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International study of childhood leukemia in residences near electrical transformer rooms

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ABSTRACT

Objectives: New epidemiologic approaches are needed to reduce the scientific uncertainty surrounding the association between extremely low frequency magnetic fields (ELF-MF) and childhood leukemia. While most previous studies focused on power lines, the Transformer Exposure study sought to assess this association using a multi-country study of children who had lived in buildings with built-in electrical transformers. ELF-MF in apartments above built-in transformers can be 5 times higher than in other apartments in the same building. This novel study design aimed to maximize the inclusion of highly exposed children while minimising the potential for selection bias.

Methods: We assessed associations between residential proximity to transformers and risk of childhood leukemia using registry based matched case-control data collected in five countries. Exposure was based on the location of the subject's apartment relative to the transformer, coded as high (above or adjacent to transformer), intermediate (same floor as apartments in high category), or unexposed (other apartments). Relative risk (RR) for childhood leukemia was estimated using conditional logistic and mixed logistic regression with a random effect for case-control set.

Results: Data pooling across countries yielded 16 intermediate and 3 highly exposed cases. RRs were 1.0 (95% CI: 0.5, 1.9) for intermediate and 1.1 (95% CI: 0.3, 3.8) for high exposure in the conditional logistic model. In the mixed logistic model, RRs were 1.4 (95% CI: 0.8, 2.5) for intermediate and 1.3 (95% CI: 0.4, 4.4) for high. Data of the most influential country showed RRs of 1.1 (95% CI: 0.5, 2.4) and 1.7 (95% CI: 0.4, 7.2) for intermediate (8 cases) and high (2 cases) exposure.

Discussion: Overall, evidence for an elevated risk was weak. However, small numbers and wide confidence intervals preclude strong conclusions and a risk of the magnitude observed in power line studies cannot be excluded.

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1. Introduction

The first study linking extremely low frequency magnetic fields (ELF-MF) to childhood cancer was published in 1979 and has been followed by more than 40 other studies (Kheifets et al., 2018; Swanson et al., 2019). The International Agency for Research on Cancer (IARC) and the World Health Organization (WHO) have classified ELF-MFs as a Group 2B carcinogen, that is, "possibly carcinogenic to humans". This classification was primarily based on consistent epidemiological evidence of an association between exposure to these fields and childhood leukemia (CL) and laboratory studies in animals and cells that did not support exposure to ELF-MF causing cancer (IARC, 2002; WHO, 2007). Because CL is the outcome for which the evidence from epidemiologic studies is strongest, it can be regarded as the critical effect in risk assessment and risk evaluation and therefore attracts particular attention.

There have been some 44 studies and several meta- and pooled analyses on childhood leukemia and ELF-MF exposure estimates based on measured fields, calculated fields or distance to power lines e.g. (Brabant et al., 2023; Seomun et al., 2021; Swanson et al., 2019). Two pooled analyses published in 2000 (Ahlbom et al., 2000; Greenland et al., 2000) of different combinations of the available studies reported a relative risk (RR) of 1.7 (95% CI: 1.2–2.3) for exposure >0.3 μT (μT) and of 2.0 (95% CI: 1.3–3.1) for >0.4 μT. While pooling of the most recent studies showed no increase in risk, a meta-analysis of the three pooled analyses reported an odds ratio (OR) of 1.45 (95% CI: 0.95–2.20) for exposures ≥0.4 μT (Amoon et al., 2022). The consistent association between average ELF-MF exposure above 0.3–0.4 μT and CL could be due to chance, selection bias, misclassification, other factors that confound the association, or a true causal relationship. Despite numerous attempts to improve study quality or examine these alternatives, the issue remains unresolved.

New epidemiologic approaches are required to reduce the scientific uncertainty surrounding the association between ELF-MF and CL. CL and average exposures to ELF-MF above 0.3–0.4 μT are rare (Kheifets et al., 2011). Epidemiologic studies designed to minimize biases from different sources and maximize the ability to detect an association are needed. Only such studies have the potential to contribute new information to an overall scientific understanding of the CL and ELF-MF issue.

In certain countries, it is relatively common for electricity transformer rooms to be placed inside multilevel apartment buildings, adjacent to living areas, usually in the basement or on the first floor. Apartments above or next to such a transformer room usually have an elevated ELF-MF exposure (Hareuveny et al., 2011; Huss et al., 2013; Ilonen et al., 2008; Lagorio and Kheifets, 2014; Röösli et al., 2011; Szabó et al., 2007; Thuróczy et al., 2008; Zaryabova et al., 2013). The Transformer Exposure (TransExpo) study aimed at assembling a cohort of children who had lived in such apartments and compare them to children who had lived in different apartments within the same building. Such children will tend to have similar socioeconomic characteristics and environmental exposures, allowing one to possibly avoid confounding by socioeconomic level and concurrent exposures. This study design also allows for assessment of exposure without requiring subject participation, which may lead to selection bias. Given the rarity of CL and low prevalence of buildings with built-in electrical transformers in most countries, an international effort was needed.

TransExpo is designed to avoid control selection and participation biases that may have affected many previous ELF-MF studies. Its focus on a population with higher than average exposure to ELF-MF is of equal importance. Pilot studies in several countries confirmed that the location of an apartment in relation to the built-in transformer is sufficient to identify higher exposed apartments with suitable specificity and sensitivity (Hareuveny et al., 2011; Huss et al., 2013; Ilonen et al., 2008; Kandel et al., 2013; Röösli et al., 2011; Szabó et al., 2007; Thuróczy et al., 2008). In fact, average exposure in apartments above transformers is 4–10 times higher than background exposures (Hareuveny et al., 2011; Huss et al., 2013; Ilonen et al., 2008; Kandel et al., 2013; Röösli et al., 2011; Szabó et al., 2007; Thuróczy et al., 2008), providing both focus on a group with clearly elevated exposure and a needed exposure contrast among children residing within the same or similar buildings. Fig. 1 presents a 24-h recording in a bedroom of an apartment above a transformer, in one on the same (first) floor as an apartment above the transformer but not directly above the transformer, and in an apartment on an upper floor. Further, information on structural characteristics of transformers, while necessary for predicting magnetic fields, is not needed for classifying apartments above a transformer into low, medium, and high exposure categories (Kandel et al., 2013; Okokon et al., 2014).

In this paper we assess associations between residential proximity to transformers and the risk of CL using data from the TransExpo study involving five countries.

2. Methods

2.1. Study design

TransExpo was envisioned as an international study to capture a sufficient number of potentially highly exposed CL cases. Prerequisites for participation were comprehensive leukemia registries that included reliable address information, the ability to select controls from a comprehensive source such as a population registry, the means to identify residential buildings with built-in transformers, and the possibility of assessing the relative locations of the case and control apartments relative to the transformers without active participation of the subjects.

Thirty-five countries were contacted to explore feasibility of participation in the study. Participation was determined to be infeasible in many countries due to lack of data or difficulties with data access. Other reasons for lack of feasibility included issues with the quality of registries and too few built-in transformers. In several countries, feasibility evaluation was promising and exposure assessment pilot work was done but did not yield data for the main study due to lack of funding, lack of access to transformer data, or other difficulties and delays. In the end, study teams from Finland, Israel, Hungary, The Netherlands, and Switzerland participated in the main study.

A protocol was developed to describe the overall study, identify the data needed, and present eligible study designs (Kheifets et al., 2013). A retrospective cohort study was the design of first choice, but required that the potential participating country had: a substantial number of transformers in residential buildings and addresses of such buildings; a high-quality leukemia (or cancer) registry for a defined calendar period of time; and a population registry or similar complete listing of the residents in the country containing reliable address information at the apartment level, including, ideally, historical data on changes of address, for the defined calendar period. The population registry was to be used to construct the study cohort of children who lived in buildings with transformers, based on a comprehensive list of buildings with transformers. Leukemia cases were to be identified by linking the cohort of children who had ever lived in those buildings to the cancer registry.

The protocol specified that if complete enumeration of the cohort was infeasible but residential history could be reconstructed for a limited number of children from the population registry, a nested case-control design could be used. In this design, controls were randomly selected from the population of children born in the same year as the case (defined as those who lived in a building with a built-in transformer and identified through the cancer registry) and who were known to be cohort members at the age when the case was diagnosed. The controls also lived in buildings with built-in transformers, but not necessarily the same buildings as the corresponding cases. In this scenario, project investigators would identify the apartment within the building where each case or control lived to get exposure information.

For countries with comprehensive cancer and population registries

but for which a complete linkage was not feasible, a neighborhood matched case-control design, which focused on buildings with transformers, offered an alternative. In this design, for each case that lived in an apartment building with a built-in transformer, a list of building residents where the case lived during the year of the case's diagnosis must have been available or able to be constructed. Children on this list were then used as controls.

2.1.1. Cases

All countries relied on leukemia registries covering the whole country with completeness of over 95% (Moore et al., 2021; Pukkala et al., 2018; Schindler et al., 2015; Schuler, 1999; Török et al., 2002). CL cases were <15 years of age based on International Classification Disease Codes Version 10 (ICD-10) codes C91–C95 or equivalent.

2.1.2. Building inclusion criteria

A priori criteria that defined which buildings could be included in the study were: a residential building that contained a built-in transformer, not in structures separate from the main building; and the building needed to have a potentially exposed apartment, e.g., the transformer could not be in the basement with no apartments directly above or adjacent. Since a list of transformer locations was needed, the transformers needed to have detailed address locations, generally obtained from electric utility companies. Locations of transformers within the buildings were further verified through records or visits.

2.1.3. Exposure classification

Pilot studies to develop exposure assessment for the study were conducted in each country. Extensive measurements (spot measurements at the perimeter and center of every room and 24-h measurements in the bedroom) were done in selected apartments and did not involve included cases and controls (Hareuveny et al., 2011; Huss et al., 2013; Ilonen et al., 2008; Röösli et al., 2011; Thuróczy et al., 2008). Using a protocol based on the country-specific pilot work, apartments were classified blind to case/control status as: 1 = above the transformer room, 2A = sharing a wall with the transformer room; 2B = same floor as apartment in 1 and sharing a corner or an edge with the transformer room; 3 = same floor as apartment in 1, 2A, 2B; 4 = directly above apartment in 1; 5 = other apartment. Fig. 2 provides a diagrammatic cross-section of a building with the transformer room on the first floor and apartment classifications relative to it.

These categories were further collapsed into high exposure (1, 2A), intermediate exposure (2B, 3, 4), and unexposed (5). Table 1 provides average exposures and exposure ranges in different exposure categories by country.

The exact location of residences of cases and controls relative to the transformer room was identified based on blueprints in Finland. In all other countries this was determined by on-site visits in combination with Google street-view assessment. Exposure assessment was done blind to the case/control status.

2.2. Statistical analyses

Each subject's exposure was coded as unexposed, intermediate or high based on their highest attained exposure during their residential history in transformer buildings. Due to the small number of highly exposed cases, we repeated the analyses combining the intermediate and high categories.

The planned approach was to pool the data for all countries. All studies used a case-control design except for Finland, for which a cohort design was possible. Due to its comprehensive nature, we used the Finnish data to explore assumptions and evaluate the potential impact of the design and analysis choices made in other countries. We then constructed a nested case-control study for the Finnish data to enable data pooling. In the nested case-control study, all cases that occurred in the cohort were identified and, for each, all controls matched on birth year were selected from among those in the cohort who had not developed the disease by the time of disease diagnosis in the case.

The main statistical method was conditional logistic regression accounting for the matching. However, some sets were dropped from the conditional logistic models due to sparse data, and in some analyses, a small number of sets were highly influential. Therefore we repeated the analyses using mixed logistic regression controlling for diagnosis age (dichotomized at <5 or ≥ 5 years) with a random effect for set and fixed effect for country, which retains all subjects with exposure information

5	5	5	5	5
5	5	4	5	5
3	2B	1	2B	3
3	2A	Transformer	2A	3

Fig. 2. Cross-section of a building with apartment classifications.

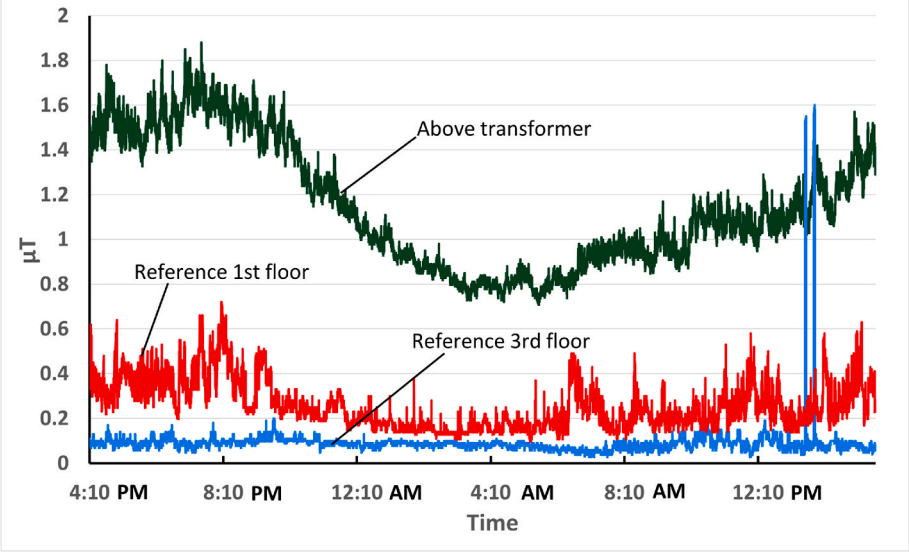

Fig. 1. 24-Hour magnetic field measurements by apartment location.
Based on data measured by Ilonen et al. (2008).

Table 1
Exposure (μT) by apartment location relative to transformer room from the TransExpo pilot studies: Mean (range).

Country	N	High Exposure: Above Transformer/Adjacent	N	Intermediate Exposure: Same Floor/Shares Corner or Edge[a]	N	Unexposed: Other Floors/ Farther Away[b]
Finland (Ilonen et al., 2008)	30	0.58 (0.17–1.55)	28	0.16 (0.03–0.62)	27	0.10 (0.02–0.70)
Israel (Kandel et al., 2013)	10	0.34 (0.07–0.73)	6	0.07 (0.03–0.11)	19	0.07 (0.01–0.13)
Hungary (Szabó et al., 2007; Thuróczy et al., 2008)	31	1.01 (0.06–4.61)	27	0.18 (0.02–1.46)	30	0.06 (0.01–0.15)
The Netherlands (Huss et al., 2013)	11	0.42 (0.11–1.19)	4	0.14 (0.07–0.28)	20	0.07 (0.03–0.13)
Switzerland (Röösli et al., 2011)	8	0.59 (0.16–1.30)	10	0.14 (0.03–0.44)	3	0.07 (0.02–0.20)

N, number of apartments with measurements.
[a] In Israel, apartments directly above apartment above transformer are in the "intermediate" category.
[b] In The Netherlands, apartments on the same floor but not sharing a corner or edge with the transformer room are in the "unexposed" category.

and also yields a shrinkage or partial-pooled estimate that limits the potential for undue influence (Agresti et al., 2000). We also used exact logistic regression and Bayesian logistic regression with noninformative prior for comparison. In the Switzerland data, there were 2 cases and 2 controls for which exposure status was uncertain but a probability of intermediate exposure was estimated (see Supplement). As sensitivity analysis, to assess the potential impact of these observations, the analyses were reconducted including "worst-case" scenarios for these observations, specifically, (1) with the two cases categorized as exposed (intermediate exposure) and the two controls categorized as not exposed and (2) with the two controls categorized as exposed (intermediate exposure) and the two cases categorized as not exposed. Statistical analyses were conducted using Stata/SE 17.0.

3. Results

The availability of information differed from country to country, leading to a need for different study design approaches. Table 2 summarizes methodologic details for each country; additional country-specific methodologic details are presented in the supplementary material.

3.1. Exploring assumptions using Finnish data

The Finnish data followed a retrospective cohort design, with many of the individual children having lived in multiple apartments in transformer buildings during their residential history. Due to its comprehensive nature, we used Finnish data to explore assumptions and to evaluate the potential impact of the design and analysis choices made in other countries.

In the Finnish cohort study, the follow-up period commenced either from the date of birth or when the child moved into the building with a transformer. It continued until the end of the study (December 31, 2016), 15th birthday, emigration from Finland, the child's death, or the date of leukemia diagnosis, whichever came first. The exposure time began on the date the child moved into a building with a transformer. If the transformer was installed in the building after the start of residence, the follow-up was initiated in the year of transformer installation. For all non-cases, the exposure period ended when the child reached the same age as the index case at the time of diagnosis. In the primary analysis, individuals were categorized as the highest attained exposure category during the pre-diagnosis period. The Finnish cohort included 58,999 children (living in 66,207 residences), out of which 29 children were leukemia cases. Even in a cohort of this size, the number of highly exposed children was small (2 cases and 2396 non-cases in the full cohort).

Table 3 presents results from analyzing the Finnish data as a cohort study using Cox proportional hazards regression modeling and as a nested case-control study using random effects logistic regression. Adjustments for gender, as well as gender and birth year, did not impact results. Therefore, we present unadjusted results. In the proportional hazards model, the hazard ratio (HR) was 0.9 for the intermediate exposure category and 1.8 for the highly exposed category, with wide confidence intervals. To explore potential cohort effects, we stratified the data by tertiles of birth year. There was no clear pattern or consistent trend by birth year for the intermediate exposure category. The numbers were too small for the high exposure category to examine cohort effects. The results obtained from analyzing the data as a nested case-control study were similar to those based the cohort design, suggesting consistency and reliability of our approach.

We conducted several additional analyses using the Finnish data to investigate parameters that influenced exposure estimates (Greenland et al., 2016). In most of our analyses, we started exposure on the move-in data, the installation date of the transformer if that was later than the move-in date, or date of birth. However, installation dates provided by the electric utility companies might not have been completely accurate. In some cases, the year of installation of the transformer was reported several years after the move-in dates. To address this issue, we conducted additional analyses by starting exposure on the move-in date. The results (Table 4) were virtually identical to the main analyses, indicating this discrepancy to be of minor concern.

We also considered the possibility that exposure levels might have decreased after the renovation of transformers in some buildings. In the sensitivity analyses, we ended the exposure time on the date of

Table 2
TransExpo methodologic study details by country.

Country	Follow-up period	Design	Residential history	Number of buildings with built-in transformers	Number of buildings visited[b]	Cases/controls (non-cases)
Finland	1967–2016	Cohort[a]	yes	677	-[c]	29/58,970
Israel	1988–2009	Modified nested case/control	yes	2293	64	5/37
Hungary	1971–2016	Neighborhood matched case/ control	no	4624	35	35/539
The Netherlands	1994–2017	Neighborhood matched case/ control	no	10	10	7/308
Switzerland	1985–2015	Neighborhood matched case/ control	yes	136	30	4/59

[a] A nested case-control study was constructed from the cohort data to facilitate data pooling.
[b] Site visits were conducted at all buildings were cases and controls resided.
[c] In Finland, the location of residences in relation to the transformer room was determined based on blueprints of the buildings, and no site visits were conducted.

Table 3
Sensitivity analyses using Finland TransExpo cohort data.

Exposure (cases/non-cases)	Cohort [Cox regression HR (95% CI)]				Nested case-control [Random effects logistic regression OR (95% CI)]	
	Total	Stratified by birth year				
	(n = 58,999)	1952–1981 (n = 20,429)	1982–1993 (n = 19,246)	1995–1999 (n = 19,324)	Cases/controls	
Unexposed (19/41,524)	1.0	1.0	1.0	1.0	19/13,477	1.0
Intermediate (8/15,050)	0.9 (0.2–3.2)	0.8 (0.1–6.9)	1.2 (0.1–12.8)	0.8 (0.1–7.7)	8/5396	1.1 (0.5–2.4)
High (2/2396)	1.8 (0.2–14.1)	–	–	–	2/844	1.7 (0.4–7.2)

CI, confidence interval; HR, hazard ratio; OR, odds ratio.

renovation to account for this potential decrease, effectively shortening the duration of the exposure period for some individuals. Results remained unchanged (as demonstrated in Table 4), suggesting that considering the date of renovation did not significantly impact our findings.

In our pilot studies, we found that exposure levels differed within an apartment depending on its location within the building relative to the transformer room. In the apartments above the transformer room, we measured higher exposure in the whole apartment. On the other hand, exposure in apartments sharing a wall with a transformer room could vary throughout the apartment. As the magnetic fields decline with distance, rooms adjacent to the wall of the transformer might have higher exposure and other areas within the same apartment might have exposures similar to apartments further away from transformers. As a result, such apartments can fall into either the high or intermediate exposure category. In most of our analyses, we categorized apartments sharing a wall with the transformer room as highly exposed. However, in sensitivity analyses, we reclassified them as belonging to the intermediate exposure category. The results remained materially unchanged with this adjustment, as indicated in Table 4. This suggests that the categorization of these apartments did not significantly impact the overall findings of our study.

For most analyses involving the Finnish data, an individual remained in the highest attained exposure category once they entered that category. However, in the sensitivity analyses, we allowed a child's exposure to increase or decrease as they moved from one apartment to another. This did not materially change the results (Table 4).

Although confounding factors such as other environmental exposures and socioeconomic characteristics are likely to be more homogeneous among transformer building residents than those of persons not living in such buildings, there may be a socioeconomic gradient by floor within buildings with transformers, with apartments above or next to transformers having lower socioeconomic status. To address this possibility, we evaluated risk of CL by floor irrespective of exposure (Table 4). Overall, there was not evidence of a gradient in CL risk by floor level. The estimated risk of childhood leukemia was slightly higher on the floors adjacent to the transformers compared to the highest floors (4th floor and above) but the point estimate for risk was even higher for floors 2–3 levels above the transformers.

3.2. Pooled analyses

To address the limitations posed by small sample sizes in individual countries, the *a priori* planned approach was to pool the results for all countries, to allow for a larger sample size, potentially providing more robust and reliable estimates. The pooled results are presented in Table 5. Risk estimates from a conditional logistic model that utilized the matching, the *a priori* planned main analysis, were not elevated. Adding adjustment for age at diagnosis and/or sex did not change results. Five sets (50 subjects) were dropped from the conditional logistic model due to concordant outcomes within these sets. Therefore we also fit a random effects logistic model that avoided dropping observations. This model estimated risks of 1.3–1.4 for the intermediate and high exposure categories (Table 5). Results using exact logistic regression and Bayesian logistic regression with noninformative priors were similar to those for random effects logistic regression (results not shown). When the intermediate and high exposure categories were combined, the risk estimates were similar to those for the separate categories.

In sensitivity analysis including four subjects (2 cases and 2 controls) from the Switzerland data who had uncertain exposure status but an estimated probability of intermediate exposure (see Supplement), when the 2 cases were categorized as intermediate exposure and the 2 controls as unexposed (an unlikely worst-case scenario), for the conditional logit,

Table 5
Odds ratios (95% CI) by exposure category in pooled analysis, TransExpo study of childhood leukemia and proximity to built-in residential transformers.

Exposure category	Cases/ Controls	Conditional logistic	Cases/ Controls	Random effect logistic
Unexposed	56/14,124	1.0	57/14,169	1.0
Intermediate	15/5461	1.02 (0.54, 1.91)	16/5464	1.39 (0.77, 2.52)
High	3/858	1.09 (0.32, 3.76)	3/858	1.32 (0.39, 4.42)
Intermed/high combined	18/6319	1.03 (0.57, 1.85)	19/6322	1.38 (0.79, 2.41)

Conditional logistic regression utilized the matched sets. Random effect logistic regression included a random effect for matched set and controlled for age at diagnosis and country as fixed effects. In the conditional logistic model, 5 sets (50 observations) were dropped due to all positive or all negative outcomes.

Table 4
Effect of Changes of Exposure Assignment in TransExpo Study of Childhood Leukemia and Proximity to Built-In Residential Transformers [Cox regression HR (95% CI)] (n = 58,999).

Exposure	Exposure time starts on move-in date	Exposure decreases on renovation date	Intermediate exposure for apartments sharing wall with transformer room	Exposure increases and decreases as subject moves apartments	Analyses by floor[a]
Unexposed n cases = 19/ non-cases = 41,524	1.0	1.0	1.0	1.0	1.0
Intermediate n cases = 8/ non-cases = 15,050	0.9 (0.2–3.2)	0.9 (0.2–3.2)	0.9 (0.2–3.2)	0.6 (0.1–2.6)	1.5 (0.4–5.9)
High n cases = 2/non-cases = 2396	1.8 (0.2–14.1)	1.8 (0.2–13.9)	2.0 (0.3–15.4)	1.7 (0.2–13.6)	1.2 (0.2–5.9)

[a] Unexposed = 4th floor or higher; intermediate exposure = Floors 2–3; high exposure = Floor 0-1.

the risk estimates were 1.12 (95% CI 0.61, 2.07) and 1.12 (95% CI 0.32, 3.85) for intermediate and high exposure compared to unexposed, respectively, and for mixed logistic regression, the risk estimates were 1.62 (95% CI 0.91, 2.87) and 1.38 (95% CI 0.41, 4.61). When the 2 controls were categorized as intermediate exposure and the 2 cases as unexposed, the results were similar to those from the main analysis.

4. Discussion

Using a novel, multi-country study approach, the TransExpo study aimed to assess associations between residential proximity to transformers and the risk of CL. TransExpo was designed to address the methodological biases inherent in most magnetic field and CL studies to date. TransExpo focused on buildings with built-in transformers to target subjects with higher exposure to magnetic fields, a rare exposure, and CL, a rare outcome. A similar design was used in studies by Khan et al. (2021, 2022), but those focused on adult cancers. These studies suggested that living in apartments above transformers during childhood might be related to acute lymphocytic leukemia and melanoma in adulthood (Khan et al., 2021). Recent population-based case-control study of childhood leukemia in Italy also focused on transformer stations (Malavolti et al., 2023). No overall association with distance to transformer station was found, but there was some evidence for elevated risk of childhood leukemia among children aged $\geq$5 years. It should be noted that exposure in the Italian study differs substantially from ours, as it considers all residences within 15 or 25 m from the center of the transformer as exposed (including transformers outside the buildings), while we consider only residences directly touching the transformer room as exposed. Thus, most of their exposed apartments would be unexposed in our study.

Results from conditional logistic regression, which focused on matched sets, did not support an association between distance from transformer rooms and CL. In other analyses, we found a weak association. As both analyses are based on a very low number of highly exposed cases and the conditional model dropped some observations due to concordant outcomes within sets, these results are not inconsistent. Notably, the risk estimates in our study were very similar for the intermediate and high exposure categories, despite 3–5 fold differences in average exposures between these categories. While the risk estimates were low, given the wide confidence intervals, we cannot exclude that there is a relationship of the magnitude reported in the previous pooled analyses.

The strengths of this study include an *a priori* approach to the design including case ascertainment, study approach, and exposure assignment. Case ascertainment demanded a high quality population-registry, CL registry, and transformer location data in collaboration with electric utility companies. TransExpo was a concerted attempt to minimize the role of selection bias likely present in most ELF-MF CL case-control studies (Mezei and Kheifets, 2006). As such, the country-specific processes for case ascertainment and inclusion criteria for the present study are documented (see supplementary material). Moreover, the TransExpo study protocol was made publicly available prior to actual data analysis allowing for transparency in its approach. The TransExpo study carried out several measurement-based pilot studies to demonstrate the approach used to assign exposure. Pilot studies confirmed with good specificity and sensitivity that the location of an apartment in relation to the built-in transformer is sufficient to identify highly exposed, intermediate and unexposed apartments within buildings. Thus, exposed and referent individuals lived in the same or similar buildings, which minimized variation in potential confounding factors such as socioeconomic status and other environmental exposures such as traffic or pesticide exposure. Furthermore, selection bias was likely avoided as all eligible subjects were included without contacting the residents or obtaining access to the residences. Finally, while either confounding or bias might not be completely eliminated, our novel design makes it likely that any remaining bias or confounding are very different from those in previous power line or ELF-MF studies, most of which used similar designs.

Several countries, including countries where pilot studies were conducted, could not participate due to lack of registry data or information on transformers. In addition, participating countries had to overcome many challenges such as setting up the data sets, identifying cases, selecting controls, verifying locations of transformers, and identifying apartment of cases and controls.

Despite our extensive efforts to include many countries, pilot work, and power calculations, the number of highly exposed cases was very small. This was due to limited access to key data in many countries and inaccurate data on buildings with transformers, including many buildings with detached or outdoor transformers or commercial (non-residential) uses of highly exposed apartments. Further, for the studies that were included, participation required an enormous amount of work that included pilot work, identifying and obtaining access to registries and transformer data, determining feasible designs, gathering and linking data sources and determining exposure (see Supplementary material for details in each country).

Given that apartments classified as unexposed, intermediate and high exposure each had a range of average magnetic field exposure levels (Table 1), our results could have been affected by exposure misclassification. However, sensitivity analyses conducted using the Finnish data found that risk estimates were robust to various changes in the exposure classification scheme.

There may be other factors at play beyond the average magnetic field exposure levels when assessing the risk of childhood leukemia. It is possible that the association between exposure and CL risk might not follow a monotonically increasing relationship, where higher exposure levels necessarily correspond to higher risks. Mechanisms that might lead to a non-classical exposure-response relationship have been proposed (Juutilainen et al., 2018). Due to wide confidence intervals, our results do not exclude any particular form of exposure-response relationship. Other variables, such as individual susceptibility, genetic factors, or additional environmental factors, may contribute to the observed risks, but given our design, this explanation is also unlikely.

Overall, this study did not find consistent evidence of an elevated risk, but due to small numbers and wide confidence intervals, a risk of the magnitude observed in power lines studies cannot be excluded. There is a need for further investigation into the relationship between exposure to transformers and the risk of childhood leukemia. Implementation of similar designs in other countries is likely to be informative but challenging.

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Human subjects review approval

This registry based study that did not involve contact with human subjects received IRB approval from University of California. Country specific IRB approvals were received as needed. In the Netherlands, the Medical Research Ethics Committee of the University Medical Center Utrecht confirmed that ethical review for this study was not necessary (protocol number 19–566/C). The Finnish study protocol was reviewed and approved by the Ethical Committee of the University of Eastern Finland (statement 4/2017). In Switzerland, the Ethics Committee of the Canton of Bern confirmed that ethical review of this study was not necessary (protocol numbers: Req-2017-00634, PB-2017-00095).

CRediT authorship contribution statement

Catherine M. Crespi: Writing – review & editing, Writing – original draft, Formal analysis. **Madhuri Sudan:** Writing – review & editing,

Writing – original draft, Methodology, Formal analysis. **Jukka Juutilainen:** Writing – review & editing, Conceptualization. **Päivi Roivainen:** Writing – review & editing, Methodology, Data curation. **Ronen Hareuveny:** Writing – review & editing, Methodology, Data curation. **Anke Huss:** Writing – review & editing, Methodology, Data curation. **Shaiela Kandel:** Writing – review & editing, Methodology, Data curation. **Henrike E. Karim-Kos:** Writing – review & editing, Data curation. **György Thuróczy:** Writing – review & editing, Methodology, Data curation. **Zsuzsanna Jakab:** Writing – review & editing, Data curation. **Ben D. Spycher:** Writing – review & editing, Methodology, Data curation. **Benjamin Flueckiger:** Writing – review & editing. **Roel Vermeulen:** Writing – review & editing. **Ximena Vergara:** Writing – review & editing, Writing – original draft, Methodology. **Leeka Kheifets:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: XPV is a former employee of the Electric Power Research Institute. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2024.118459.

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