Title
Methodologic Issues in the Studies of Childhood Leukemia and Overhead Power Lines

Author
Amoon, Aryana Turandot

Publication Date
2019

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

Methodologic Issues in the Studies of Childhood Leukemia and Overhead Power Lines

A dissertation submitted in partial satisfaction of the requirements

for the degree Doctor of Philosophy in Epidemiology

by

Aryana Turandot Amoon

2019

ABSTRACT OF THE DISSERTATION

Methodologic Issues in the Studies of Childhood Leukemia and Overhead Power Lines

by

Aryana Turandot Amoon

Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2019

Professor Leeka I. Kheifets, Co-Chair

Professor Onyebuchi Aniweta Arah, Co-Chair

Aims: While studies have consistently found an association between childhood leukemia risk and magnetic fields, similar associations between childhood leukemia and distance to overhead power lines suggest that other factors associated with magnetic fields and proximity to overhead power lines may be responsible for observed associations including bias, confounding, or other methodologic challenges, particularly when it comes to residential mobility and dwelling type.

Methods: First, we pooled data from multiple studies to assess the association with distance and evaluate whether it is due to magnetic fields or other factors associated with distance from lines. We then analyzed a single study from California to assess predictors of residential mobility between birth and diagnosis, and account for potential confounding due to residential mobility. Next, we simulated a synthetic dataset based on that study and used it to assess the sensitivity of

electromagnetic field (EMF)-leukemia associations to different scenarios of uncontrolled confounding by mobility under two major hypotheses of the infectious etiology of childhood leukemia; then used the findings to conduct sensitivity analysis and empirically offset the potential bias due to unmeasured mobility in the actual California study. Finally, we assessed whether dwelling type is a risk factor for childhood leukemia, what covariates are related to dwelling type, whether dwelling type behaves as a confounder or as a potential effect measure modifier in the EMF-leukemia relationship.

Results: Although we found no material association between childhood leukemia and distance to nearest overhead power line of any voltage, there was a slight increase in risk of leukemia among children living <50 m from 200+ kilovolt power lines, consistent with some previous findings. There was no association found with calculated magnetic fields in this set of studies, however, and odds ratios (ORs) remained unchanged with adjustment for potential confounders in the pooled analysis.

In the California study, we found that mobility was strongly associated with age, dwelling type, and SES. Both EMF-leukemia associations were stronger in the stratum of non-movers, too, but adjustment for proxy variables had no effect. In the hybrid-simulation study, as expected, the stronger the assumed relationship between mobility and exposure and outcome, the greater the potential bias. However, no scenario created a bias strong enough to completely explain away previously observed associations. In all mobility analyses, only dwelling type seemed to affect the relationship based on a small subset of subjects, However, when expanded to a larger subset, dwelling type was neither associated with childhood leukemia risk, nor functioned as a confounder. Stratification revealed potential effect measure modification by dwelling type only.

Conclusion: Although uncontrolled confounding by residential mobility had some impact on the estimated effect of EMF exposures on childhood leukemia, it is unlikely to be the primary explanation for the associations observed between power lines exposure and childhood leukemia. Similarly, dwelling type does not appear to play a significant role as either a risk factor or confounder. Future research should explore the role of dwelling and mobility as an effect measure modifier and potential interaction effects.

The dissertation of Aryana Turandot Amoon is approved.

Catherine Crespi-Chun

Zuofeng Zhang

Onyebuchi Aniweta Arah, Committee Co-Chair

Leeka I. Kheifets, Committee Co-Chair

University of California, Los Angeles

2019

DEDICATION

This dissertation is dedicated to my parents, who have always supported me.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

EMF	Electromagnetic Fields
MF	Magnetic Fields
SES	Socioeconomic Status
OR	Odds Ratio
CI	Confidence Interval
CAPS	California Power Line Study

ACKNOWLEDGMENTS

I could not have completed this dissertation without the help of the following people:

First, I would like to express my sincere gratitude to my co-chairs Dr. Leeka Kheifets and Dr. Onyebuchi Arah, without whom I would certainly still be lost. Dr. Kheifets accepted me as her student and has given me patience, motivation, and access to her immense knowledge and world of expertise. I know I gave her some headaches, but I am immensely grateful for her guidance, advice, and frequent nudges. Dr. Arah, too, has been an incredible mentor and, also with great patience, taught me so much during my years of research. I could not imagine a better duo to be my mentors and advisors during my Ph.D study. I would also like to thank the other members of my dissertation committee: Dr. Catherine Crespi and Dr. Zuo-Feng Zhang, for their mentorship, patience, understanding, and encouragement.

In addition to my committee, I would like to thank my wonderful friend, Dr. Chenxiao Ling, who I started the program with back in 2013 and who has supported me ever since. I would also like to thank Dr. Madhuri Sudan, Dr. Yongfu Yu, and Dr. Roch Nianogo for their assistance and patience with my SAS coding. I am also grateful for my colleagues, friends, and family who offered me help when I was struggling.

This work would not have been possible without the financial support of UCLA graduation division and the department of Epidemiology at the Fielding School of Public Health. Special thanks are due to our department's student affairs office Joy Miller, who has answered every silly question I have had over the past six years.

Finally, I would not be here, at the end of my Ph.D dissertation, without the love and support from my parents, who have been there for me from the very beginning.

Chapter 2 is a version of: Amoon, A.T., Crespi, C.M., Ahlbom, A., Bhatnagar, M., Bray, I., Bunch, K., Clavel, J., Feychting, M., Hemon, D., Johansen, C., Kreis, C., Malagoli, C., Marquant, F., Pedersen, C., Raaschou-Nielsen, O., Roosli, M., Spycher, B., Sudan, M., Swanson, J., Tittarelli, A., Tuck, D., Tynes, T., Vergara, X., Vinceti, M., Wunsch Filho, V., & Kheifets, L. (2017). Proximity to overhead power lines and childhood leukemia: An international pooled analysis. *British journal of cancer, 119*(3), 364-373. DOI: 10.1038/s41416-018-0097-7. Dr. Crespi helped with the analyses and drafting the manuscript. Dr.s Kheifets, Swanson, and Vergara conceived of the work. Dr. Kheifets designed the study, acquired data, and played a key role in interpreting the results. Dr. Sudan and Megha helped collect, organize, and clean the data. Everyone else provided data. All authors played a role in interpretation of results, revised the manuscript and approved the final version.

Chapter 3 is a version of: Amoon, A. T., Oksuzyan, S., Crespi C. M., Arah, O. A., Cockburn, M., Vergara, X., & Kheifets, L. (2017). Residential mobility and childhood leukemia. *Environmental research, 164*, 459-466. DOI: 10.1016/j.envres.2018.03.016. Dr.s Cockburn, Oksuzyan, Vergara, and Kheifets conceived of the work. Dr.s Oksuzyan, Crespi, and Arah helped with analysis. All authors played a role in interpretation of results and revising the manuscript.

Chapter 4 is a version of: Amoon, A. T., Arah, O. A., Kheifets, L. (submitted 2019). The sensitivity of reported effects of EMF on childhood leukemia to uncontrolled confounding by residential mobility: a hybrid simulation study and an empirical analysis using CAPS data. Manuscript submitted for publication. Dr. Arah helped conceive the idea and analysis plan. Both Dr.s assisted in interpretation of results and revising of the manuscript.

Chapter 5 is a version of: Amoon, A. T., Crespi C. M., Nguyen, A., Zhao, X., Vergara, X., & Kheifets, L. (2019). The role of dwelling type in the California Power Line Study of childhood leukemia. Manuscript in preparation for publication. Dr.s Vergara and Kheifets conceived the work. Dr. Crespi, Andrew and Xinyu obtained the dwelling samples. Dr.s Kheifets and Crespi assisted in development of an analysis plan and interpretation of results. All authors read, revised and approved the manuscript.

VITA

EDUCATION

M.P.H. Epidemiology — 2015
University of California, Los Angeles

B.A. Psychology — 2013
University of California, Berkeley

A.A. Social Science — 2010
Ohlone College

WORK EXPERIENCE

Teaching Assistant/Special Reader — 2014-2019
Department of Epidemiology, UCLA

Energy and Environment Intern — 2017
Electric Power and Research Institute

Clinical Evidence Analyst — 2015-2017
Doctor Evidence, LLC.

PUBLICATIONS

- Kheifets, L., Crespi, C. M., Hooper, C., Cockburn, M., **Amoon, A. T.**, & Vergara, X. P. (2017). Residential magnetic fields exposure and childhood leukemia: a population-based case–control study in California. *Cancer Causes & Control, 28*(10), 1117-1123.
- **Amoon, A. T.**, Crespi, C. M., Ahlbom, A., Bhatnagar, M., Bray, I., Bunch, K. J., … Kheifets, L. (2017). Proximity to overhead power lines and childhood leukemia: An international pooled analysis. *British journal of cancer, 119*(3), 364-373.
- **Amoon, A. T.**, Oksuzyan, S., Crespi C. M., Arah, O. A., Cockburn, M., Vergara, X., & Kheifets, L. (2017). Residential mobility and childhood leukemia. *Environmental research, 164*, 459-466.
- **Amoon, A. T.**, Arah, O. A., Kheifets, L. (2019). The sensitivity of reported effects of EMF on childhood leukemia to uncontrolled confounding by residential mobility: a hybrid simulation study and an empirical analysis using CAPS data. Manuscript submitted for publication.
- **Amoon, A. T.**, Crespi C. M., Nguyen, A., Zhao, X., Vergara, X., & Kheifets, L. (2019). The role of dwelling type in the California Power Line Study of childhood leukemia. Manuscript submitted for publication.

CONFERENCE PRESENTATIONS

- **Amoon, A. T.** & Kheifets, L. (2018). International pooled analysis of proximity to power lines and childhood leukemia. BioEM Conference. Portorož, Slovenia, June 24-29, 2018.
- **Amoon, A. T.** & Kheifets, L. (2018). Residential mobility and childhood leukemia analysis in California Power Line Study. BioEM Conference. Portorož, Slovenia, June 24-29, 2018.

1 Introduction

1.1 Childhood Leukemia

Childhood leukemia is the most common childhood cancer, affecting 51/1,000,000 children in the United States annually (SEER, 2018) and anywhere from 35/1,000,000 to 60/1,000,000 children annually in Europe (World Health Organization, 2014). There are two main types of childhood leukemia: acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). ALL accounts for about 75% of all childhood leukemia cases with peak incidence occurring between ages 2 and 4, while AML, the second most common type, has greater incidence in the first two years of life followed by the teenage years (American Cancer Society, 2015; SEER, 1999). Chronic leukemia is rare in children. Incidence of childhood leukemia, particularly ALL, has increased slightly over the past century (Cancer Research UK, 2014; SEER, 1999; Svendsen, Feychting, Klaeboe, Langmark, & Schuz, 2007) but cannot be explained by improved diagnosis alone (Barrington-Trimis et al., 2017; Dalmasso et al., 2005; Linet, Ries, Smith, Tarone, & Devesa, 1999; Shah & Coleman, 2007).

Risk factors known to be associated with leukemia include age, sex, race/ethnicity, and socioeconomic status (SES) (Borugian et al., 2005; Oksuzyan et al., 2015a). In addition to variation in leukemia incidence by age, boys are more likely to develop leukemia than girls, and whites have higher incidences of ALL than African Americans (Belson, Kingsley, & Holmes, 2007). SES has been shown to be associated with both increased and decreased risk, depending on the surrogate measure used: studies using individual-level measures that often required some direct contact with subjects showed that lower SES was related to greater risk of leukemia, whereas record-based studies, which often used community-based measures of SES showed greater risk with higher SES (Poole, Greenland, Luetters, Kelsey, & Mezei, 2006). However, when comparing four different

surrogate measures captured in the same records-based study, no differences were found, as well as no association with childhood leukemia (Oksuzyan et al., 2015b), suggesting previous studies were influenced by selection bias.

There are also known genetic risk factors; those with Down's Syndrome (Hitzler & Zipursky, 2005) and Li-Fraumeni syndrome (F. P. Li et al., 1988) are at substantially increased risk of leukemia. Ionizing radiation, a known carcinogen, is an also established risk factor for leukemia (Hsu et al., 2013). Other factors are suspected, but not conclusively linked to higher incidence, including factors related to immune systems (Schuz, Kaletsch, Meinert, Kaatsch, & Michaelis, 1999), postnatal infections (McNally & Eden, 2004; O'Connor & Boneva, 2007) and electromagnetic fields (Kheifets & Swanson, 2014).

1.2 Electromagnetic fields

Electromagnetic fields, a form of non-ionizing radiation, have been classified as a Group 2B: possible human carcinogen (International Agency for Research on Cancer, 2002; World Health Organization, 2007). Over 40 retrospective epidemiologic studies have been conducted to assess the possible effect of magnetic fields on childhood leukemia risk, most of which use a surrogate measure for the assessment of historical exposure: either with wire codes (London et al., 1991; Savitz, Wachtel, Barnes, John, & Tvrdik, 1988; Wertheimer & Leeper, 1979), using present day measurements (Green et al., 1999; Kabuto et al., 2006; Linet et al., 1997; McBride et al., 1999), or using historical load and other information to calculate magnetic fields (Bunch, Swanson, Vincent, & Murphy, 2016; Feychting & Ahlbom, 1993; Kroll, Swanson, Vincent, & Draper, 2010; Pedersen, Johansen, Schuz, Olsen, & Raaschou-Nielsen, 2015; Tynes & Haldorsen, 1997; Verkasalo et al., 1993).

Pooled analyses show that greater magnetic fields, above 0.3 or 0.4 microTesla (μT), are associated with a small, but consistent, increase in the risk of childhood leukemia (Ahlbom et al., 2000; Greenland, Sheppard, Kaune, Poole, & Kelsh, 2000; Kheifets et al., 2010; Schuz et al., 2007). Kheifets et al. also looked at distance from nearby overhead power lines as another surrogate measure, and found comparable trends as for MF (Kheifets et al., 2010). Other studies assessing distance found similar results (Crespi et al., 2016; Draper, Vincent, Kroll, & Swanson, 2005; Kabuto et al., 2006; Sermage-Faure et al., 2013). However, distance is known to be a poor predictor of MF exposure (Feychting & Ahlbom, 1994), and therefore the question arises as to whether the association of increased childhood leukemia risk with distance is due to MF or to other factors associated with distance from overhead power lines that are unrelated to long-term average MF. Unlike MF, prior to this work, there was not a comprehensive pooled analysis on childhood leukemia and distance to power lines, which could help to answer this question.

It is also important to consider the role of other factors which may affect the MF-leukemia relationship, either as an unconsidered/unmeasured confounder, through exposure misclassification, through affecting selection into studies, or even by effect measure modification. Two such factors are residential mobility and dwelling type. As often, only one home is analyzed in studies of residential exposures, the period of assessment may be etiologically irrelevant, or the exposure can be misclassified if the home captured was barely lived in (Urayama et al., 2009). The type of home may also affect not only the level of exposure (Brix, Wettemann, Scheel, Feiner, & Matthes, 2001; Calvente et al., 2014; Schuz, Grigat, Brinkmann, & Michaelis, 2001; Schuz et al., 2000; Tomitsch, Dechant, & Frank, 2010), but also assessment (Feychting & Ahlbom, 1993; Vergara et al., 2015) of such exposure. Both mobility and dwelling type are related to SES (McCarthy, Rohe, & van Zandt, 2001; Urayama et al., 2009), which has been shown to be

associated with participation in studies where direct subject involvement is required (Mezei & Kheifets, 2006).

The purpose of this dissertation is to quantify and describe the association between overhead power lines and childhood leukemia as well as to examine how residential mobility and dwelling type can influence this relationship. First, we provide a comprehensive assessment of the association between childhood leukemia and distance to overhead power lines not attempted previously by pooling together 11 studies from 10 countries. We also assessed whether such an association could be due to MF or other factors, and further consider whether bias, confounding, or other methodologic challenges have substantial influence on the results. Next, we dive further into the role of residential mobility, using the California Power Line Study (CAPS) to first describe what factors affect mobility and use them as proxies to adjust for, and evaluate, potential confounding due to residential mobility. As residential mobility was only available for cases, we devised a hybrid simulation study (Sudan, Arah, Olsen, & Kheifets, 2016) to further assess the impact of unmeasured residential mobility on EMF-leukemia associations using different scenarios of uncontrolled confounding by mobility. Finally, we look at the influence of dwelling type in the MF-leukemia relationship using CAPS to determine what covariates are related to dwelling type and examine whether dwelling type behaves as a confounder or an effect measure modifier in the MF-leukemia relationship.

2 Proximity to Overhead Power Lines and Childhood Leukaemia: An International Pooled Analysis

Authors: Aryana T Amoon, Catherine M Crespi, Anders Ahlbom, Megha Bhatnagar, Isabelle Bray, Kathryn J Bunch, Jacqueline Clavel, Maria Feychting, Denis Hémon, Christoffer Johansen, Christian Kreis, Carlotta Malagoli, Fabienne Marquant, Camilla Pedersen, Ole Raaschou-Nielsen, Martin Röösli, Ben D Spycher, Madhuri Sudan, John Swanson, Andrea Tittarelli, Deirdre M Tuck, Tore Tynes, Ximena Vergara1, Marco Vinceti, Victor Wünsch-Filho, and Leeka Kheifets

2.1 Abstract

Background: While studies have consistently found an association between childhood leukemia risk and magnetic fields, the associations between childhood leukemia and distance to overhead power lines have been inconsistent. We pooled data from multiple studies to assess the association with distance and evaluate whether it is due to magnetic fields or other factors associated with distance from lines.

Methods: We present a pooled analysis combining individual-level data (29,049 cases and 68,231 controls) from 11 record-based studies.

Results: There was no material association between childhood leukemia and distance to nearest overhead power line of any voltage. Among children living <50 m from 200+ kilovolt power lines, the adjusted odds ratio for childhood leukemia was 1.33 (95% CI: 0.92-1.93). The odds ratio was higher among children diagnosed before age 5 years. There was no association with calculated magnetic fields. Odds ratios remained unchanged with adjustment for potential confounders.

Conclusion: In this first comprehensive pooled analysis of childhood leukemia and distance to power lines, we found a small and imprecise risk for residences <50 m of 200+ kilovolt lines that was not explained by high magnetic fields. Reasons for the increased risk, found in this and many other studies, remains to be elucidated.

2.2 Introduction

Thirty-five epidemiologic studies have examined the association between exposure to extremely low frequency magnetic fields (MF) and childhood leukemia (Kheifets & Swanson, 2014). Analyses that have pooled data from multiple studies (Ahlbom et al., 2000; Greenland et al., 2000; Kheifets et al., 2010; Schuz et al., 2007) report a small but consistent increased risk of childhood leukemia associated with exposures above 0.3 or 0.4 microTesla (μT). In one of these analyses, Kheifets et al. (Kheifets et al., 2010) pooled six studies for an analysis of the association between distance from power lines and childhood leukemia. They found an odds ratio (OR) of 1.59 (95% CI: 1.02-2.50) for the closest distance category, which was comparable to the result for MF. High MF can occur close (e.g. <100 meters (m)) to high voltage power lines (Vergara et al., 2015). However, distance is known to be a poor predictor of MF exposure (Feychting & Ahlbom, 1994), and therefore the question arises as to whether the association of increased childhood leukemia risk with distance is due to MF or to other factors associated with distance from overhead power lines that are unrelated to long-term average MF. Unlike MF, there has not yet been a comprehensive pooled analysis on childhood leukemia and distance to power lines, which could help to answer this question.

Draper et al., reporting on a study in the United Kingdom (UK) using diagnosed cases from 1962-1995, found an association between childhood leukemia and the distance between home address at birth and the nearest high voltage overhead line (Draper et al., 2005) with the apparent risk extending out to 600 m, a distance greater than would be expected for MF from high voltage lines because MF rapidly decline with distances and are very weak at distances beyond 100 m (Burgi, Sagar, Struchen, Joss, & Roosli, 2017; Swanson, 2008). Whether the risk truly persists at greater distances from power lines and what might be an explanation for this observation is unclear.

Several explanations have been proposed, including selection of controls, but none are fully satisfactory (Kheifets, Feychting, & Schuz, 2005), leaving open the possibility that some factor associated with distance other than MF is responsible.

The Draper et al. study was extended to cover more recent time periods (diagnoses during 1962-2008) and lower line voltages (Bunch et al., 2016). The updated study confirmed the raised leukemia risks reported for the earlier decades, but found that risk declined in the latest decades. A small Danish study of calculated fields also found higher risks in earlier decades (1968-1986) compared to more recent cases (1987-2003) (Pedersen et al., 2015). Two large studies in France and the United States (US), specifically California, reported that living within 50 m of a 200+ kilovolt (kV) line may be associated with a small increased risk of childhood leukemia (Crespi et al., 2016; Sermage-Faure et al., 2013). In these studies, no increase in risk was observed beyond 50 m from 200+ kV lines or within 50 m of lower voltage lines. Both studies covered more recent time periods only (diagnosed in 1988 or later). Thus, the existence of similar temporal trends in risk in other countries is unresolved.

Geographic information systems (GIS), maps, and on-site measurements have all been used to assess proximity to power lines (Blaasaas & Tynes, 2002), each with varying degrees of accuracy. In addition, the point of the home chosen for the start of measurement of the distance varied from study to study; some used the center of the building (Verkasalo et al., 1993), while others used the corner closest to the power line (Feychting & Ahlbom, 1993; Tynes & Haldorsen, 1997) or where the mailbox was located (Sermage-Faure et al., 2013). Some studies identified observations with poor geocoding accuracy and excluded them from analyses. If the association were real, one would expect it to be stronger when data with problematic geocoding are excluded from the analysis. On the other hand, such exclusions might inadvertently introduce bias.

In Sweden (Feychting & Ahlbom, 1993), the MF association with childhood leukemia was limited to single-family homes, although calculated MF levels were somewhat higher in apartments mainly due to fields from sources other than power lines, as verified by spot measurements. This resulted in lower correlation between calculated fields and spot measurements for apartments compared to single-family homes, which may explain why the association between calculated fields and childhood leukemia was limited to homes with better exposure prediction (i.e. single-family homes).

The association between socioeconomic status (SES) and leukemia is complex and varies based on the specific measures used. Individual measures, such as family income, tend to be negatively associated with childhood leukemia in most studies, while ecological measures, such as percent of neighborhood unemployment or deprivation index, tend to be positively associated (Adam et al., 2015; Adam, Rebholz, Egger, Zwahlen, & Kuehni, 2008; Oksuzyan et al., 2015b; Poole et al., 2006). Study participants often differ in SES and other factors from non-participants, possibly resulting in selection bias (Mezei & Kheifets, 2006; Slusky et al., 2014; Stiller & Boyle, 1996), but this is less of an issue in the record-based studies that comprise this analysis, which do not require active participation. Indeed, Poole et al. (Poole et al., 2006) argues that individual measures of SES often come from case-control studies requiring participation, whereas ecological measures often come from record-based studies less prone to this bias. Additionally, residence in single-family homes may be associated with higher SES and with various exposures (including both distance and magnetic fields) and thus potentially confound an association.

Power lines may be co-located with other potential risk factors such as motorways or railways, resulting in higher traffic-related air pollution exposure in proximity to power lines (Houot et al., 2015; Langholz, Ebi, Thomas, Peters, & London, 2002), or specifically higher nitrogen dioxide

exposure from traffic (Feychting, Svensson, & Ahlbom, 1998). Several studies have reported associations between childhood leukemia and traffic density, proximity to major roads or highways, or exposure to air pollutants caused by traffic. A meta-analysis by Boothe et al. (Boothe, Boehmer, Wendel, & Yip, 2014) assessing childhood leukemia in relation to multiple pollutants found an increased risk for post-natal exposure but no association with pre-natal exposure. Most studies found an association with childhood leukemia overall, but the association tended to be stronger when examining just acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML) for specific pollutants (Filippini, Heck, Malagoli, Del Giovane, & Vinceti, 2015).

Studies of childhood leukemia and distance from power lines have assessed exposure at the birth home and/or diagnosis home. The critical time-period of exposure for a potential effect on leukemia development is unknown, and it is unclear whether birth home or diagnosis home is more representative of a child's lifetime exposure and/or which exposure period is more relevant biologically. Of course, the former depends on the pattern of movement of the family between pregnancy and diagnosis. Residential mobility can manifest as selection bias, confounding, or increased measurement error, or it could also be a potential risk factor (Kheifets, Swanson, Yuan, Kusters, & Vergara, 2017).

There are many unresolved issues regarding the association between childhood leukemia risk and distance from overhead power lines that are difficult to resolve in any single study. In this paper, we pool data from multiple studies to provide a more comprehensive assessment of the association between childhood leukemia risk and distance to power lines than previously attempted. We also assess whether the association is due to MF or other factors, and further consider whether bias, confounding, or other methodologic challenges inherent in these studies have substantial influence on the results using available data.

2.3 Methods

Search and Inclusion

The present study is a pooled analysis combining raw individual-level data from multiple studies, sometimes called an individual participant data (IPD) meta-analysis (Debray et al., 2015; Stewart et al., 2012). We searched the published literature through PubMed and a database of MF literature (EMF Portal https://www.emf-portal.org/en) to identify studies on childhood leukemia and proximity to overhead transmission lines. To locate studies potentially missed in our initial searches, we also searched the reference lists in identified papers and conducted an informal survey of epidemiologists involved in MF research. To be included in our analysis, a study must have used record-based exposure assessment, i.e., not requiring active participation of study subjects, with exposure (i.e., distance to power lines) determined at the individual level; thus, studies with ecologic or area-based exposure assessment were excluded. We excluded wire code studies (Fajardo-Gutierrez et al., 1997; Fulton, Cobb, Preble, Leone, & Forman, 1980; Green et al., 1999; Linet et al., 1997; London et al., 1991; McBride et al., 1999; Savitz et al., 1988; Wertheimer & Leeper, 1979). Although wire code studies use distance, they document only the power lines closest to the home, and thus higher voltage power lines might not have been recorded if there were any distribution lines that were closer. Studies with hospital controls were also excluded, because such controls may not be representative of the source population from which cases arose. We identified 21 studies on distance to power lines published between 1993 and 2016, of which 13 met our inclusion criteria (Table 2.1). Eight studies were excluded; reasons for their exclusion are provided in the appendix (Supplementary Table 2.1).

Table 2.1 provides a list of the 13 studies meeting our inclusion criteria along with each study's characteristics and main results. We attempted to obtain data for all 13 studies; however, original

individual data on distance for Finland and Japan were unavailable. The 11 included studies were conducted in 10 different countries: Brazil, Denmark, France, Italy (2 studies in separate regions), Norway, Sweden, Switzerland, Tasmania, the UK, and the US (California). Exposure assessment in Brazil involved interviews with mothers as well as direct MF measurements inside the homes of children. However, the distance data used in our study were calculated using only grid maps for the Metropolitan Region of São Paulo without requiring participant involvement (Wunsch-Filho et al., 2011).

Material

Among the three largest studies, accounting for 88% of all cases and 76% of cases closest to lines, two (UK and US) were based on birth residencies and one (France) on the residence at time of diagnosis; most of the other studies focused on the residence at time of diagnosis in their original publications, but nearly all had some information available on birth homes as well. To focus on populations with higher exposure prevalence, some studies (Norway and Sweden) captured data from the time the child entered an area defined as homes within specified distances to overhead power lines. For Italy 2 we received data for 1998-2013 for the Modena and Reggio Emilia provinces, which is a broader time-period than in their original publication (Malagoli et al., 2010). All studies provided information on sex, age, and SES (with the exception of France with no information on sex for controls), five studies provided information on mobility (whether subjects moved between birth and diagnosis dates), and four studies provided data on type of dwelling and traffic exposure. We collected available MF information to examine potential impact from adjustments for calculated fields on distance. Most studies provided calculated MF (Brazil provided measured fields), while France, Switzerland, and Tasmania had no measured or calculated fields available.

All variables were recoded to make them as compatible as possible. Distance to power lines was coded into four categories as the primary analysis (<50 m, 50-<150 m, 150-<300 m, and ≥300 m as the reference); these cut points were selected based on available data and previous literature. The primary analyses estimated risk of any type of childhood leukemia associated with distance of residence from power lines and was restricted to participants who had study-defined accurate geocoding. A mixture of birth and diagnosis homes was used, based on available data, with the home used in prior publications given preference. We estimated risk for distance from closest overhead power line of any voltage and from closest power line with voltage of 200 kV or greater. Analyses were adjusted for age at diagnosis, sex (except for France where a dummy variable was used), and SES (either individual or ecological, depending on availability), all of which were coded as categorical variables.

Statistical analysis

We used two statistical approaches: one-stage meta-analysis and two-stage meta-analysis (Burke, Ensor, & Riley, 2017). In the one-stage approach, a traditional pooled analysis, data from all studies were entered simultaneously into a single mixed-effects logistic regression model with random intercepts for study. In the two-stage approach, effect estimates (log ORs) were obtained for each study separately and then combined using a random-effects meta-analysis model. A sensitivity analysis using the two-stage approach included Japan and Finland for which only summary data were available. The risk estimate for Finland comes from unpublished data from a previous pooled analysis (Ahlbom et al., 2000) and provided estimates based on living <50 m to any voltage line. For the primary analyses, estimates from these two methods were compared. For all further analyses, we used the one-stage approach.

Additional subgroup, confounder, and sensitivity analyses were performed. We fitted models for various subgroups: comparing subtypes of leukemia (ALL and AML), excluding children with Down syndrome, and comparing subjects younger than five years to those five years or older at diagnosis. To evaluate whether the strength of the association changed over time, we stratified by decade of diagnosis in a manner similar to that of Bunch et al (Bunch, Keegan, Swanson, Vincent, & Murphy, 2014), except that due to small numbers, we grouped the decades as 1960-1980, 1980-2000, and 2000 and later. The latter analysis was conducted both with and without the UK study, because it was the hypothesis generating study.

We examined the effects of confounder adjustments on risk estimates. Confounders examined included residential mobility (moving between the time of birth and diagnosis) for five studies, type of dwelling (single-family home or other) for four studies, traffic exposure (high, medium, or low) for four studies, urban versus rural setting for seven studies, ecological measures of SES for six studies, individual measures of SES for five studies, and MF for eight studies. The latter analysis was performed both with and without Brazil, the only country with measured rather than calculated fields. Completeness of collected confounder information varied across studies; many studies with confounder information had substantial subject-level missing data. We further analyzed the association between childhood leukemia risk adjusting for each confounder individually, controlling for age, sex, and SES. As confounder information was available only for subsets of studies, we present ORs from both minimally adjusted models (adjusted for age, sex, and SES) and models with confounders fit to the same subset of data.

Sensitivity analyses included comparing the association based on birth homes to that in diagnosis homes, as well as the choice of the reference category (e.g. ≥300 m vs. ≥600 m). To assess how geocoding accuracy may result in exposure misclassification, we conducted an analysis of all

observations, regardless of geocoding quality, compared to one including only observations with good geocoding. Finally, we repeated the primary analysis using alternative controls. These analyses used data from studies that assessed other cancers in addition to leukemia (Italy 2, Sweden, Switzerland, Tasmania, UK, and US). We used controls matched to cases of other cancers (central nervous system tumors, lymphoma, and other cancers), and conducted an analysis combining all alternative controls.

Analyses were conducted using SAS 9.3 and Stata 14.2.

2.4 Results

Our pooled data set included 30,200 childhood leukemia cases and 69,594 controls. After restriction to participants with study-defined accurate geocoded distances from overhead power lines to the home, we were left with 97,280 participants (29,049 cases, 68,231 controls). After removing observations with missing data on age, sex, or SES, there were 27,143 cases and 65,265 controls available for the primary analysis. Studies included cases diagnosed as early as 1960s and as late as 2014; a larger percentage of cases and controls came from the time periods between 2000-2015, as shown in Figure 2.1.

Table 2.2 provides results for the primary analysis using the one-stage approach. There was no material association between childhood leukemia and distance to nearest line of any voltage for any distance category. Crude ORs and ORs adjusted for age, sex, and SES were virtually the same. Results were similar when distance of ≥600 m was used as reference (data not shown). For distance to high voltage lines (200+ kV), there was no difference between risk estimates for distances of 50-<150 and 150-<300 m compared to those living 300 m or more away. However, among those living <50 m to a 200+ kV power line, the adjusted pooled OR was 1.33 (95% CI: 0.92-1.93).

Supplementary Figure 2.1 shows the distribution over time of subjects living within 50 m of an overhead power line.

Table 2.3 provides study-specific results and estimates from random effects meta-analysis model based on the two-stage approach. Although the ORs for individual studies for distances <50 m to a 200+ kV power line ranged from 0.56 (UK) to 9.05 (Brazil), the results were sufficiently homogenous for pooling: I-squared 24.6%, p=0.25 (Figure 2.2). Several smaller studies did not have observations in the <50 m to a 200+ kV line category (Table 2.3). The inclusion of estimates from Japan and Finland, for which individual data could not be obtained, only slightly increased the meta-analysis OR. Reassuringly, results of one-stage and two-stage analysis approaches were similar. All further results examine distance to 200+ kV lines and ≥300 m as the reference utilizing one-stage analysis.

An influence analysis showed that removal of studies one at a time had little effect on the pooled estimate, except that the OR increased from 1.33 to 1.58 on removal of the UK study (Supplementary Figure 2.2). The UK study contributed the largest number of participants to the pooled analysis, accounting for over 60% of the cases overall, but only six cases and thirteen controls lived within 50 m of a 200+ kV line.

Subgroup Analyses

When the analysis was restricted to ALL, the results were similar to those found for the primary analysis, with an OR of 1.39 (95% CI: 0.92-2.10) for children living <50 m from a 200+ kV power line compared to those ≥300 m away (Table 2.3). The association was not seen for AML (OR: 0.82; 95% CI: 0.27-2.45). Excluding children with Down syndrome had no effect on the results (data not shown).

In the analysis stratified by age at diagnosis, the association between childhood leukemia and distance <50 m compared to ≥300 m from a 200+ kV line appeared to increase for children diagnosed before age five years (OR: 1.65; 95% CI: 1.02-2.67) (Table 2.4). When examining differences by time-period of diagnosis, we found the highest ORs for the years 1960-1980 for all distance categories, followed by the 2000-2010 in the <50 m category, with virtually null association in the middle decades, 1980-2000 (Table 2.4). When the UK study, which generated the hypothesis of a temporal trend, was excluded from this analysis, ORs were elevated for all time periods in the <50 m category. However, they were imprecisely estimated, with no apparent trend, and the 1960-1980 period was based on small numbers (Supplementary Table 2.2).

Confounder Analyses

Supplementary Table 2.3 provides results for the association of potential confounders with childhood leukemia risk, adjusted for age, sex, and SES. Most potential confounders examined, including traffic, urban versus rural setting, and SES, were not associated with risk of childhood leukemia. Calculated magnetic fields ≥ 0.4 μT were also not related to childhood leukemia (OR: 1.07; 95% CI: 0.65-1.76) in these studies. An association between mobility and leukemia risk was observed; the odds of leukemia among participants who had ever moved between birth and diagnosis was 1.89 times higher than among those who had never moved (95% CI: 1.50-2.38). Participants living in single-family homes had lower odds of leukemia than those living in other types of residences (OR: 0.80; 95% CI 0.61-1.06), but results were imprecise.

Table 2.5 presents ORs for the association between distance from power lines and childhood leukemia risk with and without adjusting for specific potential confounders. Different subsets of studies are included in each analysis due to the availability of variables in the studies. The association between power lines and childhood leukemia was slightly higher among the studies

that included individual measures of SES compared to those with ecological SES measures, but adjusting for SES did not change the observed risk estimates in either subset (Table 2.5). Adjustments for other confounders, including dwelling type, traffic, and urban versus rural setting, also had little impact on the risk estimates. Adjustment for mobility, which was associated with leukemia risk (Supplementary Table 2.3), did not affect the risk estimates either (Table 2.5). Further investigation determined that only two studies, Brazil and Sweden, contributed meaningfully to estimating the OR in this model, and mobility was associated with distance <50 m positively in Brazil and negatively in Sweden, which resulted in an overall lack of association. Adjusting for MF exposure using calculated fields did not materially change the OR for distance <50 m. Including Brazil, the only measurement-based study, in these analyses strengthened the association between proximity to power lines and childhood leukemia from 1.32 to 1.47 (95% CI: 0.83-2.60) when adjusting for MF (Table 2.5), but results were imprecise. Analyses of the association between distance and leukemia risk stratified by various covariates revealed stronger associations with distance for participants who had ever moved and for participants from both single-family homes and other dwelling types, suggesting potential interaction effects between these covariates and proximity to power lines (Supplementary Table 2.4). However, some results were based on small numbers, and the OR for distance among participants who had ever moved was driven by a single study (Sweden). In analysis stratified by MF level, there were too few observations in the category (<0.1 μT and <50 m to 200+ kV line), therefore we used a cut point of <0.2 μT and collapsed eight age categories to three to achieve meaningful comparisons. A raised OR was observed in the ≥0.4 μT stratum, for the <50 m to 200+ kV line category (OR: 6.25; 95% CI: 0.94-41.52), but based on small numbers.

Sensitivity Analyses

The association between distance (<50 m compared to ≥300 m) to 200+ kV power lines and childhood leukemia was stronger for diagnosis homes (OR: 1.78; 95% CI: 1.13-2.81) compared to birth homes (OR: 1.23; 95% CI: 0.79-1.91), although the confidence intervals overlap (Supplementary Table 2.5). This was true even in the subset of studies that had information on both birth and diagnosis homes (Supplementary Table 2.6). When using all available data, including observations with less accurate geocoding, the minimally adjusted model provided an OR of 1.33 (95% CI: 0.92-1.91) for the shortest distance category to a 200+ kV power line (Supplementary Table 2.5), similar to the observed association using only accurately geocoded observations (Table 2.3). In the analysis with all alternative controls, the association weakened in comparison to the one observed in the primary analysis. Results were broadly similar for controls for other cancer types (Supplementary Table 2.5).

2.5 Discussion

We conducted a pooled analysis assessing proximity to overhead power lines and its association with childhood leukemia using individual-level data from 11 case-control studies. We found virtually no increase in risk of leukemia among children who lived within any distance, (including <50 m) to power lines of all voltages combined. We found a small, but imprecise, increase in risk of leukemia among children who lived in homes <50 m from higher voltage (200+ kV) power lines. We found no material association between childhood leukemia and MF in this set of studies. We did not find any association between childhood leukemia and urban versus rural, type of dwelling, traffic density, or SES in this set of studies. Further, adjusting for SES did not alter the associations whether ecological or individual measures of SES were used. Unfortunately, only the US study measured both types of SES, thus we were unable to compare these measures of SES in the pooled analysis. A previous analysis of the US data (Oksuzyan et al., 2015b) found that SES,

as an individual or ecological measure, was not clearly associated with the risk of childhood leukemia or its major subtypes.

Of the potential confounders that we examined, only mobility was associated with childhood leukemia. Brazil obtained some of their data through interviews (however, data included in our main analysis were records-based), and therefore the data on mobility were prone to non-responder bias (9.5% of cases and 12% of controls refused participation). The stratified analyses showed a much stronger association between proximity to power lines and childhood leukemia for those who moved compared to those who never moved, but both strata had small numbers in their highest exposed categories (Supplementary Table 2.4). Given the uncertain relationship between mobility and proximity to power lines, the support for mobility as a confounder appears limited.

We found higher ORs for distance when only studies with information on mobility, type of dwelling, or traffic were included; however, adjustments for these confounders had no effect on the estimates. Thus, these variables did not appear to confound the associations, but rather indicated potential selection of studies with higher ORs for close distance, perhaps due to higher quality of studies with more detailed examination of potential confounders and more accurate geocoding.

Nevertheless, the role of mobility in the studies of childhood leukemia is not fully understood. Assessment of that role is complicated because it might be related to the age of the child, SES, type of housing (single-family vs. apartments), likelihood of successful geocoding, inclusion into the measurement component of the study, or exposure misclassification. Further exploration of the role of mobility on the association between proximity to power lines and childhood leukemia is warranted, whether it is through selection bias, confounding, or measurement error or as a risk factor itself.

In the age-stratified analyses, excess leukemia risk associated with close distance to power lines was limited to the younger age group, for whom any address might be more indicative of lifetime exposure and/or exposure during a critical time period. On the other hand, although we might expect exposure in birth homes to be more representative of exposure during the critical developmental time-period, power line proximity to diagnosis homes was more strongly associated with childhood leukemia than proximity to birth homes. This was the case when all studies were considered and when limiting to studies that had information on both birth and diagnosis homes (Supplementary Table 2.6). Another possible explanation for variation with age is the heterogeneity of childhood leukemia, involving a spectrum of lymphoid and myeloid diseases with different distributions of age at diagnosis and potentially differing etiologies.

We did not confirm a sharp monotonic decline in the association in more recent decades as was suggested by a UK study (Bunch et al., 2016) with some support from the Danish study (Pedersen et al., 2015). When the UK data were excluded, the associations by period of diagnosis were similar (Supplementary Table 2.2). We used tighter distance intervals compared to the UK study closest distance of <200 m, which spans three of our distance categories. Studies in our pooled analysis had little overlap across time periods, and mostly smaller studies contributed cases before 1990 with the non-UK studies in total contributing roughly equal numbers of highly exposed subjects as the UK study in this period. Thus, while we did not confirm the UK finding: excluding UK, there is only a slight suggestion of higher risk in the earliest period, all estimates are too imprecise to draw firm conclusions either way. Due to small numbers, it is difficult to explore this further even in this pooled analysis.

Similarly, other methodologic considerations fail to offer good explanations for the observed association in our study. We only included record-based studies to reduce the possibility of

selection bias in our results (Law, Smith, Roman, & United Kingdom Childhood Cancer Study, 2002). Some studies identified subjects with poor geocoding accuracy and excluded them from analysis. Exposure misclassification due to measurement error and potential selection bias was likely minimal, as the risk estimate did not change when including less accurately geocoded observations, although very little of the poor geocoding occurred at close distances. Similarly, and as expected, use of alternative controls reduced the risk estimates somewhat, but did not suggest strong bias. Once again, this observation may be due to the selection of the set of studies.

In addition to increasing statistical power, IPD meta-analyses (or pooling) allowed us to standardize inclusion criteria and analyses across studies, and conduct analyses that were not done or possible in the individual studies (Burke et al., 2017). Increasing the precision of the estimates is especially important if the possible effect estimate is small, such as the association between proximity to power lines and childhood leukemia. Pooling also strengthened the study with standardization of data across studies, as the definitions of outcome, exposure, and potential confounders varied substantially between individual studies. Particularly problematic were varied definitions of "exposed" and reference categories for distance to power lines used in previous studies of childhood leukemia. Further, pooled analysis enabled consistent application of statistical analyses to all included studies, minimizing bias, and resulting in more stable results.

There are inherent limitations when pooling data. First, the pooled dataset is only as good as the underlying data. Second, each study collected different information, which limited the adjustment and confounder analysis or required excluding studies. Restrictions to smaller subsets of studies in the sensitivity analyses are likely selective and not generalizable to the broader set of data.

Although the studies we have included do not show an association with MF, our results are broadly consistent with previous pooled analyses of MF and childhood leukemia (Ahlbom et al., 2000;

Greenland et al., 2000; Kheifets et al., 2010; Schuz et al., 2007) in that the elevated risk we found was limited to <50 m of a 200+ kV lines, a distance at which MF are more likely to be elevated. On the other hand, the lack of association with MF and the fact that adjusting for MF did not weaken the association for distance supports alternative explanations for the associations observed between residential distance from power lines and leukemia risk, such as other correlates of distance or unmeasured confounders. Furthermore, although we included only record-based studies, which are less prone to bias, our results are somewhat weaker and less precise than that of previous MF pooled analyses, again arguing against MF as an explanation.

In conclusion, we found a small, imprecise association between childhood leukemia and residence located within 50 m of 200+ kV lines, which was stronger for younger children, in our individual-data pooled analysis of 11 studies. This association was not explained by exposure to high MF levels or by other measured confounders. We found no evidence for bias as a potential explanation and in particular, we only included record-based studies, making selection bias unlikely. While exposure misclassification is likely to be present, the risk of bias due to distance misclassification is quite small. The previous UK findings of risk estimates for distances beyond 200 m are not supported by the pooled data from other countries. The decrease in effect over time are not clearly supported by the pooled data from other countries, although numbers of exposed cases and controls for the earlier time period are small for both UK and for other countries combined. While pooled analysis is a powerful approach to integrating data, it is only as good as the underlying data. Reasons for the small yet fairly consistent increase in the risk of childhood leukemia in relation to proximity to power lines found in many studies remain to be elucidated.

Figure 2.1 Distribution of cases and controls, and studies by years of diagnosis.

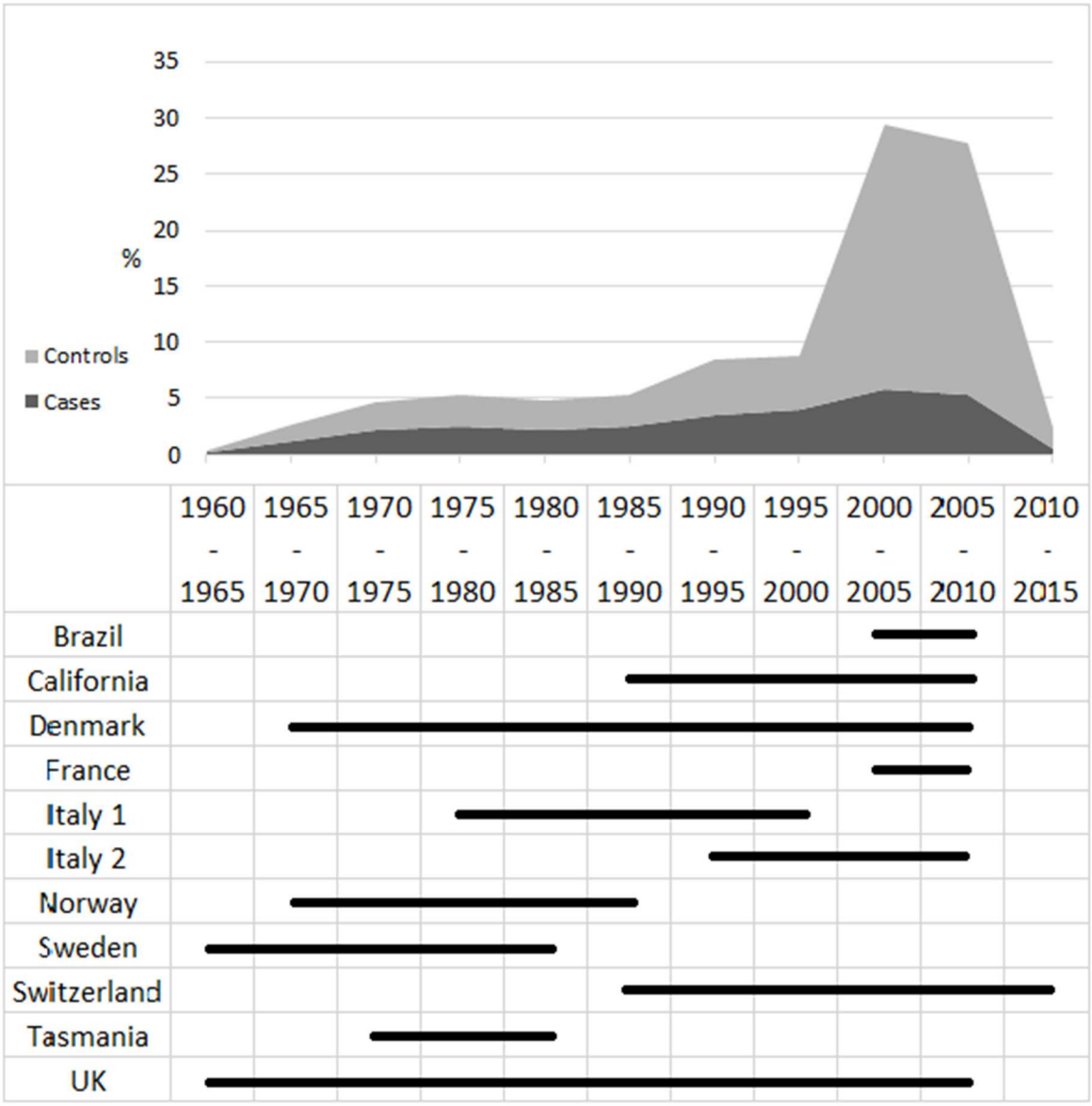


Figure 2.2 Two-stage meta-analysis <50 m vs. 300+ m to 200+ kV line.

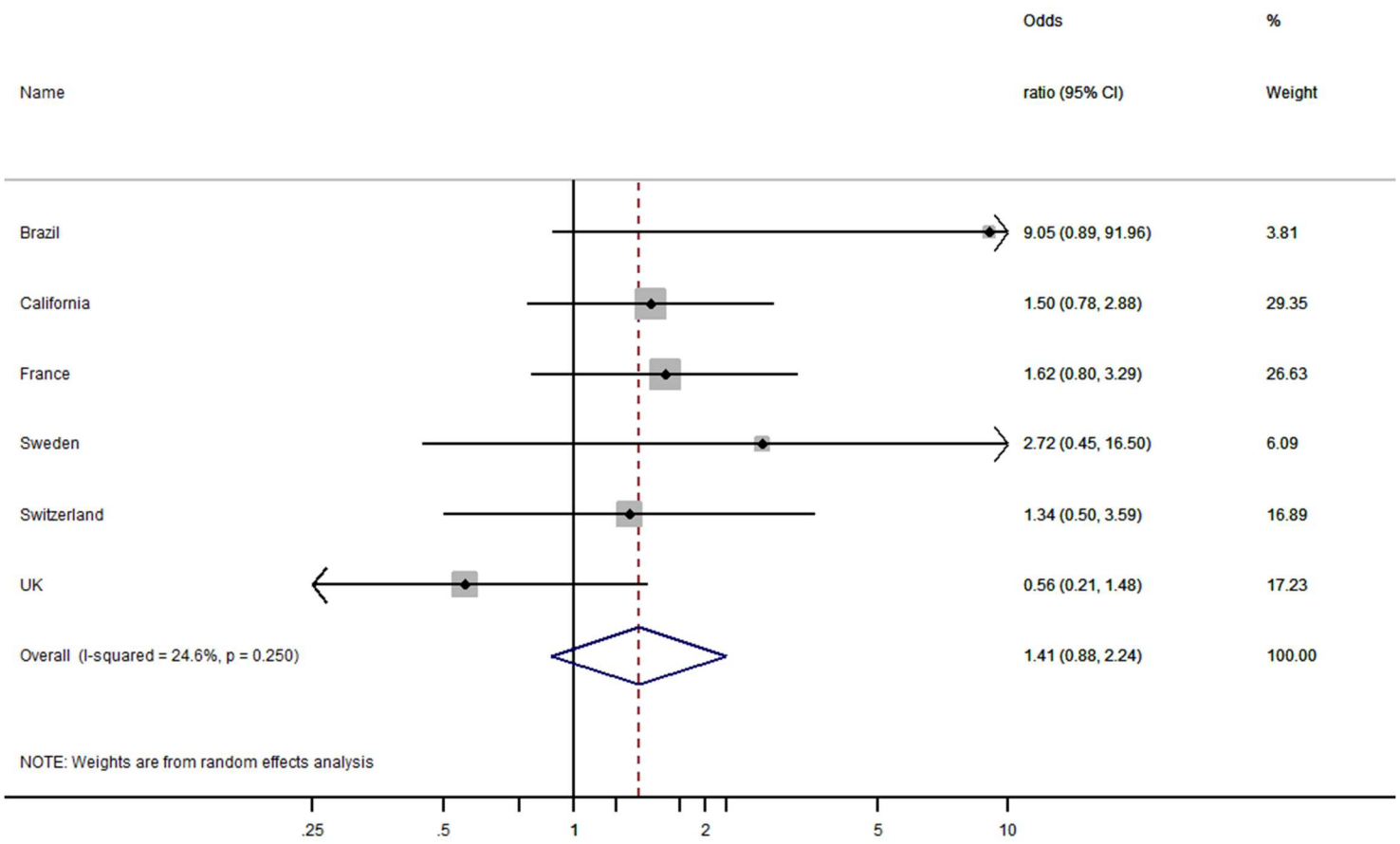


Table 2.1 Characteristics of Studies Meeting Criteria for Pooled Analysis of Childhood Leukemia and Distance to Power Lines.

Country (First Author, Year)	Population (Leukemia)	Years of Diagnosis	Age	Voltages (kV)	Home Analyzed	Homes with Data	Results (Shortest distance category to reference)	Adjusted for
Included:	**Cases/Controls**							
Brazil (Wünsch-Filho, 2011)	162/565	2001-2009	0-8	88, 138, 230, 345, 440, 750	Diagnosis	Birth Diagnosis	COR (95% CI): 0.68 (0.25-1.84) AOR (95% CI): 1.54 (0.26-9.12)	Age, Sex, Race, Mobility, Education, Day Care, Down's Syndrome, Flu History, Maternal Age, Maternal Occupational History, Maternal Smoking and Alcohol History
Denmark (Pedersen, 2014)	1698/3396	1968-2006	0-15	132, 150, 220, 400	Birth	Birth	COR (95% CI): 0.76 (0.40-1.45) AOR (95% CI): 0.76 (0.40-1.45)	Socioeconomic Status
France (Sermage-Faure, 2013)	2712/29797	2002-2007	0-14	63, 90, 150, 225, 400	Diagnosis	Diagnosis	AOR (95% CI): 1.2 (0.8-1.9)	Age, Département
Italy 1 (Bianchi, 2000)	119/476	1978-1997	0-14	132, 220, 380	Diagnosis	Birth Diagnosis	N/A- distance not assessed in publication	Age, Sex
Italy 2 (Malagoli, 2010)	46/184	1986-2007	0-14	132, 380	Exposed[1]	Birth Diagnosis	N/A- distance not assessed in publication	Age, Sex, Paternal and Maternal Education, Paternal Income
Norway (Tynes, 1997)	148/579	1965-1989	0-14	11, 18, 22, 24, 50, 60, 66, 132, 300, 420	Exposed[1]	Birth Diagnosis	COR (95% CI): 0.6 (0.3-1.3)	
Sweden (Feychting, 1993)	39/151	1960-1985	0-16	20, 50, 70, 130, 220, 400	Diagnosis	Birth Diagnosis	COR (95% CI): 2.9 (1.0-7.3)	
Switzerland (Spycher, 2011)[2]	1109/5545	1985-2014	0-15	100, 150, 220, 380	N/A	Birth Diagnosis	N/A- distance not assessed in publication	
Tasmania (Lowenthal, 2007)	47/47	1972-1980	0-17	88, 110, 220	All	Birth Diagnosis	N/A- only adults assessed in publication	

UK (Bunch, 2014)	17299/21059	1962-2008	0-14	132, 275, 400	Birth	Birth	COR (95% CI): 1.00 (0.75-1.34)	
US (Crespi, 2016)	4879/4835	1988-2008	0-15	60, 69, 70, 115, 138, 230, 288, 500	Birth	Birth Diagnosis (cases only)	AOR (95% CI): 1.4 (0.7-2.7)	Age, Sex, Race/Ethnicity, Socioeconomic Status
Not Included:								**Reason for Non-inclusion**
Finland (Verkasalo, 1993)	Total= 134,800	1970-1989	0-19		Exposed		OR (95% CI): 1.47 (0.33-6.60)[+]	Original data not found
Japan (Kabuto, 2006)	312/603	1999-2001	0-15		Diagnosis		OR (95% CI): 3.06 (1.31-7.13)	Data not received

AOR, adjusted odds ratio; COR, crude odds ratio

[1]Home in region with power lines

[+]Odds ratio for a subset of participants obtained from private communication

[2]Distance used as confounder

Table 2.2 Odds ratios for childhood leukaemia by distance to closest overhead power lines: one-stage results.

Distance (m)	Cases/Controls	Crude OR (95% CI)	Adjusted OR (95% CI)
To Any Voltage			
300+	25,713/60,603	1.00 (Reference)	1.00 (Reference)
150-<300	783/2,559	0.98 (0.89-1.07)	0.98 (0.89-1.07)
50-<150	449/1,498	0.98 (0.87-1.10)	0.98 (0.87-1.10)
<50	198/605	1.02 (0.85-1.21)	1.01 (0.85-1.21)
To 200+ kV Line			
300+	26,434/63,197	1.00 (Reference)	1.00 (Reference)
150-<300	304/898	0.97 (0.84-1.12)	0.97 (0.84-1.12)
50-<150	152/469	0.98 (0.80-1.20)	0.97 (0.79-1.19)
<50	50/123	1.35 (0.93-1.94)	1.33 (0.92-1.93)

Analyses were conducted using a random intercept logistic regression model adjusted for age, sex, and SES.

Table 2.3 One-stage and two-stage results for childhood leukemia comparing <50 m to 300+ m distance to closest overhead power line.

	Any Voltage		200+kV	
Study	**Ca/Co**	**OR (95% CI)**	**Ca/Co**	**OR (95% CI)**
Included				
Brazil	5/11	1.64 (0.54-4.95)	3/1	9.05 (0.89-91.90)
Denmark	0/2	--	0/0	--
France	23/213	1.17 (0.75-1.81)	9/60	1.62 (0.80-3.30)
Italy1	2/2	4.27 (0.57-31.91)	0/0	--
Italy2	1/4	1.00 (0.10-9.63)	0/0	--
Norway	8/43	0.70 (0.31-1.56)	0/6	--
Sweden	4/8	2.72 (0.45-16.57)	4/8	2.72 (0.45-16.57)
Switzerland	34/199	0.88 (0.61-1.28)	5/20	1.34 (0.50-3.59)
Tasmania	1/0	--	0/0	--
UK	22/34	0.82 (0.49-1.40)	6/13	0.56 (0.21-1.47)
US	97/89	1.07 (0.80-1.43)	23/15	1.50 (0.78-2.88)
Two-Stage (Meta-Analysis)		1.02 (0.85-1.22)		1.41 (0.88-2.24)
One-Stage (Pooled Analysis)		1.01 (0.85-1.21)		1.33 (0.92-1.93)
Not Included				
Japan		3.06 (1.31-7.13)		--
Finland		1.47 (0.33-6.57)		--
Meta-Analysis of All Studies		1.10 (0.88-1.38)		--

Denmark and Tasmania had no observations in <50 m category for any voltage. Italy1, Italy2, and Norway had no observations in the <50 m category for 200+kV.
Analyses were adjusted for age, sex (where available), and socioeconomic status.
Ca= cases; Co= controls. Numbers can differ slightly from original publication due to different exclusion criteria.

Table 2.4 Odds ratios for childhood leukaemia by distance to closest overhead power line of 200 kV or higher within subgroups.

Subgroup	Distance (m)	Cases	Controls	OR	95% CI
Leukemia Subtype[a]					
Acute Lymphoblastic Leukemia	≥300	21,068	56,450	1	--
	150-<300	240	785	0.99	0.84-1.17
	50-<150	120	418	0.96	0.77-1.21
	<50	40	108	1.39	0.92-2.10
Acute Myeloid Leukemia	≥300	3,916	33,986	1	--
	150-<300	48	484	1.09	0.85-1.40
	50-<150	18	251	0.85	0.57-1.27
	<50	5	68	1.28	0.67-2.46
Age at Diagnosis					
<5 Years	≥300	14,940	29,322	1	--
	150-<300	188	396	1.14	0.94-1.38
	50-<150	88	228	0.9	0.69-1.17
	<50	34	49	1.65	1.02-2.67
>=5 Years	≥300	11,683	34,418	1	--
	150-<300	115	502	0.78	0.62-0.98
	50-<150	64	241	1.09	0.80-1.49
	<50	16	74	1.01	0.55-1.83
Year of Diagnosis					
1960-1980	≥300	5,213	5,933	1	--
	150-<300	40	62	1.71	1.03-2.83
	50-<150	23	32	2.68	1.34-5.37
	<50	8	12	2.22	0.78-6.33
1980-2000	≥300	11,200	13,992	1	--
	150-<300	110	176	0.89	0.69-1.15
	50-<150	65	99	1.04	0.75-1.45
	<50	14	22	1.07	0.52-2.18
2000-2010	≥300	10,210	43,815	1	--
	150-<300	153	660	0.99	0.82-1.21
	50-<150	64	338	0.81	0.61-1.09
	<50	28	89	1.44	0.90-2.32

Analyses were conducted using a random intercept logistic regression model adjusted for age, sex, and socioeconomic status. [a]Some controls overlap for subtypes.

Table 2.5 Comparison of the odds ratios for association between childhood leukemia and distance to closest overhead 200+ kV power line with and without adjustment for specific confounders.

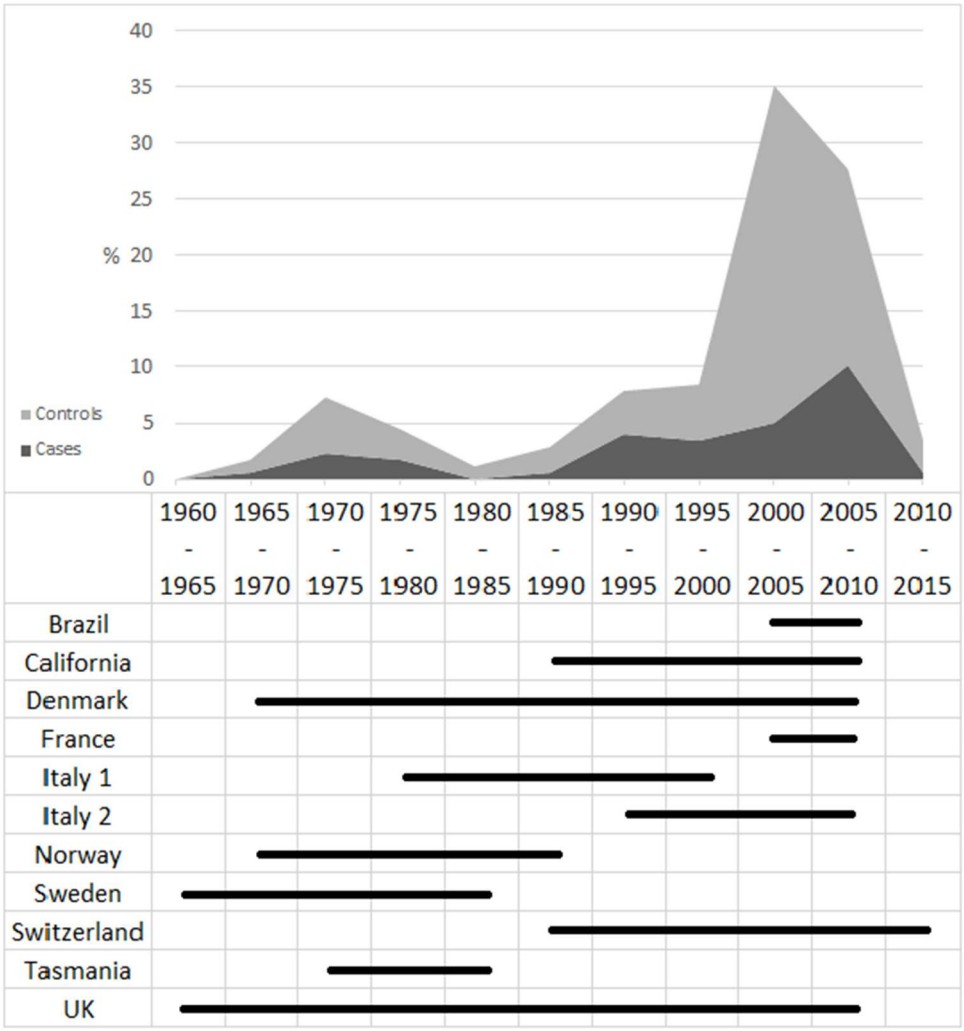
Confounder Model	**≥300 m**	**150-<300 m**	**50-<150 m**	**<50 m**
Ecological SES- Studies 2, 3, 8, 9, 10, 11				
not adjusted*	1.00 (reference)	1.01 (0.87-1.18)	0.90 (0.72-1.12)	1.28 (0.85-1.93)
adjusted⁺	1.00 (reference)	1.02 (0.87-1.18)	0.90 (0.72-1.12)	1.28 (0.85-1.93)
Individual SES- Studies 1, 5, 6, 7, 11				
not adjusted*	1.00 (reference)	0.83 (0.63-1.10)	1.09 (0.77-1.54)	1.49 (0.85-2.59)
adjusted⁺	1.00 (reference)	0.83 (0.63-1.10)	1.09 (0.77-1.55)	1.48 (0.85-2.58)
Mobility- Studies 1, 5, 6, 7, 9				
not adjusted*	1.00 (reference)	0.90 (0.43-1.90)	1.84 (1.00-3.38)	2.05 (0.78-5.36)
adjusted⁺	1.00 (reference)	0.87 (0.41-1.86)	1.72 (0.93-3.20)	2.09 (0.79-5.51)
Dwelling Type- Studies 1, 6, 7, 11				
not adjusted*	1.00 (reference)	0.95 (0.51-1.79)	1.64 (1.04-2.58)	2.59 (1.35-4.99)
adjusted⁺	1.00 (reference)	0.96 (0.51-1.81)	1.66 (1.05-2.61)	2.62 (1.36-5.03)
Traffic- Studies 3, 4, 7, 8				
not adjusted*	1.00 (reference)	0.99 (0.77-1.26)	1.02 (0.73-1.42)	1.78 (1.06-2.98)
adjusted⁺	1.00 (reference)	0.98 (0.77-1.26)	1.01 (0.72-1.41)	1.77 (1.05-2.97)

Urban Setting- Studies 1, 2, 3, 6, 7, 8, 10				
not adjusted*	1.00 (reference)	1.02 (0.87-1.21)	1.01 (0.80-1.28)	1.28 (0.81-2.02)
adjusted⁺	1.00 (reference)	1.02 (0.87-1.21)	1.01 (0.80-1.28)	1.28 (0.81-2.02)
Calculated Fields- Studies 2, 4, 5, 6, 7, 10, 11				
not adjusted*	1.00 (reference)	0.95 (0.79-1.13)	0.98 (0.75-1.26)	1.16 (0.71-1.91)
adjusted⁺	1.00 (reference)	0.95 (0.79-1.13)	1.00 (0.75-1.32)	1.23 (0.67-2.26)
Measured or Calculated Fields- Studies 1, 2, 4, 5, 6, 7, 10, 11				
not adjusted*	1.00 (reference)	0.95 (0.79-1.14)	0.97 (0.75-1.24)	1.32 (0.81-2.13)
adjusted⁺	1.00 (reference)	0.95 (0.79-1.14)	0.98 (0.75-1.28)	1.47 (0.83-2.60)

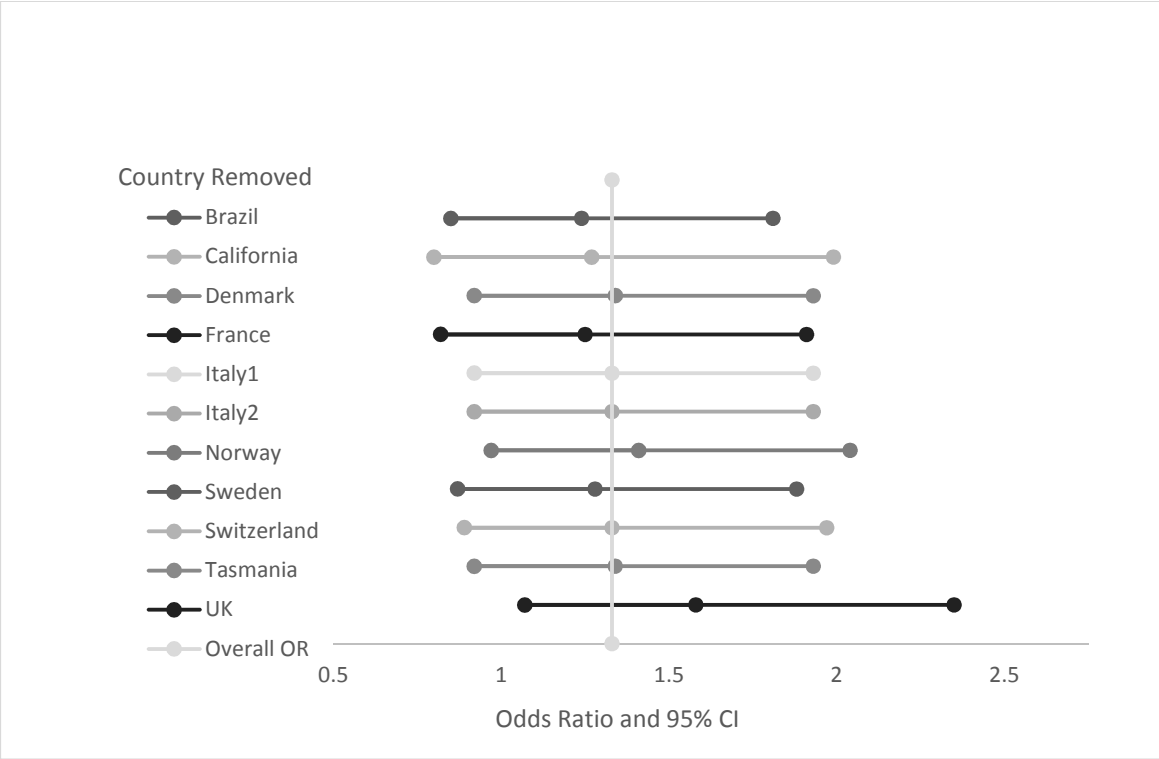
Studies: 1-Brazil, 2-Denmark, 3-France, 4-Italy1, 5-Italy2, 6-Norway, 7-Sweden, 8-Switzerland, 9-Tasmania, 10-UK, 11-US.
*Analyses were conducted using a random intercept logistic regression model, adjusting for age, sex and SES (except in SES models) in subjects who did not have missing values for the covariate of interest.
⁺Analyses were conducted using a random intercept logistic regression model, adjusting for age, sex, SES, and the covariate of interest.

2.6 Appendices

Supplementary Figure 2.1 Distribution of cases and controls <50 m of a 200+ kV line by years of diagnosis.



Supplementary Figure 2.2 Influence Analysis: <50 m vs. 300+ m to 200+ kV line.



Supplementary Table 2.1 List of excluded studies and reasons for exclusion.

Country	First Author, Year	Study Type	Stated Disease Diagnosis	Study Population	Year of Diagnosis	Age (years)	Exposure Assessment	Results	Reason for Exclusion
Greece	Petridou, 1997	Matched Case-Control study	Childhood Leukemia	Cases = 117 Controls = 202	1993-1994	0-14	Shortest distance between the power line and center of residence	OR for 4 EMF measures for the highest quintile: [V/d]: OR = 1.5, 95% CI 0.6,3.8	Hospital controls; Not record based
Iran	Sohrabi, 2010	Matched case-control study	Acute Lymphoblastic Leukemia (ALL)	Cases = 300 Controls = 300	2009	1-18	Shortest distance from the residence to nearest power line	OR =2.6; 95%CI 1.7, 3.9	Hospital controls; Interviewed for history of residences near HVPL
	Feizi, 2007	Matched case-control Study	Acute Lymphoblastic Leukemia (ALL)	Cases = 60 Controls = 59	1998-2004	0-14	Distance of the power line to nearest residence; Calculated fields	OR = 8.7; 95% CI 1.7, 58.4	Hospital based controls including non-malignant hematology
Japan	Mizoue, 2004	GIS-based Population study	Childhood hematological malignancies	Exposed = 22,222 (≤300m) Unexposed = 29,087 (>300m)	1992-2001	0-14	Distance from the HVPL(<300m); spot measurements in front of gates for home	Districts with more than 50% of area ≤300 m of HVPL (referent: districts in which no area fell in that range) IRR = 2.2; 95% CI 0.5,9.0	Study design; Exposure at district level
Malaysia	Rahman, 2008	Hospital-based case control study	Acute childhood Leukemias	Cases = 128 Controls = 128	2001-2007	0-14	Distance to the power line from the house	Distance to power lines ≤ 200 m (referent: >200 m) OR = 2.3; 95% CI 1.2, 4.5	Hospital controls; Not enough detail is given on powerline data

Taiwan	Li, 1998	GIS-based population study	Childhood Leukemia	Exposed = 11,802 (<100m) Unexposed = 108,894 (>100m)	1987-1992	0-14	Distance of each administrative region from HVPL	Living in households >100m vs < 100m from HVPL : SIR = 2.4, 95% CI 1, 5	Similar design and exposure assessment more detailed but still not at individual level
	Lin, 1996	GIS- based population study	Childhood Leukemias	Total = 145,000	1987-1992	0-14	Distance of each administrative region from HVPL	Living in households >100m vs < 100m from HVPL : SIR = 2.7, 95% CI 1.3, 5.8	Study design; Exposure at district level
UK	Skinner, 2000	Population based Case-Control study	Childhood hematological malignancies	Cases = 3,380 Controls = 3,390	1991-1996	0-14	Distance from HVPL, substations and underground cables; calculated fields from power lines	Calculated MF ≥ 0.2 µT (referent <0.1 µT) ALL : OR = 0.5, 95% CI 0.1, 2.3 All Leukemias : OR = 0.4, 95% CI 0.1, 1.9	Subset of Draper et al. (2005)

*HVPL = High Voltage Power Line; V = Voltage; d = distance
*MF = Magnetic Field
*WC = Wire Codes

Supplementary Table 2.2 Odds ratio of childhood leukemia by distance to closest overhead power line of 200kV or higher by year of diagnosis, with and without hypothesis-generating study.

Year	Distance (m)	With UK			Without UK		
		Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
1960-1980	≥300	5,213	5,933	1.00 (reference)	548	1,240	1.00 (reference)
	150-<300	40	62	1.71 (1.03-2.83)	8	49	0.71 (0.25-1.99)
	50-<150	23	32	2.68 (1.34-5.37)	11	28	1.69 (0.63-4.52)
	<50	8	12	2.22 (0.78-6.33)	4	9	1.87 (0.46-7.58)
1980-2000	≥300	11,200	13,992	1.00 (reference)	3,378	6,105	1.00 (reference)
	150-<300	110	176	0.89 (0.69-1.15)	53	110	0.91 (0.64-1.29)
	50-<150	65	99	1.04 (0.75-1.45)	33	74	0.91 (0.58-1.41)
	<50	14	22	1.07 (0.52-2.18)	14	18	1.45 (0.68-3.07)
2000-2010	≥300	10,210	43,815	1.00 (reference)	6,257	36,195	1.00 (reference)
	150-<300	153	660	0.99 (0.82-1.21)	113	588	0.98 (0.78-1.22)
	50-<150	64	338	0.81 (0.61-1.09)	53	302	0.89 (0.65-1.23)
	<50	28	89	1.44 (0.90-2.32)	26	83	1.59 (0.97-2.62)

Analyses were conducted using a random intercept model adjusted for age, sex, and SES.

Supplementary Table 2.3 Odds ratios for the association between childhood leukemia and other potential risk factors associated with proximity to overhead power lines.

Covariate		OR (95% CI)
Mobility[1]	Never Moved	1.00 (reference)
	Ever Moved	1.89 (1.50-2.38)
Dwelling[2]	Other Residence	1.00 (reference)
	Single Family Home	0.80 (0.61-1.06)
Traffic[3]	Low Exposure	1.00 (reference)
	Medium Exposure	1.00 (0.94-1.07)
	High Exposure	1.05 (0.98-1.13)
Setting[4]	Urban	1.00 (reference)
	Rural	0.98 (0.94-1.03)
Calculated Magnetic Fields[5]	<0.1 μT	1.00 (reference)
	0.1-<0.4 μT	0.95 (0.68-1.31)
	>=0.4 μT	1.07 (0.65-1.76)
SES	Low	1.00 (Reference)
	Medium-Low	1.04 (1.00-1.08)
	Medium	1.05 (1.01-1.10)
	Medium-High	1.05 (1.00-1.10)
	High	1.04 (1.00-1.09)

Analyses were conducted using a random intercept logistic regression model adjusted for age, sex and SES.

[1]Studies included: Brazil, Italy2, Norway, Sweden, Tasmania

[2]Studies included: Brazil, Norway, Sweden, US

[3]Studies included: France, Italy1, Sweden, Switzerland

[4]Studies included: Brazil, Denmark, France, Norway, Sweden, Switzerland, UK

[5]Studies included: Denmark, Italy1, Italy2, Norway, Sweden, UK, US

Supplementary Table 2.4 Odds ratios for childhood leukemia by distance to closest overhead power line of 200kV or higher, stratified by various covariates.

Model	Distance (m)	Cases	Controls	OR	95% CI
Ever Moved[1]	≥300	96	202	1	--
	150-<300	4	36	0.66	0.16-2.72
	50-<150	11	22	2.84	0.96-8.36
	<50	4	4	6.22	0.98-39.49
Never Moved[1]	≥300	202	869	1	--
	150-<300	9	30	1.51	0.63-3.64
	50-<150	9	27	1.69	0.74-3.82
	<50	3	11	1.29	0.34-4.90
Single Family Home[2]	≥300	190	747	1	--
	150-<300	13	44	1.08	0.52-2.27
	50-<150	37	57	1.78	1.04-3.04
	<50	17	17	2.67	1.25-5.71
Other Residence[2]	≥300	52	143	1	--
	150-<300	5	28	0.56	0.18-1.79
	50-<150	12	22	1.31	0.53-3.20
	<50	7	6	2.99	0.76-11.75
Low Traffic Exposure[3]	≥300	1,253	12,045	1	--
	150-<300	33	260	1.11	0.76-1.61
	50-<150	12	136	0.71	0.38-1.32
	<50	9	40	2.28	1.09-4.76
Medium Traffic Exposure[3]	≥300	1,466	12,860	1	--
	150-<300	12	201	0.51	0.28-0.92
	50-<150	11	107	0.8	0.43-1.51
	<50	6	28	1.74	0.71-4.26
High Traffic Exposure[3]	≥300	1,041	9,993	1	--
	150-<300	30	161	1.45	0.97-2.18
	50-<150	17	77	1.97	1.15-3.38
	<50	3	19	1.14	0.33-3.96

Urban[4]	≥300	18,765	46,426	1	--
	150-<300	171	604	1.03	0.86-1.24
	50-<150	78	312	0.97	0.74-1.27
	<50	20	80	1.20	0.70-2.03
Rural[4]	≥300	3,023	11,932	1	--
	150-<300	43	186	0.97	0.67-1.41
	50-<150	25	100	1.12	0.69-1.81
	<50	7	27	1.53	0.64-3.67
≥0.4 μT[5]	≥300	4	18	1	--
	150-<300	0	0	--	--
	50-<150	4	7	9.02	0.81-100.63
	<50	17	15	6.25	0.94-41.52
0.2-<0.4 μT[5]	≥300	6	6	1	--
	150-<300	1	1	--	--
	50-<150	6	19	0.14	0.01-1.62
	<50	6	10	0.19	0.12-1.93
<0.2 μT[5]	≥300	21,304	27,239	1	--
	150-<300	219	305	0.95	0.80-1.14
	50-<150	98	130	1.07	0.82-1.41
	<50	8	13	0.75	0.31-1.84

Analyses were conducted using a random intercept logistic regression adjusted for age, sex, and SES.

[+]Analysis was conducted using standard logistic regression adjusted for age, sex, and SES.

[1]Countries included: Brazil, Italy2, Norway, Sweden, Tasmania

[2]Countries included: Brazil, Norway, Sweden, US

[3]Countries included: France, Italy1, Sweden, Switzerland

[4]Countries included: Brazil, Denmark, France, Norway, Sweden, Switzerland, UK

[5]Countries included: Denmark, Italy1, Italy2, Norway, Sweden, UK, US

Supplementary Table 2.5 Odds ratios for childhood leukemia by distance to closest overhead power line of 200kV or higher applying different methodologies.

Model	Distance	Cases	Controls	OR	95% CI
Exposure at Birth Home v. Diagnosis Home					
Birth Home[1]	300+	23,807	33,960	1	--
	150-<300	259	440	0.97	0.82-1.14
	50-<150	127	212	1	0.79-1.26
	<50	38	54	1.23	0.79-1.91
Diagnosis Home[2]	300+	4,549	38,648	1	--
	150-<300	104	688	1.15	0.93-1.42
	50-<150	48	364	0.97	0.71-1.32
	<50	24	98	1.78	1.13-2.81
Ignoring Geocoding Accuracy					
All Observations	300+	29,768	74,532	1	--
	150-<300	332	945	0.99	0.86-1.14
	50-<150	158	486	0.94	0.77-1.15
	<50	52	125	1.33	0.92-1.91
Alternative Controls					
All Alternative Controls[3]	300+	22,086	55,117	1	--
	150-<300	254	778	1	0.85-1.18
	50-<150	127	361	1.04	0.82-1.32
	<50	38	87	1.11	0.70-1.74
Lymphoma[4]	300+	17,497	7,765	1	--
	150-<300	165	114	0.86	0.64-1.15
	50-<150	79	51	1.17	0.75-1.81
	<50	15	21	0.77	0.35-1.70
Other Cancers[5]	300+	17,454	26,659	1	--
	150-<300	165	395	0.97	0.79-1.19
	50-<150	79	160	1.2	0.89-1.63
	<50	15	28	1.33	0.68-2.62
CNS[6]	300+	22043	20693	1	--
	150-<300	254	269	1.08	0.89-1.31
	50-<150	127	150	0.98	0.75-1.28
	<50	38	38	1.11	0.67-1.84

Analyses were conducted using a random intercept logistic regression model, adjusted for age, sex, and socioeconomic status.
1. Studies included in birth home analysis: Brazil, Denmark, Italy1, Italy2, Norway, Sweden, Switzerland, Tasmania, UK, US
2. Studies included in diagnosis home analysis: Brazil, France, Italy1, Italy2, Norway, Sweden, Switzerland, Tasmania
3. Studies included: Italy2, Sweden, Switzerland, Tasmania, UK, US
4. Studies included: Italy2, Sweden, Switzerland, Tasmania, UK
5. Studies included: Sweden, Switzerland, Tasmania, UK
6. Studies included: Sweden, Switzerland, UK, US

Supplementary Table 2.6 Odds ratios for childhood leukemia by distance to closest power line of voltage 200 kV or higher in birth homes compared to diagnosis homes in subset of studies with both.

Home Analyzed	Distance (m)	Cases	Controls	OR	95% CI
Birth	300+	1,321	6,443	1	--
	150-<300	38	177	1.06	0.73-1.53
	50-<150	24	88	1.27	0.80-2.02
	<50	9	26	1.69	0.78-3.66
Diagnosis	300+	2,012	10,001	1	--
	150-<300	62	266	1.18	0.88-1.58
	50-<150	33	134	1.2	0.81-.178
	<50	15	38	1.94	1.06-3.56

Analyses were conducted using a random intercept logistic regression model adjusted for age, sex, and SES.

Studies included: Brazil, Italy1, Italy2, Norway, Sweden, Switzerland, Tasmania, US.

3 Residential Mobility and Childhood Leukemia

Authors: Amoon, A.T., Oksuzyan, S., Crespi, C.M., Arah, O.A., Cockburn, M., Vergara, X., Kheifets, L.

3.1 Abstract

Aims: Studies of environmental exposures and childhood leukemia studies do not usually account for residential mobility. Yet, in addition to being a potential risk factor, mobility can induce selection bias, confounding, or measurement error in such studies. Using data collected for California Powerline Study (CAPS), we attempt to disentangle the effect of mobility.

Methods: We analyzed data from a population-based case-control study of childhood leukemia using cases who were born in California and diagnosed between 1988 and 2008 and birth certificate controls. We used stratified logistic regression, case-only analysis, and propensity-score adjustments to assess predictors of residential mobility between birth and diagnosis, and account for potential confounding due to residential mobility.

Results: Children who moved tended to be older, lived in housing other than single-family homes, had younger mothers and fewer siblings, and were of lower socioeconomic status. Odds ratios for leukemia among non-movers living <50 meters from a 200+ kilovolt line (OR: 1.62; 95% CI: 0.72-3.65) and for calculated fields ≥0.4 microTesla (OR: 1.71; 95% CI: 0.65-4.52) were slightly higher than previously reported overall results. Adjustments for propensity scores based on all variables predictive of mobility, including dwelling type, increased odds ratios for leukemia to 2.61 (95% CI: 1.76-3.86) for living <50 meters from a 200+ kilovolt line and to 1.98 (1.11-3.52) for calculated

fields. Individual or propensity-score adjustments for all variables, except dwelling type, did not materially change the estimates of power line exposures on childhood leukemia.

Conclusion: The residential mobility of childhood leukemia cases varied by several sociodemographic characteristics, but not by the distance to the nearest power line or calculated magnetic fields. Mobility appears to be an unlikely explanation for the associations observed between power lines exposure and childhood leukemia.

3.2 Introduction

The majority of studies that have evaluated the role that environmental exposures play in the development of childhood leukemia have considered exposure at only a single residential address for each child (e.g., home at birth, home at time of diagnosis, longest lived home) and not the mobility of subjects. Residential mobility, or moving between time of birth and diagnosis, can involve short distances, such as moving within the same neighborhood, or longer distance moves; the likelihood of experiencing similar environmental exposures before and after a move may depend on distance. Subjects can also move out of the study area and be lost to follow-up. As only one residential address is available in most studies, few studies can directly assess residential mobility.

Mobility has been considered a source of potential bias in childhood leukemia studies as it can affect study participation and selection, result in exposure misclassification, or confound the results (Kheifets, Swanson, et al., 2017). We explore each of the possible connections in subsequent paragraphs. Figure 3.1 provides a simplified directed acyclic graph illustrating how mobility could affect studies of childhood leukemia and electro-magnetic fields (EMF) in particular, but is relevant as well for many other environmental exposures.

Exposure misclassification can occur if the period of assessment is not the etiologically relevant critical time period in a child's development. This misclassification will affect sensitivity thereby reducing the power to detect associations. The problem can further be compounded by mobility, as the relevant exposure may occur at a different home than the one captured (Urayama et al., 2009), leading to biased results when estimating risk of childhood leukemia, especially if mobility is differential between cases and controls. Several studies have reported higher residential mobility

among cases compared to age-matched controls (Green et al., 1999; Kleinerman et al., 1997; McBride et al., 1999).

Mobility can affect selection through the availability of data. Often, cases are by design residentially more stable as they must both reside and be diagnosed in the same geographic area (region, state or country) while the same requirement does not apply to controls. There is, also, the possibility that subjects move outside the study area and are not captured as cases.

Further, mobility may differ by exposure, either directly or through differential socioeconomic status (SES). In a California study, moving between time of birth and diagnosis was associated with lower community-based SES, as well as lower individual measures of SES, such as parental education and household income (Urayama et al., 2009). SES is also associated with exposure to magnetic fields as it could be related to the number, type, and quality of appliances within the home, the dwelling type (apartment vs. single-family home), and the location of the home in relation to overhead power lines (Hatch et al., 2000; Wartenberg, Greenberg, & Harris, 2010). SES has also been shown to be associated with participation in studies when direct subject involvement is required (Mezei & Kheifets, 2006).

Type of dwelling, such as apartment or single-family home, can affect not only a subject's exposure but also exposure assessment. For example, when geographic information system (GIS) methods are utilized to assess proximity to power lines and to calculate magnetic fields, mobile homes are more likely to result in poor GIS matching of the residential address. Similarly, apartments, particularly in complexes, may lead to greater misclassification of exposure (Feychting & Ahlbom, 1993; Vergara et al., 2015). Home ownership, and subsequently dwelling type, is also associated with SES and mobility (McCarthy et al., 2001).

Residential mobility can also function as a marker for other risk factors for childhood leukemia such as older age of the child at diagnosis, younger maternal age at birth, and maternal place of birth (Urayama et al., 2009). Additionally, mobility might be related to increased exposure to viruses or other infections possibly associated with higher leukemia risk (Kinlen, 2012; Sahl, 1994). The distance moved (e.g. within vs. outside of a neighborhood) could be an indicator for exposure to new infections. A study of childhood leukemia in the United Kingdom (UK) found that increased migration from greater distances was associated with higher incidence of childhood leukemia (Stiller & Boyle, 1996). Another recent UK study (Kendall, Wakeford, Bunch, Vincent, & Little, 2015) found that 44% of childhood leukemia cases had not moved at all between birth and diagnosis, and about two-thirds of those who did move were living within 2 kilometers (km) of their birth residence.

It has been hypothesized that mobility can explain an association between EMF and childhood leukemia (Sahl, 1994). A previous study (Jones, Shih, Thurston, Ware, & Cole, 1993) found that people who moved had a higher proportion of "high" wire codes (an imperfect exposure surrogate) than those who were residentially stable. Another study evaluated residential mobility of adults and proximity to power lines in the UK (Swanson, 2013), but found that proximity did not appear to clearly affect the likelihood of moving. Direct data on mobility of children is lacking.

We conducted a large epidemiologic case-control study in California to examine the associations of childhood leukemia with calculated magnetic fields and with distance from the birth address to the nearest high-voltage overhead transmission line. In common with other case-control studies of childhood cancers, cases, but not controls, had to reside in California at time of diagnosis. The aims of this analysis are to: (i) describe factors that affect or predict mobility among childhood leukemia cases; (ii) use such factors as proxies to adjust for mobility; and (iii) evaluate potential

confounding due to residential mobility in the study of the potential effect of EMF exposure from nearby power lines on childhood leukemia.

3.3 Methods

The California Power Lines Study (CAPS) included childhood leukemia cases younger than 16 years diagnosed in California between 1988 and 2008 who were also born in California. Cases were identified from the California Cancer Registry (CCR; www.ccrcal.org), which requires mandatory reporting of incident cancers and is 99% complete (Schoendorf & Branum, 2006). Information on child's age, sex, residence at the time of diagnosis, as well as information on cancer types and characteristics was extracted from the CCR. Cancer registry data were linked to the California Birth Registry (CBR; California Department of Public Health, Vital Statistics Branch) which is also over 99% complete (Schoendorf & Branum, 2006). Controls were randomly selected from the CBR and matched to cases (1:1). Controls were excluded if they were diagnosed with any type of cancer in California before the matched case's date of diagnosis. Detailed descriptions of the study design and methods have been previously published (Kheifets et al., 2015), as have the results of the calculated magnetic fields and distance analyses (Crespi et al., 2016; Kheifets, Crespi, et al., 2017a).

Although cases had to be both born in and diagnosed in California, because controls were selected from birth records, they were born in California, but were not required to be residing in the state at time of diagnosis of the corresponding case. Thus, we had birth addresses for both cases and controls, but address at diagnosis for cases only.

The CBR provided information on socio-demographic and perinatal factors of study subjects, including mother's residential address at time of birth, child's date of birth, sex, race and ethnicity, birth weight, birth order, number of live births living, parental ages, parental education, parental

race and ethnicity, and source of payment for delivery. We examine race and ethnicity separately and combined. Combined child race/ethnicity was defined as White if both parents were White, Black if either parent was Black, Asian if either parent was Asian, Hispanic if either parent was Hispanic and neither parent was Black or Asian, and Other otherwise. We also examined both individual SES and a census-based SES derived using principal component analysis based on seven indicator variables at the census block level (Yost, Perkins, Cohen, Morris, & Wright, 2001) (high if ≥60th percentile of the principal components score, low otherwise). In addition, because variables indicative of SES collected on birth records varied from year to year, we developed a composite SES indicator (high or low) based hierarchically as available for each subject: the father's years of education (high if ≥12 years, low otherwise), mother's years of education (high if ≥12 years, low otherwise), payment method for hospital delivery (low if government programs or no coverage, high otherwise), and, finally, census-based SES. More information on race/ethnicity and SES indicators in CAPS is available in previous publications (Oksuzyan, Crespi, Cockburn, Mezei, & Kheifets, 2012; Oksuzyan et al., 2015a, 2015b).

We determined geocoded latitudes and longitudes for cases' residential addresses using the University of Southern California (USC) GIS Laboratory's open-source geocoder, which uses parcel level data for Los Angeles County and street level data for the whole of California (Goldberg & Cockburn, 2010). Only addresses with parcel or street segment matching, which corresponds to more precise geocoding, were included in this analysis.

We created three categories of residential mobility for cases: 1) not moved, 2) moved within a neighborhood, defined as distance between birth and diagnosis addresses 50-2000 meters (m), and 3) moved outside of a neighborhood, defined as distance between birth and diagnosis addresses of 2000 m or further. For the primary analysis, the latter two were collapsed and cases were classified

as either residentially stable (did not move) or residentially mobile (moved). To allow for minor geocoding differences over the years, if the distance between birth and diagnosis addresses was 0 to 50 m, we assumed the subject lived in the same property and did not move. This assumption was verified by examining Google satellite images for a larger set of residences (with distances <100 m between birth and diagnosis addresses). 50 m was chosen to increase specificity and make estimates more conservative.

Proximity to power lines was defined as distance from the child's address to any power line or to the nearest power line of 200 kV and above (Kheifets et al., 2015) and was classified into 8 categories: <50 m, 50-<100 m, 100-<200 m, 200-<300 m, 300-<400 m, 400-<500 m, 500-<600 m, and no lines within 600 m. Due to small numbers in one of the categories, a sensitivity analyses was run in which the closest two categories were combined (<100 m). Birth homes located close to lines were site-visited to verify distance, collect additional information needed for magnetic fields calculations, and ascertain dwelling type (single-family homes vs other). Site visits, only available for a subset of subjects (n=178), were conducted blind to case-control status to reduce bias. Calculated fields estimating fields at time of birth were classified into three categories: ≥0.4 microTesla (μT), 0.1-<0.4 μT, and <0.1 μT (Vergara et al., 2015).

We considered the following variables as covariates: child's age at diagnosis, number of siblings living, census-based SES, race/ethnicity, mother's age, mother's years of education, father's years of education, mother's place of birth, the payment source for delivery, type of dwelling, proximity to high voltage power lines, and calculated fields. All covariates were modeled as categorical variables. For more details, see a previous study (Oksuzyan et al., 2015b).

3.3.1 Statistical Analysis

3.3.1.1 Stratified Analyses

The primary analysis assessed the impact of mobility on the associations between proximity to overhead power lines 200 kV or greater and calculated fields and childhood leukemia. For this analysis, we stratified on mobility (not moved, moved within same neighborhood, moved outside neighborhood) and used logistic regression with case/control status as the dependent variable and exposure as the independent variable. To increase power and avoid sparse data, all controls were used in each stratum. Models were adjusted for age, sex, race/ethnicity, and composite SES.

3.3.1.2 Case-Only Analyses Predicting Mobility

We conducted case-only analysis using mobility as the outcome variable to determine covariates associated with moving. We fit logistic regression models with the binary outcome of moved versus did not move and with the 3-category multinomial outcome (did not move (reference), moved within neighborhood and moved outside of neighborhood).

3.3.1.3 Comparison of Birth and Diagnosis Home Characteristics in Movers

In residentially mobile cases, birth and diagnosis homes were compared to assess changes in census-based SES, distance to nearest power lines, and calculated magnetic fields. Changes in exposure categories were analyzed by chi-square tests; mean calculated fields and proximity to power lines at birth and diagnosis were compared using Wilcoxon signed-rank tests.

3.3.1.4 Adjusted Analyses of Exposure-Leukemia Associations Indirectly Accounting for Mobility

Mobility was not available for controls and thus direct adjustment for mobility as a potential confounder in the relation between exposure and childhood leukemia was not possible. We therefore conducted analyses adjusting for variables associated with mobility as proxies We examined models adjusting for each proxy singly, with additional adjustment for age and sex, and we also used propensity score methods to simultaneously control for all the proxies (Rosenbaum & Rubin, 1983; Guo & Fraser, 2014)], to avoid over adjustment. The propensity scores were

created using multinomial logistic regression with the variables associated with mobility as predictors. We estimated propensity scores for each subject as the predicted probability from the model based on their covariate values. We then fit logistic regression models for the outcome of childhood leukemia that included the exposure variable (proximity or calculated field) with and without adjusting for the propensity score, to assess whether the adjustment changed the childhood leukemia risk estimate. This approach assumes that including propensity scores in the model provides a reasonable proxy for adjusting for residential mobility.

Analyses were conducted using SAS software version 9.3. Copyright © 2017 SAS Institute Inc. CAPS was approved by University of California, Los Angeles Office for the Protection of Research Subjects.

3.4 Results

Out of 6,645 eligible childhood leukemia cases identified from the CCR, 87.1% (5,788) were born in California and were successfully linked to birth records. Of these, 4,879 were matched at either parcel or street segment levels for both birth and diagnosis addresses and included in the analysis. A majority of cases were male (55.3%), Hispanic (52.1%), and had acute lymphoblastic leukemia (ALL) (81.5%). The median age at time of diagnosis was 3.8 years. Most cases (2,982, 61.1%) moved between birth and diagnosis. Among those who moved, 618 stayed within 2 km of their birth home, while 1,992 moved outside of their birth neighborhood. Additional characteristics are presented in Table 3.1. There were no differences in characteristics between cases and controls. However, among cases who moved, children tended to be older, live in housing other than single-family homes, and have younger mothers. Fewer siblings and lower SES were also more common among children who moved.

3.4.1 Stratified Analyses

As reported previously, using all leukemia cases and controls, we found an OR for childhood leukemia of 1.44 (95% CI 0.74-2.77) for those whose birth residence was within 50 m of a 200+ kV line, (Crespi et al., 2016) and an OR (95% CI) of 1.50 (0.70-3.21) for the highest exposure of calculated fields (≥0.4 μT) (Kheifets, Crespi, et al., 2017a). The results of analyses stratified by the mobility status of the cases are presented in Table 3.2.

Among non-movers, moderate associations for childhood leukemia and both living within 50 m of voltage 200+ kV power line (OR: 1.62, 95% CI: 0.72-3.65) and living in higher calculated fields (OR: 1.71, 95% CI: 0.65-4.52) at birth home were observed. Among those who moved, the OR was slightly lower for the proximity analysis (OR: 1.28, 95% CI: 0.60-2.75) than the overall proximity OR (1.44) reported previously, but did not change for calculated fields. These analyses used all controls in each stratum because while similar point estimates were found when stratifying controls, the results were less stable (data not shown).

We also conducted analyses stratifying cases by distance of move, with the strata of "moved within birth neighborhood" and "moved outside birth neighborhood." A slightly stronger association was noted for those who moved out of the neighborhood for both those living <50 m from a 200+ kV line and those with ≥0.4 μT calculated fields at the birth home (Table 3.2). All results from stratified analyses were imprecise.

3.4.2 Case-Only Analyses Predicting Mobility

Results of the case-only analyses with mobility status as the outcome are presented in Table 3.3. In unadjusted analyses with a binary mobility outcome (moved vs. not moved), greater likelihood of mobility was associated with older age at diagnosis (p-value for trend <0.001), leukemia subtype, Black and Hispanic race/ethnicities, younger maternal age at birth, being an only child or having many siblings, non-US maternal place of birth, and lower SES. Not living in a single-family

home was also associated with likelihood of moving (OR:1.43; 95% CI: 0.52-3.93), but results were imprecise as type of dwelling was recorded only for site-visited homes. No association was detected for sex or Down syndrome (data not shown). Similar results were obtained when race and ethnicity were assessed separately (data not shown), thus for the remaining analyses, the combined race/ethnicity variable was used. Crude and adjusted ORs were similar for all variables associated with mobility (Table 3.3).

Similar results were found in the multinomial logistic analysis using the three-level mobility as an outcome. Older child's age at diagnosis was more strongly associated with moving outside the birth neighborhood than the association within the same neighborhood. In contrast, Hispanic race/ethnicity was associated with moving within a neighborhood but not with moving more than 2 km away (Table 3.3). Neither calculated fields, nor proximity to 200+ kV power lines appeared to be associated with moving, although numbers were too small to assess movement with regards to the birth neighborhood (Table 3.3).

3.4.3 Comparison of Birth and Diagnosis Home Characteristics in Movers

Among cases who moved, there were few differences in characteristics between birth and diagnosis homes. Calculated fields changed in only 51 cases, unsurprising, since the overwhelming majority of subjects had calculated fields of <0.1 μT. Only two children changed exposure categories, possibly since only three exposure categories were used and few cases were classified at the highest exposure level (≥0.4 μT). Among those who moved, 6% of subjects moved into closer distance categories to overhead 200+ kV power lines while another 6% moved farther away. When considering all voltages, equal numbers of cases moved into the closer or farther categories (16%). Due to censoring of distance data beyond 2000 m, these percentages do not account for subjects who moved closer or father but remained beyond 2000 m. No differences were noted in

the average distances from the closest power lines, 200+ kV or any voltage, nor in average calculated fields for children who moved between birth and diagnosis (data not shown).

About 17% of all subjects changed the status of their census-based SES from low to high or the reverse. Among both non-movers and movers, relative census-based SES appeared to increase from birth to diagnosis (7.6% and 13.6%, respectively), but this difference was not significant. These changes were not absolute changes, but change in quintile. Figure 3.2 shows the distribution of changes in census-based SES using quintiles.

3.4.4 Adjusted Analyses of Exposure-Leukemia Associations Indirectly Accounting for Mobility

Both unadjusted and adjusted results in subsets of observations using variables associated with mobility are presented for comparison (Table 3.4). Adjustment for most variables had no impact on the results. Analyses focusing on dwelling type of site-visited residences, showed a higher association between power lines and childhood leukemia in this subset across all strata, although estimates were imprecise due to smaller numbers. However, adjustment for dwelling type did not change the estimates in comparison to unadjusted analyses in the same subset. For distance, adjustment for maternal age at birth and number of siblings showed a minimal increase in associations with childhood leukemia among those who did not move. Adjustment for race/ethnicity showed a similar slight increase in associations in the analysis of calculated fields. All results were imprecise (Table 3.4).

When all variables related to mobility except for dwelling type were included in the models via propensity scores, the OR for living <50 m from a 200+ kV line and for high calculated fields largely remained similar to unadjusted results in previous findings (Table 3.5). Dwelling type, assessed for a small subset of residences within specific distances from overhead power lines and with likely higher exposure to MF, was not available beyond 200 m for most subjects. With

dwelling included in the propensity score in the smaller subset of data, the OR for living <50 m from a 200+ kV line and for calculated fields ≥0.4 μT increased to 2.61 (95% CI: 1.76-3.86) and 1.98 (95% CI: 1.11-3.52), respectively.

3.5 Discussion

In our study of residential mobility in CAPS, many childhood leukemia cases were mobile, with 61% having changed residence between birth and diagnosis. This excludes about 13% of leukemia cases identified in the CCR born outside of California and an unknown, but likely smaller, number of children born in California who moved out of state before developing leukemia.

Similar to previous findings (Urayama et al., 2009), cases diagnosed at older ages had higher odds of moving between birth and diagnosis, while older maternal age at birth was associated with decreased odds of moving. In our study, we also noted increased likelihood of moving with Black and Hispanic race/ethnicity, being an only child, and a non-US maternal place of birth when analyzed alone, although some associations disappeared when adjusting for other covariates. Racial and ethnic differences in moving preferences have been examined in previous studies, including specific factors such as neighborhood racial/ethnic compositions in California. Most respondents generally preferred neighborhoods comprised of their own race/ethnicity and were likely to move within such neighborhoods or into similar ones. Suburbanization also differed by race/ethnicity (Alba & Logan, 1991; Charles, Good, Hanusa, Chang, & Whittle, 2003; Clark, 1992). Dwelling type was also associated with mobility, but the numbers were small, leading to imprecise estimates. Similar results were found when considering moving within and outside neighborhoods, with some variables showing slightly more pronounced results for those moving outside the birth neighborhood while Hispanic race/ethnicity and non-US maternal place of birth were more strongly associated with moving within the same neighborhood. Interestingly, neither

high calculated fields nor close proximity to 200+ kV power lines were associated with greater likelihood of moving.

It seems obvious for age at diagnosis to be positively correlated with likelihood of residential mobility as more time means more opportunity to change residence. However, several studies indicated greater likelihood of moving around the time of birth, as families prepare or adjust to their new addition, particularly true for the birth of the first child (Clark & Huang, 2003; Kulu, 2005; Rabe & Taylor, 2009). A Texas study on residential mobility, environmental exposures, and birth defects found ~30% each of case and control mothers moved between the time of conception and delivery (Canfield, Ramadhani, Langlois, & Waller, 2006). In a UK study, approximately 20% of mothers of infants moved (Champion, 2005). Further exploration of how mobility intersects with age of the child, parental age, birth order, and dwelling type is warranted.

Using the composite SES, we found that lower SES was associated with greater likelihood of moving, as in previous studies (Urayama et al., 2009). Although for most participants, individual measures of SES were used, the composite SES variable also included census-based SES, which could differ between time of birth and diagnosis, even for residentially stable subjects, because census-based SES may change over time. The census-based SES measure was based on seven different factors, any number of which could have shifted for each census tract. Similarly, definitions of the factors may have also changed (e.g. federal poverty level, calculation of education index, etc.). However, there did not appear to be any material trend in changes in SES from birth to diagnosis or for distance to power lines or calculated fields among those who moved.

To assess how mobility may affect the relationship of exposure to MF and childhood leukemia, we stratified by the mobility of the cases. In the strata of cases who did not move, a slightly stronger association was found for both proximity to power lines and MF, suggesting that birth home may

be a better indicator of exposure in these children. When looking at cases who moved greater than 2 km away from their birth home, we also saw an increase in effect. Children moving outside their birth neighborhoods may have more opportunity to encounter new infections, consistent with the infectious disease etiology. Another possibility is that these cases moved due to pre-diagnostic conditions or perhaps other environmental characteristics associated with their proximity to power lines, but not captured in our dataset. This sub-group of movers might have unmeasured susceptibility to leukemia also associated with their moving farther away. However, all results were imprecise, so larger datasets would be needed to explore any of these hypotheses.

While the mobility of controls was unknown, the variables associated with mobility were known for both cases and controls. Thus, we used them as a surrogate of mobility to evaluate if they modified the relationship between proximity to power lines and MF on childhood leukemia. We observed an increase in the ORs for both MF and distance. Dwelling type, in particular, seems to be a major predictor of mobility, however, this information was available only for site-visited homes within certain distances of overhead power lines (n=178). Dwelling type can indicate quality of exposure assessment, in particular for MF, where calculation of MF in non-single-family homes more likely to lead to misclassification (Feychting & Ahlbom, 1993; Vergara et al., 2015). Further exploration is needed in datasets with more complete residential information.

Strengths of this study include the use of population registries to obtain data, thus avoiding participation bias and exposure assessment blind to case-control status to reduce information bias. To increase accuracy of exposure and outcome assessment, we excluded from analyses all cases and controls with imprecise geocode matching for birth or diagnosis address. Another strength was the large sample size, which increased the power to detect associations, should they exist. Despite the large sample size, in some analyses, especially those involving dwelling type, the analytic

sample was reduced because the variable was only available for site-visited residences. Since site visits were conducted blind to case-control status, the potential for biases was probably small, and the impact was mainly on the precision of the estimates.

A potential limitation of our study was misclassification of residential mobility. We defined residential mobility by distance between the geocoded points of birth and diagnosis addresses of cases. Although some misclassification was inevitable, we minimized it by manually investigating, mapping, and visually inspecting all distances between birth and diagnosis residences that were less than 100 m. Based on our visual inspection and geocoding accuracy considerations, we developed the 50 m cut point to decide whether a case moved or not to maintain high specificity. *A priori* sensitivity analysis performed using differing cut points showed similar results (Oksuzyan, 2013). The propensity scores allowed us to adjust for the propensity to move for both cases and controls and thus partially overcome lack of mobility information for controls.

Although CAPS focused on power lines and EMF exposure, we believe the findings on mobility are relevant to other environmental exposures and other childhood outcome studies. Exposure misclassification due to mobility in particular has been expressed as a concern in birth outcome studies (Chen, Bell, Caton, Druschel, & Lin, 2010; Lupo et al., 2010; Madsen et al., 2010; Schulman, Selvin, Shaw, & Malcoe, 1993). It may also be pertinent to consider maternal mobility during pregnancy as prenatal exposures are associated with a variety of birth and childhood outcomes.

In conclusion, because our controls were potentially less residentially stable than our cases, we examined whether the observed association of childhood leukemia with exposure to MF or distance to power lines could be due to this potential difference. We found that the effects of distance to power lines and MF exposure on childhood leukemia were similar for a residentially

stable subset of cases and overall results were unchanged when we controlled for proxies of mobility, except for dwelling. These results suggest that confounding by mobility is an unlikely explanation for the associations observed.

Figure 3.1 Simplified directed acyclic graph (DAG) depicting possible connections of residential mobility in the study of EMF exposures on childhood leukemia.

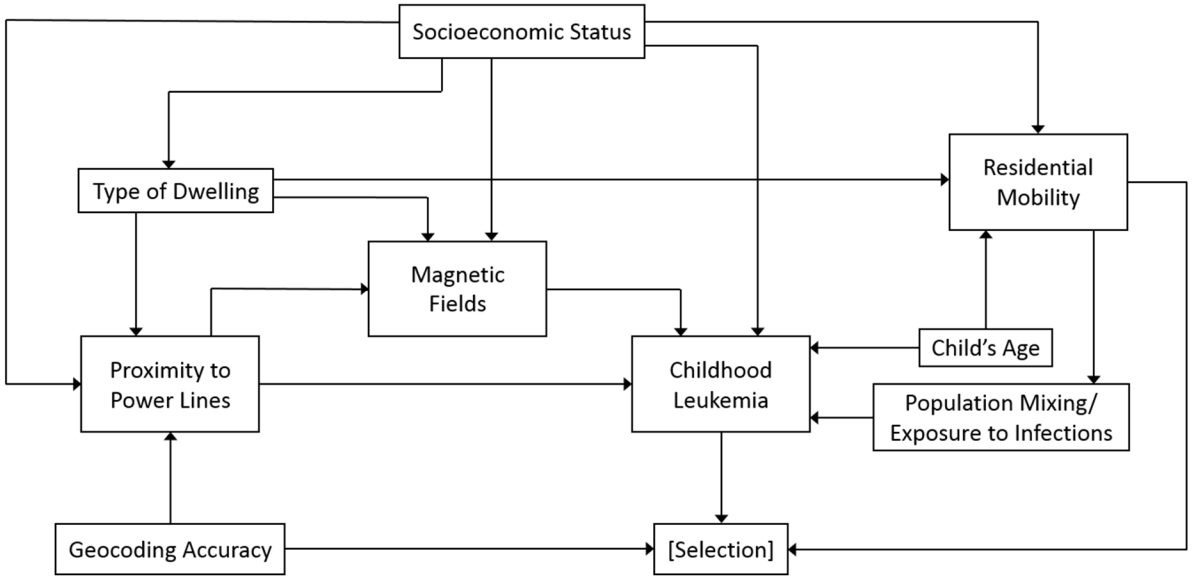


Figure 3.2 Changes in census-based socioeconomic status from time of birth to diagnosis in cases, stratified by mobility.

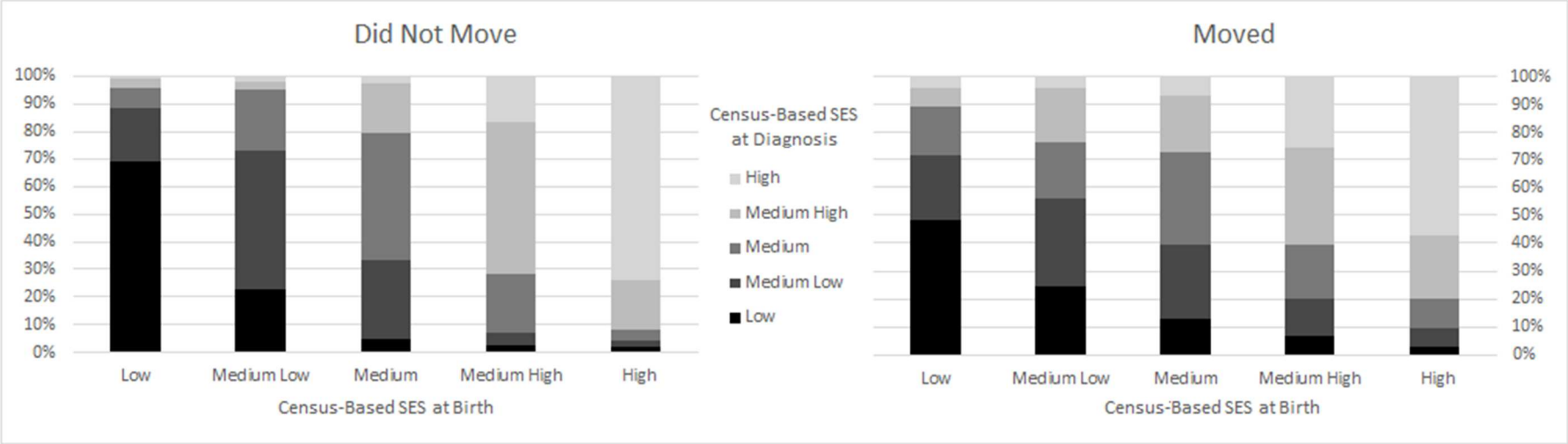


Table 3.1 Characteristics of Cases by Mobility Status in California Power Lines Study, 1986-2008.

	Controls		Cases		Did Not Move		Moved	
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Gender								
Male	2,718	56.2	2,700	55.3	1,038	54.7	1,662	55.7
Female	2,117	43.8	2,179	44.7	859	45.3	1,320	44.3
Age (years)								
<1	349	7.2	323	6.6	240	12.7	83	2.8
1-5	3,095	64	3,145	64.5	1,363	71.9	1,782	59.8
6-9	821	17	828	17	205	10.8	623	20.9
10-15	570	11.8	583	12	89	4.7	494	16.6
Race/Ethnicity								
White	1,513	32.1	1,425	29.8	633	33.9	792	27.1
Black	423	9	248	5.2	65	3.5	183	6.3
Asian	467	9.9	535	11.2	245	13.1	290	9.9
Other	87	1.9	86	1.8	35	1.9	51	1.8
Hispanic	2,220	47.1	2,493	52.1	890	47.6	1,603	54.9
Leukemia Type								
ALL	--	--	3,974	81.5	1,505	79.3	2,469	82.8
AML	--	--	722	14.8	303	16	419	14.1
Other	--	--	183	3.8	89	4.7	94	3.2
Downs Syndrome								
Yes	4	0.1	36	1	16	1.1	20	0.9
No	3,567	99.9	3,541	99	1,437	98.9	2,104	99.1
Dwelling Type at Birth								
Single-Family Home	66	72.5	59	67.8	19	73.1	40	65.6
Other	25	27.5	28	32.2	7	26.9	21	34.4
Maternal Age (years)								
<25	1,704	35.3	1,562	32	429	22.6	1,133	38
25-34	2,497	51.7	2,577	52.8	1,055	55.6	1,522	51.1
>=35	633	13.1	739	15.2	413	21.8	326	10.9

Siblings								
0	1,974	40.8	1,886	38.9	660	34.8	1,226	41.1
1	1,545	32	1,549	31.8	636	33.5	913	30.6
2	753	15.6	805	16.5	335	17.7	470	15.8
3	327	6.8	368	7.5	166	8.8	202	6.8
4+	236	4.9	271	5.6	100	5.3	171	5.7
Maternal Place of Birth								
US	2,737	56.6	2,633	54	1,057	55.7	1,576	52.9
Non-US	2,098	43.4	2,246	46	840	44.3	1,406	47.2
Socioeconomic Status								
Low	3,294	70	3,296	69.4	1,187	63.4	2,109	73.3
High	1,413	30	1,453	30.6	684	36.6	769	26.7

ALL= acute lymphoblastic leukemia. AML= acute myeloid leukemia.

Table 3.2 Odds ratios of Leukemia by Calculated Fields and Proximity to Power Lines, Stratified by Mobility of Cases.

		Total	Cases Who Did Not Move	Cases Who Moved	Cases Who Moved <2 km	Cases Who Moved ≥2 km
		AOR (95% CI)	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)
Calculated fields	<0.1	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	0.1-0.4	0.90 (0.57-1.41)	0.58 (0.29-1.18)	1.09 (0.66-1.78)	1.24 (0.55-2.80)	1.03 (0.54-2.00)
	>=0.4	1.49 (0.69-3.19)	1.71 (0.65-4.52)	1.50 (0.63-3.58)	N < 5	1.64 (0.63-4.26)
Distance to 200+ kV Power Line	600+	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	500-<600	1.18 (0.82-1.71)	1.34 (0.83-2.16)	1.08 (0.70-1.65)	0.94 (0.42-2.10)	1.12 (0.71-1.76)
	400-<500	0.87 (0.60-1.28)	0.74 (0.43-1.29)	0.95 (0.62-1.46)	0.78 (0.35-1.74)	1.01 (0.64-1.60)
	300-<400	1.11 (0.78-1.59)	1.17 (0.73-1.87)	1.07 (0.71-1.61)	1.28 (0.66-2.47)	1.03 (0.66-1.61)
	200-<300	0.85 (0.59-1.22)	0.96 (0.59-1.55)	0.78 (0.51-1.21)	N < 5	0.89 (0.56-1.39)
	100-<200	0.77 (0.53-1.11)	0.72 (0.42-1.23)	0.79 (0.52-1.21)	1.17 (0.61-2.25)	0.68 (0.41-1.11)
	50-<100	0.96 (0.56-1.64)	0.42 (0.16-1.10)	1.31 (0.74-2.33)	N < 5	1.42 (0.78-2.61)
	<50	1.38 (0.71-2.67)	1.62 (0.72-3.65)	1.28 (0.60-2.75)	N < 5	1.54 (0.70-3.36)

All controls were used in each stratum to increase stability of estimates and avoid small cell counts

Analyses were adjusted for age, sex, race/ethnicity, and composite SES.

Table 3.3 Odds ratios for associations of residential mobility with selected characteristics in childhood leukemia cases in the California Power Lines Study, 1986-2008 – Case-Only.

	Moved vs. Not Moved (reference)		Moved Within Neighborhood vs. Not Moved (reference)	Moved Outside Neighborhood vs. Not Moved (reference)
Characteristic	**Crude OR (95% CI)**	**Adjusted[+] OR (95% CI)**	**AOR[+] (95% CI)**	**AOR[+] (95% CI)**
Age (years)				
<1	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1-5	3.78 (2.92-4.90)	3.84 (2.90-5.09)	2.76 (1.78-4.27)	4.39 (3.18-6.06)
6-9	8.79 (6.54-11.81)	8.26 (6.03-11.33)	6.04 (3.75-9.72)	9.37 (6.57-13.37)
10-15	16.05 (11.46-22.47)	14.98 (10.51-21.35)	8.11 (4.83-13.62)	18.40 (12.47-27.17)
Race/Ethnicity				
White	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Black	2.25 (1.66-3.04)	1.69 (1.22-2.35)	1.41 (0.83-2.40)	1.75 (1.25-2.45)
Asian	0.95 (0.78-1.16)	0.92 (0.72-1.16)	0.92 (0.63-1.36)	0.94 (0.73-1.20)
Other	1.17 (0.75-1.81)	0.97 (0.60-1.57)	1.59 (0.81-3.12)	0.84 (0.50-1.40)
Hispanic	1.44 (1.26-1.64)	1.13 (0.95-1.33)	1.54 (1.18-2.02)	1.03 (0.86-1.23)
Leukemia Type				
ALL	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
AML	0.84 (0.72-0.99)	0.93 (0.77-1.12)	0.90 (0.68-1.19)	0.94 (0.77-1.15)
Other	0.64 (0.48-0.87)	0.79 (0.57-1.11)	0.74 (0.44-1.26)	0.81 (0.57-1.16)
Maternal Age (years)				
<25	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
25-34	0.55 (0.48-0.63)	0.59 (0.50-0.69)	0.59 (0.47-0.74)	0.59 (0.50-0.69)
>=35	0.30 (0.25-0.36)	0.34 (0.27-0.42)	0.44 (0.32-0.61)	0.31 (0.24-0.39)
Siblings				
0	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1	0.77 (0.67-0.89)	0.86 (0.74-1.00)	0.92 (0.73-1.16)	0.84 (0.72-0.99)
2	0.76 (0.64-0.89)	0.95 (0.79-1.15)	1.12 (0.85-1.48)	0.90 (0.74-1.10)
3	0.66 (0.52-0.82)	0.85 (0.66-1.10)	0.80 (0.54-1.19)	0.87 (0.66-1.14)
4+	0.92 (0.71-1.20)	1.30 (0.96-1.77)	1.40 (0.91-2.14)	1.26 (0.91-1.75)

Maternal Place of Birth				
US	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Non-US	1.12 (1.00-1.26)	1.13 (0.97-1.32)	1.58 (1.27-1.98)	1.01 (0.86-1.19)
SES				
Low	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
High	0.63 (0.56-0.72)	0.85 (0.74-0.98)	0.75 (0.60-0.94)	0.88 (0.76-1.03)
Calculated Field (μT)				
<0.1	1.00 (reference)	1.00 (reference)˜	NA	NA
0.1-<0.4	1.77 (0.86-3.67)	1.81 (0.83-3.93)˜	NA	NA
≥0.4	0.94 (0.36-2.47)	1.07 (0.39-2.93)˜	NA	NA
Distance to Closest 200+kV Power Line (m)				
≥600	1.00 (reference)	1.00 (reference)˜	NA	NA
500-<600	0.90 (0.55-1.49)	0.74 (0.43-1.26)˜	NA	NA
400-<500	1.36 (0.76-2.43)	1.31 (0.71-2.40)˜	NA	NA
300-<400	1.00 (0.61-1.63)	0.79 (0.47-1.33)˜	NA	NA
200-<300	0.88 (0.52-1.50)	0.85 (0.48-1.51)˜	NA	NA
100-<200	1.21 (0.68-2.15)	1.22 (0.66-2.28)˜	NA	NA
50-<100	2.90 (1.10-7.66)	2.23 (0.82-6.06)˜	NA	NA
<50	0.79 (0.34-1.83)	0.97 (0.40-2.33)˜	NA	NA

⁺Adjusted for all other non-exposure-of-interest covariates in model.

˜Adjusted for age of child, leukemia type, maternal age at birth, race/ethnicity, number of siblings, mother's place of birth and SES. Numbers too small to analyze with regards to neighborhood.

Table 3.4 Odds ratios for childhood leukemia by levels of calculated fields and proximity to 200+ kV power lines adjusted for various characteristics associated with mobility, stratified by mobility status of cases.

	Characteristic	Adjustment	Total	Did Not Move	Moved
Distance to 200+ kV Line <50 m (vs. ≥600 m)	Race/Ethnicity	Not adjusted[1]	1.43 (0.74-2.77)	1.61 (0.71-3.62)	1.31 (0.61-2.82)
		Adjusted[2]	1.37 (0.71-2.66)	1.59 (0.70-3.57)	1.28 (0.60-2.76)
	SES	Not adjusted[1]	1.52 (0.79-2.91)	1.62 (0.72-3.64)	1.43 (0.68-3.02)
		Adjusted[2]	1.52 (0.79-2.92)	1.69 (0.75-3.81)	1.42 (0.67-3.00)
	Maternal Age at Birth	Not adjusted[1]	1.51 (0.79-1.61)	1.63 (0.72-3.67)	1.42 (0.67-3.00)
		Adjusted[2]	1.51 (0.79-2.90)	1.75 (0.77-3.96)	1.43 (0.68-3.02)
	Mother's Place of Birth	Not adjusted[1]	1.51 (0.79-2.91)	1.63 (0.73-3.67)	1.42 (0.67-3.00)
		Adjusted[2]	1.51 (0.79-2.91)	1.63 (0.72-3.67)	1.42 (0.68-3.01)
	Number of Siblings	Not adjusted[1]	1.51 (0.79-2.91)	1.63 (0.73-3.67)	1.42 (0.67-3.00)
		Adjusted[2]	1.51 (0.79-2.91)	1.74 (0.77-3.93)	1.41 (0.67-2.98)
	Dwelling Type*	Not adjusted[1]	2.82 (1.08-7.35)	3.99 (1.09-14.57)	2.31 (0.79-6.74)
		Adjusted[2]	2.94 (1.12-7.72)	4.18 (1.11-15.81)	2.49 (0.84-7.36)
Calculated Fields ≥0.4 μT (vs. <0.1 μT)	Race/Ethnicity	Not adjusted[1]	1.51 (0.70-3.22)	1.65 (0.63-4.35)	1.51 (0.64-3.58)
		Adjusted[2]	1.48 (0.69-3.18)	1.72 (0.65-4.55)	1.50 (0.63-3.59)
	SES	Not adjusted[1]	1.52 (0.71-3.25)	1.66 (0.63-4.36)	1.53 (0.64-3.62)
		Adjusted[2]	1.52 (0.71-3.26)	1.68 (0.64-4.42)	1.51 (0.64-3.57)
	Maternal Age at Birth	Not adjusted[1]	1.52 (0.71-3.25)	1.67 (0.63-4.41)	1.52 (0.64-3.60)
		Adjusted[2]	1.51 (0.71-3.23)	1.62 (0.61-4.33)	1.52 (0.64-3.61)
	Mother's Place of Birth	Not adjusted[1]	1.52 (0.71-3.25)	1.67 (0.63-4.41)	1.52 (0.64-3.60)
		Adjusted[2]	1.51 (0.71-3.23)	1.67 (0.63-4.40)	1.52 (0.64-3.61)
	Number of Siblings	Not adjusted[1]	1.52 (0.71-3.25)	1.67 (0.63-4.41)	1.52 (0.64-3.60)
		Adjusted[2]	1.50 (0.70-3.21)	1.66 (0.63-4.41)	1.53 (0.64-3.62)
	Dwelling Type*	Not adjusted[1]	2.20 (0.80-6.08)	4.45 (1.07-18.54)	1.78 (0.54-5.81)
		Adjusted[2]	2.17 (0.79-6.01)	4.63 (1.11-19.29)	1.74 (0.53-5.69)

[1]Adjusted for age and sex.

[2]Adjusted for age, sex, and the variable in question.

*Only available for small subset of site-visited residences.

Table 3.5 Odds ratios for childhood leukemia by levels calculated fields exposure and proximity to 200+ kV power lines, adjusted for variables associated with mobility using propensity scores.

	Without Dwelling		With Dwelling	
Variable	**Case/Control**	**AOR (95% CI)†**	**Case/Control**	**AOR (95% CI)‡**
Distance (m)				
≥600	4,318/4,244	1.00 (reference)	33/43	1.00 (reference)
100-<200	51/66	0.76 (0.67-0.87)	17/15	1.48 (1.05-2.07)
50-<100	27/27	0.98 (0.81-1.19)	17/18	1.23 (0.89-1.71)
<50	22/15	1.44 (1.14-1.82)	16/8	2.61 (1.76-3.86)
Calculated Fields (μT)				
<0.1	4,604/4,533	1.00 (reference)	47/50	1.00 (reference)
0.1-<0.4	37/40	0.91 (0.70-1.18)	24/29	0.88 (0.60-1.30)
≥0.4	17/11	1.52 (0.98-2.36)	13/7	1.98 (1.11-3.52)

†Adjusted for age of child, sex, race/ethnicity, SES, maternal age at birth, mother's place of birth, and number of siblings.

‡Adjusted for age of child, sex, race/ethnicity, SES, maternal age at birth, mother's place of birth, number of siblings, and dwelling type.

4 The Sensitivity of Reported Effects of EMF on Childhood Leukemia to Uncontrolled Confounding by Residential Mobility: A Hybrid Simulation Study and an Empirical Analysis Using CAPS Data

Authors: Aryana T. Amoon, Onyebuchi A. Arah, Leeka Kheifets

4.1 Abstract

Purpose: Residential mobility is considered as a potential source of confounding in studies assessing environmental exposures, including in studies of electromagnetic field (EMF) exposures and childhood leukemia.

Methods: We present a hybrid-simulation study where we simulate a synthetic dataset based on an existing study and use it to assess the sensitivity of EMF-leukemia associations to different scenarios of uncontrolled confounding by mobility under two major hypotheses of the infectious etiology of childhood leukemia. We then used the findings to conduct sensitivity analysis and empirically offset the potential bias due to unmeasured mobility in the California Powerline Study (CAPS) dataset.

Results: As expected, the stronger the assumed relationship between mobility and exposure and outcome, the greater the potential bias. However, no scenario created a bias strong enough to completely explain away previously observed associations.

Conclusions: We conclude that uncontrolled confounding by residential mobility had some impact on the estimated effect of EMF exposures on childhood leukemia, but that it was unlikely to be the primary explanation behind previously observed largely consistent, but unexplained associations.

4.2 Introduction

Residential mobility is considered as a potential source of bias in studies assessing environmental exposures since the majority of studies consider exposures at only a single residential address. Mobility has been hypothesized to explain observed association (Sahl, 1994) between electromagnetic fields (EMF) and childhood leukemia. Mobility can affect an association through study selection and participation, through exposure misclassification, or even as a confounder (Amoon, Oksuzyan, et al., 2018; Kheifets, Swanson, et al., 2017).

Mobility has been known to be associated with characteristics such as lower socioeconomic status (SES) (Urayama et al., 2009), which are related to a subject's exposure to magnetic fields (Hatch et al., 2000; Wartenberg et al., 2010). SES can be related to the type, quality, and number of appliances within a home, as well as the location of the home with regards to overhead powerlines (Hatch et al., 2000; Wartenberg et al., 2010). Type of dwelling (single-family home vs. apartment) is also associated with exposure to EMF (Feychting & Ahlbom, 1993; Vergara et al., 2015) as well as with mobility (Amoon, Oksuzyan, et al., 2018; McCarthy et al., 2001).

Increased mobility is also associated with older age of child at diagnosis, and younger maternal age at birth (Urayama et al., 2009) which can impact a child's risk for leukemia. Mobility may also be related to increased exposure to viruses or other infections possibly associated with risk of childhood leukemia (Greaves, 2018; Kinlen, 2012; Sahl, 1994). There are two competing theories on the possible infectious etiology of childhood leukemia. In the "population mixing" hypothesis, the disease can develop as a rare response to a relatively common infection introduced to a previously isolated population (Kinlen, 2012). In such a case, exposure to infections would be associated with a greater risk of childhood leukemia. Alternatively, the "delayed infection" hypothesis suggests a protective effect of infections in early-childhood in the development of

leukemia through normal immune system development (Greaves, 2006). Possible routes of early childhood infection include having older siblings, breastfeeding, and attending daycare (Amitay & Keinan-Boker, 2015; Ma et al., 2005; Urayama, Buffler, Gallagher, Ayoob, & Ma, 2010; Urayama et al., 2011; Westergaard et al., 1997).

We previously attempted to assess the effect of mobility on the EMF-leukemia relationship in a California Powerlines Study (CAPS) (Amoon, Oksuzyan, et al., 2018). As the information on mobility was available only for cases, we determined variables predictive of mobility among cases: child's age, maternal age at birth, socioeconomic status (SES), race/ethnicity, parity, and dwelling type. We used a variety of approaches, including propensity score methods to control for those variables. Given the limitations in the available data and previous work, we extend this effort by simulation and sensitivity analysis.

In this paper, we present a hybrid simulation study (Sudan et al., 2016) assessing the impact of unmeasured residential mobility on EMF-leukemia associations. The aims of this study are (1) to simulate a synthetic case-control study based on available CAPS data, and to use it to assess the sensitivity of the plausible EMF-leukemia associations to different scenarios of uncontrolled confounding by mobility, and (2) to use the simulation findings to conduct sensitivity analysis and offset the potential bias due to uncontrolled confounding by mobility in the empirical study of the associations between EMF exposures on childhood leukemia in CAPS.

4.3 Methods

We first conducted a simulation study that generated case-control data using inputs on the interrelations of childhood leukemia, EMF, and mobility conditional on other covariates from an existing case-control study, the California Powerlines Study (CAPS). We then analyzed the simulated dataset to investigate the extent to which not adjusting for various scenarios of

confounding by mobility could explain the magnitude and the direction of the associations between EMF exposures and childhood leukemia. Finally, we assessed the empirical relationship between EMF exposures and childhood leukemia in CAPS by offsetting potential confounding by mobility as seen in the simulation study.

CAPS is a case-control study that enrolled childhood leukemia cases younger than 16 years diagnosed in California between 1988 and 2008. Cases were identified from the California Cancer Registry [CCR; www.ccrcal.org] and matched to the California Birth Registry [CBR; California Department of Public Health, Vital Statistics Branch]. Controls were randomly selected from the CBR and matched to cases 1:1. Controls were excluded if they were diagnosed with any type of cancer in California before the matched case's date of diagnosis. Out of 6,645 eligible childhood leukemia cases identified from the CCR, 4,879 were matched to birth records and had accurate geocoding of both birth and diagnosis addresses. Similarly, 4,835 controls met these criteria (for birth address only). Details of this study have been previously described (Kheifets et al., 2015). Cases were required to be both born and diagnosed in California, but as controls were selected from the CBR, they were not required to be residing in California at the time of their case's diagnosis. Hence, the mobility of controls is unknown.

First, we analyzed CAPS data to extract information on the prevalences of our EMF exposures: living <50 meters (m) from an overhead powerline of 200 kilovolts (kV) or greater and exposure to calculated magnetic fields of 0.4 microTesla (μT) or greater. The prevalence of childhood leukemia, as well as, residential mobility among cases, was also retrieved.

We used CAPS to estimate odds ratios (ORs) between the variables used in previous analyses (Crespi et al., 2016; Kheifets, Crespi, et al., 2017b) and distance to high-voltage overhead powerlines, calculated magnetic fields, and childhood leukemia to the extent possible with the

available data using both cases and controls. Table 4.1 lists the ORs and prevalences of our selected characteristics to both exposures of interest as well as to leukemia.

Second, we simulated data for a new mobility variable as well as new exposure and outcome variables using the parameters in Table 4.1 based on a causal structure of mobility as a confounder in the EMF-leukemia association shown in the two directed acyclic graphs (DAGs). These DAGs were used to depict plausible scenarios based on accepted theory or evidence. Figure 4.1 is based on the population mixing hypothesis while Figure 4.2 is based on the delayed infection hypothesis. We simulated the new variables using equations with the defined parameter values in Table 4.1. All variables were binary. Mobility was drawn from a Bernoulli trial, B[1, p], where p was the probability of observing the variable as 1 (versus the reference 0) in the study. Since mobility information was not available for controls, we used the prevalence among cases for initial simulation values. In future analyses, mobility can be simulated using similar equations as those below taken from previous analyses (Amoon, Oksuzyan, et al., 2018). For the exposures, we used indicator variables for the most highly exposed children (living <50 m to a 200+ kV line; exposed to ≥0.4 μT calculated fields).

In particular, the probability of living <50 m to an overhead powerline of 200 kV or greater used in the simulations was specified as:

$$1/(1 + \exp(-(\log\text{-odds}(PL_{background} = 1) + \log(OR_{age\ <1\text{-}PL})*age<1 + \log(OR_{age\ 1\text{-}5\text{-}PL})*age1\text{-}5 + \log(OR_{age\ 6\text{-}9\text{-}PL})*age6\text{-}9 + \log(OR_{male\text{-}PL})*male + \log(OR_{high\ SES\text{-}PL})*highSES + \log(OR_{Hispanic\text{-}PL})*Hispanic + \log(OR_{other\ race\text{-}PL})*otherrace + \log(OR_{asian\ race\text{-}PL})*asianrace + \log(OR_{black\ race\text{-}PL})*blackrace + \log(OR_{moved\text{-}PL})*moved))),$$

where PL stands for powerlines.

The corresponding equation for exposure to ≥0.4 μT calculated fields was:

$1/(1 + \exp(-(\text{log-odds}(CF_{background} = 1) + \log(OR_{age <1\text{-}CF})*age<1 + \log(OR_{age\ 1\text{-}5\text{-}CF})*age1\text{-}5 + \log(OR_{age\ 6\text{-}9\text{-}CF})*age6\text{-}9 + \log(OR_{male\text{-}CF})*male + \log(OR_{high\ SES\text{-}CF})*highSES + \log(OR_{Hispanic\text{-}CF})*Hispanic + \log(OR_{other\ race\text{-}CF})*otherrace + \log(OR_{asian\ race})*asianrace + \log(OR_{black\ race})*blackrace + \log(OR_{moved\text{-}PL})*moved)))$, where CF stands for calculated fields.

Similarly, the probability of leukemia given these exposures and the other variables was specified as:

$1/(1 + \exp(-(\text{log-odds}(Leuk_{background} = 1) + \log(OR_{EMF\text{-}Leuk})*newlygenertedEMFexposures + \log(OR_{age <1\text{-}Leuk})*age<1 + \log(OR_{age\ 1\text{-}5\text{-}Leuk})*age1\text{-}5 + \log(OR_{age\ 6\text{-}9\text{-}Leuk})*age6\text{-}9 + \log(OR_{male\text{-}Leuk})*male + \log(OR_{high\ SES\text{-}Leuk})*highSES + \log(OR_{Hispanic\text{-}Leuk})*Hispanic + \log(OR_{other\ race\text{-}Leuk})*otherrace + \log(OR_{asian\ race\text{-}Leuk})*asianrace + \log(OR_{black\ race\text{-}Leuk})*blackrace + \log(OR_{moved\text{-}Leuk})*moved)))$, where EMF would be either distance or calculated fields.

The ORs for the covariates in the equations above are the same as Table 1, save for mobility, which is discussed below. The background prevalences of the exposure and outcome variables were based on their proportions in CAPS. To determine if confounding by mobility or other variables could affect previous findings of EMF-leukemia associations, we set the true effect of those associations as null.

We copied our dataset 1000 times and simulated as many Monte Carlo samples of our new variables. We repeated this for different values for the association of mobility with leukemia ($OR_{moved\text{-}Leuk}$s) as well as mobility with the EMF exposures ($OR_{moved\text{-}PL/CF}$s). For the population mixing hypothesis (Figure 1), we ran models where the association between mobility and outcome were assumed to be 1.3, 2.0, or 3.0 in accordance with moderate previous findings (Kinlen, 2012). In the case of the delayed infection hypothesis (Figure 4.2), we assumed the mobility-leukemia association to be negative and varied it at 0.3, 0.6 and 0.9 also based on previous literature

(McNally & Eden, 2004). The mobility-EMF associations were the same under both hypotheses: they were assumed to be positive but small. We assessed scenarios of the EMF-mobility association at 1.3, 2.0 and 3.0 to simulate a small, moderate, or large effect of mobility, respectively. Each of the generated samples were run through a "fully-adjusted-minus-mobility" model that included all other variables except mobility. In this model, any difference from null in the coefficient of the exposure would be due to mobility. The resulting 1000 ORs from each model of the 1000 replicates of the hybrid simulated datasets were summarized using the median as the point estimate and the 2.5^{th} and 97.5^{th} percentiles as the lower and upper limits of the 95% simulation interval in each scenario.

Finally, to address the second main aim of this study, we used methods and formulas described by Arah and others (Arah, 2017; Arah, Chiba, & Greenland, 2008) to obtain the estimated bias generated by uncontrolled mobility in our simulated dataset and used it as a fixed offset in the empirically estimated associations between EMF exposures and childhood leukemia based on the real CAPS dataset. The formula used to derive the offset was given by:

Offset = $\log(OR_{EMF\_Leuk})$*$Exposure$ where OR_{EMF_Leuk} is the observed biased OR for the association between EMF and leukemia when all other variables, except for mobility, are accounted for in the simulated datasets wherein EMF had no effect on leukemia. The observed OR_{EMF_Leuk} from the simulated datasets could, thus, only be due to uncontrolled confounding by mobility and is a bias factor on the OR scale. Offsetting this bias factor from the empirical estimated EMF-Leukemia OR is equivalent to dividing this biased empirical EMF-Leukemia OR by the bias factor to obtain a mobility-adjusted EMF-Leukemia OR (Arah, 2017; Arah et al., 2008). The main empirical analysis adjusted the variables sex, age, SES and race/ethnicity using a complete-case analysis. Sensitivity analyses involved using multiple imputations on observations

with missing values for the variables SES and race/ethnicity (10 imputations per missing value). We also included other predictors of mobility documented previously (Amoon, Oksuzyan, et al., 2018): maternal age at birth, parity, and dwelling type in complete-case scenarios.

All analyses were conducted using SAS software version 9.3. Copyright © 2017 SAS Institute Inc.

4.4 Results

The complete-case analysis included 9,244 subjects of which 4,659 were cases and 4,585 were controls. 61% of cases had moved between time of birth and diagnosis. The simulated impact of uncontrolled confounding by mobility on the associations between EMF exposures and childhood leukemia under the population mixing hypothesis is presented at the top of Table 4.2. For the analyses involving distance, removing mobility from the model increased the ORs up to 1.31. However, even with mobility associated with both exposure and outcome with an OR of 3.0, there was not enough bias introduced to explain a previously observed association of 1.41 (Crespi et al., 2016). Naturally, as the effect of mobility increased, so did the amount of bias generated by leaving it out of the model. A similar trend was seen for calculated fields, where again, previously observed associations (such as OR of 1.50) were not reached (Kheifets, Crespi, et al., 2017b).

The bottom of Table 4.2 shows the results of the simulations under the delayed infection hypothesis. It shows similar trends to the population mixing hypothesis but in the opposite direction. Scenario 3 with a mobility-exposure OR of 3.0 and mobility-leukemia exposure of 0.3 showed similar levels of bias to the maxed-out scenarios under the population mixing hypothesis. Several scenarios with mobility-leukemia at an OR of 0.9 showed almost no bias remaining in the model, even when mobility was omitted, but this could be due to the fact that the chosen association was so weak.

The results of using offsets in CAPS to account for the potential bias of mobility is also presented in Table 4.2. For the population mixing hypothesis, as expected, the greater the potential bias introduced by mobility, the closer to null the association became when accounting for it, for both distance and calculated fields. However, even in our scenario with the greatest bias introduced, the effect of large calculated fields on the incidence of childhood leukemia is not erased completely, even if the effect is imprecise. In the case of the delayed infection hypothesis, accounting for the bias pulled the ORs away from the null.

Using multiple imputation on the same variables did not change the results (results not shown). When maternal age at birth and parity were included in the model, the results were almost identical (Supplementary Table 4.1), suggesting that although these variables are predictive of mobility, they do not appear to alter the EMF-leukemia relationship.

The associations were stronger for a site-visited subset: 1.73 (0.82-3.66) for distance and 1.99 (0.84-4.72) for magnetic fields. When site-visited dwelling classification was included, all the estimates increased in magnitude (Supplementary Table 4.2), with the bias-adjusted distance ORs ranging from 1.28 to 1.62 for the population mixing hypothesis and from 1.66 to 2.25 under the delayed infection hypothesis. However, the sample size was greatly reduced for these analyses. In all cases, both exposures still showed associations with increased risk of childhood leukemia, even after accounting for the potential bias introduced by unmeasured mobility.

4.5 Discussion

In this paper, we created a synthetic case-control study based on information from CAPS on EMF exposures and childhood leukemia as well as related characteristics and used the computed bias from the simulation experiments to adjust the real CAPS dataset for uncontrolled confounding by residential mobility. We simulated different scenarios using the synthesized variables and

examined whether the reported associations between EMF exposures and childhood leukemia could be affected by unmeasured residential mobility, which could represent either infectious etiology of childhood leukemia or other ways mobility could affect such a relationship.

In our study, although mobility appeared to be an important factor to adjust for, we find associations close to those previously found in CAPS: 1.41 for the association between living <50 m from a high-voltage powerline and 1.50 for the association between exposure to ≥0.4 μT of calculated magnetic fields, except for strong postulated associations between mobility and both exposure and outcome. For mobility were to be truly responsible for the observed associations, the relationship between mobility and both EMF exposures and childhood leukemia would have to be strong (ORs > 3.0 in both cases). However, as previously assessed among the cases in CAPS, mobility did not appear to be associated greatly with EMF exposures (Amoon, Oksuzyan, et al., 2018). Stronger trends were seen under both hypotheses. Of note were scenarios in the delayed infection hypothesis where mobility-leukemia had an OR of 0.9. In the distance analyses, omitting mobility from the fully adjusted model still showed a null effect. For calculated fields, we saw an OR of 1.02 as well as 1.01. This does not lend support to the delayed infection hypothesis, at least in CAPS.

The most interesting finding was using the bias offsets in CAPS. It appeared as though mobility might play a role in the observed association between both EMF exposures and childhood leukemia. The 'unadjusted' ORs, however, were also lower than previously observed in CAPS analyses (Crespi et al., 2016; Kheifets, Crespi, et al., 2017b). Even with our "strongest mobility" scenario, neither bias-adjusted association of EMF exposure with leukemia appeared to be null, although the confidence intervals were relatively wider than before bias-adjustment. This further suggests that mobility alone might not completely explain away previously observed associations,

unless the true associations are extreme. This also does not rule out other risk factors that could explain them away. Information on infections, for example, was not available in this study to assess the infectious etiology theories more rigorously.

The additional models with maternal age and parity included did not appear to change the results at all, suggesting that while they may be related to mobility, they are not substantially related to EMF exposures to have an effect on their relationship. Dwelling type, however, increased all ORs in magnitude, including the estimated bias introduced by mobility in the simulated datasets. This suggests that dwelling type is a major cofactor of mobility. Unfortunately, the subset for this analysis included only 240 subjects which also led to wide confidence intervals. Further analysis of dwelling type with additional identification of this information for subjects in CAPS is planned.

Strengths of this study include the use of CAPS, which itself has a relatively large sample size to increase power, and used population registries to obtain data, eliminating potential for participation bias due to self-selection. Exposure assessment was also conducted blindly with respect to case-control status, reducing the risk for information bias due to recorder bias.

Potential limitations of this study involve residential mobility itself. In CAPS, it was defined by the distance between a case's birth address and diagnosis address of more than 50 meters, but this could be misclassified. Additionally, we used the prevalence of mobility only among cases because it was unavailable among controls which may not accurately reflect the source population distribution of residential mobility. Also, previous studies have shown a discrepancy in mobility among cases and controls (Green et al., 1999; Kleinerman et al., 1997; McBride et al., 1999). Finally, as only initial and final address information was available, it is possible for a case to have moved, then returned to their birth home before being diagnosed, but we expect this to be rare.

Uncontrolled confounding by residential mobility appears to have impact on the estimated effects of EMF exposures, namely proximity to high-voltage powerlines and increased magnetic field exposure, on childhood leukemia. However, it is unlikely to be the primary driving force behind previously observed largely consistent, but unexplained associations.

Figure 4.1 DAG of a main causal structure under the population mixing hypothesis where mobility is positively associated with both EMF exposure and childhood leukemia and Z is the set of other associated measured factors.

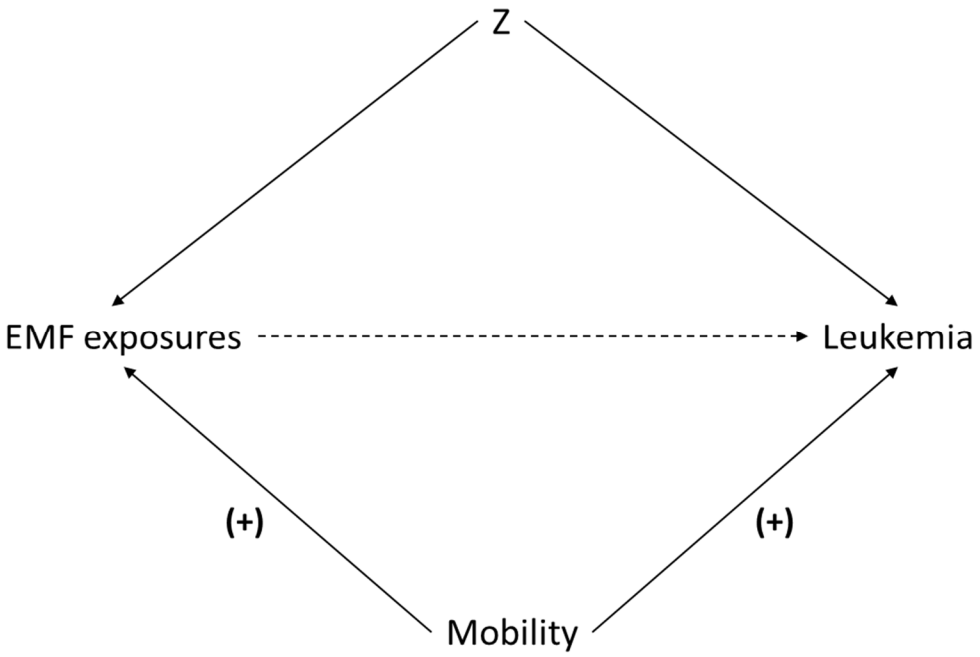


Figure 4.2 DAG of a main causal structure under the delayed infection hypothesis where mobility is positively associated with EMF exposure and a protective factor for childhood leukemia and Z is the set of other associated measured factors.

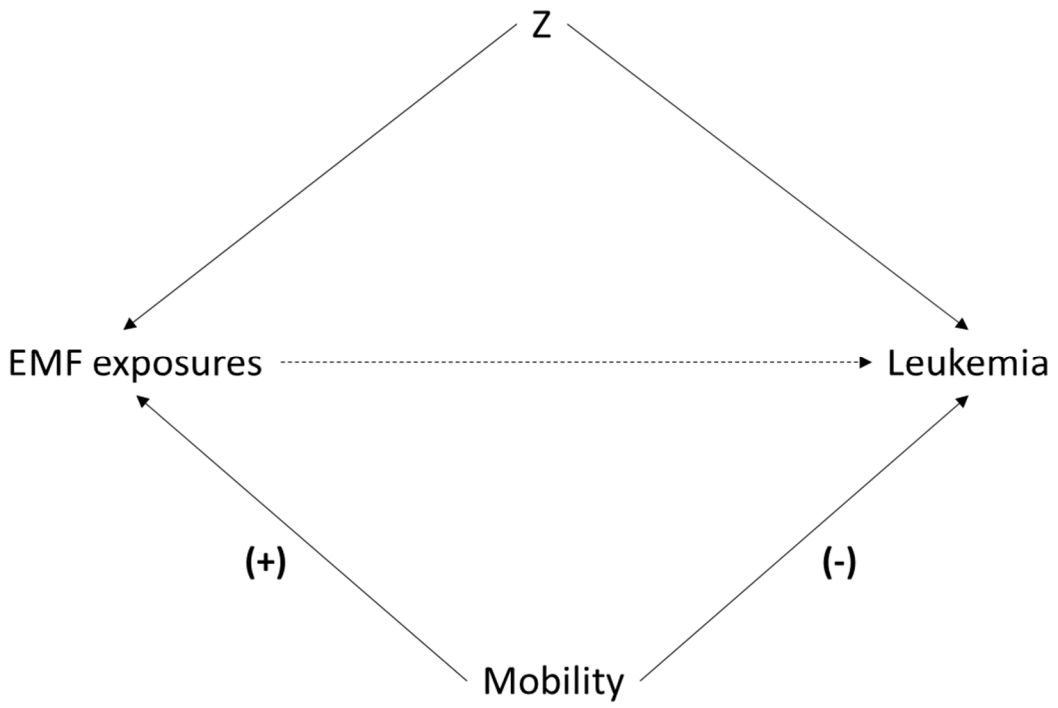


Table 4.1 Input values for the relationship between the covariates and distance to powerlines, calculated magnetic fields, and leukemia in CAPS used to develop the synthetic cohort.

Covariate	<50 m to 200+ kV Line (OR)[1]	≥0.4 µT (OR)[2]	Distance -> Leukemia (OR)[3]	CF -> Leukemia (OR)[4]	Prevalence in CAPS (0 < p <1)
Male Sex	1.01	0.37	0.96	0.96	0.56
Asian Race (v. non-Hispanic White)	2.19	1.98	1.24	1.24	0.11
Black Race (v. non-Hispanic White)	0.52*	1.34*	0.63	0.63	0.07
Hispanic (v. non-Hispanic White)	1.44	1.45	1.20	1.20	0.50
Other Race (v. non-Hispanic White)	1.96*	N/A*	1.06	1.06	0.02
<1 Years Old (v. 10-15 Years Old)	1.12*	1.11*	0.91	0.91	0.07
1-5 Years Old (v. 10-15 Years Old)	1.81	1.24	0.99	0.99	0.64
6-9 Years Old (v. 10-15 Years Old)	0.45	0.67	0.97	0.97	0.17
High SES	0.62	0.63	1.05	1.05	0.30

CAPS California Powerlines Study, *m* meters, *kV* kilovolts, *µT* microTesla, *CF* calculated fields, *OR* odds ratio, *p* probability, *SES* socioeconomic status.

[1]Effect of covariates on living <50 m from a 200+ kV line, adjusted for all other covariates.

[2]Effect of covariates on having ≥0.4, adjusted for all other covariates.

[3]Effect of covariates on leukemia risk, adjusted for all other covariates and distance.

[4]Effect of covariates on leukemia risk, adjusted for all other covariates and calculated fields.

*Cells n<5

Mobility ORs not estimated due to no information for controls.

Table 4.2 Complete-case analysis of the impact of mobility on the association between EMF exposures and childhood leukemia.

	Varied Inputs		<50 m distance to 200+ kV power lines			≥0.4 µT calculated fields		
			Bias introduced	Offset Analysis		Bias introduced	Offset Analysis	
Hypothesis	Mobility -> Exposure (OR)	Mobility -> Leukemia (OR)	Distance -> Leukemia OR (95% CI)	Before Adjustment OR (95% CI)	After Adjustment OR (95% CI)	CF -> Leukemia OR (95% CI)	Before Adjustment OR (95% CI)	After Adjustment OR (95% CI)
Population Mixing	1.30	1.30	1.03 (0.66-1.69)		1.34 (0.70-2.60)	1.06 (0.51-2.41)		1.40 (0.65-3.00)
	2.00	1.30	1.05 (0.72-1.60)		1.31 (0.68-2.54)	1.06 (0.55-2.14)		1.40 (0.65-3.01)
	3.00	1.30	1.08 (0.77-1.48)		1.29 (0.67-2.49)	1.06 (0.64-1.92)		1.40 (0.65-3.01)
	1.30	2.00	1.07 (0.66-1.79)		1.29 (0.67-2.50)	1.08 (0.49-2.81)		1.38 (0.64-2.97)
	2.00	2.00	1.13 (0.74-1.76)	1.39 (0.72-2.68)	1.22 (0.63-2.36)	1.14 (0.60-2.40)	1.49 (0.69-3.19)	1.30 (0.61-2.80)
	3.00	2.00	1.19 (0.83-1.70)		1.17 (0.60-2.26)	1.17 (0.72-2.25)		1.27 (0.59-2.72)
	1.30	3.00	1.08 (0.68-1.86)		1.28 (0.66-2.47)	1.14 (0.50-3.14)		1.31 (0.61-2.81)
	2.00	3.00	1.21 (0.78-1.94)		1.15 (0.59-2.22)	1.24 (0.64-2.81)		1.20 (0.56-2.57)
	3.00	3.00	1.31 (0.90-1.91)		1.06 (0.55-2.05)	1.30 (0.74-2.70)		1.14 (0.53-2.45)
Delayed Infection	1.30	0.90	1.00 (0.62-1.67)		1.39 (0.72-2.68)	1.02 (0.49-2.42)		1.46 (0.68-3.13)
	2.00	0.90	1.00 (0.67-1.49)		1.38 (0.71-2.67)	1.01 (0.52-1.97)		1.48 (0.69-3.17)
	3.00	0.90	0.99 (0.70-1.37)		1.40 (0.72-2.70)	0.98 (0.56-1.74)		1.52 (0.71-3.25)
	1.30	0.60	0.98 (0.58-1.57)		1.42 (0.73-2.74)	0.99 (0.45-2.13)		1.51 (0.70-3.23)
	2.00	0.60	0.94 (0.62-1.40)	1.39 (0.72-2.68)	1.48 (0.76-2.86)	0.94 (0.47-1.85)	1.49 (0.69-3.19)	1.58 (0.74-3.39)
	3.00	0.60	0.91 (0.63-1.24)		1.52 (0.79-2.95)	0.89 (0.50-1.56)		1.67 (0.78-3.58)
	1.30	0.30	0.94 (0.54-1.50)		1.47 (0.76-2.84)	0.96 (0.40-2.02)		1.55 (0.72-3.33)
	2.00	0.30	0.85 (0.52-1.29)		1.64 (0.85-3.17)	0.85 (0.39-1.63)		1.75 (0.82-3.75)
	3.00	0.30	0.77 (0.52-1.06)		1.81 (0.93-3.49)	0.77 (0.39-1.29)		1.93 (0.90-4.14)

EMF electromagnetic fields, *m* meters, *kV* kilovolts, *µT* microTesla, *CF* calculated fields, *OR* odds ratio, *CI* confidence interval
All models were adjusted for age, sex, socioeconomic status, and race/ethnicity.

4.6 Appendices

Supplementary Table 4.1 Complete-case analysis of the impact of mobility on the association between EMF exposures and childhood leukemia with additional variables: maternal age at birth and parity (n=9,242).

		<50 m distance to 200+ kV power lines			≥0.4 µT calculated fields		
		Bias introduced	Offset Analysis		Bias introduced	Offset Analysis	
Hypothesis	Set	Distance -> Leukemia OR (95% CI)	Before Adjustment OR (95% CI)	After Adjustment OR (95% CI)	CF -> Leukemia OR (95% CI)	Before Adjustment OR (95% CI)	After Adjustment OR (95% CI)
Population Mixing	1	1.03 (0.68-1.50)		1.34 (0.69-2.60)	1.03 (0.60-1.86)		1.43 (0.67-3.07)
	2	1.05 (0.76-1.44)		1.32 (0.68-2.55)	1.05 (0.65-1.77)		1.40 (0.65-3.01)
	3	1.07 (0.81-1.42)		1.30 (0.67-2.52)	1.06 (0.69-1.66)		1.39 (0.65-2.97)
	4	1.05 (0.71-1.62)		1.32 (0.68-2.56)	1.05 (0.62-1.86)		1.41 (0.66-3.02)
	5	1.12 (0.82-1.58)	1.39 (0.72-2.69)	1.24 (0.64-2.40)	1.12 (0.70-1.88)	1.47 (0.69-3.16)	1.32 (0.61-2.83)
	6	1.17 (0.90-1.56)		1.18 (0.61-2.29)	1.17 (0.77-1.82)		1.25 (0.58-2.69)
	7	1.08 (0.73-1.70)		1.28 (0.66-2.48)	1.09 (0.63-2.16)		1.35 (0.63-2.90)
	8	1.20 (0.86-1.76)		1.16 (0.60-2.25)	1.20 (0.74-2.15)		1.23 (0.57-2.64)
	9	1.29 (0.96-1.80)		1.08 (0.56-2.09)	1.30 (0.84-2.08)		1.14 (0.53-2.44)
Delayed Infection	1	1.00 (0.66-1.47)		1.38 (0.71-2.68)	1.01 (0.56-1.75)		1.46 (0.68-3.14)
	2	1.00 (0.71-1.38)		1.40 (0.72-2.70)	0.99 (0.59-1.68)		1.49 90.70-3.20)
	3	0.98 (0.73-1.31)		1.41 (0.73-2.73)	0.98 (0.63-1.47)		1.50 (0.70-3.22)
	4	0.97 (0.63-1.41)		1.43 (0.74-2.77)	0.97 (0.55-1.69)		1.51 (0.71-3.25)
	5	0.93 (0.66-1.29)	1.39 (0.72-2.69)	1.49 (0.77-2.89)	0.93 (0.56-1.53)	1.47 (0.69-3.16)	1.58 (0.74-3.39)
	6	0.90 (0.68-1.18)		1.55 (0.80-3.00)	0.89 (0.58-1.37)		1.66 (0.77-2.56)
	7	0.93 (0.58-1.40)		1.49 (0.77-2.89)	0.93 (0.49-1.63)		1.58 (0.74-3.38)
	8	0.84 (0.56-1.19)		1.66 (0.86-3.21)	0.84 (0.48-1.34)		1.75 (0.82-3.76)
	9	0.76 (0.55-1.03)		1.82 (0.94-3.53)	0.76 (0.48-1.16)		1.93 (0.90-4.15)

EMF electromagnetic fields, *m* meters, *kV* kilovolts, *µT* microTesla, *CF* calculated fields, *OR* odds ratio, *CI* confidence interval,
All models were adjusted for age, sex, socioeconomic status, race/ethnicity, maternal age at birth, and parity.

Supplementary Table 4.2 Complete-case analysis of the impact of mobility on the association between EMF exposures and childhood leukemia with additional variables: maternal age at birth, parity, and site-visited dwelling (n=240).

		<50 m distance to 200+ kV power lines			≥0.4 µT calculated fields		
		Bias introduced	Offset Analysis		Bias introduced	Offset Analysis	
Hypothesis	Set	Distance -> Leukemia OR (95% CI)	Before Adjustment OR (95% CI)	After Adjustment OR (95% CI)	CF -> Leukemia OR (95% CI)	Before Adjustment OR (95% CI)	After Adjustment OR (95% CI)
Population Mixing	1	1.07 (0.59-1.95)		1.62 (0.77-3.42)	1.02 (0.47-2.34)		1.95 (0.82-4.61)
	2	1.10 (0.62-1.96)		1.58 (0.75-3.34)	1.06 (0.50-2.26)		1.89 (0.80-4.47)
	3	1.11 (0.62-2.05)		1.56 (0.74-3.30)	1.09 (0.54-2.21)		1.83 (0.77-4.33)
	4	1.09 (0.59-2.03)		1.59 (0.75-3.36)	1.04 (0.47-2.63)		1.91 (0.81-4.52)
	5	1.17 (0.64-2.07)	1.73 (0.82-3.66)	1.48 (0.70-3.13)	1.09 (0.54-2.43)	1.99 (0.84-4.72)	1.82 (0.77-4.32)
	6	1.23 (0.68-2.23)		1.41 (0.67-2.98)	1.17 (0.61-2.45)		1.71 (0.72-4.04)
	7	1.11 (0.59-2.05)		1.56 (0.74-3.29)	1.09 (0.47-2.75)		1.84 (0.78-4.34)
	8	1.22 (0.68-2.37)		1.43 (0.67-3.01)	1.20 (0.57-2.60)		1.66 (0.70-3.93)
	9	1.35 (0.73-2.55)		1.28 (0.61-2.71)	1.32 (0.65-2.88)		1.52 (0.64-3.59)
Delayed Infection	1	1.05 (0.56-1.88)		1.66 (0.78-3.50)	0.98 (0.44-2.24)		2.03 (0.86-4.79)
	2	1.03 (0.56-1.92)		1.69 (0.80-3.56)	0.99 (0.47-2.13)		2.01 (0.85-4.77)
	3	1.03 (0.57-1.84)		1.69 (0.80-3.57)	0.99 (0.49-2.01)		2.01 (0.85-4.75)
	4	1.01 (0.54-1.92)		1.71 (0.81-3.61)	0.97 (0.41-2.18)		2.05 (0.87-4.86)
	5	0.96 (0.51-1.82)	1.73 (0.82-3.66)	1.80 (0.85-3.80)	0.93 (0.40-1.95)	1.99 (0.84-4.72)	2.14 (0.91-5.07)
	6	0.93 (0.50-1.69)		1.86 (0.88-3.93)	0.90 (0.43-1.84)		2.22 (0.94-5.24)
	7	0.95 (0.49-1.80)		1.82 (0.86-3.85)	0.93 (0.35-1.93)		2.15 (0.91-5.09)
	8	0.85 (0.44-1.62)		2.03 (0.96-4.29)	0.84 (0.33-1.80)		2.37 (1.00-5.61)
	9	0.77 (0.39-1.48)		2.25 (1.06-4.74)	0.76 (0.35-1.55)		2.64 (1.12-6.24)

EMF electromagnetic fields, *m* meters, *kV* kilovolts, *µT* microTesla, *CF* calculated fields, *OR* odds ratio, *CI* confidence interval,
All models were adjusted for age, sex, socioeconomic status, race/ethnicity, maternal age at birth, parity, and dwelling.

5 The Role of Dwelling in the California Power Line Study of Childhood Leukemia

Authors: Amoon, A., Crespi, C.M., Nguyen, A., Zhao, X., Vergara, X., Kheifets, L.

5.1 Abstract

Aims: The type of dwelling where a child lives is an important factor when considering residential exposure to environmental agents in studies of childhood leukemia. In this paper, we explore the role of dwelling type in the magnetic field (MF)- leukemia relationship using data from the California Power Line Study (CAPS), a population-based case-control study of childhood leukemia. Dwelling type could affect the magnetic field (MF)-childhood leukemia relationship in a number of ways: as a surrogate for other factors; as a confounder; through exposure misclassification; or as an effect measure modifier.

Methods: In the original study, residence type was ascertained only for a small subset. For this analysis, we obtained information on over 2,000 subjects. Using logistic regression, we assessed whether dwelling type is a risk factor for childhood leukemia, what covariates are related to dwelling type, whether dwelling type behaves as a confounder or as a potential effect measure modifier in the MF-leukemia relationship.

Results: A majority of children lived in single-family homes or duplexes (70%). As expected, dwelling type was associated with race/ethnicity and socioeconomic status. Dwelling type was neither associated with childhood leukemia risk, nor functioned as a confounder. Stratification revealed potential effect measure modification by dwelling type.

Conclusion: Dwelling type does not appear to play a significant role in the MF-leukemia relationship in the CAPS dataset as either a risk factor or confounder. Future research should explore the role of dwelling as an effect measure modifier and potential interaction effects.

5.2 Introduction

Dwelling is an important factor when considering residential exposure to environmental agents in studies of childhood leukemia. However, it has been little studied in the context of magnetic fields (MF). Type of dwelling (single-family home, apartment, etc.) could affect the MF-childhood leukemia relationship in a number of ways: as a surrogate for other factors, such as socioeconomic status (SES) or radon; as a confounder; through potential exposure misclassification; or as an effect measure modifier. A directed acyclic graph illustrating these possibilities is presented in Figure 5.1.

Dwelling type could be a risk factor for leukemia by acting as a proxy for other unknown or unmeasured exposures. In studies of childhood leukemia, attributes related to a residential dwelling such as the structure, materials, and even age can affect the levels of exposure to gamma radiation or radon gas (Calvente et al., 2014; Kavet, Zaffanella, Pearson, & Dallapiazza, 2004; C. Y. Li et al., 2007). Previous research has shown both that dwelling type is (Del Risco Kollerud, Blaasaas, & Claussen, 2014; Feychting & Ahlbom, 1993; Raaschou-Nielsen et al., 2008) and is not (Amigou et al., 2011; London et al., 1991) related to childhood leukemia when comparing single-family vs multi-family housing. Type of residence may also affect the MF-leukemia relationship through association with other covariates implicated in MF-childhood leukemia research. Socioeconomic status is associated with dwelling type (McCarthy et al., 2001); dwelling type or home ownership has often been used as a surrogate for SES. Residential mobility, or moving between time of birth and diagnosis, is also associated with dwelling type. When used as a proxy for mobility in adjusting MF-leukemia estimates, we saw a difference in the models excluding dwelling compared to those including it. However, the sample size was limited (Amoon,

Oksuzyan, et al., 2018). Homeownership, and subsequently dwelling type, is also strongly associated with race/ethnicity (United States Census Bureau, 2018).

Dwelling type could function as a confounder if it is associated with MF exposures in addition to childhood leukemia. While two pooled analyses did not show dwelling type to be a confounder in the MF-leukemia relationship (Ahlbom et al., 2000; Amoon, Crespi, et al., 2018), residence type has been shown to be a strong predictor of measured magnetic fields (McBride et al., 1999). Several studies have found greater exposure to magnetic fields in apartments when using both measurements (Brix et al., 2001; Calvente et al., 2014; Schuz et al., 2001; Schuz et al., 2000; Tomitsch et al., 2010) and calculations (Feychting & Ahlbom, 1993). Not only can the dwelling type affect the level of MF exposure, it can also affect assessment of said exposure, especially when voltage of, and proximity to, power lines is used to calculate magnetic fields (Kheifets, Swanson, et al., 2017). For example, measured or calculated MF might be higher in a smaller dwelling (apartment) compared to larger dwelling (single-family home). On the other hand, calculated MF may be less accurate for an apartment if its exact location within a structure is unknown. Thus, certain dwelling types (non-single-family homes) are more likely to result in exposure misclassification (Amoon, Oksuzyan, et al., 2018; Feychting & Ahlbom, 1993; Vergara et al., 2015). To date, there are no data on the association between dwelling type and proximity to overhead power lines.

Previous studies suggest that dwelling type could potentially function as an effect measure modifier with different strengths of the MF-leukemia association for different dwelling types (Amoon, Oksuzyan, et al., 2018). The relationship seems to depend on the surrogate of MF exposure: a Swedish study showed stronger association for calculated fields and leukemia in single-family homes despite lower recorded calculated magnetic fields than apartments (Feychting

& Ahlbom, 1993), while a study in Colorado showed lower risks of childhood leukemia when using spot measurements in single-family homes (Savitz et al., 1988). No recent studies have undertaken such stratified analysis.

In this paper, we explore the role of dwelling type in the MF-leukemia relationship using data from the California Power Line Study (CAPS). The aims of this study are (1) to determine whether dwelling type is a risk factor for leukemia, (2) determine what covariates are related to dwelling type, (3) examine whether dwelling type behaves as a confounder in the MF-leukemia relationship, and (4) to analyze the role of dwelling type as a potential effect modifier in the MF-leukemia relationship.

5.3 Methods

CAPS is a state-wide case-control study that included childhood leukemia cases younger than 16 years of age diagnosed in California between 1988 and 2008. Cases were identified from the California Cancer Registry [CCR; www.ccrcal.org] and matched to the California Birth Registry [CBR; California Department of Public Health, Vital Statistics Branch]. Controls were randomly selected from the CBR and matched to cases 1:1. Controls were excluded if they were diagnosed with any type of cancer in California before the matched case's date of diagnosis. Out of 6,645 eligible childhood leukemia cases identified from the CCR, 4,879 were matched to birth records and had accurate geocoding of birth addresses. Similarly, 4,835 controls met these criteria. Details of this study have been previously described (Kheifets et al., 2015). Exposure assessment for distance to overhead power lines was three-tiered. First, geographic information systems (GIS) information was obtained from electric power companies and distance from home address was calculated for all subjects living within 2000 meters (m) of one. Google Earth aerial imagery was used to confirm distance for about a third of the subjects. Finally, for homes within distances close

enough to generate non-zero magnetic fields, site visits were conducted to measure the actual distance as well as to collect other relevant information.

In the original study, residence type was ascertained only for site-visited homes (n=252) for whom addresses were available. For this analysis, we obtained information on residence type for 1,799 additional subjects. The 1,799 additional subjects included (1) all subjects with potential for high exposure and (2) a stratified random sample (without replacement), where the stratification was by distance to nearest power line of 200 kV or greater. Sampling weights were calculated as the inverse of the probability of selection. Once these subjects were selected, this sample was combined with the site-visited sample, their order was randomized, and a unique ID was generated for each subject. A dataset that contained only the unique ID, and latitude and longitude were provided to an analyst who used Google Earth and Google Map's Street View to determine dwelling type using the current day image (no historical data was used). Thus, the analyst was blinded to the cases/control status of the subjects. Homes were classified as single-family residence, apartment, duplex, or mobile home. In some instances, real estate websites were used to confirm single- vs multi-family home. Additionally, for each subject, a confidence score was recorded (high: the residence was identified and was in the middle of a neighborhood with homogeneous dwelling types; medium: residence not clearly identified, but homogeneous neighborhood; low: unsure of precise location of residence in the mixed neighborhood).

For the main analyses, for the subjects with both site-visited and Google Earth-determined dwelling type, the site-visit information was used. Sensitivity analyses include (1) using all 2,051 observations but with only Google Earth information; (2) using only those with high confidence score for dwelling code (n=1,883); and (3) using only the site-visited subset. Sampling weights were used in all analyses. All models were adjusted for age, sex, SES, and race/ethnicity unless

otherwise stated. Multiple imputation was used for observations with missing SES (n=308) or race/ethnicity (n=44) information. Analyses used all four dwelling types as well as a binary classification in which duplexes and single-family homes were combined into one category and mobile homes with apartments in another. The binary category was based on previous literature showing similar risk estimates for both detached and semi-detached dwellings compared with other types of housing (Calvente et al., 2014; Maslanyj et al., 2007; Myers, Clayden, Cartwright, & Cartwright, 1990; Schuz et al., 2000). We also looked at a binary classification where mobile homes, apartments, and duplexes were all considered "non-single-family" residences, but found duplexes to be more similar to single-family homes for most factors (data not presented).

We first assessed whether dwelling type could be a risk factor for childhood leukemia. These analyses used unconditional logistic regression with dwelling type as the independent variable and case/control status as the dependent variable. We fit both crude and adjusted models. Next, we examined whether dwelling type was associated with other variables known to be relevant in the MF-leukemia relationship using chi-square tests and logistic regression. The variables examined included age, sex, SES, race/ethnicity, maternal age at birth, and mobility. Third, to assess whether dwelling is a confounder, unconditional logistic regression was performed using categorical exposures for MF as the independent variables and case/control status as the outcome, with and without dwelling included in the model. Distance to high-voltage (≥200 kV) lines was categorized into 0-<50, 50-<200, 200-<600, 600-<2000, and 2000+ m (reference). Categories for calculated fields were as follows: <0.1 (reference), 0.1-<0.4, and ≥0.4 μT. Finally, to assess whether dwelling is an effect modifier, we conducted unconditional logistic regression analyses stratified by the different dwelling types and examined the estimated relationship between distance and MF exposures and childhood leukemia risk.

Analyses were performed using SAS software version 9.3. Copyright © 2017 SAS Institute Inc. CAPS was approved by University of California, Los Angeles Office for the Protection of Research Subjects.

5.4 Results

A majority of children in the 1,799 newly sampled set lived in single-family homes or duplexes (69.7%), which is comparable to the site-visited subset (72.2%). Of the 252 site-visited residences, thirty-four were misclassified using Google Earth inspection (13.5%). Of these, 22 were marked as high confidence. Eighteen single-family residences were misclassified by the Google Earth inspection, 14 as apartments and 4 as duplexes, with 10 marked as high-confidence. Even after double-checking the 34 discrepant observations using Zillow.com and other such sites, 18 remained misclassified (7.1% of 252).

Childhood leukemia cases appeared less likely to live in mobile homes or duplexes (Table 5.1); however, results were imprecise. No differences in risk estimates were observed when dwelling was dichotomized (single-family homes and duplexes vs apartments and mobiles homes). Adjustments left estimates unchanged. There was no difference in results when only Google Earth classification was used or when the analysis was restricted to those with a high confidence score (results not shown). In the site-visited subset, however, the adjusted odds ratios for childhood leukemia for living in an apartment as compared to a single-family home increased slightly, but remained imprecise (Table 5.1). This increase was also noticeable when dwelling type was binary. Table 2 shows the relationships of dwelling type with other residential characteristics. As expected, SES, race/ethnicity, and residential mobility were all associated with dwelling type. Those with low SES were more likely to live in housing other than duplex or single-family homes (odds ratio (OR): 1.71, 95% confidence interval (CI): 1.29-2.28). Similarly, subjects who were Black, Asian

or Hispanic or had moved at least once between birth and diagnosis were also less likely to live in single-family homes. Conversely, living close to high-voltage overhead power lines (OR: 0.62, 95% CI: 0.28-1.37) and increased calculated fields (OR: 0.63, 95% CI: 0.25-1.37) were more likely in single-family homes, but these estimates were imprecise. All results were drawn towards the null in the adjusted models (Table 5.2).

The results of the confounder analysis are presented in Table 5.3. In the distance analyses, adjustment for dwelling had no effect (OR: 1.50, 95% CI: 0.88-2.58). The same was true for calculated fields (from OR: 1.39 to OR: 1.41). The high confidence subset exhibited the same results, as did the site-visited subset. However, the site-visited subset revealed larger ORs, suggesting that better exposure and confounder assessment may be a factor in the observed results.

Table 5.4 shows the results of the stratified analyses aimed at assessing whether dwelling type is an effect modifier for the EMF-childhood leukemia relationship. While there are small numbers for apartment and mobile home-dwellers living close to high-voltage lines and in the highest calculated magnetic fields, there does appear to be a difference in strength of association between those who live in duplexes and single-family homes compared to the total. For distance less than 50 m from 200+ kV lines, in the total sample of 2,051 subjects, the OR (95% CI) decreased from 1.50 (0.88-2.57) overall to 1.31 (0.72-2.37) for children living in duplexes and single-family homes. Meanwhile, despite higher calculated fields among those living in duplexes and single-family homes (Table 5.2), there was no difference in OR compared to the total sample (1.39 vs 1.38, respectively). The high confidence and site-visited subsets showed similar trends, albeit with greater differences given the smaller sample sizes. Interestingly, the binary classification of single-family home vs non-single-family home showed different results in the site-visited subset of this

analysis (Supplementary Table 5.1), with the effect estimate for distance in single-family homes dropping to null, while the effect estimate for calculated fields was increased.

5.5 Discussion

In this paper, we explored the possible roles of dwelling type on the MF-leukemia relationship. Duplexes and mobile homes appeared to be less common among cases than controls, even after adjusting for SES, but results were imprecise. Within the smaller, more accurately assessed, site-visited subset, however, apartments and mobile homes were more common in cases, compared to single-family homes and duplexes, after adjusting for age, sex, SES, and race/ethnicity (Table 5.1). Although we found no differences in the overall effects when using only Google Earth classifications compared to the best info for the 252 site-visited, the possibility of dwelling type misclassification is high considering 13.5% of the 252 site-visited dwellings were misclassified. We do not, however, expect this misclassification to be differential as the analyst was blind to case/control status.

As expected, dwelling type was associated with both race/ethnicity and SES, although Schuz et al. found that residence type only appeared to be associated with other measures of SES in urban areas compared to rural areas (Schuz et al., 2001). Our study had no information on urban/rural status. However, Tomitsch et al. reported that differences between urban and rural areas could be explained by residence type (Tomitsch et al., 2010), so we did not seek this information to be included in the model when both SES and dwelling type were present. Neither age nor maternal age at birth were associated with dwelling type (Table 5.2).

Most previous findings for measured fields showed higher MF in non-single-family dwellings (Brix et al., 2001; Calvente et al., 2014; Schuz et al., 2001; Tomitsch et al., 2010), whereas our results showed the opposite. While we used calculated fields, based on the voltage of and distance

from nearby overhead power lines, instead, our findings were still contrary to a previous study using calculated fields (Feychting & Ahlbom, 1993). On the other hand, Table 5.2 shows that close proximity to higher-voltage lines was also less common among non-single-family residences, consistent with previous studies (Myers et al., 1990). Compared to a previous California study where over 80% of subjects lived in single-family homes (Does et al., 2011), the subjects in this study were more likely to live in apartments (29.2%). As mentioned previously, exposure assessment is limited in apartment dwellings, and calculations are often not as accurate (Feychting & Ahlbom, 1993).

We did not find evidence of confounding by dwelling for either distance or magnetic fields (Table 5.3). Similarly, dwelling type did not affect a previously observed multiplicative interaction between calculated fields and distance (Crespi, Swanson, Vergara, & Kheifets, 2019), although numbers were small. These observations are consistent with previous findings for dwelling type in pooled analyses (Ahlbom et al., 2000; Amoon, Crespi, et al., 2018). Both ORs at the highest exposure levels were consistent with previous findings (Crespi et al., 2016; Kheifets, Crespi, et al., 2017a), albeit our results were slightly higher for proximity to power lines (OR: 1.50) and slightly lower for higher calculated fields (OR: 1.39) due to the dwelling sample subset. These results, combined with the elevated effect estimates in the site-visited subset, suggest that the ability to detect an association, should one exist, may depend on the of quality of exposure assessment.

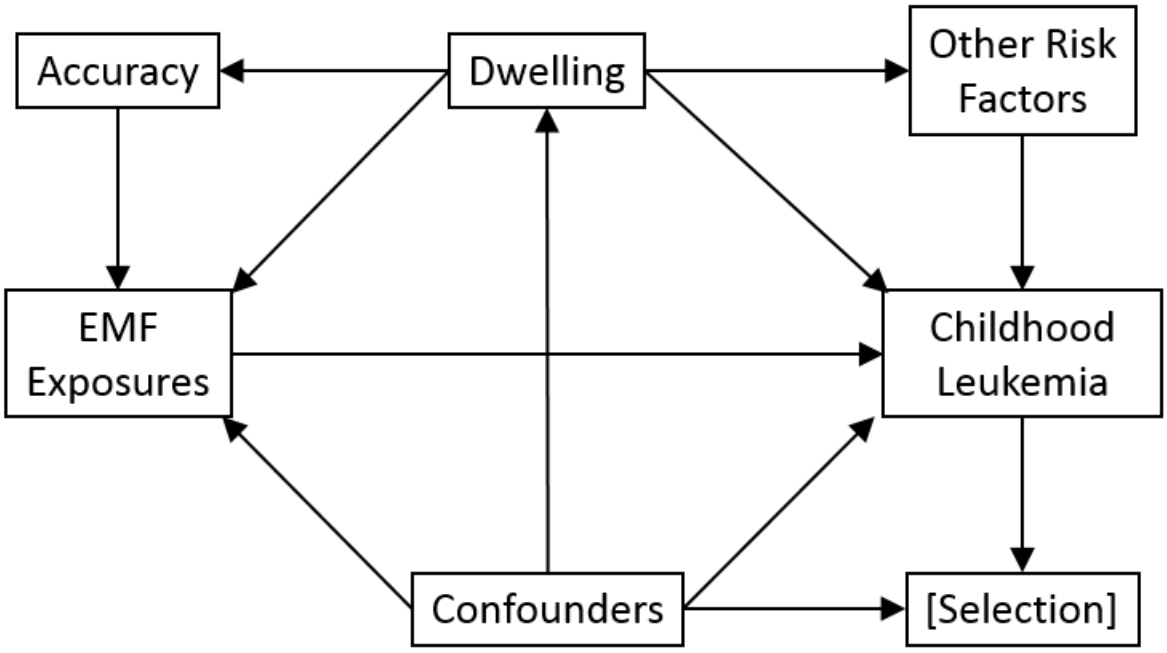
Although evidence of confounding was minimal, we appeared to find effect measure modification by dwelling type when comparing the MF-leukemia relationship in those who lived in single-family homes compared to those who did not (Table 5.4). Due to small numbers, however, the results were extremely imprecise and will need to be replicated in future studies. The two exposures revealed different trends, with distance showing weaker associations in single-family

homes and calculated fields remaining mostly unchanged. This, too, was in contrast to some previous findings which showed an OR of 5.6 for exposure to calculated fields ≥0.2 μT in single-family homes, but only 1.1 in apartments (Feychting & Ahlbom, 1993).

Strengths of our study include the use of population registries for identification of cases and controls, avoiding participation bias and exposure and confounder assessment blind to case-control status to reduce information bias. However, misclassification of dwelling type and magnetic field exposure is possible, but we do not expect such misclassification to be differential with respect to case/control status. Additionally, while we attempted to estimate calculated fields and distance using historical data, we did not ascertain dwelling types in actual birth years due to the issues with historic Google Earth images. Again, we do not expect this bias to be differential and changes of residences from apartments to single family homes are uncommon. Another limitation was small sample sizes for our effect modification analysis. Even with dwelling types grouped together, the numbers in the highest exposed categories remained small. Interaction effects between the MF exposures and dwelling type should be studied in future analyses where the sample size allows.

In conclusion, dwelling type does not appear to play a significant role in the MF-leukemia relationship in the CAPS dataset as either a risk factor or confounder. As mentioned previously, different countries have different types of building structures, materials, and electrical wiring practices. Accurate exposure and confounder assessment are crucial to the study of this matter. Future research should explore the role of dwelling as an effect modifier and potential interaction effects.

Figure 5.1 Directed acyclic graph depicting possible influence of dwelling on EMF-leukemia relationship



Confounders include: child's age, sex, race/ethnicity, socioeconomic status, etc.
Other Risk Factors include: radon gas, gamma radiation, and other pollutants.

Table 5.1 Risk of childhood leukemia by dwelling type in CAPS (n=2,051).

Set	Dwelling Type	Cases	Controls	COR (95% CI)	AOR (95% CI)*
All observations (n=2,051)	Apartment	293	306	1.06 (0.83-1.36)	1.04 (0.81-1.34)
	Duplex	20	25	0.75 (0.35-1.60)	0.74 (0.34-1.60)
	Mobile Home	9	8	0.68 (0.20-2.27)	0.65 (0.19-2.25)
	Single-Family (reference)	697	693	1.00 (reference)	1.00 (reference)
	Apartment or Mobile	302	314	1.06 (0.83-1.36)	1.04 (0.81-1.33)
	Duplex or Single (reference)	717	718	1.00 (reference)	1.00 (reference)
Site-visited (n=252)	Apartment	34	35	1.09 (0.62-1.91)	1.31 (0.71-2.44)
	Duplex	2	4	N/A	N/A
	Mobile Home	0	1	N/A	N/A
	Single-Family (reference)	83	93	1.00 (reference)	1.00 (reference)
	Apartment or Mobile	34	36	1.08 (0.62-1.88)	1.29 (0.70-2.38)
	Duplex or Single (reference)	85	97	1.00 (reference)	1.00 (reference)

CAPS California Power Line Study, *COR* crude odds ratio, *AOR* adjusted odds ratio.

*Adjusted for age, sex, socioeconomic status and race/ethnicity. Missing variables multiply imputed.

Table 5.2 Association of various residential characteristics with dwelling type.

Characteristic		Apt + Mob	SFH + Dup	(Apt + Mobile) vs. (Duplex + Single-Fam) [reference]	
				COR (95% CI)	AOR (95% CI)*
Age (years)	<2	126	279	0.75 (0.51-1.09)	0.98 (0.77-1.26)
	2	102	238	0.71 (0.48-1.07)	0.88 (0.67-1.15)
	3	92	229	0.76 (0.51-1.14)	0.98 (0.75-1.29)
	4-6	145	366	0.75 (0.53-1.08)	0.98 (0.79-1.23)
	7+	151	323	1.00 (reference)	1.00 (reference)
Sex	Male	337	797	0.92 (0.72-1.18)	0.97 (0.86-1.10)
	Female	279	638	1.00 (reference)	1.00 (reference)
SES	Low	456	930	1.71 (1.29-2.28)	1.25 (1.07-1.45)
	High	139	475	1.00 (reference)	1.00 (reference)
Race/ethnicity	White	130	475	1.00 (reference)	1.00 (reference)
	Black	56	71	2.28 (1.37-3.82)	1.64 (1.03-2.59)
	Asian	62	153	1.95 (1.24-3.08)	1.49 (0.97-2.26)
	Hispanic	343	687	1.98 (1.47-2.69)	1.36 (0.98-1.86)
	Other	7	23	0.63 (0.17-2.30)	0.39 (0.13-1.15)
Maternal Age at Birth (years)	<25	248	439	1.26 (0.86-1.86)	1.07 (0.88-1.30)
	25-35	293	780	0.97 (0.67-1.40)	0.93 (0.78-1.11)
	≥35	75	291	1.00 (reference)	1.00 (reference)
Moved	No	79	311	0.44 (0.30-0.65)	N/A
	Yes	223	406	1.00 (reference)	N/A
Distance to 200+ kV Line (meters)	<50	8	30	0.62 (0.28-1.37)	0.74 (0.39-1.38)
	50-<100	16	41	0.90 (0.51-1.59)	1.03 (0.63-1.67)
	100-<200	33	90	0.85 (0.56-1.29)	0.99 (0.68-1.44)
	200-<600	153	346	1.02 (0.81-1.29)	1.13 (0.87-1.46)
	≥600	406	928	1.00 (reference)	1.00 (reference)
Calculated Fields (μT)	≥0.4	6	22	0.63 (0.25-1.57)	0.98 (0.55-1.75)
	0.1-<0.4	18	62	0.67 (0.39-1.15)	0.78 (0.49-1.23)
	<0.1	592	1,351	1.00 (reference)	1.00 (reference)

Dup duplex, *Apt* apartment, *Mob* mobile home, *SFH* single-family home, *SES* socioeconomic status, *kV* kilovolts, *μT* microTesla

*All models are adjusted for age, sex, SES, and race/ethnicity. Mobility was not included as it is only known for cases. Missing values multiply imputed.

Table 5.3 Effect of MF exposures on childhood leukemia with and without dwelling as a confounder.

Sample Set	Exposure Distance (m)	Counts Cases	Counts Controls	Without Dwelling	With Dwelling
All 2,051, using site-visit info for 252	<50	23	15	1.50 (0.88-2.57)	1.50 (0.88-2.58)
	50-<100	28	29	0.93 (0.60-1.44)	0.94 (0.60-1.45)
	100-<200	53	70	0.77 (0.54-1.08)	0.77 (0.54-1.08)
	200-<600	251	248	0.99 (0.78-1.24)	0.98 (0.78-1.24)
	600+	664	670	1.00 (reference)	1.00 (reference)
1,883 high confidence	<50	20	13	1.53 (0.86-2.74)	1.53 (0.85-2.73)
	50-<100	24	27	0.89 (0.56-1.41)	0.90 (0.57-1.42)
	100-<200	45	62	0.75 (0.52-1.08)	0.75 (0.52-1.08)
	200-<600	236	236	1.00 (0.78-1.27)	1.00 (0.78-1.27)
	600+	612	608	1.00 (reference)	1.00 (reference)
252 site-visited subset	<50	23	14	1.72 (0.85-3.49)	1.75 (0.84-3.64)
	50-<100	26	29	0.97 (0.53-1.77)	1.00 (0.53-1.89)
	100-<200	29	38	0.79 (0.43-1.46)	0.79 (0.41-1.49)
	200-<600	2	3	N/A	N/A
	600+	39	49	1.00 (reference)	1.00 (reference)
Sample Set	**Calculated Fields (μT)**	**Counts Cases**	**Counts Controls**	**Without Dwelling**	**Four Dwellings**
All 2,051, using site-visit info for 252	≥0.4	17	11	1.39 (0.82-2.35)	1.41 (0.83-2.38)
	0.1-<0.4	38	42	0.82 (0.55-1.21)	0.81 (0.55-1.20)
	<0.1	964	979	1.00 (reference)	1.00 (reference)
1,883 high confidence	>=0.4	15	10	1.39 (0.81-2.41)	1.39 (0.80-2.40)
	0.1-<0.4	32	38	0.79 (0.52-1.19)	0.79 (0.52-1.20)
	<0.1	890	898	1.00 (reference)	0.79 (0.53-1.20)
252 site-visited subset	≥0.4	17	10	1.63 (0.92-2.90)	1.70 (0.95-3.07)
	0.1-<0.4	37	42	0.81 (0.53-1.25)	0.79 (0.51-1.22)
	<0.1	65	81	1.00 (reference)	1.00 (reference)

MF magnetic fields, *m* meters, *μT* microTesla

All models adjusted for age, sex, socioeconomic status, and race/ethnicity, using multiple imputations for missing values.

Table 5.4 Odds ratios for childhood leukemia by MF exposures, stratified by dwelling type.

Sample Set	Exposure	Total OR (95% CI)	Apt + Mob ca/co	Apt + Mob OR (95% CI)	Dup + SFH ca/co	Dup + SFH OR (95% CI)
Distance to 200+ kV lines (m)						
All (n=2,051)	<50	1.50 (0.88-2.57)	6/2	N/A	17/13	1.31 (0.72-2.37)
	50-<100	0.93 (0.60-1.44)	8/8	0.86 (0.35-2.11)	20/21	0.95 (0.56-1.58)
	100-<200	0.77 (0.54-1.08)	16/17	0.80 (0.39-1.66)	37/53	0.72 (0.48-1.07)
	200-<600	0.99 (0.78-1.24)	65/88	0.59 (0.35-0.98)	186/160	1.18 (0.90-1.55)
	600+	1.00 (reference)	207/199	1.00 (reference)	457/471	1.00 (reference)
High confidence (n=1,833)	<50	1.53 (0.86-2.74)	8/1	N/A	12/12	1.05 (0.54-2.04)
	50-<100	0.89 (0.56-1.41)	5/8	0.55 (0.20-1.50)	19/19	1.05 (0.61-1.79)
	100-<200	0.75 (0.52-1.08)	13/15	0.63 (0.28-1.44)	32/47	0.74 (0.48-1.13)
	200-<600	1.00 (0.78-1.27)	60/83	0.55 (0.30-1.01)	176/153	1.21 (0.91-1.62)
	600+	1.00 (reference)	183/175	1.00 (reference)	429/433	1.00 (reference)
Site-visit (n=252)	<50	1.72 (0.85-3.49)	6/2	N/A	17/12	1.33 (0.54-3.30)
	50-<100	0.97 (0.53-1.77)	6/8	16.87 (4.15-68.58)	20/21	0.90 (0.40-2.01)
	100-<200	0.79 (0.43-1.46)	7/8	33.27 (8.37-132.25)	22/30	0.65 (0.30-1.41)
	200-<600	N/A	0/2	N/A	2/1	2.00 (0.21-19.27)
	600+	1.00 (reference)	15/16	1.00 (reference)	24/33	1.00 (reference)
Calculated Fields (μT)						
All (n=2,051)	≥0.4	1.39 (0.82-2.35)	4/2	N/A	13/9	1.38 (0.77-2.47)
	0.1-<0.4	0.82 (0.55-1.21)	11/7	0.99 (0.40-2.46)	27/35	0.77 (0.49-1.19)
	<0.1	1.00 (reference)	287/305	1.00 (reference)	677/674	1.00 (reference)
High confidence (n=1,833)	≥0.4	1.39 (0.81-2.41)	5/3	N/A	10/7	1.41 (0.73-2.75)
	0.1-<0.4	0.79 (0.52-1.19)	9/5	1.18 (0.46-3.04)	23/33	0.72 (0.44-1.17)
	<0.1	1.00 (reference)	255/274	1.00 (reference)	635/624	1.00 (reference)
Site-visit (n=252)	≥0.4	1.63 (0.92-2.90)	4/2	N/A	13/8	1.57 (0.82-3.03)
	0.1-<0.4	0.81 (0.53-1.25)	11/7	1.16 (0.41-3.28)	26/35	0.75 (0.46-1.24)
	<0.1	1.00 (reference)	19/27	1.00 (reference)	46/54	1.00 (reference)

MF magnetic fields, *Dup* duplex, *Apt* apartment, *Mob* mobile home, *SFH* single-family home, *ca* cases, *co controls, OR* odds ratio, *CI* confidence interval, *kV* kilovolts, *m* meters, *μT* microTesla

All models adjusted for age, sex, socioeconomic status, and race/ethnicity, using multiple imputations for missing values.

*Cells n<5

5.6 Appendix

Supplementary Table 5.1 Odds ratio for childhood leukemia by MF exposures, stratified by alternative binary dwelling type in site-visited subset.

	Total	Dup + Apt + Mob		SFH	
Exposure	**OR (95% CI)**	**ca/co**	**OR (95% CI)**	**ca/co**	**OR (95% CI)**
Distance to 200+ kV lines (m)					
<50	1.72 (0.85-3.49)	7/2	N/A	16/12	1.00 (0.40-2.53)
50-<100	0.97 (0.53-1.77)	7/8	22.90 (6.56-79.96)	19/21	0.86 (0.37-1.98)
100-<200	0.79 (0.43-1.46)	7/9	25.27 (7.09-89.98)	22/29	0.66 (0.30-1.49)
200-<600	N/A	0/2	N/A	2/1	N/A
600+	1.00 (reference)	15/19	1.00 (reference)	24/30	1.00 (reference)
Calculated Fields (μT)					
≥0.4	1.63 (0.92-2.90)	5/3	N/A	12/7	1.79 (0.84-3.79)
0.1-<0.4	0.81 (0.53-1.25)	11/7	1.32 (0.50-3.50)	26/35	0.68 (0.40-1.17)
<0.1	1.00 (reference)	20/30	1.00 (reference)	45/51	1.00 (reference)

MF magnetic fields, *Dup* duplex, *Apt* apartment, *Mob* mobile home, *SFH* single-family home, *ca* cases, *co controls, OR* odds ratio, *CI* confidence interval, *kV* kilovolts, *m* meters, *μT* microTesla
All models adjusted for age, sex, socioeconomic status, and race/ethnicity, using multiple imputations for missing values.

6 Conclusion and Public Health Implications

This dissertation first examined whether proximity to overhead power lines showed similar increases in risk for childhood leukemia as compared to magnetic fields and found a small, but imprecise, effect for those living closer than 50 meters from higher voltages lines only. No associations were found when using lines of all voltages or calculated magnetic fields in the same subset of studies. Further, in the set of countries analyzed, urban versus rural setting, traffic density, and SES type did not affect the association, only residential mobility did.

Using the record-based California study, we then assessed how residential mobility may affect the EMF-leukemia relationship. As expected, several risk factors for childhood leukemia were also associated with residential mobility. We highlight the importance of accounting for residential mobility in the estimation of environmental exposures, as most of the cases had moved between time of birth and diagnosis. However, we found that the association between EMF exposures and leukemia was stronger in the stratum of cases who did not move. We saw a similar increase in risk for children who moved out of their birth neighborhood, giving some credence to the infectious etiology hypotheses for childhood leukemia.

As residential mobility information was only available for cases, we used variables associated with mobility among cases as surrogates in the model to control for mobility, but saw no change in effect. We decided to synthesize a dataset based on CAPS to compute potential bias that could be introduced via uncontrolled confounding of residential mobility. However, we found that mobility would have to be strongly associated (ORs > 3.0) with both EMF exposures and childhood leukemia. However, we did not find the former to be the case.

In all mobility analyses, only dwelling type seemed to influence the association in any way. Dwelling type, like mobility, can act as a proxy for other unknown or unmeasured exposures, act

as a confounder, affect the quality of exposure assessment, or influence the relationship through effect measure modification. In the final part of this dissertation, based on a newly collected data, we analyzed the role of dwelling type in CAPS. We found that higher calculated fields were less common in non-single-family residences, contrary to previous findings (Feychting & Ahlbom, 1993), but did not find evidence of confounding. However, there was some evidence of effect measure modification: although single-family homes showed larger magnetic fields, the effect of EMF exposures on leukemia was weaker in those homes, again, in contrast to previous findings (Feychting & Ahlbom, 1993).

While these results broadly corroborate previous pooled analyses of MF and childhood leukemia (Ahlbom et al., 2000; Greenland et al., 2000; Kheifets et al., 2010; Schuz et al., 2007), they support alternative explanations for the associations observed between residential distance from power lines and leukemia risk, such as other correlates of distance or unmeasured confounders. Future analyses should explore the interaction of EMF exposures and dwelling type and mobility on risk of childhood leukemia. Although this dissertation focused on EMF exposures, we believe the findings on mobility and dwelling are relevant to other environmental exposures and other childhood outcome studies.

7 References

Adam, M., Kuehni, C. E., Spoerri, A., Schmidlin, K., Gumy-Pause, F., Brazzola, P., . . . Zwahlen, M. (2015). Socioeconomic Status and Childhood Leukemia Incidence in Switzerland. *Front Oncol, 5*, 139. doi:10.3389/fonc.2015.00139

Adam, M., Rebholz, C. E., Egger, M., Zwahlen, M., & Kuehni, C. E. (2008). Childhood leukaemia and socioeconomic status: what is the evidence? *Radiat Prot Dosimetry, 132*(2), 246-254. doi:10.1093/rpd/ncn261

Ahlbom, A., Day, N., Feychting, M., Roman, E., Skinner, J., Dockerty, J., . . . Verkasalo, P. K. (2000). A pooled analysis of magnetic fields and childhood leukaemia. *Br J Cancer, 83*(5), 692-698. doi:10.1054/bjoc.2000.1376

Alba, R. D., & Logan, J. R. (1991). Variations on two themes: racial and ethnic patterns in the attainment of suburban residence. *Demography, 28*(3), 431-453.

American Cancer Society (2015). What Are the Key Statistics for Childhood Leukemia? Retrieved from https://www.cancer.org/cancer/leukemia-in-children/about/key-statistics.html.

Amigou, A., Sermage-Faure, C., Orsi, L., Leverger, G., Baruchel, A., Bertrand, Y., . . . Clavel, J. (2011). Road traffic and childhood leukemia: the ESCALE study (SFCE). *Environ Health Perspect, 119*(4), 566-572. doi:10.1289/ehp.1002429

Amitay, E. L., & Keinan-Boker, L. (2015). Breastfeeding and Childhood Leukemia Incidence: A Meta-analysis and Systematic Review. *JAMA Pediatr, 169*(6), e151025. doi:10.1001/jamapediatrics.2015.1025

Amoon, A. T., Crespi, C. M., Ahlbom, A., Bhatnagar, M., Bray, I., Bunch, K. J., . . . Kheifets, L. (2018). Proximity to overhead power lines and childhood leukaemia: an international pooled analysis. *Br J Cancer, 119*(3), 364-373. doi:10.1038/s41416-018-0097-7

Amoon, A. T., Oksuzyan, S., Crespi, C. M., Arah, O. A., Cockburn, M., Vergara, X., & Kheifets, L. (2018). Residential mobility and childhood leukemia. *Environ Res, 164*, 459-466. doi:10.1016/j.envres.2018.03.016

Arah, O. A. (2017). Bias Analysis for Uncontrolled Confounding in the Health Sciences. *Annu Rev Public Health, 38*, 23-38. doi:10.1146/annurev-publhealth-032315-021644

Arah, O. A., Chiba, Y., & Greenland, S. (2008). Bias formulas for external adjustment and sensitivity analysis of unmeasured confounders. *Ann Epidemiol, 18*(8), 637-646. doi:10.1016/j.annepidem.2008.04.003

Barrington-Trimis, J. L., Cockburn, M., Metayer, C., Gauderman, W. J., Wiemels, J., & McKean-Cowdin, R. (2017). Trends in childhood leukemia incidence over two decades from 1992 to 2013. *Int J Cancer, 140*(5), 1000-1008. doi:10.1002/ijc.30487

Belson, M., Kingsley, B., & Holmes, A. (2007). Risk factors for acute leukemia in children: a review. *Environ Health Perspect, 115*(1), 138-145. doi:10.1289/ehp.9023

Blaasaas, K. G., & Tynes, T. (2002). Comparison of three different ways of measuring distances between residences and high voltage power lines. *Bioelectromagnetics, 23*(4), 288-291.

Boothe, V. L., Boehmer, T. K., Wendel, A. M., & Yip, F. Y. (2014). Residential traffic exposure and childhood leukemia: a systematic review and meta-analysis. *Am J Prev Med, 46*(4), 413-422. doi:10.1016/j.amepre.2013.11.004

Borugian, M. J., Spinelli, J. J., Mezei, G., Wilkins, R., Abanto, Z., & McBride, M. L. (2005). Childhood leukemia and socioeconomic status in Canada. *Epidemiology, 16*(4), 526-531.

Brix, J., Wettemann, H., Scheel, O., Feiner, F., & Matthes, R. (2001). Measurement of the individual exposure to 50 and 16 2/3 Hz magnetic fields within the Bavarian population. *Bioelectromagnetics, 22*(5), 323-332.

Bunch, K. J., Keegan, T. J., Swanson, J., Vincent, T. J., & Murphy, M. F. (2014). Residential distance at birth from overhead high-voltage powerlines: childhood cancer risk in Britain 1962-2008. *Br J Cancer, 110*(5), 1402-1408. doi:10.1038/bjc.2014.15

Bunch, K. J., Swanson, J., Vincent, T. J., & Murphy, M. F. (2016). Epidemiological study of power lines and childhood cancer in the UK: further analyses. *J Radiol Prot, 36*(3), 437-455. doi:10.1088/0952-4746/36/3/437

Burgi, A., Sagar, S., Struchen, B., Joss, S., & Roosli, M. (2017). Exposure Modelling of Extremely Low-Frequency Magnetic Fields from Overhead Power Lines and Its Validation by Measurements. *Int J Environ Res Public Health, 14*(9). doi:10.3390/ijerph14090949

Burke, D. L., Ensor, J., & Riley, R. D. (2017). Meta-analysis using individual participant data: one-stage and two-stage approaches, and why they may differ. *Stat Med, 36*(5), 855-875. doi:10.1002/sim.7141

Calvente, I., Davila-Arias, C., Ocon-Hernandez, O., Perez-Lobato, R., Ramos, R., Artacho-Cordon, F., . . . Fernandez, M. F. (2014). Characterization of indoor extremely low frequency and low frequency electromagnetic fields in the INMA-Granada cohort. *PLoS One, 9*(9), e106666. doi:10.1371/journal.pone.0106666

Cancer Research UK. (2018). Children's cancer statistics. Retrieved April 2017, from https://www.cancerresearchuk.org/health-professional/cancer-statistics/childrens-cancers/incidence.%20Accessed%20February%202017.

Canfield, M. A., Ramadhani, T. A., Langlois, P. H., & Waller, D. K. (2006). Residential mobility patterns and exposure misclassification in epidemiologic studies of birth defects. *J Expo Sci Environ Epidemiol, 16*(6), 538-543. doi:10.1038/sj.jes.7500501

Champion, T. (2005). Population movement within the UK. In *Focus on people and migration* (pp. 91-113): Springer.

Charles, H., Good, C. B., Hanusa, B. H., Chang, C. C., & Whittle, J. (2003). Racial differences in adherence to cardiac medications. *J Natl Med Assoc, 95*(1), 17-27.

Chen, L., Bell, E. M., Caton, A. R., Druschel, C. M., & Lin, S. (2010). Residential mobility during pregnancy and the potential for ambient air pollution exposure misclassification. *Environ Res, 110*(2), 162-168. doi:10.1016/j.envres.2009.11.001

Clark, W. A. (1992). Residential preferences and residential choices in a multiethnic context. *Demography, 29*(3), 451-466.

Clark, W. A., & Huang, Y. (2003). The life course and residential mobility in British housing markets. *Environment and Planning A, 35*(2), 323-339.

Crespi, C. M., Swanson, J., Vergara, X. P., & Kheifets, L. (2019). Childhood leukemia risk in the California Power Line Study: Magnetic fields versus distance from power lines. *Environ Res, 171*, 530-535. doi:10.1016/j.envres.2019.01.022

Crespi, C. M., Vergara, X. P., Hooper, C., Oksuzyan, S., Wu, S., Cockburn, M., & Kheifets, L. (2016). Childhood leukaemia and distance from power lines in California: a population-based case-control study. *Br J Cancer, 115*(1), 122-128. doi:10.1038/bjc.2016.142

Dalmasso, P., Pastore, G., Zuccolo, L., Maule, M. M., Pearce, N., Merletti, F., & Magnani, C. (2005). Temporal trends in the incidence of childhood leukemia, lymphomas and solid tumors in north-west Italy, 1967-2001. A report of the Childhood Cancer Registry of Piedmont. *Haematologica, 90*(9), 1197-1204.

Debray, T. P., Moons, K. G., van Valkenhoef, G., Efthimiou, O., Hummel, N., Groenwold, R. H., . . . GetReal Methods Review, G. (2015). Get real in individual participant data (IPD) meta-analysis: a review of the methodology. *Res Synth Methods, 6*(4), 293-309. doi:10.1002/jrsm.1160

Del Risco Kollerud, R., Blaasaas, K. G., & Claussen, B. (2014). Risk of leukaemia or cancer in the central nervous system among children living in an area with high indoor radon concentrations: results from a cohort study in Norway. *Br J Cancer, 111*(7), 1413-1420. doi:10.1038/bjc.2014.400

Does, M., Scelo, G., Metayer, C., Selvin, S., Kavet, R., & Buffler, P. (2011). Exposure to electrical contact currents and the risk of childhood leukemia. *Radiat Res, 175*(3), 390-396. doi:10.1667/RR2357.1

Draper, G., Vincent, T., Kroll, M. E., & Swanson, J. (2005). Childhood cancer in relation to distance from high voltage power lines in England and Wales: a case-control study. *BMJ, 330*(7503), 1290. doi:10.1136/bmj.330.7503.1290

Fajardo-Gutierrez, A., Navarrete-Martinez, A., Reynoso-Garcia, M., Zarzosa-Morales, M. E., Mejia-Arangure, M., & Yamamoto-Kimura, L. T. (1997). Incidence of malignant neoplasms in children attending Social Security Hospitals in Mexico City. *Med Pediatr Oncol, 29*(3), 208-212.

Feychting, M., & Ahlbom, A. (1993). Magnetic fields and cancer in children residing near Swedish high-voltage power lines. *Am J Epidemiol, 138*(7), 467-481.

Feychting, M., & Ahlbom, A. (1994). THE AUTHORS REPLY. *American Journal of Epidemiology, 140*(1), 75-75. doi:10.1093/oxfordjournals.aje.a117169

Feychting, M., Svensson, D., & Ahlbom, A. (1998). Exposure to motor vehicle exhaust and childhood cancer. *Scand J Work Environ Health, 24*(1), 8-11.

Filippini, T., Heck, J. E., Malagoli, C., Del Giovane, C., & Vinceti, M. (2015). A review and meta-analysis of outdoor air pollution and risk of childhood leukemia. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev, 33*(1), 36-66. doi:10.1080/10590501.2015.1002999

Fulton, J. P., Cobb, S., Preble, L., Leone, L., & Forman, E. (1980). Electrical wiring configurations and childhood leukemia in Rhode Island. *Am J Epidemiol, 111*(3), 292-296.

Greaves, M. (2006). Infection, immune responses and the aetiology of childhood leukaemia. *Nat Rev Cancer, 6*(3), 193-203. doi:10.1038/nrc1816

Greaves, M. (2018). A causal mechanism for childhood acute lymphoblastic leukaemia. *Nat Rev Cancer, 18*(8), 471-484. doi:10.1038/s41568-018-0015-6

Green, L. M., Miller, A. B., Agnew, D. A., Greenberg, M. L., Li, J., Villeneuve, P. J., & Tibshirani, R. (1999). Childhood leukemia and personal monitoring of residential exposures to electric and magnetic fields in Ontario, Canada. *Cancer Causes Control, 10*(3), 233-243.

Greenland, S., Sheppard, A. R., Kaune, W. T., Poole, C., & Kelsh, M. A. (2000). A pooled analysis of magnetic fields, wire codes, and childhood leukemia. Childhood Leukemia-EMF Study Group. *Epidemiology, 11*(6), 624-634.

Hatch, E. E., Kleinerman, R. A., Linet, M. S., Tarone, R. E., Kaune, W. T., Auvinen, A., . . . Wacholder, S. (2000). Do confounding or selection factors of residential wiring codes and magnetic fields distort findings of electromagnetic fields studies? *Epidemiology, 11*(2), 189-198.

Hitzler, J. K., & Zipursky, A. (2005). Origins of leukaemia in children with Down syndrome. *Nat Rev Cancer, 5*(1), 11-20. doi:10.1038/nrc1525

Houot, J., Marquant, F., Goujon, S., Faure, L., Honore, C., Roth, M. H., . . . Clavel, J. (2015). Residential Proximity to Heavy-Traffic Roads, Benzene Exposure, and Childhood Leukemia-The GEOCAP Study, 2002-2007. *Am J Epidemiol, 182*(8), 685-693. doi:10.1093/aje/kwv111

Hsu, W. L., Preston, D. L., Soda, M., Sugiyama, H., Funamoto, S., Kodama, K., . . . Mabuchi, K. (2013). The incidence of leukemia, lymphoma and multiple myeloma among atomic bomb survivors: 1950-2001. *Radiat Res, 179*(3), 361-382. doi:10.1667/RR2892.1

International Agency for Research on Cancer (IARC) (2002). IARC monographs on the evaluation of carcinogenic risks to humans: Non-ionizing radiation, part 1: Static and extremely low-frequency (ELF) electric and magnetic fields (Vol. 80). Retrieved April 2017, from https://monographs.iarc.fr/iarc-monographs-on-the-evaluation-of-carcinogenic-risks-to-humans-41/.

Jones, T. L., Shih, C. H., Thurston, D. H., Ware, B. J., & Cole, P. (1993). Selection bias from differential residential mobility as an explanation for associations of wire codes with childhood cancer. *J Clin Epidemiol, 46*(6), 545-548.

Kabuto, M., Nitta, H., Yamamoto, S., Yamaguchi, N., Akiba, S., Honda, Y., . . . Kubo, O. (2006). Childhood leukemia and magnetic fields in Japan: a case-control study of childhood leukemia and residential power-frequency magnetic fields in Japan. *Int J Cancer, 119*(3), 643-650. doi:10.1002/ijc.21374

Kavet, R., Zaffanella, L. E., Pearson, R. L., & Dallapiazza, J. (2004). Association of residential magnetic fields with contact voltage. *Bioelectromagnetics, 25*(7), 530-536. doi:10.1002/bem.20033

Kendall, G. M., Wakeford, R., Bunch, K. J., Vincent, T. J., & Little, M. P. (2015). Residential mobility and associated factors in relation to the assessment of exposure to naturally occurring radiation in studies of childhood cancer. *J Radiol Prot, 35*(4), 835-868. doi:10.1088/0952-4746/35/4/835

Kheifets, L., Ahlbom, A., Crespi, C. M., Draper, G., Hagihara, J., Lowenthal, R. M., . . . Wunsch Filho, V. (2010). Pooled analysis of recent studies on magnetic fields and childhood leukaemia. *Br J Cancer, 103*(7), 1128-1135. doi:10.1038/sj.bjc.6605838

Kheifets, L., Crespi, C. M., Hooper, C., Cockburn, M., Amoon, A. T., & Vergara, X. P. (2017a). Residential magnetic fields exposure and childhood leukemia: a population-based case-control study in California. *Cancer Causes Control*. doi:10.1007/s10552-017-0951-6

Kheifets, L., Crespi, C. M., Hooper, C., Cockburn, M., Amoon, A. T., & Vergara, X. P. (2017b). Residential magnetic fields exposure and childhood leukemia: a population-based case-control study in California. *Cancer Causes Control, 28*(10), 1117-1123. doi:10.1007/s10552-017-0951-6

Kheifets, L., Crespi, C. M., Hooper, C., Oksuzyan, S., Cockburn, M., Ly, T., & Mezei, G. (2015). Epidemiologic study of residential proximity to transmission lines and childhood cancer in California: description of design, epidemiologic methods and study population. *J Expo Sci Environ Epidemiol, 25*(1), 45-52. doi:10.1038/jes.2013.48

Kheifets, L., Feychting, M., & Schuz, J. (2005). Childhood cancer and power lines: results depend on chosen control group. *BMJ, 331*(7517), 635; discussion 636; author reply 636-637. doi:10.1136/bmj.331.7517.635

Kheifets, L., & Swanson, J. (2014). *Childhood leukemia and extremely low-frequency magnetic fields: Critical evaluation of epidemiologic evidence using Hill's framework* (Vol. 141). Boca Raton, FL, USA: CRC Press.

Kheifets, L., Swanson, J., Yuan, Y., Kusters, C., & Vergara, X. (2017). Comparative analyses of studies of childhood leukemia and magnetic fields, radon and gamma radiation. *J Radiol Prot, 37*(2), 459-491. doi:10.1088/1361-6498/aa5fc7

Kinlen, L. J. (2012). An examination, with a meta-analysis, of studies of childhood leukaemia in relation to population mixing. *Br J Cancer, 107*(7), 1163-1168. doi:10.1038/bjc.2012.402

Kleinerman, R. A., Linet, M. S., Hatch, E. E., Wacholder, S., Tarone, R. E., Severson, R. K., . . . Robison, L. L. (1997). Magnetic field exposure assessment in a case-control study of childhood leukemia. *Epidemiology, 8*(5), 575-583.

Kroll, M. E., Swanson, J., Vincent, T. J., & Draper, G. J. (2010). Childhood cancer and magnetic fields from high-voltage power lines in England and Wales: a case-control study. *Br J Cancer, 103*(7), 1122-1127. doi:10.1038/sj.bjc.6605795

Kulu, H. (2005). Fertility and spatial mobility: Evidence from Austria. *Rostock: MPIDR working paper, 2002*.

Langholz, B., Ebi, K. L., Thomas, D. C., Peters, J. M., & London, S. J. (2002). Traffic density and the risk of childhood leukemia in a Los Angeles case-control study. *Ann Epidemiol, 12*(7), 482-487.

Law, G. R., Smith, A. G., Roman, E., & United Kingdom Childhood Cancer Study, I. (2002). The importance of full participation: lessons from a national case-control study. *Br J Cancer, 86*(3), 350-355. doi:10.1038/sj.bjc.6600092

Li, C. Y., Mezei, G., Sung, F. C., Silva, M., Chen, P. C., Lee, P. C., & Chen, L. M. (2007). Survey of residential extremely-low-frequency magnetic field exposure among children in Taiwan. *Environ Int, 33*(2), 233-238. doi:10.1016/j.envint.2006.09.012

Li, F. P., Fraumeni, J. F., Jr., Mulvihill, J. J., Blattner, W. A., Dreyfus, M. G., Tucker, M. A., & Miller, R. W. (1988). A cancer family syndrome in twenty-four kindreds. *Cancer Res, 48*(18), 5358-5362.

Linet, M. S., Hatch, E. E., Kleinerman, R. A., Robison, L. L., Kaune, W. T., Friedman, D. R., . . . Tarone, R. E. (1997). Residential exposure to magnetic fields and acute lymphoblastic leukemia in children. *N Engl J Med, 337*(1), 1-7. doi:10.1056/NEJM199707033370101

Linet, M. S., Ries, L. A., Smith, M. A., Tarone, R. E., & Devesa, S. S. (1999). Cancer surveillance series: recent trends in childhood cancer incidence and mortality in the United States. *J Natl Cancer Inst, 91*(12), 1051-1058.

London, S. J., Thomas, D. C., Bowman, J. D., Sobel, E., Cheng, T. C., & Peters, J. M. (1991). Exposure to residential electric and magnetic fields and risk of childhood leukemia. *Am J Epidemiol, 134*(9), 923-937.

Lupo, P. J., Symanski, E., Chan, W., Mitchell, L. E., Waller, D. K., Canfield, M. A., & Langlois, P. H. (2010). Differences in exposure assignment between conception and delivery: the impact of maternal mobility. *Paediatr Perinat Epidemiol, 24*(2), 200-208. doi:10.1111/j.1365-3016.2010.01096.x

Ma, X., Buffler, P. A., Wiemels, J. L., Selvin, S., Metayer, C., Loh, M., . . . Wiencke, J. K. (2005). Ethnic difference in daycare attendance, early infections, and risk of childhood acute lymphoblastic leukemia. *Cancer Epidemiol Biomarkers Prev, 14*(8), 1928-1934. doi:10.1158/1055-9965.EPI-05-0115

Madsen, C., Gehring, U., Walker, S. E., Brunekreef, B., Stigum, H., Naess, O., & Nafstad, P. (2010). Ambient air pollution exposure, residential mobility and term birth weight in Oslo, Norway. *Environ Res, 110*(4), 363-371. doi:10.1016/j.envres.2010.02.005

Malagoli, C., Fabbi, S., Teggi, S., Calzari, M., Poli, M., Ballotti, E., . . . Vinceti, M. (2010). Risk of hematological malignancies associated with magnetic fields exposure from power lines: a case-control study in two municipalities of northern Italy. *Environ Health, 9*, 16. doi:10.1186/1476-069X-9-16

Maslanyj, M. P., Mee, T. J., Renew, D. C., Simpson, J., Ansell, P., Allen, S. G., & Roman, E. (2007). Investigation of the sources of residential power frequency magnetic field exposure in the UK Childhood Cancer Study. *J Radiol Prot, 27*(1), 41-58. doi:10.1088/0952-4746/27/1/002

McBride, M. L., Gallagher, R. P., Theriault, G., Armstrong, B. G., Tamaro, S., Spinelli, J. J., . . . Choi, W. (1999). Power-frequency electric and magnetic fields and risk of childhood leukemia in Canada. *Am J Epidemiol, 149*(9), 831-842.

McCarthy, G. W., Rohe, W. M., & van Zandt, S. (2001). *The economic benefits and costs of homeownership: A critical assessment of the research*: Research Institute for Housing America.

McNally, R. J., & Eden, T. O. (2004). An infectious aetiology for childhood acute leukaemia: a review of the evidence. *Br J Haematol, 127*(3), 243-263. doi:10.1111/j.1365-2141.2004.05166.x

Mezei, G., & Kheifets, L. (2006). Selection bias and its implications for case-control studies: a case study of magnetic field exposure and childhood leukaemia. *Int J Epidemiol, 35*(2), 397-406. doi:10.1093/ije/dyi245

Myers, A., Clayden, A. D., Cartwright, R. A., & Cartwright, S. C. (1990). Childhood cancer and overhead powerlines: a case-control study. *Br J Cancer, 62*(6), 1008-1014.

O'Connor, S. M., & Boneva, R. S. (2007). Infectious etiologies of childhood leukemia: plausibility and challenges to proof. *Environ Health Perspect, 115*(1), 146-150. doi:10.1289/ehp.9024

Oksuzyan, S. (2013). Study of factors related to childhood leukemia and to central nervous system tumors in California (Doctoral dissertation). Available from ProQuest, LLC. (UMI No. 3604775).

Oksuzyan, S., Crespi, C. M., Cockburn, M., Mezei, G., & Kheifets, L. (2012). Birth weight and other perinatal characteristics and childhood leukemia in California. *Cancer Epidemiol, 36*(6), e359-365. doi:10.1016/j.canep.2012.08.002

Oksuzyan, S., Crespi, C. M., Cockburn, M., Mezei, G., Vergara, X., & Kheifets, L. (2015a). Race/ethnicity and the risk of childhood leukaemia: a case-control study in California. *J Epidemiol Community Health, 69*(8), 795-802. doi:10.1136/jech-2014-204975

Oksuzyan, S., Crespi, C. M., Cockburn, M., Mezei, G., Vergara, X., & Kheifets, L. (2015b). Socio-economic status and childhood leukemia in California. *Journal of Cancer Prevention & Current Research, 3*(4). doi:10.15406/jcpcr.2015.03.00087

Pedersen, C., Johansen, C., Schuz, J., Olsen, J. H., & Raaschou-Nielsen, O. (2015). Residential exposure to extremely low-frequency magnetic fields and risk of childhood leukaemia, CNS tumour and lymphoma in Denmark. *Br J Cancer, 113*(9), 1370-1374. doi:10.1038/bjc.2015.365

Poole, C., Greenland, S., Luetters, C., Kelsey, J. L., & Mezei, G. (2006). Socioeconomic status and childhood leukaemia: a review. *Int J Epidemiol, 35*(2), 370-384. doi:10.1093/ije/dyi248

Raaschou-Nielsen, O., Andersen, C. E., Andersen, H. P., Gravesen, P., Lind, M., Schuz, J., & Ulbak, K. (2008). Domestic radon and childhood cancer in Denmark. *Epidemiology, 19*(4), 536-543. doi:10.1097/EDE.0b013e318176bfcd

Rabe, B., & Taylor, M. P. (2009). *Residential mobility, neighbourhood quality and life-course events*. Retrieved from

Sahl, J. D. (1994). Viral contacts confound studies of childhood leukemia and high-voltage transmission lines. *Cancer Causes Control, 5*(3), 279-283.

Savitz, D. A., Wachtel, H., Barnes, F. A., John, E. M., & Tvrdik, J. G. (1988). Case-control study of childhood cancer and exposure to 60-Hz magnetic fields. *Am J Epidemiol, 128*(1), 21-38.

Schulman, J., Selvin, S., Shaw, G. M., & Malcoe, L. H. (1993). Exposure misclassification due to residential mobility during pregnancy in epidemiologic investigations of congenital malformations. *Arch Environ Health, 48*(2), 114-119. doi:10.1080/00039896.1993.9938404

Schuz, J., Grigat, J. P., Brinkmann, K., & Michaelis, J. (2001). Residential magnetic fields as a risk factor for childhood acute leukaemia: results from a German population-based case-control study. *Int J Cancer, 91*(5), 728-735.

Schuz, J., Grigat, J. P., Stormer, B., Rippin, G., Brinkmann, K., & Michaelis, J. (2000). Extremely low frequency magnetic fields in residences in Germany. Distribution of measurements, comparison of two methods for assessing exposure, and predictors for the occurrence of magnetic fields above background level. *Radiat Environ Biophys, 39*(4), 233-240.

Schuz, J., Kaletsch, U., Meinert, R., Kaatsch, P., & Michaelis, J. (1999). Association of childhood leukaemia with factors related to the immune system. *Br J Cancer, 80*(3-4), 585-590. doi:10.1038/sj.bjc.6690395

Schuz, J., Svendsen, A. L., Linet, M. S., McBride, M. L., Roman, E., Feychting, M., . . . Ahlbom, A. (2007). Nighttime exposure to electromagnetic fields and childhood leukemia: an extended pooled analysis. *Am J Epidemiol, 166*(3), 263-269. doi:10.1093/aje/kwm080

SEER Program (National Cancer Institute (US)). (1999). Cancer incidence and survival among children and adolescents: United States SEER Program, 1975-1995 (No. 99). National Cancer Institute.

SEER Program (National Cancer Institute (US)). (2018). Cancer stat facts: Childhood leukemia (ages 0-19). Retrieved April 2019, from https://seer.cancer.gov/statfacts/html/childleuk.html.

Sermage-Faure, C., Demoury, C., Rudant, J., Goujon-Bellec, S., Guyot-Goubin, A., Deschamps, F., . . . Clavel, J. (2013). Childhood leukaemia close to high-voltage power lines--the Geocap study, 2002-2007. *Br J Cancer, 108*(9), 1899-1906. doi:10.1038/bjc.2013.128

Shah, A., & Coleman, M. P. (2007). Increasing incidence of childhood leukaemia: a controversy re-examined. *Br J Cancer, 97*(7), 1009-1012. doi:10.1038/sj.bjc.6603946

Slusky, D. A., Does, M., Metayer, C., Mezei, G., Selvin, S., & Buffler, P. A. (2014). Potential role of selection bias in the association between childhood leukemia and residential magnetic fields exposure: a population-based assessment. *Cancer Epidemiol, 38*(3), 307-313. doi:10.1016/j.canep.2014.02.010

Stewart, G. B., Altman, D. G., Askie, L. M., Duley, L., Simmonds, M. C., & Stewart, L. A. (2012). Statistical analysis of individual participant data meta-analyses: a comparison of methods and recommendations for practice. *PLoS One, 7*(10), e46042. doi:10.1371/journal.pone.0046042

Stiller, C. A., & Boyle, P. J. (1996). Effect of population mixing and socioeconomic status in England and Wales, 1979-85, on lymphoblastic leukaemia in children. *BMJ, 313*(7068), 1297-1300.

Sudan, M., Arah, O. A., Olsen, J., & Kheifets, L. (2016). Reported associations between asthma and acute lymphoblastic leukemia: insights from a hybrid simulation study. *Eur J Epidemiol, 31*(6), 593-602. doi:10.1007/s10654-016-0126-x

Svendsen, A. L., Feychting, M., Klaeboe, L., Langmark, F., & Schuz, J. (2007). Time trends in the incidence of acute lymphoblastic leukemia among children 1976-2002: a population-based Nordic study. *J Pediatr, 151*(5), 548-550. doi:10.1016/j.jpeds.2007.07.006

Swanson, J. (2008). Methods used to calculate exposures in two epidemiological studies of power lines in the UK. *J Radiol Prot, 28*(1), 45-59. doi:10.1088/0952-4746/28/1/002

Swanson, J. (2013). Residential mobility of populations near UK power lines and implications for childhood leukaemia. *J Radiol Prot, 33*(3), N9-14. doi:10.1088/0952-4746/33/3/N9

Tomitsch, J., Dechant, E., & Frank, W. (2010). Survey of electromagnetic field exposure in bedrooms of residences in lower Austria. *Bioelectromagnetics, 31*(3), 200-208. doi:10.1002/bem.20548

Tynes, T., & Haldorsen, T. (1997). Electromagnetic fields and cancer in children residing near Norwegian high-voltage power lines. *Am J Epidemiol, 145*(3), 219-226.

Urayama, K. Y., Buffler, P. A., Gallagher, E. R., Ayoob, J. M., & Ma, X. (2010). A meta-analysis of the association between day-care attendance and childhood acute lymphoblastic leukaemia. *Int J Epidemiol, 39*(3), 718-732. doi:10.1093/ije/dyp378

Urayama, K. Y., Ma, X., Selvin, S., Metayer, C., Chokkalingam, A. P., Wiemels, J. L., . . . Buffler, P. A. (2011). Early life exposure to infections and risk of childhood acute lymphoblastic leukemia. *Int J Cancer, 128*(7), 1632-1643. doi:10.1002/ijc.25752

Urayama, K. Y., Von Behren, J., Reynolds, P., Hertz, A., Does, M., & Buffler, P. A. (2009). Factors associated with residential mobility in children with leukemia: implications for assigning exposures. *Ann Epidemiol, 19*(11), 834-840. doi:10.1016/j.annepidem.2009.03.001

United States Census Bureau (2018). Housing vacancies and homeownership: Annual statistics: 2017. Retrieved March 2019, from https://www.census.gov/housing/hvs/index.html.

Vergara, X. P., Kavet, R., Crespi, C. M., Hooper, C., Silva, J. M., & Kheifets, L. (2015). Estimating magnetic fields of homes near transmission lines in the California Power Line Study. *Environ Res, 140*, 514-523. doi:10.1016/j.envres.2015.04.020

Verkasalo, P. K., Pukkala, E., Hongisto, M. Y., Valjus, J. E., Jarvinen, P. J., Heikkila, K. V., & Koskenvuo, M. (1993). Risk of cancer in Finnish children living close to power lines. *BMJ, 307*(6909), 895-899.

Wartenberg, D., Greenberg, M. R., & Harris, G. (2010). Environmental justice: a contrary finding for the case of high-voltage electric power transmission lines. *J Expo Sci Environ Epidemiol, 20*(3), 237-244. doi:10.1038/jes.2009.11

Wertheimer, N., & Leeper, E. (1979). Electrical wiring configurations and childhood cancer. *Am J Epidemiol, 109*(3), 273-284.

Westergaard, T., Andersen, P. K., Pedersen, J. B., Olsen, J. H., Frisch, M., Sorensen, H. T., . . . Melbye, M. (1997). Birth characteristics, sibling patterns, and acute leukemia risk in childhood: a population-based cohort study. *J Natl Cancer Inst, 89*(13), 939-947.

World Health Organization. (2007). Environmental health criteria 238: Extremely low frequency fields.

World Health Organization, Environment and Health Information System (2014). Incidence of childhood leukemia (4.1). Retreived April 2019, from http://data.euro.who.int/eceh-enhis/Default2.aspx?indicator_id=15

Wunsch-Filho, V., Pelissari, D. M., Barbieri, F. E., Sant'Anna, L., de Oliveira, C. T., de Mata, J. F., . . . Kheifets, L. (2011). Exposure to magnetic fields and childhood acute lymphocytic leukemia in Sao Paulo, Brazil. *Cancer Epidemiol, 35*(6), 534-539. doi:10.1016/j.canep.2011.05.008

Yost, K., Perkins, C., Cohen, R., Morris, C., & Wright, W. (2001). Socioeconomic status and breast cancer incidence in California for different race/ethnic groups. *Cancer Causes Control, 12*(8), 703-711.