeper [2] conducted in Colorado slightly reduced the association between ELF-MF and leukemia in children (pooled OR=1.21; 95% CI 1.03–1.42; p=0.02). When the global meta-analysis was performed exclusively on acute lymphoblastic leukemia cases (10 studies), the estimated pooled OR for the association between ELF-MF and childhood acute lymphoblastic leukemia was 1.16 (95% CI 0.97–1.39; p=0.09; Supplementary Figure 2). Heterogeneity between studies was not significant and the publication bias was not present (Supplementary Figure 3; Egger's test: p=0.855) in the global meta-analysis restricted to acute lymphoblastic leukemia.

Meta-analyses based on magnetic flux density measurements

Twelve studies included in our meta-analysis used direct magnetic flux density measurements or calculated magnetic fields to assess the association between magnetic field exposure and childhood leukemia. Being exposed to magnetic fields ranging from 0.1 to 0.2 µT (pooled OR=1.04; 95% CI 0.88–1.24; p=0.62; 12 studies), from 0.2 to 0.3 µT (pooled OR=0.92; 95% CI 0.68–1.24; p=0.60; five studies), from 0.3 to 0.4 µT (pooled OR=1.10; 95% CI 0.72–1.66; p=0.67; four studies) and from 0.2 to 0.4 µT (pooled OR=1.07; 95% CI 0.87–1.30; p=0.54; nine studies) did not increase the risk of childhood leukemia (Supplementary Table 3). Exposure to magnetic fields higher than 0.4 µT was associated with an increased risk of childhood leukemia (pooled OR=1.37; 95% CI 1.05–1.80; p=0.02; 12 studies; Figure 3). Heterogeneity between studies was not significant and the publication bias was not present (Supplementary Figures 4–11; Egger's tests: p=0.922 for 0.1–0.2 µT; p=0.753 for 0.2–0.4 µT; p=0.803 for >0.4 µT). Only one

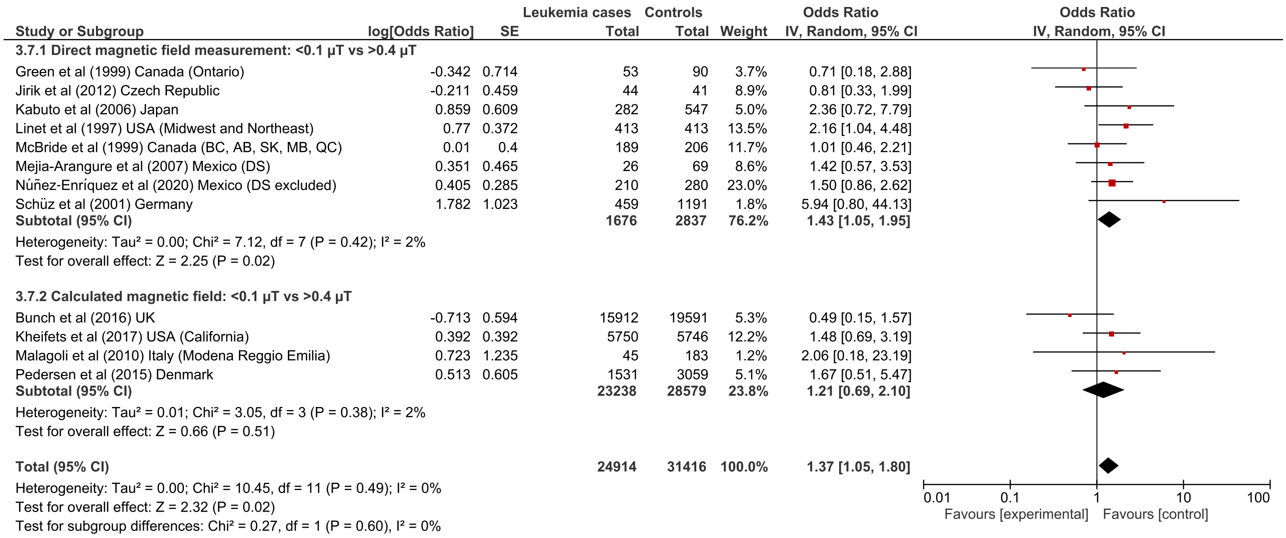

Figure 3: Exposure to magnetic fields higher than 0.4 μT increased the risk of developing childhood leukemia (all leukemia subtypes were combined in this analysis). Two studies performed in Mexico are included in this meta-analysis but one is based exclusively on Down syndrome (DS) children [48] and the other one has excluded DS children [27]. The exclusion of the study by Mejia-Arangure et al. [48] based only on DS children did not change the association between magnetic fields higher than 0.4 μT and childhood leukemia (pooled OR=1.37; 95% CI 1.02–1.83; p=0.04). The study by Green et al. [31] is based on subjects from Canada, Ontario whereas the study by McBride et al. [6] is based on subjects from other Canadian provinces: British Columbia (BC), Alberta (AB), Saskatchewan (SK), Manitoba (MB) and Quebec (QC).

subgroup analysis has detected a significant subgroup difference (Supplementary Table 4). There was a significant association between magnetic fields comprised between 0.1 and 0.2 μT and childhood leukemia but only for 50 Hz. Nevertheless, this difference between frequencies (50 Hz vs. 60 Hz) was not present for higher magnetic fields, which suggests that this difference was due to chance (Supplementary Table 4). It is noteworthy that the study by Mejia-Arangure and colleagues [48] was a small study based on children with Down syndrome (DS) and the removal of this study from our meta-analysis did not change the association between magnetic fields higher than 0.4 μT and childhood leukemia (pooled OR=1.37; 95% CI 1.02–1.83; p=0.04; 11 studies; heterogeneity: Q (10)=10.44; p=0.40; I^2=4%).

Seven studies included in our quantitative synthesis have analyzed the relation between acute lymphoblastic leukemia alone and exposure to ELF-MF using direct magnetic flux density measurements or calculated magnetic fields. Being exposed to magnetic fields higher than 0.4 μT increased the risk of developing childhood acute lymphoblastic leukemia (Supplementary Figure 12). We have found a higher association between acute lymphoblastic leukemia and >0.4 μT (pooled OR=1.88, 95% CI 1.31–2.70; p=0.0006; seven studies) than the association we have found when all leukemia subtypes were analyzed in the same meta-analysis (>0.4 μT: pooled OR=1.37; 95% CI 1.05–1.80; p=0.02, 12 studies). It is noteworthy that being exposed to magnetic fields higher than 0.3 μT was also significantly associated with acute lymphoblastic leukemia (pooled OR=1.42, 95% CI 1.03–1.95; p=0.03; three studies) but exposure to magnetic fields lower than 0.4 μT was not associated with a more elevated risk of acute lymphoblastic leukemia (Supplementary Table 3).

Meta-analyses based on distances to power lines

Five studies included in our systematic review have examined the relation between living in proximity to overhead power lines and childhood leukemia (Supplementary Table 3). Living between 200 and 600 m away from power lines was not associated with an increased risk of childhood leukemia (pooled OR=1.02; 95% CI 0.95–1.10; five studies; Supplementary Figure 13). The estimated pooled ORs for living within 50 m and 200 m of power lines were 1.11 (95% CI 0.81–1.52; four studies) and 0.98 (95% CI 0.85–1.12; five studies), respectively (Supplementary Figures 14 and 15). Heterogeneity between studies was not significant (Supplementary Table 3). Subgroup analyses did not detect significant subgroup differences (Supplementary Table 5).

Two studies included in our quantitative synthesis have analyzed the relation between living near overhead power lines and childhood acute lymphoblastic leukemia alone (Supplementary Table 3). Living between 200 and

Table 5: Exposure to electric appliances and childhood leukemia.

Electric appliances	Number of studies	Number of subjects	Heterogeneity	Pooled OR (95% CI)	Overall effect
All leukemias combined					
Reference category: no exposure to the electric appliance					
Electric blanket	4	Cases: 1,064 Controls: 1,207	Q (3)=0.98, p=0.81, I^2=0%	2.75 [1.71, 4.42]	**p<0.0001**
Water bed	4	Cases: 1,066 Controls: 1,207	Q (3)=1.13, p=0.77, I^2=0%	1.11 [0.85, 1.47]	p=0.44
Bedside electric clock	4	Cases: 993 Controls: 1,123	Q (3)=1.45, p=0.69, I^2=0%	1.27 [1.01, 1.60]	**p=0.04**
Hair dryer	4	Cases: 1,065 Controls: 1,205	Q (3)=9.61, p=0.02, I^2=69%	1.40 [0.79, 2.48]	p=0.25
Acute lymphoblastic leukemia					
Reference category: no exposure to the electric appliance					
Electric blanket	2	Cases: 697 Controls: 854	Q (1)=0.29, p=0.59, I^2=0%	2.56 [1.50, 4.38]	**p=0.0006**
Water bed	2	Cases: 699 Controls: 854	Q (1)=0.96, p=0.33, I^2=0%	1.15 [0.85, 1.56]	p=0.35
Bedside electric clock	2	Cases: 626 Controls: 770	Q (1)=0.29, p=0.59, I^2=0%	1.22 [0.92, 1.61]	p=0.17
Hair dryer	2	Cases: 699 Controls: 853	Q (1)=2.94, p=0.09, I^2=66%	1.16 [0.55, 2.46]	p=0.69

600 m away from power lines was not associated with an increased risk of childhood acute lymphoblastic leukemia (pooled OR=1.08; 95% CI 0.89–1.31). When acute lymphoblastic leukemia was analyzed separately, the estimated pooled ORs for living within 50 m and 200 m of power lines were 1.44 (95% CI 0.72–2.88) and 0.93 (95% CI 0.70–1.22), respectively. It is noteworthy that Kabuto and colleagues [4] have found an association between living less than 50 m away from power lines and childhood acute lymphoblastic leukemia with an OR of 3.06 (95% CI 1.31–7.13) against the reference category >100 m (instead of >600 m as defined in the present meta-analysis). The inclusion of the study of Kabuto et al. [4] in an additional meta-analysis supported an association between living within 50 m of power lines and childhood acute lymphoblastic leukemia (pooled OR=2.01; 95% CI 1.05–3.85; p=0.03; three studies; Supplementary Figure 16).

Meta-analyses based on wire codings

Five studies included in our systematic review used the wire coding classification system of Wertheimer and Leeper [2]. The low current configurations and the OHCC defined by Wertheimer and Leeper were not associated with an increased risk of childhood leukemia (VLCC: pooled OR=0.66; 95% CI 0.43–1.03; three studies; OLCC: pooled OR=0.98; 95% CI 0.74–1.29; four studies; OHCC: pooled OR=0.87; 95% CI 0.66–1.16; four studies; Supplementary Table 3; Supplementary Figures 17–19). The estimated pooled OR for the VHCC was 1.23 (95% CI 0.72–2.10; five studies) (Supplementary Figure 20). Heterogeneity between studies was not significant. Subgroup analyses could not be performed for studies based on wire codings given the limited number of studies (the NOS score was lower than seven points in all studies, 60 Hz was used in all studies and all studies were performed before 2000).

The OLCC and OHCC were not associated with childhood acute lymphoblastic leukemia analyzed separately (Supplementary Table 3). The estimated pooled OR for the VHCC and acute lymphoblastic leukemia was 1.22 (95% CI 0.70–2.10; three studies). The meta-analysis could not be performed for the VLCC when acute lymphoblastic leukemia was analyzed alone (there was only one study).

Meta-analyses based on exposure to electric appliances

Four articles have studied the relation between exposure to electric appliances and childhood leukemia [8, 9, 29, 41]. We have performed meta-analyses based on the electric appliances that have been examined in each of these studies: electric blanket, water bed, bedside electric clock and hair dryer (Table 5; Supplementary Figures 21–24). Exposure to the electric blanket increased the risk of childhood leukemia (pooled OR=2.75; 95% CI 1.71–4.42; $p<0.0001$; four studies). The association between exposure to the bedside electric clock and childhood leukemia was also significant (pooled OR=1.27; 95% CI 1.01–1.60; p=0.04; four studies). Heterogeneity between studies was not significant except in the analysis performed on the use of hair dryers (Q (3)=9.61; p=0.02; I^2=69%; Supplementary Figure 24). Subgroup analyses could not be performed for studies based on electric appliances given the limited number of studies (only one study had a NOS score higher than 6, only one study used 50 Hz and all studies were performed before 2000). There was a significant association between childhood acute lymphoblastic leukemia analyzed separately and exposure to electric blankets (pooled OR=2.56; 95% CI 1.50–4.38; p=0.0006; two studies). There were no significant associations between childhood acute lymphoblastic leukemia analyzed separately and the other electric appliances (Table 5).

Discussion

Our global meta-analysis based on the exposure categories that have most often been used in the literature about ELF-MF and childhood leukemia indicates a significant association between ELF-MF and childhood leukemia (21 studies, pooled OR=1.26; 95% CI 1.06–1.49; p=0.007). Heterogeneity between studies was moderate (Q (20)=34.7; p=0.02; I^2=42%). Importantly, our subgroup analyses indicate that this association mainly results from the studies that have been performed before 2000 (Table 4). We have found a pooled OR of 1.51 (95% CI 1.26–1.80) for the association between ELF-MF and childhood leukemia in the earlier studies performed before 2000 and a pooled OR of 1.04 (95% CI 0.84–1.29) for the recent studies. These results are in agreement with the study performed by Swanson and colleagues [62] who found a decline in the risk for childhood leukemia and ELF-MF from the mid-1990s to 2017. Furthermore, the test for subgroup differences based on the method to assess magnetic field exposure indicates a Q value (df=3) of 6.16 (p=0.10) and an I^2 of 51.3% (Table 4). These results suggest that the method used to assess the magnetic field exposure could play a role in the heterogeneity we have observed across the studies included in our global meta-analysis.

Our meta-analysis based only on magnetic flux densities shows that exposure to magnetic fields higher than 0.4 μT was associated with a more elevated risk of leukemia in children (12 studies, pooled OR=1.37; 95% CI 1.05–1.80). Magnetic fields lower than 0.4 μT were not associated with childhood leukemia. The results of these meta-analyses are in line with the meta-analysis of Zhao and colleagues [14] who found that ELF-MF higher than 0.4 μT increased the risk of leukemia in children. Seven studies were included in their analysis for magnetic flux densities higher than 0.4 μT and they have reported a pooled OR of 1.57 (95% CI 1.03–2.40) when all leukemia subtypes were combined in the same analysis. The main differences between Zhao's meta-analysis and ours are that more exposure categories (0.3–0.4 μT) and more studies have been included in our meta-analyses, including studies whose authors needed to be contacted to provide the necessary information for the extraction of data (like Jirik et al. [26] and Núñez-Enríquez et al. [27]). Seven studies included in our systematic review have examined the relation between residential magnetic fields and childhood acute lymphoblastic leukemia alone. We have found a higher association between acute lymphoblastic leukemia and >0.4 μT (pooled OR=1.88, 95% CI 1.31–2.70; p=0.0006; seven studies) than the association found when all leukemia subtypes were analyzed together in the same analysis (>0.4 μT: pooled OR=1.37; 95% CI 1.05–1.80; p=0.02, 12 studies). Magnetic flux densities lower than 0.4 μT were not associated with childhood acute lymphoblastic leukemia. Our results are partially in agreement with those of Zhao and colleagues [14] who found a higher pooled OR of 2.43 (95% CI 1.30–4.55) between childhood acute lymphoblastic leukemia and magnetic flux densities higher than 0.4 μT but no association for lower magnetic flux densities. Nevertheless, only three studies had been included in their meta-analysis. Another difference between Zhao's meta-analysis and ours is that Zhao's meta-analysis was only based on crude OR whereas ours was based on crude OR and adjusted OR when they were available in the articles included in our meta-analysis. As a result, confounders like the degree of urbanization and the socio-economic status [46] have been taken into account, at least to some extent, in the present meta-analysis.

Our meta-analyses planned *a priori* based only on distances to power lines or only on wire codings did not find significant associations between ELF-MF and childhood leukemia. Interestingly, the estimated pooled OR for the VHCC was 1.23 (95% CI 0.72–2.10) and was higher than the pooled OR calculated for the other current configurations. Our results suggest that only ELF-MF higher than 0.4 μT are associated with childhood leukemia but the mean measured magnetic flux densities for the VHCC defined by Wertheimer and Leeper [2] were rarely higher than 0.4 μT in the studies performed by Green et al. [31] and McBride et al. [6]. Green and colleagues [31] measured a mean magnetic flux density of 0.38 μT (±SD 0.26) for the VHCC and the mean magnetic flux density measured in the study by McBride and colleagues [6] for the VHCC was even lower (only 0.263 μT in the child's bedroom). Since only a limited number of cases assigned to the VHCC have been exposed to magnetic fields higher than 0.4 μT, it is not surprising that the pooled OR of 1.23 we have found for the VHCC was higher than the pooled OR we have found for 0.2–0.4 μT (pooled OR=1.07; 95% CI 0.87–1.30) but lower than the pooled OR we have found for magnetic fields higher than 0.4 μT (pooled OR=1.37; 95% CI 1.05–1.80). It is noteworthy that the pooled OR we have found for living less than 50 m away from power lines and childhood acute lymphoblastic leukemia was 1.44 (95% CI 0.72–2.88). Since there were only two studies in this meta-analysis, a lack of statistical power could explain why conventional statistical significance had not been reached in this analysis. In agreement with this view, Kabuto and colleagues [4] have found an association between living within 50 m of power lines and childhood acute lymphoblastic leukemia (OR=3.06; 95% CI 1.31–7.13) but against the reference category >100 m (instead of >600 m as defined in the present meta-analysis). The inclusion of the study of Kabuto et al. [4] in an additional meta-analysis supports an association between living less than 50 m away from power lines and childhood acute lymphoblastic leukemia (pooled OR=2.01; 95% CI 1.05–3.85; p=0.03; three studies; Supplementary Figure 16). Taken together, our secondary meta-analyses suggest that acute lymphoblastic leukemia is the subtype of leukemia associated with ELF-MF if the relation between childhood leukemia and residential magnetic fields is real (Supplementary Figures 12 and 16).

Our results are at least partially in agreement with the pooled analyses published earlier on ELF-MF and childhood leukemia. The results of Greenland and colleagues [18] do not support an association between magnetic fields lower than 0.3 μT and childhood leukemia and they have found a pooled OR of 1.7 (95% CI 1.2–2.3) for magnetic fields higher than 0.3 μT. The pooled OR for magnetic fields higher than 0.3 μT and childhood leukemia was 1.39 (95% CI 0.98–1.98) in our meta-analysis and almost reached conventional statistical significance (p=0.07). However, these results very unlikely mean that the magnetic field threshold linked to a higher leukemia risk is circa 0.3 μT, because our meta-analysis indicates that magnetic fields between 0.3 and 0.4 μT were not associated with an increased risk of leukemia in children. Greenland and colleagues [18] have also performed a pooled analysis on wire coding data but their results are difficult to compare with our meta-analysis based only on wire codings, because they did not use the same reference category. Their reference category is the low current configuration and comprises the underground category, the VLCC and the OLCC (underground + VLCC + OLCC) whereas we have compared each wire coding (VLCC, OLCC, OHCC and VHCC) to the underground/extremely low category. They have found a pooled OR of 1.02 (95% CI 0.87–1.22) for the OHCC and 1.50 (95% CL 1.17–1.92) for the VHCC after exclusion of the studies of Wertheimer and Leeper [2] and Fulton et al. [63] (but inclusion of the study by Fajardo-Gutierrez et al. [64] published in Spanish) whereas we have found a pooled OR of 0.87 (95% CI 0.66–1.16) for the OHCC and a pooled OR of 1.23 (95% CI 0.72–2.10) for the VHCC. Our meta-analysis indicates that only magnetic fields higher than 0.4 μT are associated with a more elevated risk of childhood leukemia, a result that is in line with two other pooled analyses [3, 19]. Interestingly, Amoon and colleagues [17] have performed a meta-analysis of three pooled analyses: the pooled analysis by Ahlbom et al. [3] with studies published before 2000, the pooled analysis by Kheifets et al. [19] based on studies published between 2000 and 2010 and their pooled analysis based on four studies published after 2010. Their meta-analysis of these three pooled analyses found a pooled OR of 1.45 (95% CI 0.95–2.20) for magnetic fields higher than 0.4 μT. These results are close to ours since we have found a pooled OR of 1.37 (95% CI 1.05–1.80) for the association between magnetic fields higher than 0.4 μT and childhood leukemia in our work. Unlike the previous pooled analyses, the last pooled analysis by Amoon and colleagues [17] based on four studies published after 2010 does not support an association between magnetic fields higher than 0.4 μT and childhood leukemia (pooled OR=1.01; 95% CI 0.61–1.66), a finding interpreted as a decrease in effect over time. Our global meta-analysis also indicates a decline of the ORs for the association between ELF-MF and childhood leukemia although we have used a lower cutoff (most studies included in our global meta-analysis used a cutoff of 0.2 μT). We have found a pooled OR of 1.51 (95% CI 1.26–1.80) for the association between ELF-MF and childhood leukemia in the studies conducted before 2000 and a pooled OR of 1.04 (95% CI 0.84–1.29) for the recent studies. Taken together, the meta-analysis of the three pooled analyses by Amoon et al. [17] and our global meta-analysis suggest that the studies performed in the twentieth century have probably overestimated the association between ELF-MF and childhood leukemia.

Our meta-analysis based only on distances completes the pooled analysis by Amoon and colleagues [16] on proximity to power lines and the risk of leukemia in children. They did not find an association between childhood leukemia and living near power lines. In agreement with these results, we did not find a significant association between these variables either when all leukemia subtypes were combined in the same meta-analysis. Amoon and colleagues [16] have only found a small increase in the risk of leukemia (pooled OR=1.33; 95% CI 0.92–1.93) among children who lived within 50 m of high voltage power lines (>200 kV). When their analysis was restricted to acute lymphoblastic leukemia, they have found a pooled OR of 1.39 (95% CI 0.92–2.10) when children lived less than 50 m away from high voltage power lines (>200 kV), a value very close to the pooled OR we have found (pooled OR=1.44; 95% CI 0.72–2.88) when our meta-analysis planned *a priori* was restricted to acute lymphoblastic leukemia (Supplementary Table 3). It is noteworthy that original individual data on distances for the Japanese study by Kabuto et al. [4] were unavailable and not included in the pooled analysis of Amoon et al. [16]. They have performed sensitivity analyses and the inclusion of the summary data available in the article of Kabuto et al. [4] only slightly increased the OR calculated in their analysis. Our sensitivity analysis has included the study by Kabuto et al. [4] in our meta-analysis restricted to acute lymphoblastic leukemia. Kabuto and colleagues [4] had reported an OR of 3.06 (95% CI 1.31–7.13) for the association between living within 50 m of power lines and childhood acute lymphoblastic leukemia. The inclusion of the study by Kabuto et al. [4] in our additional meta-analysis supports an association between living less than 50 m away from power lines and childhood acute lymphoblastic leukemia (pooled OR=2.01; 95% CI 1.05–3.85; p=0.03; three studies; Supplementary Figure 16). However, this additional analysis based on three studies must be interpreted cautiously because Kabuto et al. [4] did not use the same reference category (>100 m instead of >600 m as defined in the present meta-analysis) as the studies included in our meta-analyses planned *a priori*. In the future, it might be interesting to perform more studies that specifically examine the relation between living less than 50 m away from overhead power lines and childhood acute lymphoblastic leukemia using the >600 m reference category.

We have performed the first meta-analysis that specifically examined the relation between exposure to ELF-MF generated by household electric appliances and childhood leukemia. Four articles included in our systematic review were interested in electric appliances and they all have studied the association between childhood leukemia and exposure to electric blankets, water beds, bedside electric clocks and hair dryers. Exposure to electric blankets increased the risk of childhood leukemia (pooled OR=2.75; 95% CI 1.71–4.42). The OR calculated for bedside electric clocks also reached statistical significance (pooled OR=1.27; 95% CI 1.01–1.60). Magnetic field levels generated by electric blankets vary between 0.45 and 2.2 μT [65, 66]. Thus, the subjects included in our meta-analysis have very likely been exposed to magnetic flux densities at least higher than 0.4 μT when using their electric blankets [8, 65, 66]. Electric clocks can emit magnetic flux densities averaging 0.74 μT at a typical user distance (40 cm [67]), which could explain why the OR for electric clocks was significant in our meta-analysis. On the other hand, magnetic fields generated by water beds are typically lower, especially when manufactured after 1990 (below 0.4 μT) [67, 68].

Eight studies that met the inclusion criteria of our systematic review have used atypical magnetic field or distance categories and could not be included in our meta-analyses. Most of these studies are compatible with the results our meta-analysis showing that residential magnetic fields higher than 0.4 μT increase the risk of childhood leukemia. Feizi and Arabi [47] have found that a magnetic field higher than 0.45 μT was associated with an increased risk of childhood acute leukemia (OR=3.60; 95% CI 1.11–12.39) and Bianchi and colleagues [44] have found an association between a magnetic field higher than 0.1 μT and childhood leukemia (relative risk=4.51; 95% CI 0.88–23.17). Two studies conducted in the Tehran province of Iran support an association between living near power lines and childhood acute lymphoblastic leukemia (Table 3), although we cannot completely rule out that there is an overlap between the subjects of these two Iranian studies [51, 57]. This potential overlap could not be identified from the available data. In a cohort study, Li and colleagues [60] have shown a more elevated leukemia risk in children living less than 100 m away from high voltage transmission lines (0–100 m: standardized incidence ratio = 2.69; 95% CI 1.08–5.55). The study of Petridou et al. [39] used wire codes adapted to Greek conditions and found an OR of 1.56 (95% CI 0.26–9.39) for the association between the highest wire code and childhood leukemia. Nevertheless, Kleinerman and colleagues [45] did not find a relation between living less than 40 m away from power lines and childhood acute lymphoblastic leukemia and the study conducted by Tynes and Haldorsen [40] does not support an association between ELF-MF and leukemia in children (Table 3). It is noteworthy that the ORs reported in Table 3 seem to be higher than those reported in our meta-analyses and this is particularly evident for the results of the three Iranian studies [47, 51, 57]. This effect could result from the fact that Iran is a lower middle income country in which many children have been exposed to particularly high residential magnetic fields (higher than 0.45 μT in the Iranian study by Feizi and Arabi [47]). In contrast, the studies included in our meta-analyses indicate that few children from high income countries have been exposed to magnetic fields above 0.4 μT [4–6, 26, 31, 46, 50, 54, 55, 59].

A strength of this work is the comprehensive nature of our systematic review that covers several sources of ELF-MF (power lines and electric appliances) and all the different methods that have been used to assess magnetic field exposure since 1979. In addition, we have performed a global meta-analysis based on 21 studies that takes into account these methods. This analysis completes the meta-analysis of Zhao and colleagues [14] performed on magnetic flux density measurements by covering the studies published after 2010 and by including the data performed on proximity to power lines and wire codings in the same global statistical analysis. Furthermore, we have analyzed the publication bias in detail. Finally, we have contacted several authors to obtain the data needed to calculate ORs and information that was missing from the published articles. In particular, we have received information from two authors that allowed us to include their results in our meta-analyses (Jirik et al. [26] and Núñez-Enríquez et al. [27] for the global meta-analysis and the meta-analysis based on magnetic flux density measurements). Moreover, we have received valuable information from several authors of the studies included in our review to detect all the articles that were (at least partially) based on the same subjects to be certain that there was no overlap between the populations of the different studies included in our meta-analyses.

A limitation of this systematic review pertains to the methodological quality of the studies that have examined the association between ELF-MF and childhood leukemia. The quality of these studies evaluated with the NOS was relatively low. One study scored only 2/9. Most studies scored 6/9 or 7/9 and none of them scored 9/9. Nevertheless, our subgroup analyses based on the NOS score did not detect significant subgroup differences between studies that scored above six points and lower quality studies (Table 4; Supplementary Table 4; test for subgroup difference: Q (1)=0.00; p=0.96, I^2=0% for the meta-analysis based on magnetic fields higher than 0.4 μT and childhood leukemia). Our work has other limitations related to the wide variety of methods that have been used over the years to study the association between ELF-MF and leukemia in children. Four methods have been taken into account in the present review: direct magnetic field measurements, calculated magnetic fields, distances to power lines and wire codings. Nevertheless, different approaches have been used to perform magnetic field measurements and they have not been separated in our meta-analyses. For example, several studies included in our systematic review (like the study by Schüz et al. [46]) have used 24 h magnetic field measurements to examine the relation between ELF-MF and childhood leukemia. In contrast, Mejia-Arangure and colleagues [48] relied only on spot measurements taken over short periods of time to assess magnetic field exposure.

Our results have practical implications. Our meta-analysis suggests that exposure to residential magnetic fields higher than 0.4 μT can increase the risk of leukemia in children. Nevertheless, it is important to emphasize the fact that very few homes are exposed to magnetic fields higher than 0.4 μT generated by overhead power lines in high income countries [11, 30]. Moreover, the annual incidence of childhood leukemia is very low and ranges between 35 and 50 cases per million children in western European countries and North America [69]. Since the absolute risk of childhood leukemia is very low and children are rarely continuously exposed to magnetic fields higher than 0.4 μT in high income countries, the increased leukemia risk found in our meta-analysis does not represent a major public health concern in these countries. Magnetic flux densities higher than 0.4 μT are usually within 50 m of overhead power lines [11] even if Crespi et al. [30] found some subjects living between 50 and 200 m away from overhead power lines (over 200 kV) that were exposed to ELF-MF higher than 0.4 μT. Magnetic flux density measurements should be performed if children live within 200 m of overhead power lines to guarantee that they are not exposed to ELF-MF higher than 0.4 μT. In contrast, living more than 200 m away from overhead power lines could be considered a safe distance for children that is not linked to a higher leukemia risk. Our systematic review suggests that children from middle income countries like Mexico and Iran are more likely to be exposed to magnetic fields above 0.4 μT and the risk of leukemia attributable to ELF-MF is probably higher in these countries. It is noteworthy that none of the studies included in our review have been performed in low income countries or in Africa. More research on ELF-MF and childhood leukemia is needed in these countries, particularly in African countries.

Our meta-analyses suggest that exposure to electric appliances like electric blankets and bedside electric clocks increase the risk of leukemia in children. However, it is important to note that the studies that have found an association between these electric appliances and childhood leukemia have been performed more than 20 years ago and our findings should be interpreted based on the electric equipment used today. Electric blankets and bedside electric clocks used at the end of the twentieth century could generate magnetic fields higher than 0.4 μT and children were typically exposed to these electric appliances during several hours in a row [67]. In contrast, hair dryers can also generate magnetic fields higher than 0.4 μT but are usually used during a shorter period of time [67] and we did not find a significant association between the use of hair dryers and childhood leukemia. These findings are relevant today in the sense that the duration of exposure to ELF-MF plays a role and that children should not be exposed to electric appliances that generate magnetic fields higher than 0.4 µT during long periods of time. Importantly, Magne and colleagues [70] have measured personal exposure to ELF-MF in French children between 2007 and 2009. They have found that alarm clocks were the main variable linked to the magnetic field exposure of the children. The proportion of children exposed to magnetic fields higher than 0.4 µT was 3.1% when all children were included in the analysis and 0.8% when the analysis was restricted to children for which no alarm clock had been identified. Taken together, these results and ours suggest that "bedside" electric clocks and alarm clocks that generate magnetic fields higher than 0.4 µT at close distance should be located at least 1 m away from the bed of the child, because the magnetic flux density generated by electric clocks was lower than 0.4 µT at this distance in the study by Preece et al. [71]. To the best of our knowledge, there is no recent update of the study by Behrens et al. [67] that has performed reliable magnetic flux density measurements for electric appliances manufactured recently that generate ELF-MF. Studies with reliable exposure characterization with respect to sources of ELF-MF are needed, especially for the electric appliances manufactured recently that we use on a daily basis.

In summary, our study suggests that exposure to ELF-MF higher than 0.4 µT increases the risk of developing leukemia in children. Acute lymphoblastic leukemia is probably the subtype of leukemia associated with ELF-MF. Prolonged exposure to electric appliances that generate magnetic fields higher than 0.4 µT like electric blankets is associated with a more elevated risk of childhood leukemia. The distance from power lines linked to leukemia is difficult to determine but living more than 200 m away from power lines is likely a safe distance for children not associated with a higher leukemia risk.

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