

July 16, 2026

Re: Scientific Evidence Supporting More Protective Setback Requirements for High-Voltage Transmission Lines and Substations Near Homes and Schools.

I am a public health physician and Director of the Institute for Health and the Environment at the University at Albany, SUNY, a World Health Organization Collaborating Centre. I have researched non-ionizing electromagnetic fields (EMFs) for over four decades. In the 1980s, I served as Executive Secretary of the New York Powerlines Project, a \$5 million study of 60 Hz magnetic fields that included research reporting an increased risk of childhood leukemia associated with elevated residential magnetic fields from power lines. I later served as New York State's spokesperson on EMF issues, Director of the Wadsworth Laboratory at the New York State Department of Health, Dean of the School of Public Health at the University at Albany and have testified before the President's Cancer Panel and the U.S. Congress on EMF and health.

Exposure to elevated power-frequency magnetic fields is associated with an increased risk of cancer, particularly childhood leukemia, as well as leukemia, brain cancer, and breast cancer in adults. The association between residential magnetic field exposure and childhood leukemia has been replicated in numerous studies conducted in multiple countries. There is also strong evidence linking long-term exposure to an increased risk of Alzheimer's disease. These are serious, often fatal diseases.

Reliance on the exposure limits of the Institute of Electrical and Electronics Engineers (IEEE) or International Commission on Non-Ionizing Radiation Protection (ICNIRP) does not protect the public, especially children, from the health impacts of long-term exposure. There is definitive evidence in the peer-reviewed scientific literature that power-frequency EMF can produce biological effects at field strengths well below these limits. Importantly, the IEEE and ICNIRP guidelines are outdated and inadequate, as they were only designed to address short-term exposure effects and not the chronic, continuous exposures experienced by people living near high-voltage power lines for many hours each day over many years.

It is the responsibility of every government to protect its citizens from avoidable risks. In total, the scientific evidence, especially leukemia, brain and breast cancer, and Alzheimer's disease, associated with EMF exposure is sufficiently strong to warrant policy action. I urge governments to do everything in their power to mitigate the serious health risks from high-voltage transmission lines and substations by adopting protective setbacks for homes and schools and implementing evidence-based measures to minimize EMF exposures, such as undergrounding and low-EMF engineering design.

High-voltage transmission lines and electric substations should be located as far away from homes, schools, and childcare facilities as possible. I am attaching a publication that presents the scientific evidence behind these recommendations.

Yours sincerely,



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Review article

Extremely low frequency electromagnetic fields and cancer: How source of funding affects results

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ARTICLE INFO

Keywords:

Magnetic fields
Leukemia
Breast cancer
Brain cancer
Power lines

ABSTRACT

While there has been evidence indicating that excessive exposure to magnetic fields from 50 to 60 Hz electricity increases risk of cancer, many argue that the evidence is inconsistent and inconclusive. This is particularly the case regarding magnetic field exposure and childhood leukemia. A major goal of this study is to examine how source of funding influences the reported results and conclusions. Several meta-analyses dating from about 2000 all report significant associations between exposure and risk of leukemia. By examining subsequent reports on childhood leukemia it is clear that almost all government or independent studies find either a statistically significant association between magnetic field exposure and childhood leukemia, or an elevated risk of at least $OR = 1.5$, while almost all industry supported studies fail to find any significant or even suggestive association. A secondary goal of this report is to examine the level of evidence for exposure and elevated risk of various adult cancers. Based on pooled or meta-analyses as well as subsequent peer-reviewed studies there is strong evidence that excessive exposure to magnetic fields increases risk of adult leukemia, male and female breast cancer and brain cancer. There is less convincing but suggestive evidence for elevations in several other cancer types. There is less clear evidence for bias based on source of funding in the adult cancer studies. There is also some evidence that both paternal and maternal prenatal exposure to magnetic fields results in an increased risk of leukemia and brain cancer in offspring.

When one allows for bias reflected in source of funding, the evidence that magnetic fields increase risk of cancer is neither inconsistent nor inconclusive. Furthermore adults are also at risk, not just children, and there is strong evidence for cancers in addition to leukemia, particularly brain and breast cancer.

1. Introduction

The first indication that extremely low frequency (ELF) electromagnetic fields (EMFs) coming from power lines and electricity could result in human disease was the report by Wertheimer and Leeper (1979) who found elevations in rates of childhood cancer in children living in homes in Denver, Colorado that were close to power lines which were presumed, based on a variety of considerations, to generate elevated magnetic fields within the home. While this conclusion was received skeptically, subsequent studies in several countries confirmed the observation. Four meta-analyses were published between 1998 and 2000 that concluded that there was a consistent and statistically significantly elevated risk of childhood leukemia in relation to residential proximity to elevated magnetic fields that could not be explained by random variation. Wartenberg (1998) considered 16 studies and reported an odds ratio (OR) of 1.44 (95%CL = 1.10–1.87) from studies that used indirect, wire-code analysis for exposure. Angelillo and Villari

(1999) reported an $OR = 1.46$ (1.05–2.04) for six studies on wire code configuration and $OR = 1.59$ (1.14–2.22) for 4 studies with 24 h measured magnetic fields. Greenland et al. (2000) conducted their meta-analysis on 15 studies and found an $OR = 1.52$ (0.99–2.33) based on measured magnetic field for children living in homes with magnetic fields $> 0.3 \mu T$ as compared to 0.1–0.2 μT , and 1.65 (1.15–2.35) based on wire code comparing children in homes with very high current code as compared to ordinary low current code. Ahlbom et al. (2000) performed a pooled analysis of results of nine studies that included 3203 children with leukemia as compared to 10,338 controls. They found an $OR = 2.00$ (1.27–3.13) for increased risk of leukemia in children with a residential magnetic field $> 0.4 \mu T$. Based primarily on the data included in these reviews the International Agency for Research on Cancer rated extra-low frequency electromagnetic fields (ELF-EMFs) as a Group 2b, possible human carcinogen (IARC, 2002).

In spite of this body of information, many have remained skeptical of the conclusion that exposure to power line magnetic fields really

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<https://doi.org/10.1016/j.envres.2019.108688>

Received 11 July 2019; Received in revised form 20 August 2019; Accepted 22 August 2019

Available online 24 August 2019

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increases risk of childhood leukemia. There are several reasons for this, including the general problem that most animal exposure studies have not found increases in cancer, and uncertainty as to the mechanism(s) responsible. Comments are often made that there are a number of studies that do not report positive associations, and thus the conclusions are inconsistent. Therefore the question of whether or not magnetic fields associated with electricity pose hazards to human health has remained controversial. In addition to childhood leukemia, several other human diseases have been reported to be elevated among individuals with excessive exposure to magnetic fields. The goal of this review is to summarize the results of more recent investigations into the magnetic fields and childhood leukemia but also review associations with other cancers. In addition the source of funding of studies will be identified.

The question of whether or not magnetic field exposure causes cancer is extremely important, because in our modern world each of us is continuously exposed. Since there is no one that is unexposed studies must compare individuals with more vs. less exposure. While the risk estimates reported above are not particularly high, when the whole society is exposed to a carcinogen the implication for public health may be large.

2. Materials and methods

This review has been limited to those experimental studies of human cancer in relation to exposure to magnetic fields from power lines or other sources of electricity. Searches were done on pubmed and Google Scholar using the terms magnetic fields, ELF-EMF, power lines or electricity and cancer, leukemia, breast cancer, or brain cancer. For each cancer under consideration the results of recently published pooled or meta-analyses have been accepted and only more recently published additional peer-reviewed publications considered. For childhood leukemia search was for childhood leukemia studies after the meta-analyses published by Wartenberg (1998), Angelillo and Villari (1999), Ahlbom et al. (2000) and Greenland et al. (2000). For adult leukemia and brain cancer, studies were identified subsequent to the meta-analyses of Kheifets et al. (2008), for childhood brain cancer after the meta-analysis of Kheifets et al. (2010b). For male breast cancer studies were considered after the meta-analyses of Erren (2001) and Sun et al. (2013). For female breast cancer studies subsequent to Chen et al. (2013) and Zhao et al. (2014). Su et al. (2018) have published a meta-analysis specifically on parental occupational exposure to magnetic fields and risk of childhood central nervous system cancer. Zhang et al. (2016) published a meta-analysis of ELF-EMFs and all forms of cancer.

References were checked in several very recent reviews on magnetic fields to be sure that English-language, peer-reviewed publications were not missed. These include Kheifets et al. (2006, 2010a, b), Calvente et al. (2010), Zhao et al. (2014), Zhang et al. (2016) and Amoon et al. (2018).

3. Results

Table 1 shows results of peer-reviewed publications published since 2000 that report statistically significant associations between exposure to magnetic fields, either indirectly measured by wire code configuration, distance from the center of the power line (as magnetic fields decline to background over a distance of about 300 m) or directly measured, and childhood leukemia. The table includes numbers of cases and controls and the source of funding. Of these positive studies only one for which the funding source was identified was funded by an industry source.

Table 2 lists studies of childhood leukemia and magnetic field exposure that reported an elevated risk with an OR > 1.5, but for which the results are not statistically significant. All of these studies were funded by government agencies or private sources.

Table 3 lists studies of childhood leukemia and magnetic field exposure which do not show either a statistically significant association, nor have an OR greater than 1.5. All were primarily funded by industrial sources, although in some cases there was partial funding by governmental agencies.

There are three recent studies (Amoon et al., 2018; Crespi et al., 2019; Swanson et al., 2019), all supported by EPRI and National Grid, that have taken a new look at magnetic fields and childhood leukemia, and argue that neither distance from a power line nor measured magnetic fields alone predict risk. The authors acknowledge that there is “a small but consistent increased risk of childhood leukemia associated with exposures above 0.3 or 0.4 μ T”. Amoon et al. (2018) pooled results from 11 studies, and find a small but imprecise risk of childhood leukemia for residences < 50 m from 200 + KEV power lines, but argue that this result is not explained by high magnetic fields. The others argue that the risk values have been declining over time (Swanson et al., 2019) and, based on a model, that there is some other factor that is responsible for this elevated risk, not only magnetic field strength (Crespi et al., 2019). However they do not identify what other possible factor this might be.

In spite of these apparently discordant data, a recent meta-analysis of associations between measured magnetic fields and childhood leukemia show statistically significant associations (Zhou et al., 2014, government funded). In 11,699 case and 13,194 controls, they report an OR = 1.57 (1.03–2.40) when comparing exposures > 0.4 μ T to < 0.1 μ T, and OR = 2.43 (1.30–4.55) specifically for acute lymphocytic leukemia. When comparing exposures > 0.4 μ T to < 0.2 μ T they find OR = 1.31 (1.06–1.61).

4. Childhood brain cancer

Kheifets et al. (2010b) performed a utility-funded pooled analysis of ELF-EMFs and childhood brain cancer in relation to measured magnetic fields. In relation to 0.1–0.2 μ T, those exposed to > 0.4 μ T showed an OR = 1.14 (0.61–2.13). Other more recent reports were not found.

5. Adult cancers

The first publication reporting elevated rates of adult cancer in relation to magnetic field exposure was also by Wertheimer and Leeper (1982). They used a wire code to determine magnetic field exposure from neighborhood distribution lines but did not directly measure the magnetic fields: The wire code evaluated how close the line was to the home, how many wires were present, how thick the wires were (thicker wires indicating higher current flow) and how far the home was along the distribution system. The distance from the substation is important because the current flowing through the line decreases as it feeds other residences along the line. They determined wire code assignments into five categories of increasing magnetic fields in the homes of individuals who died from cancer as well as age, sex- and year of death-matched controls. They excluded most cases of lung cancer. They studied five different communities near to Denver, Colorado, and determined the ratio of cancer cases to controls. When comparing the highest to lowest surrogate of magnetic field exposure, the values varied between 121 and 164. (Using this method the value would be 100 if the rates were the same, would be greater than 100 if higher magnetic field posed a risk and less than 100 if magnetic fields were protective). There were statistically significant elevations for brain cancer, lymphoma, cancer of the uterus and breast, as well as non-significantly elevated cancers of the pancreas, bladder, kidney and prostate.

These results showing elevations in rates of several different types of cancer have been confirmed in more recent studies. Hakansson et al. (2002; government funded) investigated cancer in workers exposed to high levels of magnetic fields in industries using resistance welding in Sweden between 1985 and 1994. They studied 537,692 men and 180,529 women, and separated them into groups of low, medium, high and very high exposure based on their job title. Men in the high exposure category had increased incidence of kidney, pituitary gland and liver and biliary cancers, and the rates of these cancers increased with increased exposure. Women in the high exposure group had increased incidence of astrocytoma groups I–IV, and there was a clear exposure-response pattern. There were suggestions of an increase in uterine cancer and multiple myeloma, but these results were not statistically

Table 1

Studies reporting statistically significant positive associations between exposure to 50 or 60 Hz magnetic fields and childhood leukemia, and source of funding.

Authors	Type of measure	Level of Association	Funding
Schuz et al. (2001)	Measured ($> 0.2 \mu\text{T}$; 24 h Night only 514 cases, 1301 controls	OR = 1.55 (0.65–3.67) OR = 3.21 (1.33–7.80)	Government
Draper et al. (2005)	Distance ($< 200 \text{ m}$) Distance ($< 600 \text{ m}$) 29081 cases of cancer, 9700 with leukemia, matched controls	RR = 1.69 (1.13–2.53) RR = 1.23 (1.02–1.49)	Government
Kabuto et al. (2006)	Measured ($> 4 \mu\text{T}$) 312 ALL cases, 603 controls	OR = 4.67 (1.15–19.0)	Government
Mejia-Arangure et al., 2007 ^a	Measured ($> 6 \text{ mG}$) 42 cases, 124 controls	OR = 3.7 (1.05–13.1)	Government
Lowenthal et al. (2007)	Distance ($< 300 \text{ m}$ for ages 0–15 years)	OR = 3.23 (1.26–8.29)	Private Foundations
Svendsen et al., 2007 (Survival)	854 cases lympho- or myeloproliferative diseases, matched controls Measured $> 0.1 \text{ re } < 0.2 \mu\text{T}$ $> 0.1 \text{ re } > 0.2 \mu\text{T}$ 595 ALL cases	OR = 2.8 (1.2–6.2) OR = 3.0 (0.9 = 9.8)	Government
Schuz et al. (2007)	Measured nighttime $0.1 - < 0.2 \mu\text{T}$ $0.2 - < 0.4 \mu\text{T}$ $> 0.4 \mu\text{T}$ 1842 cases, 3099 controls	OR = 1.11 (0.91–1.36) OR = 1.37 (0.99–1.90) OR = 1.93 (1.11–3.35)	EPRI
Feizi and Arabi (2007)	Calculated ($> 0.45 \mu\text{T}$) (70 cases, 69 controls)	OR = 3.60, 1.11–12.39)	Not identified
Rahman et al., 2008	Distance ($< 200 \text{ m}$ to $> 200 \text{ m}$) (128 cases, 128 controls)	OR = 2.30 (1.1–4.49)	Not identified
Yang et al. (2008) ^b	Distance ($< 50 \text{ m}$) Distance ($< 100 \text{ m}$)	OR = 4.39 (1.43–13.54) OR = 4.31 (1.54–12.08)	Government
Sohrabi et al. (2010)	Distance ($< 600 \text{ m}$) (300 cases, 300 controls)	OR = 2.61 (1.73–3.94)	Not identifiedGov
Tabrizi and Bidgoli, 2015	22 ALL cases 100 controls, prenatal and postnatal to power lines	OR = 3.6 (1.6–7.8)	

EPRI = Electric Power Research Institute.

ALL = Acute lymphocytic leukemia.

^a Study of children with Down's Syndrome.^b Study of children with polymorphisms of DNA repair genes.

significant. Zhang et al. (2016) performed a government-funded meta-analysis of all forms of cancer in association with ELF exposure. They reported on 42 studies with 13,259 cases, 100,882 controls, and found an overall OR = 1.08 (1.01–1.15). The strongest associations were for breast cancer and leukemia, and studies done in North America were more consistently positive than those from Europe.

6. Adult leukemia

There is a considerable body of evidence specifically on adult leukemia in relation to magnetic field exposure, a focus triggered by the studies of childhood leukemia. Feychting et al. (1997; government

funded) studied adult leukemia in relation to both residential and occupational exposures. While neither alone showed significant results, when both sources of exposure were considered there was a significantly elevated risk of adult leukemia (OR = 3.7; 1.5–9.4). In a meta-analysis of data published up through 1997, Kheifets et al. (1997) concluded that most studies showed a small overall increase in risk [risk ratio (RR) = 1.18; 1.12–1.24]. Lowenthal et al. (2007) reported that children living within 300 m of a power line had an elevated (but not statistically significant) risk of developing leukemia (OR = 4.74; 0.98–22.9), while adults living within the same distance showed a smaller but significantly elevated risk (OR = 3.23; 1.26–8.29) (funded by private foundation).

Table 2Studies showing non-significant elevations in risk with OR > 1.5 .

Mizoue et al. (2004)	Distance ($< 300 \text{ m}$) Lived there long	OR = 2.2 (0.5–9.0) OR = 3.4 (0.9–13.2)	Government
Malagoli et al. (2010)	Calculated $> 0.1 \mu\text{T}$ from HVPL 64 cases, 64 controls	OR = 3.2 (0.4–23.4)	Government
Wuunsch-Filho et al., 2011	Measured ($> 0.3 \mu\text{T}$) Distance ($< 50 \text{ m}$) Distance ($< 200 \text{ m}$)	OR = 1.09 (0.33–3.61) OR = 3.57 (0.41–31.44) OR = 1.67 (0.49–5.75)	Government
Sermage-Faure et al. (2013)	ALL, HVPLs in France 2779 cases, 30,000 controls. Distance ($< 50 \text{ m}$ of 225–400 KEV) Distance ($< 50 \text{ m}$ of 63–150 KEV)	OR = 1.7 (0.9–3.6)	Gov/Private
Salvan et al. (2015)	409 cases, 569 controls Measured relative to $< 0.1 \mu\text{T}$ $0.1\text{--}0.2 \mu\text{T}$ $> 0.2 \mu\text{T}$ $> 3 \mu\text{T}$	OR = 1.0 (0.6–1.7) OR = 1.87 (0.53–1.25) OR = 2.24 (1.03–4.88) OR = 0.75 (0.38–1.50)	Government

HVPL = high voltage power line.

KEV = kilovolts

Table 3
Negative studies of magnetic or electric field exposures and childhood leukemia and source of funding.

UK Childhood Cancer, 2002	Measured (> 20 V/m cf to < 10 V/m) 273 cases, 276 controls	OR = 1.32 (0.73–2.39) All leukemia	Power Comp and private.
Foliart et al. (2007)	Measured 386 cases	No trend observed	EPRI/EDF
Kroll et al. (2010)	Modelled (each > 0.2 μ T)	OR = 1.14 (0.57–2.32)	Gov/National Grid
Schuz et al. (2012) (Survival)	28,968 cases, 28,968 controls Various (> 0.3 μ T) 3074 cases	OR = 0.96 (0.49–1.89)	EPRI
Bunch et al. (2014)	Distance (< 200 m) Distance (< 599 m) 53,515 cases of childhood cancer matched to at least one control	RR = 1.12 (0.90–1.38) RR = 0.99 (0.89–1.10)	National Grid
Pedersen et al. (2014)	Distance (< 200 m) Distance (< 599 m) 1698 cases, 3396 controls	OR = 0.76 (0.40–1.45) OR = 0.92 (0.67–1.25)	Danish Energy and Private
Crespi et al. (2016)	Distance (< 50 m) 5788 cases, 3308 controls	OR 1.4 (0.7–2.7)	EPRI and NCI

Kheifets et al. (2008) have done an extensive meta-analysis of 59 studies of ELF exposure and adult leukemia, including those reported earlier as well as those published since the 1997 report. When considering both the older and newer studies, the RR = 1.16 (1.11–1.22) for all leukemia. The strongest association was for chronic lymphocytic leukemia (CLL) (RR = 1.35; 1.10–1.65). This study was supported by EPRI.

There have been only a few studies since 2008 investigating adult leukemia and ELF exposure. Marcilio et al. (2011) reported on 1857 cases of leukemia and 4706 controls in a study funded by a utility. They report an RR = 1.47 (0.99–2.18) for residence within 50 m, and RR = 1.61 (0.91–2.86) for measured magnetic field > 3 mG. Huss et al. (2018) reported results from the Swiss national registry of 3.1 million death records using a job exposure matrix to different levels of ELF-EMFs as high, medium or low. They report a hazards ratio (HR) = 1.31 (1.02–1.67) for myeloid leukemias and HR = 1.26 (0.93–1.70) for acute myeloid leukemia. There was a non-significant elevation in HR for acute lymphocytic leukemia [HR = 1.21 (0.78–1.89)], chronic myeloid leukemia (CML) [HR = 1.20 (0.71–2.02)] and Hodgkin's lymphoma [HR = 1.27 (0.71–2.29)]. There was little evidence of associations with chronic lymphocytic leukemia, non-Hodgkin's lymphoma or multiple myeloma. Interestingly they also report a dose-dependent increase in lung cancer, although they suspect this is secondary to smoking, not ELF.

6.1. Adult brain cancer

There is also a significant body of evidence showing that exposure to excessive magnetic fields increases the risk of development of adult brain cancer. Kheifets et al. (1995) performed a meta-analysis of 29 reports of brain cancer. She found statistically significant elevations in the incidence of brain cancer among electrical engineers, welders, and power station workers, all of whom are routinely exposed to elevated magnetic fields.

Kheifets et al. (2008) performed a second meta-analysis of occupational ELF exposure and brain cancer in adults, funded by EPRI. On consideration of 47 studies they report an overall RR = 1.14 (1.07–1.22) for all brain cancers, and RR = 1.18 (1.1–1.26) for only glioma. In studies since that date, Coble et al. (2009) (government funded) reported finding no significant associations between job title classified based on expected magnetic field exposure, total years of exposure, cumulative lifetime exposure and average lifetime exposure for glioma (489 cases) or meningioma (197 cases) as compared to 799 controls. Baldi et al. (2011) in a government-funded study investigated adult brain cancer in France with measurement of both occupational exposure and residential distance from the power line. This is one of the few studies that found a higher odds ratio for meningioma [3.02 (1.10–8.26)] (84 cases and 174 controls) than glioma [1.20 (0.66–2.17)] (51 cases and 120 controls). There was no association

between living within 100 m of power lines as compared to more than 100 m for glioma [OR = 0.66 (0.21–2.07)] but a non-significant elevated risk for meningioma [OR = 2.99 (0.86–19.40)]. Elliott et al. (2013) reported on adult brain cancer based on 6781 cases and 79,507 controls living or not living within 1000 m of a high-voltage power line, and found an OR = 1.22 (0.86–1.69)] (partial funding from utilities). Turner et al. (2014) (also partial funding from utilities) reported on adult primary glioma (1,939) and meningioma (1,822) from seven countries and based occupational exposure on a job matrix. They found no association with either cancer for life time exposure, but did report elevated associations for glioma [OR = 1.67 (1.36–2.07)] and meningioma [OR = 1.23 (0.97–1.57)] for exposures during the previous four years. They suggest that ELF may function as a promotor or stimulate progression of brain tumors. However Carlberg et al. (2018) (foundation funded) did not find any significant association between occupational exposure to magnetic fields and meningioma based on cumulative exposure, average exposure or maximum exposure.

A report by Carlberg et al. (2017) (foundation funded) drew a similar conclusion to that of Turner et al. (2014) with regard to recent EMF exposure. They studied life time occupational job matrix magnetic field exposure of 1346 glioma cases and 3485 controls, and results were analyzed relative to the grade of glioma. They found no significant association with cumulative μ T-years or maximum exposed job, but an OR = 1.3 (1.003–1.6) (p for trend = 0.04) for occupational exposure where the average level was 0.27 μ T or greater. For astrocytomas grades I to III (n = 363), there were no significant associations with cumulative exposure, average exposure or maximum exposure, but for astrocytoma grade IV (n = 687), commonly known as glioblastoma, there were significant associations with cumulative exposure of 8.52 μ T-years or more (OR = 1.5; 1.05–2.1) and average exposure of 0.27 μ T or more (OR = 1.4; 1.03–2.0). However the significant associations were only for 1–4 years, 5–9 years and 10–14 years before diagnosis, with no significant association of 20 or more years. Thus these results are quite consistent with the conclusion that exposure in the recent past is important, as suggested by Turner et al. (2014). There was a significant p for trend between level of exposure and grade IV astrocytomas for years 1–14, but not for 15 or more years, and no significant association with all glioma in either 1–14 or 15 or more years. Their conclusion was that occupation exposure to ELF EMF serves as a promotion or progression factor, rather than as an initiator.

Hardell and colleagues have reported a number of studies showing an increased risk of gliomas and especially glioblastomas in individuals that have used mobile phone extensively (Hardell and Carlberg, 2009), and therefore they examined interactions between mobile phone use and ELF exposure on gliomas and astrocytomas grade IV. They did not find any interaction between ELF and mobile phone use for gliomas, indicating that they are independent risk factors. They conclude that radiofrequency EMFs are the major risk factor for gliomas.

6.2. ELF exposure and breast cancer

Erren (2001) reported a meta-analysis of ELF and female breast cancer from 24 studies, and found $RR = 1.12$ (1.09–1.15). Chen et al. (2010) reported a meta-analysis of 24,338 cases and 60,628 controls in 15 publications in relation to female breast cancer risk. They found no statistically significant associations ($OR = 0.988$; 0.898–1.088). However a different Chen et al. (2013) also reported a meta-analysis of case-control studies published between 1990 and 2010 and found an $OR = 1.07$ (1.02–1.13) for 23 studies. Associations were positive for estrogen-positive and premenopausal breast cancer, but not for other forms. Zhao et al. (2014) have also published a meta-analysis of results of 16 studies published between 2000 and 2007 that reported on pre- and post-menopausal breast cancer. They find an $OR = 1.10$ (1.01–1.20) overall, and $OR = 1.25$ (0.93–1.18) for pre-menopausal women. There was no significant association for post-menopausal women. Zhang et al. (2016) also performed a meta-analysis of 23 studies of female breast cancer and reported an $OR = 1.07$ (1.00–1.15).

Erren (2001) reported a meta-analysis of 15 studies of male breast cancer in relation to ELF, and found a $RR = 1.37$ (1.11–1.71). Sun et al. (2013) performed a meta-analysis of 18 studies of male breast cancer in relation to EMF exposures. This included seven case-control and 11 cohort studies. They report a pooled $OR = 1.32$ (1.14–1.52, $p < 0.001$). All of these breast cancer studies were funded by government agencies. Grundy et al. (2016) investigated occupational exposure to magnetic fields and male breast cancer in 115 cases and 570 controls. They classified magnetic field exposures into three categories based on job histories and duration. They found an elevated risk of breast cancer in men who were exposed to $> 0.6 \mu T$ [$OR = 1.80$ (0.82–3.95)] as compared to men exposed to $< 0.3 \mu T$. In addition they found that men with any occupational exposure to magnetic fields for at least 30 years had an elevated risk of breast cancer [$OR = 2.77$ (0.98–7.82)] as compared to men with only background exposure.

6.3. Other cancers

There are also a few studies focused on other specific cancers. Baumgardt-Elms et al. (2002) found no elevated risk of testicular cancer in men who had ever worked near high voltage power lines [$OR = 0.7$ (0.38–1.18). Charles et al. (2003) reported an elevated risk of prostate cancer mortality in workers at US electric utility companies when comparing those with greater than 4.4 μT -years exposure as compared to those with $< 0.6 \mu T$ -years exposure (funded by EPRI and government). The author suggest that further study is needed on this association.

6.4. Parental ELF exposure and childhood cancer risk

There have been a number of studies of parental exposure to ELF-EMF and cancers in offspring. Feychting et al. (2000) followed 235,635 children from birth to 14 years based on parent's job title. They did not find elevations in any childhood cancer based on mother's occupational exposure but did find a significant elevation in risk of leukemia (but not brain cancer) based on father's exposure [$RR = 2.0$ (1.1–3.5)]. By contrast Infante-Rivard and Deadman (2003) found an $OR = 2.5$ (1.2–5.0) for childhood leukemia based on mother's occupational exposure during pregnancy in a government-funded study. In a later study the same group performed a similar investigation of brain cancer in offspring of mothers' with ELF exposure estimated by a job title matrix and reported an $OR = 1.5$ (1.0–3.4) for astroglial tumors (Li et al., 2009). Among sewing machine operators, who are exposed to high magnetic fields, there was an $OR = 2.3$ (1.0–5.4) for all childhood brain tumors (government funded). Su et al. (2018) (government funded) performed a meta-analysis of 22 studies (21 case-control and one cohort study) of parental occupational exposure and childhood brain cancer. They report a strong association with maternal exposure [$OR = 1.16$

(1.06–1.26) and childhood brain cancer and a non-significantly elevated association with paternal exposure [$OR = 1.15$ (0.98–1.34)]].

Pearce et al. (2007) reported on a population based registry of young people with cancer from Northern England, and examined risk of leukemia in offspring of men likely exposed to EMFs based on parental occupation on the child's birth records (funded by foundations). There was a significant elevation in childhood lymphoid leukemia in children whose fathers' occupation was as an electrician [$OR = 1.59$ (1.12–2.26)]. Hug et al. (2010) (government funded) studied German children's (ages 0 to 14) risk of developing cancer in relation to parents' pre-conceptual ELF exposure, based on occupation. They had 2382 controls and 2,049 cases, of which 846 were acute leukemia, 159 with non-Hodgkin's lymphoma, 444 with brain tumors and 600 with other solid tumors. They found no elevated risk in children whose fathers had occupational exposure to ELF-EMFs greater than $0.2 \mu T$. Reid et al. (2011), in a government funded study, found no elevated risk of acute lymphocytic leukemia of either maternal [$OR = 0.96$ (0.74–1.25)] or paternal [$OR = 0.78$ (0.56–1.09)] occupational exposure. Auger et al. (2019) have reported on 784,944 Canadian newborns followed for one decade (government funded). There were 1114 children who developed cancer. They found a borderline elevated risk for development of any cancer [$OR = 1.08$ (0.98–1.20)], hematopoietic cancer [$OR = 2.04$ (0.88–1.23)] and solid tumors [$OR = 1.11$ (0.99–1.25)] for children living within 80 m of a transformer station as compared to > 200 m. However they did not find any association with living near to transmission lines.

7. Discussion

It is remarkable that in the 40 years after Wertheimer and Leeper (1979) first reported an association between exposure to magnetic fields from residential power lines and elevated risk of childhood cancer, and the large number of subsequent investigations, that there is still controversy over the question “Does exposure to magnetic fields cause cancer?” One contributing cause of the confusion is clear from the analysis of the source of funding. When childhood leukemia studies are funded by governments or private sources they consistently find that elevated exposure increases risk. When those studies are funded by utilities they consistently do not find positive associations. In some cases the same investigators find positive associations when funded by government and then go on to report negative finding when funded by utilities. The differences in findings cannot be explained by numbers of cases or other methodological factors, leading to the conclusion that conflicts of interest based on source of funding have influenced the results, whether this was due to conscious or unconscious design.

A similar finding of different results obtained based on funding source has been reported for use of mobile phones and brain cancer, where reports funded by the industry were least likely to find associations (Huss et al., 2007). Other have also commented on the degree to which ties to industry influences conclusions as to risks of cancer from EMF exposures, and how this goes beyond reports of original research to influences on national and international committees that issue summary reports (Hardell et al., 2006; Maisch, 2006; Starkey, 2016; Hardell, 2017). The overall result arising from these conflicts of interest is that the public is confused and many times the press declares that results are “inconsistent” when in fact they are very consistent if one does not consider the results of industry-funded studies.

While much of the debate as to whether magnetic fields increase the risk of cancer has focused on childhood leukemia, the evidence for an elevated risk for several adult cancers is strong and surprisingly consistent. While there remains a possibility of conflicts of interest here as well, it is not as apparent as in the case of childhood leukemia. But meta-analyses on magnetic field exposure and adult leukemia, brain cancer and breast cancer in both men and women are almost all positive. The data on parental exposure and childhood cancer is less strong and consistent, but there is sufficient indication that there may be an

association so as to merit additional study.

The specific mechanisms whereby exposure to magnetic fields increases risk of cancer are still uncertain, but we know that generation of reactive oxygen species and gene induction are involved (Belpomme et al., 2018). The recent animal studies from the Ramazzini Institute also provide additional insight, when considered in light of some of the human studies. Bua et al. (2018) did not detect any increase in cancer in Sprague-Dawley rats exposed to 50 Hz ELF-EMFs over their lifetime. However the same groups demonstrated that there was synergistic cancer promotion when magnetic fields were added to exposure to formaldehyde (Soffritti et al., 2016a) or an acute low-dose of ionizing radiation (Soffritti et al., 2016b). These results are consistent with the suggestion in the reports of Turner et al. (2014) and Carlberg et al. (2017) that magnetic fields function of promoters, not inducers, of cancer.

There are other implications of this analysis. We have accepted results of meta-analyses done by a number of different authors. However in none of these meta-analyses have industry-funded studies been excluded. If studies were included that were biased, the overall conclusions may have been underestimations of the true associations.

While the significant elevations in risk for the various forms of cancer are not large (significant ORs usually not much greater than 2), the reality is that everyone is exposed at various degrees, and therefore there is no unexposed population for comparison. This means that in each study one is comparing disease in individuals with more as compared to less exposure. This also will result in an underestimation of the true risk. The overall evidence presented above shows a clear increase in risk of various cancers associated with elevated field magnetic exposure, but these consideration lead to the conclusion that the actual risk is likely even greater than indicated by the meta-analyses because of bias in some reports as well as in the individual studies and because of the lack of an unexposed comparison population.

In spite of the evidence for there being an elevated risk of various cancers upon excessive exposure to magnetic fields, there has not been a general acceptance that such exposure is a hazard to human health of sufficient magnitude to merit doing anything about it. This represents a failure on the part of international and national institutions, as well as the medical and public health communities, and is in great part a consequence of the distortions promoted by those with clear conflicts of interest. But to have regulators, scientists and the public remain ignorant of the evidence of harm from excessive exposure is unacceptable. The concept of “prudent avoidance”, developed by Granger Morgan (1988) from Carnegie Mellon University some 30 years ago, remains invaluable. We are not going to reduce our use of electricity, but there are many simple ways to reduce excessive exposure to magnetic fields that do not interfere with the quality of life but will reduce the risk of developing cancer.

Funding source

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

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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

<https://doi.org/10.1515/reveh-2021-0112>

Received August 27, 2021; accepted February 13, 2022;

published online March 15, 2022

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 ($<0.2 \mu\text{T}$ vs. $>0.2 \mu\text{T}$), distances between the child's home and power lines ($>200 \text{ m}$ vs. $<200 \text{ m}$) 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 $0.4 \mu\text{T}$ (12 studies, $>0.4 \mu\text{T}$: pooled OR=1.37; 95% CI 1.05–1.80; acute lymphoblastic leukemia alone: seven studies, $>0.4 \mu\text{T}$: pooled OR=1.88; 95% CI 1.31–2.70). Lower magnetic fields were not associated with leukemia (12 studies, $0.1\text{--}0.2 \mu\text{T}$: pooled OR=1.04; 95% CI 0.88–1.24; $0.2\text{--}0.4 \mu\text{T}$: 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 $0.4 \mu\text{T}$ can increase the risk of developing leukemia in children, probably acute lymphoblastic leukemia. Prolonged exposure to electric appliances that generate magnetic fields higher than $0.4 \mu\text{T}$ like electric blankets is associated with a greater risk of childhood leukemia.

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Keywords: cancer; childhood leukemia; electromagnetic fields; magnetic fields; power lines.

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) ($1\ \mu\text{T} = 10\ \text{mG}$). 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 synthesizes 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 μ T [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 μ T (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 μ T, 0.2–0.3 μ T, 0.3–0.4 μ T, 0.2–0.4 μ T, >0.2 μ T, >0.3 μ T and >0.4 μ T) 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: $<0.2 \mu\text{T}$ vs. $>0.2 \mu\text{T}$ for magnetic flux densities, $>200 \text{ m}$ vs. $<200 \text{ m}$ 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, $<0.2 \mu\text{T}$ served as the reference category for magnetic flux densities. Living more than 200 m away from power lines ($>200 \text{ m}$) 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 $0.2 \mu\text{T}$ 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 $0.4 \mu\text{T}$ in residences located within 200 m of power lines [11, 30]. Moreover, mean measured magnetic flux densities were always lower than $0.2 \mu\text{T}$ 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 $0.2 \mu\text{T}$. 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: $<0.1 \mu\text{T}$ 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 ($0.1\text{--}0.2 \mu\text{T}$, $0.2\text{--}0.3 \mu\text{T}$, $0.3\text{--}0.4 \mu\text{T}$, $0.2\text{--}0.4 \mu\text{T}$, $>0.3 \mu\text{T}$ and $>0.4 \mu\text{T}$) and distance categories ($0\text{--}50 \text{ m}$, $0\text{--}200 \text{ m}$, $200\text{--}600 \text{ m}$) 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

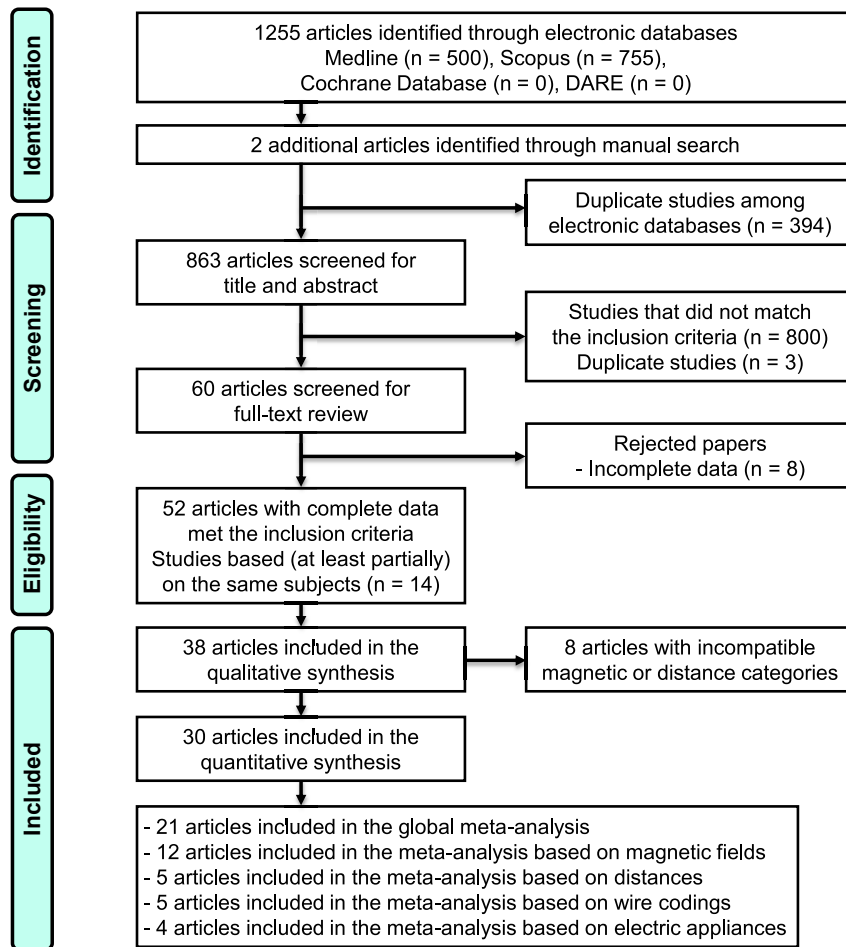


Figure 1: Flowchart of selection of studies for inclusion in the meta-analysis. See Appendix for the studies excluded from our systematic review and the reasons of exclusion.

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 $0.4 \mu\text{T}$ than children from lower income countries. Only 0.3% of children from high income countries have been exposed to

ELF-MF higher than $0.4 \mu\text{T}$ [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 $0.4 \mu\text{T}$.

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 ($0.2 \mu\text{T}$ 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.

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
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)
Savitz, 1988 [36]	36	207	USA, Colorado, <15 y, NR	Colorado Cancer Registry, 35%, >0.2 μ T: 13.8%	RDD, 74%, >0.2 μ T: 7.7%	1976–1983	Direct MF measure, wire coding
							This study supports an association between low power use conditions and childhood leukemia (>0.2 μ T, OR=1.93; 0.67–5.56)
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)
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 μ T: 18.4%	CSR, 99%, >0.3 μ T: 5.7%	1960–1985	Calculated MF, direct MF measure	This study supports an association between childhood leukemia and magnetic fields (>0.3 μ T: RR=3.8; 1.4–9.3)	Study funded in part by the National Board for Industrial and Technical Development (NUTEK)
Linnet, 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 μ T: 1.4%	RDD, 63%, >0.5 μ T: 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 μ T: 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 μ T: 3.1%	CSR, 54%, >0.2 μ T: 1.8%	1988–1993	Direct MF measure	This study provides some evidence for an association between ELF-MF and childhood leukemia (>0.2 μ T: 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 European Union 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 μ T: 0.7%	CSR, 95%, >0.14 μ T: 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 lines and childhood acute lymphoblastic leukemia)	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-Ara-ngue, 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 μ T: 23.8%	Instituto John Langdon Down and Centro de Atencion Integral del Nino con Sindrome de Down, 56%, >0.6 μ T: 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 μ T: 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 μ T: 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
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 μ T: 6.7%	São Paulo Birth Registry, CSR, 23%, >0.3 μ T: 6.0%	2003–2009	Direct MF measure, distances
Jirík, 2012 [26]	82	81	Czech Republic, <15 y, NR	University hospitals, NR, >0.4 μ T: 17.0%	Hospital controls, NR, >0.4 μ T: 18.5%	2003–2007	Direct MF measure
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
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
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
Pedersen, 2015 [55]	1,536	3,072	Denmark, <15 y, NR	Danish Cancer Registry, NR, >0.4 μ T: 0.3%	CSR, NR, >0.4 μ T: 0.1%	1968–2003	Calculated MF

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)

This study does not support an association between ELF-MF and childhood leukemia

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)

This study provides little support for a relation between proximity to power lines and childhood leukemia

This study provides little support for a relation between proximity to power lines and childhood leukemia

This study provides some support for an association between childhood leukemia and ELF-MF (>0.4 μ T: OR=1.67; 0.51–5.47)

Funded by the Brazilian Electricity Regulatory Agency

Not reported

Funded by the Institut de Veille Sanitaire and several other organizations

Funded by a Programme Grant awarded from Children with Cancer UK

Funded by the foundation Children with Cancer UK and by other organizations

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 μ T: 2.4%	CSR, 61%, >0.2 μ T: 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 μ T: 0.02%	Birth registers, CSR, NR, >0.4 μ T: 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 μ T: 0.2%	California Birth Registry, CSR, NR, >0.4 μ T: 0.1%	1988–2008	Calculated MF	This study provides some support for a relation between ELF-MF and childhood leukemia (>0.4 μ T: 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. ^aThe 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. ^bThe 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). ^cThe 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. ^dAIEOP, Associazione Italiana Ematologia Pediatrica (nation-wide hospital-based registry of childhood malignancies). ^eThe 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. ^fThe 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 μ T:	139	546	OR=1 (Ref.)
	0.05–0.14 μ T:	8	19	OR=1.8 (0.7–4.2)
	>0.14 μ T:	1	14	OR=0.3 (0.0–2.1)
	Total:	148	579	
Bianchi, 2000 [44]	<0.001 μ T:	92	401	RR=1 (Ref.)
	0.001–0.1 μ T:	6	8	RR=3.29 (1.1–9.7)
	>0.1 μ T:	3	3	RR=4.51 (0.8–23.1)
	Total:	101	412	
Feizi, 2007 [47]	<0.45 μ T:	45	54	OR=3.60 (1.1–12.3)
	>0.45 μ T:	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. ^aThe 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. ^bAn 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. ^cAdaptation 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

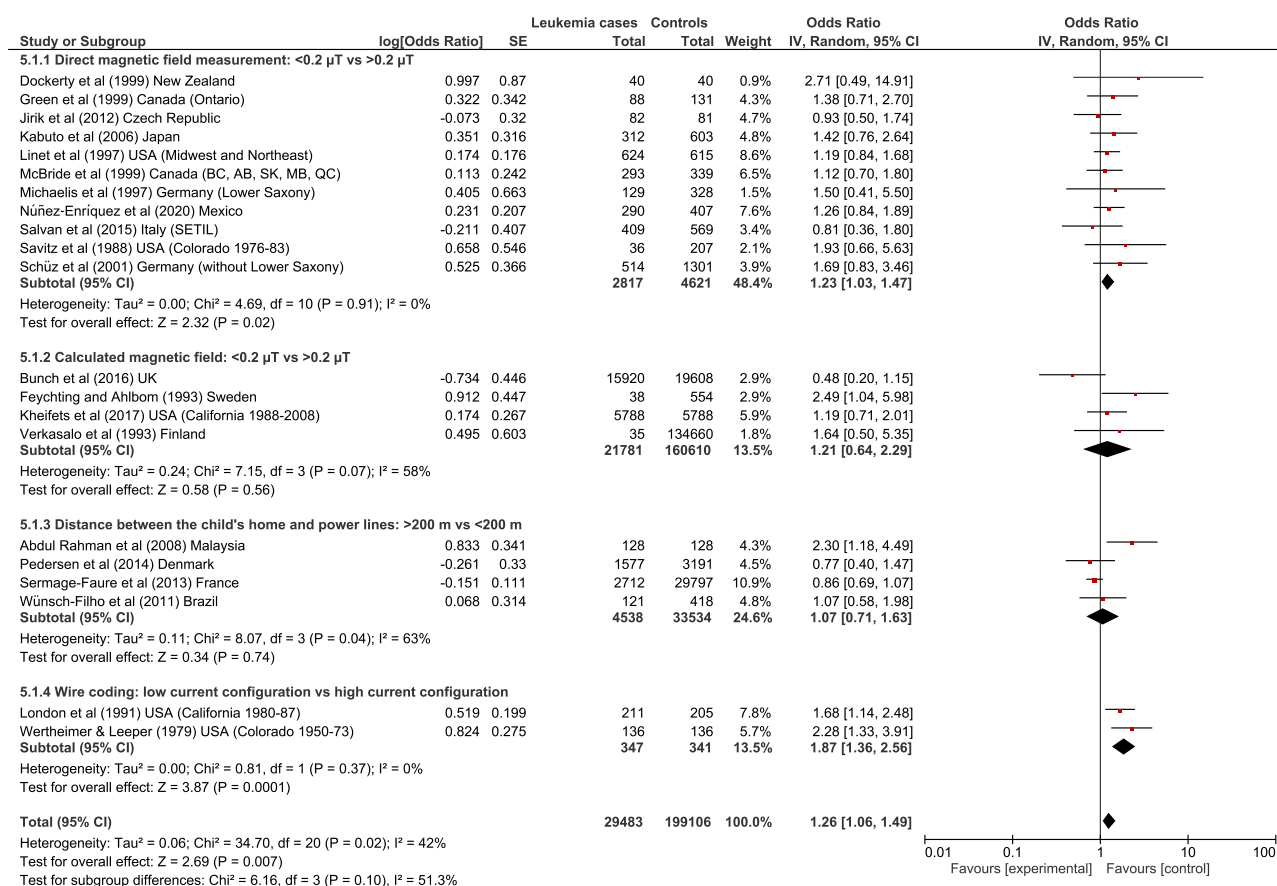


Figure 2: Global meta-analysis based on the exposure levels (cutoff points) that have most often been used in the studies included in the present systematic review (<0.2 µT vs. >0.2 µT for magnetic fields, >200 m vs. <200 m for distances to power lines and the low current configuration vs. the high current 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

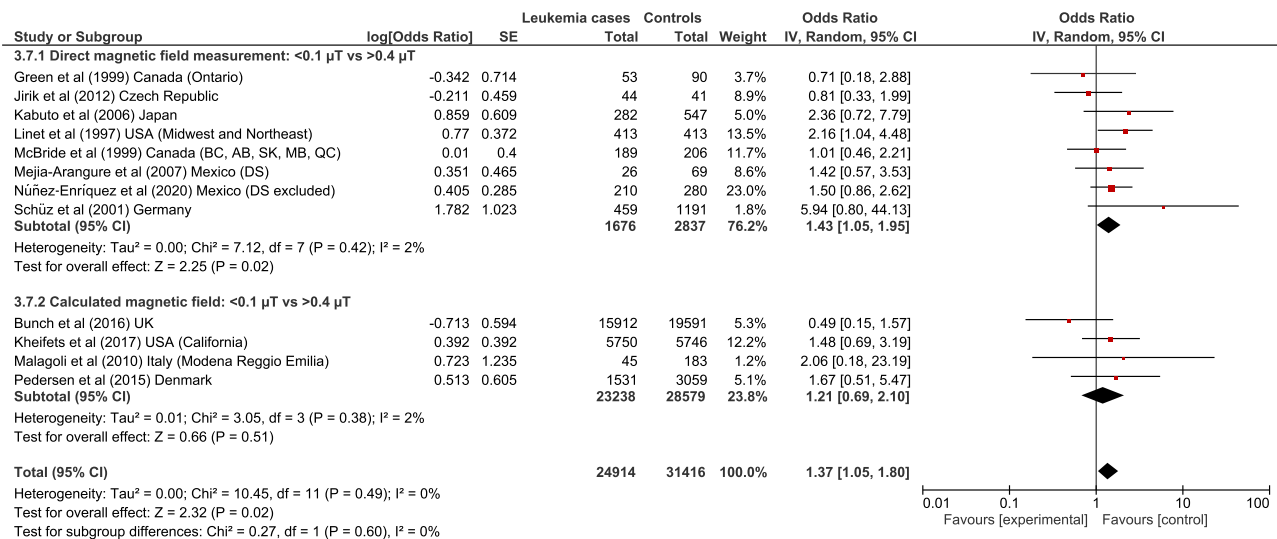


Figure 3: Exposure to magnetic fields higher than 0.4 μ T increased the risk of developing childhood leukemia (all leukemia subtypes were combined in this analysis). Two studies performed in Mexico are included in this meta-analysis but one is based exclusively on Down syndrome (DS) children [48] and 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 μ T 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 μ T 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 μ T 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 μ T 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 μ T (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 μ T: 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 μ T 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 μ T 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 $>0.4 \mu\text{T}$ (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 ($>0.4 \mu\text{T}$: 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 ($\pm\text{SD } 0.26$) 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 $0.4 \mu\text{T}$ 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 $0.4 \mu\text{T}$ 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 $0.4 \mu\text{T}$ 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 $0.4 \mu\text{T}$ 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 $0.4 \mu\text{T}$ 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 $0.4 \mu\text{T}$. 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 $0.4 \mu\text{T}$. 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 $0.4 \mu\text{T}$ 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 $0.4 \mu\text{T}$ 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 $0.4 \mu\text{T}$ 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.

Research funding: The present work was supported by a grant obtained by the University of Liège from the Belgian BioElectroMagnetics Group (BBEMG). The funding organization played no role in the study design, in the collection, analysis and interpretation of data, in the writing of the report or in the decision to submit the report for publication.

Author contributions: Each author has consented to their names upon the article and has made a significant contribution to this article. Professor Olivier Bruyère, Dr Christian Brabant and Dr Charlotte Beaudart have designed the study. Dr Christian Brabant and Anton

Geerinck have collected the data. Dr Christian Brabant and Dr Charlotte Beaudart have performed the statistical analysis. All authors have interpreted the data, wrote and revised the manuscript critically for important intellectual content. All authors have approved the final version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests: This work was supported by a grant obtained by the University of Liège from the Belgian BioElectroMagnetics Group (BBEMG).

Ethical approval: Not applicable. No ethical approval was required as this was a systematic review and did not use primary data.

Informed consent: Not applicable, as this work was a systematic review and did not use primary data.

Data availability: Data are available from Dr Christian Brabant (christian.brabant@uliege.be) with a reasonable request.

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Supplementary Material: The online version of this article offers supplementary material (<https://doi.org/10.1515/reveh-2021-0112>).

SCIENTIFIC REPORTS

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Exposure to Magnetic Field Non-Ionizing Radiation and the Risk of Miscarriage: A Prospective Cohort Study

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Magnetic field (MF) non-ionizing radiation is widespread and everyone is exposed to some degree. This prospective cohort study of 913 pregnant women examined the association between high MF exposure and miscarriage risk. Cox (proportional hazards) regression was used to examine the association. After controlling for multiple other factors, women who were exposed to higher MF levels had 2.72 times the risk of miscarriage (hazard ratio = 2.72, 95% CI: 1.42–5.19) than those with lower MF exposure. The increased risk of miscarriage associated with high MF was consistently observed regardless of the sources of high MF. The association was much stronger if MF was measured on a typical day of participants' pregnancies. The finding also demonstrated that accurate measurement of MF exposure is vital for examining MF health effects. This study provides fresh evidence, directly from a human population, that MF non-ionizing radiation could have adverse biological impacts on human health.

Magnetic field (MF) non-ionizing radiation is a ubiquitous environmental exposure and a serious looming public health challenge. MFs are emitted from both traditional sources that generate low frequency MFs (e.g., power lines, appliances, transformers, etc.) and from emerging sources that generate higher frequency MFs (e.g., wireless networks, smart meter networks, cell towers, wireless devices such as cell phones, etc.). Humans are now widely exposed to MF with ever-increasing intensity, due to the proliferation of MF-generating apparatuses.

The steep increase in MF exposure has renewed concerns about the potential health effects of this invisible, man-made environmental exposure. A recent NIEHS multi-year project conducted by the National Toxicology Program (NTP) has revealed an increased risk of cancer associated with MF non-ionizing radiation exposure^{1,2}. More specifically, the NTP study found that the cancer risk due to MF exposure observed in their experimental animals matched the cancer cell types that had been reported in previous epidemiologic studies in human populations¹. This finding has made it more difficult to continue to dismiss possible biological effects of MF exposure. Such outright dismissal could be especially troublesome given the high prevalence of human exposure (with almost everyone being exposed to MF non-ionizing radiation to some degree). This includes vulnerable populations such as pregnant women and young children. The International Agency for Research on Cancer (IARC) has classified MF as a possible carcinogen^{3,4}.

Miscarriage is one of the potential adverse health outcomes that are sensitive to MF exposure and also an endpoint that the WHO has recommended to be further studied in the context of MF health effects⁵. Over the years, a few observational studies in human populations have suggested a possible link between MF exposure during pregnancy and an increased risk of miscarriage^{6–11} including two studies published in 2002 that increased the public awareness of such an association^{12,13}. In addition, one study examined human embryonic tissues to assess the association between EMF exposure and embryonic growth, and observed an increased risk of impaired embryonic bud growth and apoptosis associated with exposure to higher MF level¹⁴, providing some direct evidence of adverse biological impact of EMF exposure on embryonic development.

Nevertheless, the association between MF exposure and risk of miscarriage remains largely unknown and overlooked. We conducted this prospective cohort study among a large population of pregnant women to further examine whether exposure to MF non-ionizing radiation during pregnancy increases the risk of miscarriage.

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Materials and Methods

This prospective cohort study was approved by the Kaiser Permanente Northern California (KPNC) Institutional Review Board and conducted among KPNC's pregnant members in the San Francisco Bay Area, all of whom provided informed consent. The study was performed in accordance with all relevant guidelines and regulations. KPNC is an integrated health care delivery system whose members comprise 28–30% of the population in the catchment area and have consistently been shown to be representative of the underlying population^{15,16}.

Study population. All pregnant women, aged 18 years or older, and residing in the participating Bay Area counties, were identified through the KPNC electronic medical record (EMR) laboratory database based on positive pregnancy tests. At KPNC, all women suspected to be pregnant were routinely asked to have a pregnancy test done at a KPNC facility. Flyers informing women about the study were posted at the participating facilities and given to women at the time of their pregnancy test. Given that miscarriage can occur very early in pregnancy, recruiting pregnant women as early as possible in their pregnancy was crucial to ensuring as complete ascertainment of miscarriage as possible. Our identification of pregnant women through positive pregnancy lab tests ensured early recruitment. To determine whether a woman's recurrent miscarriage(s), an indication of higher susceptibility to miscarriage, increases her vulnerability to MF exposure, we oversampled women with two or more prior miscarriages. The pregnant women identified were contacted by a trained recruiter/interviewer to determine their eligibility and willingness to participate in the study. Those who indicated their intention to carry the pregnancy to term and whose gestational age at identification was less than 10 completed weeks (still at risk for miscarriage) were invited to participate in the study. Among 1,627 eligible pregnant women, 1,054 agreed to participate in the study.

Measuring magnetic field exposure during pregnancy. All participating pregnant women were asked to carry an EMDEX Lite meter (Enertech Consultants Inc.) for 24 hours during pregnancy. The EMDEX Lite meter is specifically designed to measure MF, which is measured in milligauss (mG).

To ensure better representation of MF exposure during pregnancy and to apply the knowledge gained from the previous study¹², we designed the MF measurement to be conducted on a typical day (a day reflecting participants' typical pattern of work and leisure activities during pregnancy). In the event that a participant's daily activities might have been altered from what was originally planned, we also verified with the participants, at the end of the measurement period, whether the measurement day was indeed a typical day of their pregnancy. If not, the measurement day was classified as non-typical.

The EMDEX Lite meter was used to measure MF exposure levels by participating pregnant women from all emitting sources. Participants were also asked to keep a diary during the 24-hour measurement period to allow the researchers to (1) identify locations of daily activities (at home, at home in bed, in transit, at work, and other), (2) verify if activities were reflective of a typical day, and (3) examine if locations and activities were associated with high MF exposure.

MF data together with participants' diary of activities on the measurement day were examined for quality control, including consistency and potential errors. We excluded 31 subjects who failed to carry the meter as instructed. We also excluded 107 subjects who had incomplete (<90% of their 24-hour measurements) MF measurement data. Those exclusions were made without knowledge of subjects' pregnancy outcomes.

Previous studies have found that the highest MF levels that pregnant women encounter are the most relevant to miscarriage risk^{12,13}, indicating a possible threshold effect at a given MF level above which developmental embryos may cease to be viable. Thus, this study focused on high levels of MF exposure. We used the 99th percentile of MF measurements during the 24-hour period to classify exposure level, balancing between the need to examine as high of MF level as possible and, at the same time, avoid using less stable indices (e.g., maximum exposure level).

To more accurately reflect participants' true MF exposure during pregnancy, we made significant efforts to separate those participants whose measurements were conducted during a typical day of their pregnancy from those whose measurements were not conducted on a typical day. Measurements obtained on a *typical day* are likely more representative of MF exposure during pregnancy while measurements obtained on a *non-typical* day are more subject to misrepresentation of the true MF exposure level during pregnancy, resulting in misclassifying participants into incorrect MF exposure categories. Such misclassification usually reduces scientists' ability to detect an underlying association. As demonstrated in a previous study, measurements conducted on a typical day showed a stronger association between MF exposure and miscarriage risk, while measurements conducted on a non-typical day showed virtually no association due to incorrectly classifying participants into MF exposure categories¹².

Measurement of miscarriage. Using KPNC EMR data, we were able to identify participants' pregnancy immediately after a positive pregnancy test, thereby starting follow-up at an earlier gestational age than the first prenatal visit, the earliest time at which most other studies have been able to identify pregnant women. This early follow-up allowed us to ascertain early miscarriages that most other studies would have missed, making it an important strength of this study.

All participants were followed for their pregnancy outcomes from the time of their positive pregnancy test to the end of their pregnancy. In the case of miscarriage, this is, by definition, before 20 completed weeks of gestation. We ascertained pregnancy outcomes through the KPNC EMR databases. For participants whose outcomes were not available in the EMR, we contacted them directly. We were able to identify pregnancy outcomes for all participants except one who had moved out of the area, thus she was excluded from further analysis.

In-person interview. An *in-person* interview was conducted with all participants to ascertain extensive information on potential confounders, including pregnancy history and risk factors for miscarriage. Previous studies have shown that MF exposure level is seldom related to common socio-demographic characteristics and risk factors^{12,17,18}; thus, the number of potential confounders in this study was small. Nevertheless, we still collected many factors for examination to ensure thorough control of confounders. Two participants were not able to complete the interview, thus they were excluded from the analyses.

The prospective study design also ensured that the *in-person* interview was blinded to MF exposure for both interviewers and participants, since the EMF measurement was conducted after the interview. This study design enhances the quality of the study findings.

Statistical analysis. We used the Cox Proportional Hazards regression model, with accommodation for left truncation, to examine the association between MF exposure level and miscarriage. Hazard ratios with 95% confidence intervals were used to determine the magnitude and significance of associations. Left truncation arises when study participants enter observation at a point in time (i.e. gestational age at cohort entry) after the time of origin, conception. Participants were followed until either (a) miscarriage, (b) end of pregnancy due to other outcomes (e.g., ectopic pregnancy), at which point they were censored or (c) 20 weeks of gestation, for participants who remained pregnant at that time.

We examined confounders using the change-in-estimate criterion, including the confounder if the miscarriage hazard ratio (HR) for MF changed by 10% or more. While most factors examined were not confounders due to a lack of association with MF exposure, we nevertheless included in the model commonly known risk factors for miscarriage and socio-demographic characteristics.

Given the previous finding that the strength of association between MF and miscarriage varied by whether the MF measurements were taken on a typical or non-typical day¹², we first conducted analyses separately by day type. The previous finding was confirmed in the current study, and we therefore conducted the remaining analyses only among those whose MF exposure was measured on *a typical day* of their pregnancy.

Since we oversampled those with multiple prior miscarriages, we first stratified analysis by those with and without multiple prior miscarriages to determine if the MF association with miscarriage risk differed between these two groups. Once it was determined that the observed associations were largely similar, we included all participants in the analyses and adjusted for prior miscarriage in all the models.

A total of 913 subjects with valid MF measurements and pregnancy outcomes were included in the final analysis.

Statistical analyses were conducted using SAS 9.3.

Results

Table 1 presents the description and characteristics of participants based on their MF exposure levels (high vs. low). The low MF exposure group consisted of women whose 99th percentile of MF exposure levels was in the low-est quartile (<2.5 mG), while those in the higher three quartiles were classified in the high MF exposure group. There were no noticeable associations or consistent patterns between MF exposure level and most of the factors examined, including risk factors for miscarriage (Table 1).

After adjustment for maternal age, race, education, smoking during pregnancy, and prior miscarriage, overall, pregnant women who had higher MF exposure during pregnancy (higher 3 quartiles) had a 48% greater risk of miscarriage than women who had lower MF exposure (in the lowest quartile): adjusted HR = 1.48, 95% confidence interval (CI): 1.03–2.14 (Table 2). Notably, consistent with the finding in a prior study¹², the observed association was much stronger among participants whose MF exposure was measured on a typical day of the pregnancy (aHR = 2.72, 1.42–5.19). In contrast, there was no observed association among those whose MF was measured on a non-typical day (Table 2). Thus, the following analyses were restricted to those whose MF was measured on a typical day of their pregnancy.

Next, we examined the association separately among women with and without multiple prior miscarriages (≥ 2). Table 3 showed that the association was largely similar between these two groups, with the association being slightly stronger among women without multiple prior miscarriages.

Table 4 shows the possible dose-response relationship by examining the association for each quartile using the lowest quartile (2.5 mG) as the reference group. While all higher quartiles showed an increased risk of miscarriage compared to the lowest MF exposure group, there was no dose-response relationship observed. These results are similar to those of a prior study¹².

The above-observed association was consistent regardless of the source of the MF. Although we did not have information on the exact sources from which MF was generated, based on participants' diary, we were able to examine whether MF exposure was from any of the following location categories: at home, at home in bed, at work, in transit, or from other sources. The association was observed consistently, regardless of the location. In addition to the adjusted variables mentioned above, further adjustment for nausea and vomiting as well as the following variables did not change the results in Tables 2–4: maternal income, marital status, maternal nausea/vomiting, alcohol use, caffeine intake, maternal fever, vaginal bleeding, urinary tract infection, carrying loads > 10 pounds, exposure to solvents or degreasers, vitamin intake, and Jacuzzi/hot tub/steam room/sauna use during pregnancy.

Discussion

After initial reports that provided evidence of an increased risk of miscarriage associated with high MF exposure during pregnancy^{12,13}, the current NIEHS-funded study provides additional evidence that exposure to high MF levels in pregnancy is associated with increased risk of miscarriage. This finding is also supported by four other studies published during the past 15 years that examined the relationship between high MF exposure and the risk of miscarriage^{8–11,19}. Two of those studies measured EMF both inside, and in the surrounding areas, of the

Characteristic	Total N (N = 913) ^a	99 th Percentile MF Level			
		Lowest quartile (N = 219)		Higher quartiles (N = 694)	
		N	%	N	%
Maternal age					
<30	296	61	27.9%	235	33.9%
30–34	288	71	32.4%	217	31.3%
≥35	329	87	39.7%	242	34.9%
Race					
White	326	91	41.7%	235	34.0%
Black	90	16	7.3%	74	10.7%
Hispanic	226	51	23.4%	175	25.3%
Asian /Pacific Islander	202	44	20.2%	158	22.8%
Other	66	16	7.3%	50	7.2%
Education					
<High school	42	5	2.3%	37	5.4%
High school or GED	142	32	14.7%	110	15.9%
Trade/Technical school	46	5	2.3%	41	5.9%
College degree	495	128	58.7%	367	53.1%
Graduate school	184	48	22.0%	136	19.7%
Marital Status					
Single	72	12	5.5%	60	8.7%
Partnered	147	31	14.2%	116	16.8%
Married	690	175	80.3%	515	74.5%
Worked in last year					
No	183	47	21.6%	136	19.7%
Yes	727	171	78.4%	556	80.3%
Smoked since LMP					
No	807	196	91.2%	611	89.3%
Yes	92	19	8.8%	73	10.7%
Coffee intake since LMP					
0 cup/day	637	142	64.8%	495	71.3%
0–1 cup/day	201	52	23.7%	149	21.5%
>1 cups/day	75	25	11.4%	50	7.2%
Alcohol use since LMP					
No	514	127	58.3%	387	55.8%
Yes	397	91	41.7%	306	44.2%
Number of previous pregnancies					
0	94	21	9.6%	73	10.5%
1	103	18	8.2%	85	12.2%
2	140	36	16.4%	104	15.0%
≥3	576	144	65.8%	432	62.2%
Number of previous miscarriages					
0	276	60	27.4%	216	31.1%
1	79	21	9.6%	58	8.4%
2	403	101	46.1%	302	43.5%
≥3	155	37	16.9%	118	17.0%
History of subfertility					
No	633	147	67.1%	486	70.0%
Yes	280	72	32.9%	208	30.0%
Vaginal bleeding since LMP					
No	670	165	75.7%	505	72.9%
Yes	241	53	24.3%	188	27.1%
Urinary tract infection since LMP					
No	860	211	96.8%	649	93.9%
Yes	49	7	3.2%	42	6.1%
Fever since LMP					
No	851	198	92.1%	653	94.8%
Continued					

Characteristic	Total N (N = 913) ^a	99 th Percentile MF Level			
		Lowest quartile (N = 219)		Higher quartiles (N = 694)	
		N	%	N	%
Yes	53	17	7.9%	36	5.2%
Carry loads (>10 pounds) since LMP					
No	416	92	42.2%	324	46.8%
Yes	494	126	57.8%	368	53.2%
Used Jacuzzi/hot tub/steam room/sauna since LMP					
No	807	200	91.7%	607	87.7%
Yes	103	18	8.3%	85	12.3%
Exposure to solvents or degreasers since LMP					
No	609	148	68.5%	461	67.7%
Yes	288	68	31.5%	220	32.3%
Vitamin use since LMP					
No	91	16	7.3%	75	10.8%
Yes	820	202	92.7%	618	89.2%
Gestational age at study entry					
0–48 days	763	173	79.0%	590	85.0%
49–69 days	135	41	18.7%	94	13.5%
≥70 days	15	5	2.3%	10	1.4%

Table 1. Characteristics of the Study Population by Daily Magnetic Field Exposure Level (Lowest or Higher Quartiles of MF 99th Percentile). Abbreviation: LMP, Last menstrual period. ^aThe numbers in each individual category may not sum to the total number because of missing data.

99 th Percentile MF Level	Total N	Miscarriage N (%)	cHR (95% CI)	aHR ^a (95% CI)
Among all participants				
Lowest quartile	219	36 (16.4%)	Ref	Ref
Higher quartiles	694	164 (23.6%)	1.43 (1.00–2.06)	1.48 (1.03–2.14)
MF measured on typical days				
Lowest quartile	106	11 (10.4%)	Ref	Ref
Higher quartiles	347	84 (24.2%)	2.46 (1.31–4.62)	2.72 (1.42–5.19)
MF measured on non-typical days				
Lowest quartile	113	25 (22.1%)	Ref	Ref
Higher quartiles	347	80 (23.1%)	1.02 (0.65–1.62)	1.08 (0.67–1.73)

Table 2. Exposure to High Magnetic Fields (MFs) During Pregnancy and the Risk of Miscarriage. cHR: crude (unadjusted) hazard ratio; aHR: adjusted hazard ratio. 95% CI: 95% Confidence interval. ^aAdjusted for maternal age at interview, race, education, smoking since LMP and prior miscarriage. Further adjustment for the following variables did not change the results: maternal nausea/vomiting, maternal income, marital status, alcohol use, caffeine intake, maternal fever, vaginal bleeding, urinary tract infection, carrying loads > 10lbs, exposure to solvents or degreasers, vitamin intake and Jacuzzi/hot tub/steam room/sauna use during pregnancy.

residence of participating pregnant women, and observed a higher risk of miscarriage associated with higher EMF exposure levels^{8,9}. Two other studies examined the impact of EMF emitted from cell phones and wireless networks, and observed that more frequent cell phone use and close proximity to wireless base stations were both associated with an increased risk of miscarriage^{10,11}. Although none of these studies conducted any personal MF measurements to capture actual MF exposure from all sources, as the current study has done, all four studies reported an increased risk of miscarriage associated with high MF exposure.

One of the most challenging aspects of assessing the health impact of MF exposure is the ability to measure MF exposure accurately as well as in the relevant etiological period. Prospectively measuring MF exposure in the etiologically relevant timeframe is essential and preferable to retrospective measurements. It is especially problematic to ascertain MF exposure long after the relevant window of exposure has passed. While logistically challenging, a prospective study design with a device that captures actual MF levels from all emitting sources in an etiologically relevant period will notably improve the accuracy of MF exposure assessment in epidemiological studies in a human population. In addition, as both this study and a previous study¹² demonstrated, even with a prospective design, if measurements were not conducted on a typical day to reflect true MF exposure during pregnancy, such study design could still fail to detect any MF health risk due to misclassification of MF exposure (see Table 2). Therefore, to ensure accurate exposure assessment, MF measurements need to be conducted prospectively during an etiologically relevant window *and* to reflect a participant's typical MF exposure patterns. The

99 th Percentile MF Level	Total N	Miscarriage N (%)	cHR (95% CI)	aHR ^a (95% CI)
≤1 prior miscarriages				
Lowest quartile	39	3 (7.7%)	Ref	Ref
Higher quartiles	143	27 (18.9%)	2.69 (0.82–8.87)	3.76 (1.07–13.18)
≥2 prior miscarriages				
Lowest quartile	67	8 (11.9%)	Ref	Ref
Higher quartiles	204	57 (27.9%)	2.43 (1.16–5.11)	2.56 (1.19–5.50)

Table 3. Exposure to High Magnetic Fields (MFs) During Pregnancy and the Risk of Miscarriage, Stratified by Number of Prior Miscarriages, *MF Measured on Typical Days Only*. cHR: crude (unadjusted) hazard ratio; aHR: adjusted hazard ratio. 95% CI: 95% Confidence interval. ^aAdjusted for maternal age at interview, race, education, smoking since LMP, and gravidity. Further adjustment for the following variables did not change the results: maternal nausea/vomiting, maternal income, marital status, alcohol use, caffeine intake, maternal fever, vaginal bleeding, urinary tract infection, carrying loads > 10lbs, exposure to solvents or degreasers, vitamin intake and Jacuzzi/hot tub/steam room/sauna use during pregnancy.

99 th Percentile MF Level	Total N	Miscarriage N (%)	cHR (95% CI)	aHR ^a (95% CI)
1 st quartile (<2.5 mG)	106	11 (10.4%)	Ref	Ref
2 nd quartile (2.5–3.6 mG)	116	32 (27.6%)	2.87 (1.45–5.70)	3.29 (1.59–6.79)
3 rd quartile (3.7–6.2 mG)	119	31 (26.1%)	2.70 (1.36–5.39)	3.01 (1.48–6.12)
4 th quartile (≥6.3 mG)	112	21 (18.8%)	1.83 (0.88–3.79)	2.02 (0.95–4.28)

Table 4. Exposure to High Magnetic Fields (MFs) During Pregnancy and the Risk of Miscarriage – Assessing Dose-Response, *MF Measured on Typical Days Only*. cHR: crude (unadjusted) hazard ratio; aHR: adjusted hazard ratio. 95% CI: 95% Confidence interval. ^aAdjusted for maternal age at interview, race, education, smoking since LMP, and prior miscarriage. Further adjustment for the following variables did not change the results: maternal nausea/vomiting, maternal income, marital status, alcohol use, caffeine intake, maternal fever, vaginal bleeding, urinary tract infection, carrying loads > 10lbs, exposure to solvents or degreasers, vitamin intake and Jacuzzi/hot tub/steam room/sauna use during pregnancy.

determination of whether the activity pattern was typical needs to be verified after measurement is complete since planned activities can change during the measurement day. It is clear that, if MF exposure is measured subjectively (e.g., interview based on participants' recall) or based on surrogate measures (e.g., wire codes, distance from power lines, job matrix, spot measurement at home, etc.), it would be very difficult for such studies to detect any MF health effect in epidemiological studies due to gross inaccuracies in measuring actual MF exposure levels. By definition, inaccurate MF measures lead to misclassification of MF exposure, which generally result in null findings. Unfortunately, the vast majority of epidemiological studies on MF health effects in the literature so far have been based on subjective and unreliable MF measurements. Thus, it is not surprising that many of the past studies failed to detect MF health effects. In addition, the focus on studying MF effects on cancer has exacerbated the problem, since the development of cancer usually has a long latency period between exposure and outcome that could span several decades. This has made accurately measure MF exposure in the etiologically relevant period (decades before the diagnosis of cancer) almost impossible. Those "null findings" have left a false impression of the "safety" of MF exposure.

The strength of this current study is that, in addition to using an objective measuring device (EMDEX Lite meter), we examined an outcome (miscarriage) with a short latency period (days or weeks rather than years or decades as in the case of cancers or autoimmune diseases). Thus, we were able to measure MF exposure prospectively in the relevant time period (during pregnancy). Furthermore, at the end of the measurement day, we ascertained whether activity patterns on that day reflected a typical day, which allowed us to identify participants with MF exposure measurements that more accurately reflected MF exposure during their pregnancies.

In this study, we found an almost three-fold increased risk of miscarriage if a pregnant woman was exposed to higher MF levels compared to women with lower MF exposure. The association was independent of any specific MF exposure sources or locations, thus removing the concern that other factors connected to the sources of the exposure might account for the observed associations. While nausea and vomiting were hypothesized to be potential confounders, adjustment for both nausea and vomiting did not change the results in this study or in a previous study²⁰. Although we did not observe a dose-response relationship for MF exposure above 2.5 mG, this could be due to a threshold effect of MF exposure in which MF levels at or above 2.5 mG could lead to fetal demise, thus examining further higher levels of MF exposure were not able to confer additional risk.

Given the ubiquitous nature of exposure to this non-ionizing radiation, a small increased risk due to MF exposure could lead to unacceptable health consequences to pregnant women. Although the number of epidemiological studies examining the adverse impact of MF exposure in humans remains limited, the findings of this study should bring attention to this potentially important environmental hazard to pregnant women, at least in the context of miscarriage risk, and stimulate much needed additional research.

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Acknowledgements

This study was supported through funds provided by the *National Institute of Environmental Health Sciences (NIEHS)*, Grant #5 R01 ES12226–5. Some of the results were presented at annual conferences of International Society of Environmental Epidemiology and Bioelectromagnetics Society 2015 and 2016.

Author Contributions

De-Kun Li conceived the concept, designed the study, obtained funding, oversaw the data gathering and analyses, and is responsible for the interpretation of results, and drafting and finalizing the manuscript. Jeannette Ferber and Hong Chen were responsible for data management. Hong Chen was involved in data analysis and interpretation of the results. Roxana Odouli was involved in the study management and preparation of the manuscript. Charles Quesenberry was involved in interpretation of results and preparation of the manuscript. De-Kun Li is the guarantor of this paper who took full responsibility for the conduct of the study, had access to the data, and controlled the decision to publish.

Additional Information

Competing Interests: The authors declare that they have no competing interests.

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