Exposure Science Issues Concerning 60 Hz Magnetic Fields

by

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DEDICATION

I dedicate this research to my wonderful wife, Sarah Ma, who agreed to uproot our family from San Francisco, California (i.e., Heaven on Earth) for me to further my education in the area of environmental health sciences. I am indebted to her for unconditional support throughout the many challenges that I faced during the Ph.D. program. I am extremely fortunate to have her in my life, and I look forward to the day when I can bring her back home to San Francisco. I also dedicate this research to women and men with fertility issues around the world with the hope that this work will inform the design of future epidemiology studies, thus refining our understanding of the potential relationship between power-frequency magnetic fields and reproductive health.

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ABSTRACT

Several recent epidemiology studies suggest that exposure to magnetic fields may be one of the etiologic factors involved in adverse reproductive health outcomes, but these studies potentially had several important design limitations that undermine the validity of their findings and subsequent conclusions. This research examined these limitations in detail using hypothesis-driven data collection and statistical analyses with the underlying goal of informing the design of future epidemiology studies concerning exposure to magnetic fields and adverse reproductive health. The study design and other related exposure science issues examined by this research included: 1) the adequacy of using a single day's worth of personal magnetic field exposure data to characterize longer periods of exposure; 2) the potential influence of physical activity on personal magnetic field exposure; and 3) the comparison of personal magnetic field exposures between women and men and within female-male couples. These issues were assessed with data from two longitudinal cohorts of men and/or women recruited from prenatal care clinics in North Carolina and an infertility center in Massachusetts. We observed that measures of central tendency associated with daily personal magnetic field exposures were more stable over time compared with measures of peak, and the stability of these metrics was greater over short-relative to long-term durations. The findings suggest that if there is interest in peak exposure metrics, more than one day of measurement is needed over the window of disease susceptibility to reduce measurement error. We also observed a positive relationship between physical activity and peak magnetic field exposure metrics, suggesting physical activity could be an important confounder in the relationship with any outcome independently associated with activity, such as miscarriage, and, as a result, should be adjusted for in statistical models to reduce bias. In addition, we demonstrated that distributions of personal exposures among women and men are similar, and that there is promise that one partner's exposure data could be used as a surrogate for the other's in the absence of such data. Future reproductive health epidemiology studies that concern exposure to magnetic fields should consider this research in the design and interpretation of their findings.

CHAPTER I – BACKGROUND

Electric and Magnetic Fields

Electricity is an essential part of our lives. Without electricity, modern conveniences such as a light bulbs, subway transportation, and electric stoves, would not exist. Electric devices that are powered by batteries use direct current (DC), and current flow is unidirectional. On the other hand, electric devices that are plugged into electric outlets use 50 or 60 Hz alternating current (AC), and current flow changes direction 50 or 60 times per second, respectively, depending on the country (60 Hz is used in the U.S. and 50 Hz is used in other areas of the world). Collectively, 50 and 60 Hz AC are classified as power-frequencies. The current from a power supply carries electric energy to these devices where it is then converted to other forms of energy so that these devices can perform their intended functions (Beiser, 1986). Electric energy transferred to a light bulb, for example, is converted into radiant energy. Electric energy transferred to a subway car or an electric stove is converted into mechanical and thermal energy, respectively.

Surrounding electric devices that are powered by either DC or AC are electric fields and magnetic fields, which are due to the presence and flow of charge, respectively (Duffin, 1980). These fields are collectively referred to as electromagnetic fields or EMFs and provide a provide a framework for understanding how forces from charges due to electricity are transmitted to other charges located in the surrounding space. By convention, electric fields radiate outwardly from current-carrying wires like spokes on a wheel, whereas magnetic fields form concentric circles around such wires. Electric fields are measured by determining the potential gradient, which is the force per unit charge in taking a charge from one point to another (units: V/m). Magnetic fields are essentially the modification of electric fields that arise due to charges in motion instead of charges at rest and are measured by determining the force on a charge with velocity (units: mG).

The electric and magnetic fields that we encounter in our lives due to the existence of electricity interact with our bodies in different ways (Shapiro, 2002). For example, if you place your arm in an electric field created by a current-carrying wire, the electrons on the surface of your skin will redistribute and create a second electric field that nearly completely cancels the original electric field at all points within your arm. The residual electric field will induce small currents inside of your arm, but from an electric field that is attenuated by 10^4 to more than 10^6 relative to original electric field (Kaune, 1993). In essence, your arm will distort the electric field created by a current-carrying wire such that it mostly passes around your arm rather than through it.

However, a magnetic field generated by a current-carrying wire will completely penetrate your arm and induce an electric field that causes the charges inside of your arm to form closed-loop currents, called eddy currents, that circulate in planes perpendicular to the direction of the magnetic field (Shapiro, 2002) (Figure 1). Faraday’s Law, which states that current will be induced in an electric conductor (e.g., your arm) when exposed to an alternating magnetic field (i.e., power-frequency magnetic field), describes this phenomenon (Shapiro, 2002). While these induced currents are smaller than those generated by the brain, nerves, and heart (NIEHS, 2002), it is believed by some that they may hold biological significance and, as a result, magnetic fields and not electric fields are typically studied in relation to human health effects.

Non-time-varying magnetic fields produced by DC power sources can induce currents inside of our bodies, but either the battery-powered electric device or our body must be changing direction 50 or 60 times per second in order for the induced current to be similar in frequency to those that are generated by an AC magnetic field from an electric device of the same voltage. Thus, in most practical situations, DC magnetic fields are not believed to hold biological importance.

Exposure to Magnetic Fields

The magnitude of the magnetic field is directly proportional to the current and inversely proportional to the distance from the source (it decreases with the cube of the distance for point sources and decreases with the square of the distance for lines sources) (NIEHS, 1998). For example, in the vicinity of an AC-powered digital clock, a device with relatively low current demand, the magnetic field level is typically in the range of 1-8 mG, which is much lower than a high current AC-device that we may encounter, such as a power saw that generates a magnetic field around 50-1000 mG (NIEHS, 2002). The magnetic field level directly underneath an overhead power distribution line is typically less than 20 mG, but may be as high as 70 mG depending on the amount of current carried by the power line (NIEHS, 2002). The magnetic field associated with an overhead power line decreases with distance at a much lesser rate and contributes to exposure over a much larger area compared with a point source (e.g., digital clock, power saw) whose magnetic fields originate from a much smaller defined area (NIEHS, 1998).

Given our extensive reliance on electricity, virtually everyone will experience exposures to magnetic fields on daily basis. However, studies on the distribution of personal magnetic field exposures among women and men in the U.S. and other areas of the world are limited. As part of the “1000-Person Survey,” a representative survey of personal magnetic field exposures in the U.S. population conducted in 1997-1998, the median of the average levels measured over a single 24-hour period among women and men 18-64 years old was 0.94 mG (Zaffanella and Kalton, 1998). The only other study to report on estimated distributions of personal exposures in adults was that by Bracken (2002) who reported a median of the single 24-hour averages and maximums of 1.14 mG and 26.90 mG, respectively, in a sample of women from the California Kaiser Spontaneous Abortion Study (n=960) (Lee et al., 2002; Li et al., 2002). No studies have characterized personal magnetic field exposures in subfertile populations, which are believed to be most susceptible to the adverse reproductive health effects associated with exposures to environmental agents, such as magnetic fields (Li et al. 2002).

Infertility and Pregnancy Loss

Infertility is one of the most common reproductive diseases, affecting approximately 10-15% of couples during their reproductive lifespan (Hull et al., 1985). The already high frequency of this disease is likely to rise as the postponement of childbearing increases in developed areas of the world (Evers, 2002; Pinelli and Di Cesare, 2005). As of 2002, more than 7 million women of reproductive age in the U.S. had the inability to become pregnant or carry a pregnancy to term (Chandra et al., 2006). Studies have also shown that most measures of male reproductive health have declined dramatically over the past five decades (Carlsen et al., 1992; Swan et al., 1997; Travison et al., 2007). Among couples that are infertile, about half are attributable to the male partner and related to poor sperm quality (Krausz, 2011; Ventura et al., 1999). In fertile women, 22% of pregnancies fail before they reach a stage where they are clinically recognizable (Wilcox et al., 1988). It is important to emphasize that most early pregnancy losses are unrecognized and manifest as increased time to pregnancy and infertility, but later pregnancy losses are recognized as miscarriages (pregnancy loss prior to the 20^{th} week of gestation) or still births. The associated direct health care cost of infertility in the U.S. was estimated at $2.9 billion in 2002 and does not include the tremendous emotional burden that is experienced by the affected couple (Chandra et al., 2006). The determinants of infertility and pregnancy loss are not well understood, but likely arise as a complex interplay of environmental and lifestyle factors evident at the population level.

Magnetic Fields and Reproductive Health

Over the past 30 years, a substantial amount of research has addressed whether or not exposure to magnetic fields is a risk factor for adverse reproductive health outcomes. The basis for this research priority arose from reports in 1979-1982 of miscarriage and birth defect clusters among video display terminal (VDT) operators in the U.S. and Canada (Bergqvist, 1984), and from laboratory studies that demonstrated developmental abnormalities in chicken embryos following environmentally-relevant exposures to magnetic fields (Ahlbom et al., 2001; Delgado et al., 1982; Ubeda et al., 1994). VDTs, which are essentially predecessors to modern-day computers, emit magnetic field levels that range from about 7-20 mG (NIEHS, 2002).

From that point forward, much effort was invested to support epidemiology studies that examined the potential association between exposure to magnetic fields from VDTs and adverse pregnancy outcomes (Bryant and Love, 1989; Ericson and Kallen, 1986a, 1986b; Goldhaber et al., 1988; Grasso et al., 1997; Lindbohm et al., 1992; McDonald et al., 1986; Nielsen et al., 1990; Roman et al., 1992; Schnorr et al., 1991; Winham et al., 1990), as well as from sources of exposure in and around the home, such as electric blankets, heated water beds, and power lines (Belanger et al., 1998; Juutilainen et al., 1993; Lee et al., 2000; Savitz and Ananth, 1994; Wertheimer and Leeper, 1986, 1989).

However, the consensus of expert opinion following this effort was that the evidence potentially linking exposure to magnetic fields and adverse reproductive health outcomes was deemed inadequate (Ahlbom et al., 2001; NIEHS, 1998). These epidemiology studies produced conflicting results and many were characterized by study design limitations that possibly resulted in biased effect estimates, most notably from exposure misclassification due to the use of surrogate measures of personal exposure, such as residential wire code classification and self-reported use of electric devices. The best effort to estimate personal exposure to magnetic fields quantitatively came from the use of spot measurements in residences and the workplace. However, the limitations with such an approach are that humans are not stationary objects and spot measurements do not incorporate differences in magnetic field exposures that result from moving between different environments. Because personal exposure monitors can capture variability in exposure over space and time, they provide a much more valid estimate of personal exposure (Savitz, 2002).

In 2002, the debate surrounding exposure to magnetic fields and adverse pregnancy outcomes was revived following the publication of two epidemiology studies conducted in pregnant women enrolled in the California Kaiser Permanente Medical Care Program (Lee et al., 2002; Li et al., 2002). At the time, these two studies were among the first of their kind to characterize magnetic field exposures using personal exposure monitors.

In the first study, Lee et al. (2002) conducted a nested case-control study (167 cases, 384 controls) where magnetic field exposure was estimated retrospectively using wire code and one-minute spot measurements around the home, as well as personal exposure monitors that collected data at a rate of once every 10 seconds for a single, 24-hour period at 30 weeks' gestation for women whose pregnancy continued and at the equivalent point relative to the onset of pregnancy for those that miscarried. There were no statistically significant associations between miscarriage and wire code classification or spot measurements or 24-hour time-weighted average $\geq$2.0 mG (a threshold previously used in childhood leukemia epidemiology studies). There was, however, a statistically significant dose-dependent increase in miscarriage risk by quartiles of 24-hour personal maximum magnetic field exposure [adjusted odds ratios (ORs) and associated 95% confidence intervals (CIs) from second lowest to highest exposure quartile; 1.4 (0.7-2.8), 1.9 (1.0-3.5), and 2.3 (1.2-4.4)], but not for the time-weighted average.

In the same publication, Lee et al. (2002) also conducted a prospective sub-study on 176 subjects from the parent cohort (10 eventually became cases) at 12 weeks of gestation to validate the assumption in the nested case-control study that magnetic field exposures at 30 weeks of gestation were similar to those early in pregnancy, and to see whether or not the findings of the sub-study were similar to the nested case-control study. Personal exposure data collected at 12 and 30 weeks were not strongly correlated, which suggests that the results of the nested case-control study were likely biased due to exposure misclassification. Lee et al. (2002) claimed that despite the poor correlation between the two time points, especially for the maximum, the results of the prospective sub-study were similar to those of the nested case-control study, and therefore, enhanced confidence in their findings.

In the second study, Li et al. (2002) conducted a prospective cohort study in 969 pregnant women (159 cases) at 10 weeks or less of gestation from the same parent cohort used in Lee et al. (2002). Li et al. (2002) employed similar exposure assessment techniques as Lee et al. (2002), in addition to modeling personal magnetic field exposure using tertiles of total sum of exposure over 16 mG. Consistent with Lee et al. (2002), Li et al. (2002) also did not report an association between wire code classification and the 24-hour time-weighted average and risk of miscarriage. However, the authors reported a positive association between a 24-hour maximum $\geq$16 mG and miscarriage (adjusted rate ratio (RR): 1.8, 95% CI: 1.2-2.7). When stratifying on gestational age, the association was stronger among those with a miscarriage between 0-9 weeks of gestation (adjusted RR: 2.2, 95% CI: 1.2-4.0) than those with a miscarriage at 10 weeks of gestation or greater (adjusted RR: 1.4, 95% CI: 0.8-2.5). Miscarriage risk was also greater in women with subfertility and previous miscarriages (RR: 3.1, 95% CI: 1.3, 7.7), which, as they hypothesized, may represent "susceptible" sub-populations. A similar increase in risk of miscarriage was also noted by tertiles of total sum of exposure over 16 mG for the entire cohort [adjusted RRs and associated 95% CIs from lowest to highest tertile of exposure; 1.7 (1.1, 2.8), 1.8 (1.1, 2.9), and 2.0 (1.2, 3.1)], and for women with sub-fertility [2.3 (0.7, 7.2), 3.7 (1.4, 10.2), and 3.3 (1.2, 9.2)].

Following the publication of the Kaiser epidemiology studies, the California Department of Health Services released a report stating that a "substantial proportion of miscarriages" might be caused by exposure to magnetic fields and that, if true, this would be cause for "personal and regulatory concern" (Neutra et al., 2002). However, there were several limitations that tempered the findings of these two epidemiology studies. The observed associations might be due to an unmeasured confounder (Savitz, 2002) and, due to the likelihood of high day-to-day variability in personal magnetic field exposures, especially for the maximum, the exposure assessment strategy likely resulted in a high degree of exposure misclassification, which, if non-differential, would likely underestimate the association. Differential misclassification of exposure cannot be ruled out as well, which would bias the effect estimate away from or towards the null depending on the degree of misclassification by outcome or relationship of the error to the outcome. This is conceivable especially if exposure is influenced by whether or not a woman has miscarried.

An accompanying commentary proposed that the basis for the miscarriage association with the maximum personal magnetic field exposure could be rooted in different mobility patterns in women with healthy pregnancies compared to women who miscarried (Savitz, 2002). In early pregnancy (first trimester), women with morning sickness, an indicator of a healthy pregnancy, would be less physically active compared to women with less healthy pregnancies and more likely to have a miscarriage. In late pregnancy, women close to term would have more discomfort and difficulty moving from place to place compared to women that had experienced miscarriage. Savitz (2002) suggested that a decreased mobility in healthy pregnancies would translate to a decreased probability of encountering sources of high magnetic fields, and, as a result, lower maximum magnetic field exposures. On the other hand, increased mobility in women that miscarried would result in greater maximum magnetic field exposures, but not due to a causal relationship between magnetic fields and miscarriage.

Li and Neutra (2002) responded to Savitz's commentary with a supplemental analysis of the Kaiser data, and demonstrated that nausea at unspecified times in pregnancy was not related to maximum magnetic field exposure. However, analysis of pregnancy-related nausea symptoms on the measurement day would be required to accurately test the association between nausea and magnetic field exposure (Savitz et al., 2006). Regarding reduced physical activity accompanying increased gestational age, Li and Neutra (2002) pointed to the prospective sub-study by Lee et al. (2002) claiming that the mean values of the exposure metrics corresponding to 12 and 30 weeks of gestation were similar (time-weighted average: 1.1 vs. 1.2 mG, maximum: 34 vs. 28 mG), and the results of the nested case-control study that used exposures measured at 30 weeks produced effect estimates that were in the same direction as the prospective sub-study that used exposures measured at 12 weeks.

Findings from a small number of exposure science studies support Savitz's hypothesis, with results suggesting a positive association between physical activity and maximum personal magnetic field exposure. In 2006, Savitz et al. recruited 100 pregnant women in North Carolina to wear an accelerometer and personal magnetic field exposure monitor, both recording once per minute for seven, consecutive 24-hour periods. The authors reported a positive association between physical activity as measured by an accelerometer and incurring an elevated maximum magnetic field exposure, but no relationship with time-weighted average. An inverse association was also noted for gestational age and maximum magnetic field exposure, which is in line with previous studies showing that physical activity decreases with increasing gestational age (Evenson et al., 2002; Hatch et al., 1993; Mottola and Campbell, 2003). Similar to Li and Neutra

(2002), Savitz et al. (2006) also reported that nausea at unspecified time during pregnancy was not related to physical activity or magnetic field exposure. A limitation of this study is that personal magnetic field exposure and physical activity for the participants may have been underestimated because the monitors sampled once every 60 seconds. For instance, recorded maximum magnetic field exposure is inversely related to sampling interval (Mezei et al., 2006), which suggests that the exposure assessment strategy adopted by Savitz et al. (2006) may have biased their results.

Using data from the Kaiser study, Mezei et al. (2006) also found a positive relationship between physical activity and maximum exposure, but physical activity was measured with time-activity diary data instead of accelerometer data. It was observed that the total daily number of activities/environments experienced (e.g., home + work + travel) was positively associated with maximum magnetic field exposure. Although accelerometers, such as those used by Savitz et al. (2006), provide an objective measure of physical activity, the data generated may not necessarily be the most appropriate for understanding whether or not physical activity influences magnetic field exposure. For example, data from an accelerometer may report that an individual had high physical activity over the course of the day, but it does not necessarily imply they also experienced many different environments, which may ultimately drive the probability of experiencing sources of high magnetic fields. Thus, perhaps data that quantifies the variety of environments that one encounters over the course of the day may provide a more valid measure of physical activity in this context than data generated by an accelerometer. Nonetheless, taken together, the studies by Savitz et al. (2006) and Mezei et al. (2006) suggest that effect estimates for epidemiology studies of maximum magnetic field exposure and miscarriage may be biased due to unmeasured confounding.

Although the Kaiser studies improved the exposure assessment strategy by incorporating personal exposure monitors into their study design, given that exposures were characterized with data derived from a single 24-hour period, it is reasonable to question the reliability of any derived exposure metrics as the window at risk for miscarriage can range anywhere up to 20 weeks of gestation. In fact, Lee et al. (2002) reported that the Pearson correlation coefficients between 24-hour personal magnetic field exposures measured at 12 and 30 weeks of gestation from the same woman were 0.64 and 0.09 for the average and maximum, respectively. Lee et al. (2002) additionally used the personal exposure data to calculate the proportion of participants that had an elevated or reduced average or maximum at 30 weeks of gestation (threshold defined as the median value across all data sets at 30 weeks of gestation for that metric) and would be identified as such using the exposure at 12 weeks of gestation (i.e., a temporal variability analyses consistent with their approach to modeling magnetic field exposure as a categorical rather than a continuous variable in their statistical models). The sensitivities for the average and maximum were 0.77 and 0.60, respectively, and the corresponding specificities were 0.96 and 0.51, respectively. These findings demonstrate that the effect estimates reported by Lee et al. (2002) were likely greatly biased due to exposure misclassification for the maximum and to a much lesser extent for the average. The same may be true for Li et al. (2002) and any future epidemiology studies that are examining the potential association between personal magnetic field exposures and miscarriage and incorporate a similar exposure assessment strategy.

Mezei et al. (2006) re-analyzed data from the Electric Power Research Institute (EPRI) Long-Term Wire Code Study, where personal magnetic field exposure levels were measured in men and women in 218 U.S. households on up to four home visits (mean and standard deviation measurement duration per visit were 33.5 and 13.0 hours, respectively) over a 20-month period.

Spearman correlation coefficients between the first and last visits for the maximum and 99th and 95th percentiles were 0.31, 0.68, and 0.78, respectively. Correlations between pairs of visits ranged from 0.27 (415 months between visits) to 0.35 (<6 months between visits) for the maximum, 0.62 to 0.65 for the 99th percentile, 0.75 to 0.84 for the 95th percentile, 0.80 to 0.87 for the median, and 0.70 to 0.82 for the time-weighted average. The findings reported by Mezei et al. (2006) suggest that measures of central tendency tend to be more stable over time relative to measures of peak. However, these findings may not be generalizable because they considered personal magnetic field exposures that occurred at home only, which may misclassify exposures as magnetic fields are not fixed to the residential environment. Activities performed outside the home, such as work and travel, are important contributors to personal exposure (Zaffanella and Kalton, 1998), and failure to include associated exposure data in derived exposure metrics may introduce bias. Another limitation of this study, which is also applicable to the temporal variability analyses by Lee et al. (2002), is the personal exposure monitors sampled at a frequency of once every 10 seconds (the same for the Kaiser studies), which, as observed by Mezei et al. (2006) in a separate analysis, may underestimate metrics of exposure, especially the maximum.

While the epidemiological literature in the context of magnetic fields and reproductive health has been dominated by studies of miscarriage, there has been a lack of research on male reproductive health outcomes. In a study of 148 men recruited from a sperm bank in Shanghai, China, Li et al. (2010) reported that 24-hour 90th percentile personal magnetic field exposures ≥1.6 mG were associated with an increased risk of abnormal sperm quality (adjusted OR: 2.0, 95% CI: 1.0-3.9). A statistically significant (trend p=0.03) dose-dependent increase in risk of poor sperm quality was also observed with increasing duration of exposure ≥1.6 mG [adjusted

ORs and associated 95% CIs for 1-3, 3-6, and >6 hours $\geq$1.6 mG, respectively: 1.5 (0.6, 4.1), 1.8 (0.7-5.2), and 2.7 (0.9-7.8)]. Analogous to the Kaiser studies, exposures were characterized using a single 24-hour measurement, which may undermine the validity of the estimated exposures as the duration of spermatogenesis is three months (Li et al., 2010). No other peer-reviewed studies exist concerning exposure to magnetic fields and adverse male reproductive health outcomes.

Since 2010, there has been a continued interest in the potential reproductive hazard posed by exposure to magnetic fields in humans. Epidemiology studies have been conducted in Canada (Auger et al., 2010), China (Wang et al., 2013; Su et al., 2014), England (de Vocht et al., 2014; de Vocht and Lee, 2014), and Iran (Shamsi Mahmoudabadi et al., 2013) and focused on several female reproductive health outcomes, including embryonic development, miscarriage, preterm birth, low birth weight, and small for gestational age. Despite the contributions to the state-of-the science, these epidemiology studies produced conflicting results and, similar to previous studies, employed wire code classification, spot measurements, or personal magnetic field exposure measurements over a single 24-hour time period, which are questionable strategies for estimating personal magnetic field exposure and likely biased the derived effect estimates.

Identified Data Gaps

To date, there is a need to characterize and report on personal magnetic field exposures in adults, which in turn will help with understanding the burden of magnetic field exposures across different geographic regions. This is especially true for women and men with subfertility as they are believed to be most susceptible to the potential reproductive health effects posed by magnetic fields (Li et al., 2002). In addition, studies on the temporal variability of daily personal magnetic field exposure metrics among adults are limited in both number and scope and, as a result, more in-depth studies are needed. The small number of studies in the literature that has been conducted (Lee et al., 2002; Mezei et al., 2006) are also weakened by several important study design limitations (e.g., relatively infrequent personal exposure monitor sampling rates or measuring personal exposures inside the home only), which potentially undermine the validity of the current data. Studies are also needed on the relationship between physical activity and personal magnetic field exposure as differential physical activity patterns among women that miscarry and women with healthy pregnancies may be a confounder in the reported link between personal maximum magnetic field exposure and miscarriage as hypothesized (Savitz, 2002) and explored previously (Mezei et al., 2006; Savitz et al., 2006). Both unmeasured physical activity and lack of attention to within-individual variability in personal magnetic field exposures are potentially key sources of bias in epidemiology studies, and additional research that improves upon previous studies is expected to improve our understanding of the potential relationship between magnetic fields and infertility through informing future epidemiology study designs.

Lastly, the spectrum of reproductive health outcomes of concern in epidemiology studies concerning magnetic field exposures range from effects on gametes (sperm, ovum) to effects that occur after the gametes fuse from fertilization all the way through birth. To examine associations between magnetic field exposures and adverse effects on gametes (e.g., sperm DNA damage), a study would need to collect a biological sample (e.g., semen sample) and personal magnetic field exposure data from the corresponding sex (e.g., a study on sperm DNA damage collect personal magnetic field exposure data from the corresponding men). This approach was adopted by Li et al. (2010) in their study of personal exposure to magnetic fields and poor sperm quality among men in China. A similar study design has not been adopted for any female-focused cohorts, but it is conceivable that a relationship between exposure to magnetic fields and various female pre-fertilization female measures could be examined in future studies. Examples include number of oocytes retrieved (Mok-Lin et al., 2010) and antral follicle count (Souter et al., 2013), both of which have been examined in epidemiology studies in relation to exposure to bisphenol A, an environmental agent with ubiquitous exposure in the population (CDC, 2014) akin to magnetic fields.

However, after fertilization, teasing apart whether or not the observed associations are due to the magnetic field exposures experienced by the mother, the father, or both would be a challenge because any damage to the sperm and ovum is no longer observable, but may influence later pregnancy outcomes. Based on previous epidemiology studies, the norm for examining the potential association between exposure to magnetic fields and adverse pregnancy outcomes is to estimate exposures to the mother as it is assumed that only maternal exposures are biologically-relevant. However, in this situation, the interpretation of the results is dependent on whether magnetic field exposures are correlated within female-male couples. If exposures are not correlated within couples, associations could reflect adverse effects related to the exposures experienced by the mother that was sampled; no conclusions can be made regarding the father's exposures as his were not measured. In this situation, there is an opportunity to study maternal versus paternal contributions to the observed associations with the outcome of interest if the exposures for both parents are measured. On the other hand, if exposures are correlated within couples, the exposure for the mother that was sampled may serve as an exposure surrogate for the father that was not sampled and vice versa, and associations may reflect effects related to the exposures that were experienced by the mother, the father, or both. One advantage, however, of such a scenario is that maternal exposure data could potentially be used as an exposure surrogate in the absence of paternal exposure data to examine associations with adverse male reproductive health outcomes prior to fertilization (e.g., sperm quality parameters). This could be especially valuable if there is differential recruitment between women and men based on their willingness to wear a personal magnetic field exposure monitor independent of their willingness to provide a biological measurement, or if there is availability of exposure data from one of the partners and also an opportunity to obtain outcome data (e.g., semen quality measures) from archived data or biological samples. Correlation of magnetic field exposures within female-male couples has yet to be reported on in the peer-reviewed literature despite the fact that this information would add value to designing and interpreting the results of comprehensive reproductive health studies.

Aims and Hypotheses

Aim 1: Examine the temporal variability of daily personal magnetic field exposure metrics in women over durations relevant to pregnancy.

- Hypothesis 1: Personal magnetic field exposure measures of central tendency are more stable over time compared with measures of peak.
- Hypothesis 2: Personal magnetic field exposure measures of central tendency and peak are more stable over short time periods compared with long time periods.

Aim 2: Examine the potential relationship between physical activity and personal magnetic field exposure in women.

- Hypothesis 3: Physical activity is positively associated with personal magnetic field exposure measures of peak.
- Hypothesis 4: Physical activity is not associated with personal magnetic field exposure measures of central tendency.

Aim 3: Compare personal magnetic field exposures between sexes and within female-male couples.

- Hypothesis 5: Estimated distributions of personal magnetic field exposures are similar between women and men.
- Hypothesis 6: Temporal variability of personal magnetic field exposure measures in men is similar to that in women.
- Hypothesis 7: Personal magnetic field exposures within female-male couples are correlated inside the home, but not outside the home.

CHAPTER II – SOURCES OF DATA

Boston Cohort

To improve our understanding of the potential relationship between exposure to magnetic fields and miscarriage, semen quality, and other reproductive health parameters, epidemiology studies are greatly needed that address the shortcomings of the previous studies, such as those conducted by Lee et al. (2002) and Li et al. (2002, 2010). EPRI, a research non-profit funded by the electric utility industry to do research on aspects of electricity production and use, including environment and health issues, approached faculty at Harvard School of Public Health (HSPH) and University of Michigan School of Public Health (UMSPH) about funding a longitudinal epidemiology study of exposure to magnetic fields and reproductive health among individuals attending a fertility clinic. However, prior to releasing such funds, a pilot study was necessary to determine the feasibility of recruiting such subjects in a fertility clinic, and the best methods to employ in a full-scale epidemiology study. The research findings reported in this current analysis concern the women and men that were recruited during the pilot phase of the project.

Women and men in this pilot study were enrolled in the Environment and Reproductive Health (EARtH) Study, which is an ongoing collaboration between Massachusetts General Hospital (MGH) Fertility Center and HSPH studying how the environment influences infertility (Ehrlich et al., 2012; Meeker et al., 2012). Participants were partners in couples seeking infertility treatment due to a female factor, a male factor, or combination of both female and male factors. At the time of recruitment into the EARtH Study (2012-2014), women and men were also recruited into a pilot study to determine the feasibility of recruiting subjects to wear a personal magnetic field exposure monitor and an accelerometer and to record their activities in a diary every 30 minutes for three, 24-hour periods, preferably preconception, shortly following embryo implantation, and during first trimester. In other words, the pilot study was nested within the larger EARtH Study. The research protocol was approved by the Institutional Review Boards of MGH, HSPH, Centers for Disease Control and Prevention, and UMSPH. Those women and men agreeing to participate in the study signed an informed consent after the study procedures were explained to them and their questions were answered by a trained research nurse.

There are many advantages of focusing on this population, including: 1) the ability to assess stages of early pregnancy (e.g., fertilization, implantation, early miscarriage) that are not observable in studies of the general population; 2) documentation of highly accurate pregnancy outcomes based on clinical data; 3) it is well-positioned to evaluate the potential relationship between exposure to magnetic fields and male reproductive health; 4) study participants may represent the most susceptible population as described by Li et al. (2002); 5) the ongoing study has benefited from a highly motivated study population (e.g., minimal loss to follow-up and high study compliance); and 6) a study among this population offers considerable cost savings by leveraging infrastructure, staff, and collection of data on outcomes and other variables.

Participants were asked to complete a time-activity diary (Figures 2 and 3), which was modeled after the one used for pregnant women in the U.S. National Children’s Study and consisted of describing the daily activities and locations at 30-minute intervals. Possible locations included inside at home, inside at work or school, inside somewhere else (i.e., not inside at home or inside at work or school), outside at home, outside at work or school, outside somewhere else (i.e., not outside at home or outside at work or school), and in transit.

Participants were asked to wear at the hip level a small personal magnetic field exposure monitor (EMDEX LITE, Enertech, Campbell, CA, USA). The EMDEX LITE was calibrated to measure the magnetic field level in mG every 4 seconds at 60 Hz with a frequency band ranging from 40-1000 Hz (frequencies outside of this range are strongly attenuated). The EMDEX LITE is encased in a plastic housing coated with electrically conductive material to shield against interferences, such as radio-frequency signals from mobile phones. As an additional precaution, participants were also instructed to place the meter on the side of their hip opposite their cell phone in the event that they keep a cell phone in their pocket during the day. The EMDEX LITE measures the magnetic field level for the X-(horizontal), Y-(vertical), and Z-(lateral) planes and then calculates the resultant, which reflects the combined field levels across these three axes at 4-second intervals. The resultant, which we defined as the magnetic field level, was calculated as follows using Eq. 1:

$$MF_r = \sqrt{MF_x^2 + MF_y^2 + MF_z^2} \qquad \text{(Eq. 1)}$$

where MF_r denotes the resultant magnetic field level (mG), MF_x denotes the magnetic field level for the X-plane (mG), MF_y denotes the magnetic field level for the Y-plane (mG), and MF_z denotes the magnetic field level for the Z-plane (mG).

Participants were also asked to wear at the hip level an ActiGraph accelerometer (Model Number GT3X, Pensacola, FL, USA). The ActiGraph is a tri-axial accelerometer that reports movement as “counts per epoch” (counts every 2 seconds for this study) from the measured accelerations (g) in the X-, Y-, and Z-planes. Similar to the EMDEX LITE, we defined physical activity level as the resultant counts across these three axes using Eq. 2:

$$PA_r = \sqrt{PA_x^2 + PA_y^2 + PA_z^2} \quad \text{(Eq. 2)}$$

where PA_r denotes the resultant physical activity level (counts), PA_x denotes the physical activity level for the X-plane (counts), PA_y denotes the physical activity level for the Y-plane (counts), and PA_z denotes the physical activity level for the Z-plane (counts).

Women were instructed to wear both monitors throughout the entire monitoring period inside and outside the home, except at bedtime and when bathing, showering, and/or swimming. These monitors, as well as similar monitors, have been used in several other studies conducted among adults (Evenson et al., 2013; Hawkins et al., 2009; Jilcott et al., 2007; Lee et al., 2002; Li et al., 2002, 2010, 2011; Mezei et al., 2006; Toriano et al., 2008).

To gather insights regarding feasibility of the study, perceived intrusiveness or effort, and on how to improve the study protocols for the future, larger study, research staff conducted brief, in-person interviews using standardized questionnaires with both women and men that were eligible for the study (Figure 4) and participants that completed participation (Figure 5).

Over 60% of those women and men approached were also recruited into the pilot study, which was our a priori goal for the pilot study. The most prevalent reason for non-participation among the women was their lack of time available to be involved, followed by lack of interest and unwillingness to wear the monitors. To attract more interest among the approached women that were not interested in participating in the study, a brochure was developed that explained the basics of and reasons for studying magnetic fields, benefits of participating, and participation requirements (Figure 6). The men that refused to participate either did not want to wear the monitors or did not have time to be involved. Of the women that completed their participation, the majority consented because they were interested in the subject matter and believed that the research would be beneficial to them and/or others. Some women also reported that they had the time to be involved in the study, were interested in the compensation, and/or their partner believed that their involvement was a good idea. Most women agreed that it was easy to participate in the study, and similar sentiments were reported by the men who completed their participation. A few women reported that the size of that the personal magnetic field exposure monitor made it rather difficult to wear, but despite this limitation, it did not discourage them from participating in the study.

Overall, the setup, deployment, and operation of the pilot study occurred without any significant problems. On a few occasions, accelerometer data was not collected from some of the participants. With the assistance of the manufacturer, we identified one of the accelerometers to be the source of the issue and it was replaced, after which no additional issues occurred.

Women (n=40) and men (n=20) wore the personal magnetic field exposure monitors and accelerometers for a median of 15.0 hours per day [interquartile range (IQR): 14.0, 16.0] for a median of 3 days total (IQR: 1, 3) and a median of 15.5 hours per day (IQR: 14.0, 16.0) for a median of 3 days total (IQR: 2, 3), respectively. Measurement days were separated by median of 4.4 weeks (IQR: 3.3, 5.7) among women and 4.6 weeks (IQR: 3.1, 5.7) among men. While it was expected that data from three separate sampling days would have been collected from each woman and man in the pilot study, there was some missing data for several reasons: 1) insufficient funds towards the end of the pilot study for some women to complete all three sampling time points, 2) participant non-compliance (e.g., did not turn on the personal magnetic field exposure monitor or wear the exposure monitor or accelerometer based on review of the data), or 3) there was a functional issue with one of the accelerometers, which was identified and replaced with the assistance of the manufacturer. As a result, the analyses described in the subsequent aims were only performed on participants for whom we had complete data for that specific analysis.

North Carolina Cohort

Data associated with the North Carolina cohort was collected by Savitz et al. (2006). Therefore, the current analysis involving this cohort is a secondary data analysis. The research protocol has been described previously (Savitz et al., 2006). Briefly, women were recruited using flyers posted in prenatal care clinics located in Chapel Hill and Durham, North Carolina in 2003-2004. In order to participate in this study, participants were required to agree to wear a personal magnetic field exposure monitor and accelerometer for seven consecutive days. Those women agreeing to participate provided informed consent, and the research protocol was approved by the Institutional Review Board at University of North Carolina School of Medicine.

Participants were asked to wear at the hip level a small personal magnetic field exposure monitor (EMDEX II, Enertech, Campbell, CA, USA) and an accelerometer (ActiGraph Model Number 7164, Pensacola, FL, USA), which were technological predecessors of the ones used in the Boston cohort. The EMDEX II was calibrated to measure the magnetic field level in mG every 60 seconds at 60 Hz with a frequency band ranging from 40-800 Hz. The Actigraph Model Number 7164 is a uniaxial accelerometer that reports movement as “counts per epoch” (counts every 60 seconds for this study) from the measured accelerations (g) in the vertical plane. Similar to the Boston cohort, we defined the magnetic field level as the resultant using Eq. 1.

Participants were instructed to wear the personal magnetic field exposure monitor and accelerometer on the hip throughout the entire monitoring period inside and outside the home, except at bedtime and when bathing, showering, and/or swimming. Those agreeing to participate (n=100) wore the personal magnetic field exposure monitors and accelerometers for a median of 13.1 hours per day (IQR: 11.4, 14.4) for a median of 7 days total (IQR: 7, 7). Similar to the Boston cohort, the relevant analyses described in the subsequent aims were only performed on participants for whom we had complete data for that specific analysis.

CHAPTER III – AIM 1 (TEMPORAL VARIABILITY OF MAGNETIC FIELD EXPOSURE METRICS IN WOMEN)

Study Participants

Aim 1 concerned data associated with both the North Carolina cohort and Boston cohort (female only), which permitted analyses concerning short-term and long-term variability of daily personal magnetic field exposure metrics, respectively.

Statistical Methods

Statistical analyses were performed using SAS version 9.3 for Windows (SAS Institute, Cary, NC, USA). Prior to conducting any statistical analyses, non-wear time data was removed from each data set (Buchowski et al., 2009; Jilcott et al., 2007; Savitz et al., 2006). For the Boston cohort, non-wear time periods were identified using the participants' time-activity diaries. However, because a time-activity diary was not employed in the North Carolina cohort, alternative methods were required to estimate non-wear-time periods. Periods in which the ActiGraph recorded $\geq$20 minutes of zero counts were defined as non-wear time for both of the monitors, an approach that has been adopted by others (Buchowski et al., 2009; Jilcott et al., 2007; Savitz et al., 2006).

For each participant, daily central tendency (average and median) and peak (90^{th}, 95^{th}, and 99^{th} percentiles, and maximum) personal magnetic field exposure metrics were estimated. To assess between- and within-person variability in daily personal magnetic field exposure over the course of repeated sampling days, consecutive sampling days for the North Carolina cohort and sampling days separated by weeks for the Boston cohort, intraclass correlation coefficients (ICCs) were calculated using the estimated between- ($\hat{\sigma}^2_{between}$) and within-subject ($\hat{\sigma}^2_{within}$) variance components as follows using Eq. 3:

$$ICC = \frac{\hat{\sigma}^2_{between}}{\hat{\sigma}^2_{between} + \hat{\sigma}^2_{within}} \qquad \text{(Eq. 3)}$$

The variance components were derived from linear mixed models with only one random effect as the random intercept for each subject as follows using Eq. 4:

$$log(MF)_{ti} = \beta_0 + b_{0i} + \varepsilon_{ti} \qquad \text{(Eq. 4)}$$

where MF_{ti} denotes the daily personal magnetic field exposure metric (mG) for the *t*th sampling day and *i*th subject, which was log-transformed to address issues concerning non-normality, β_0 denotes the overall intercept, b_{0i} denotes the random deviation from the overall intercept for subject *i*, and ε_{ti}denotes the random error for the *t*th sampling day and the *i*th subject. The ICC is a measure of reliability of repeated measures over time and ranges from 0 (low reliability) to 1 (high reliability). The magnitudes of the ICCs were evaluated using the following criteria: poor reproducibility (ICC <0.40), fair to good reproducibility (0.40$\leq$ ICC <0.75), and excellent reproducibility (ICC $\geq$0.75) (Rosner, 2000).

While the ICC is an indicator of the temporal reliability for continuous measures, it does not quantify the magnitude of exposure misclassification if subjects are categorized into different exposure groups (e.g., low versus high exposure). To address this issue, we adopted a sensitivity and specificity analysis to determine the probabilities of accurately classifying subjects as having a high or low exposure using data from single measurement day. When treating exposure data as categorical variables, sensitivity and specificity of a single-day personal magnetic field exposure metric (i.e., surrogate) as a predictor of a high or low short-term (North Carolina cohort) or long-term (Boston cohort) personal magnetic field exposure metric (i.e., observed) were evaluated by comparing the surrogate and the observed exposure levels for agreement. For the North Carolina cohort, each daily personal magnetic field exposure metric for each woman served as a surrogate for the short-term exposure metric and was not included in the observed calculation, which was derived using the data from the remaining six sampling days. For instance, if data from Monday was used in the derivation of the surrogate level, then only data from Tuesday-Sunday was used for calculating the observed level. However, because only three sampling days were available for the Boston cohort (as opposed to seven), the observed long-term exposure metric was calculated using data across all three sampling days. This approach was repeated for each sampling day for each woman, resulting in three (Boston cohort) or seven (North Carolina cohort) separate 2 x 2 contingency tables (one for each sampling day). All tables were then combined into a single table for the Boston and North Carolina cohorts, respectively, where overall sensitivity and specificity were calculated for both durations. Sensitivities and specificities were calculated for the personal magnetic field exposure metrics assessed in the ICC analysis for thresholds corresponding to the 50^{th}, 75^{th}, and 90^{th} percentiles of the daily exposure metrics.

Mezei et al. (2006) demonstrated that less frequent sampling may underestimate the daily personal magnetic field exposure maximum, but it does not affect the time-weighted average, or 95th or 99th percentiles. Thus, it is plausible that estimates of within-subject temporal variability of daily personal magnetic field exposure metrics (e.g., ICC, or sensitivity or specificity) may be biased as well. For example, our estimated personal magnetic field exposure metrics were based on data that was collected at 60-second and 4-second intervals for the North Carolina and Boston cohorts, respectively. Therefore, estimates of temporal variability of the daily personal magnetic field exposure metrics may be biased for the North Carolina cohort; this is conceivable for the maximum as the infrequent sampling rate relative to the Boston cohort may underestimate the true maximum. We modeled the Boston data using a 60-second (i.e., random sampling of a data point every 60 seconds) instead of a 4-second sampling rate as well to evaluate whether or not a decrease in sampling frequency affected the estimated ICCs, sensitivities, and specificities, and shed light on the potential bias of the 60-second rate.

Results

ICCs, which are presented in Table 1, varied widely between daily central tendency and peak personal magnetic field exposure metrics. For both the North Carolina and Boston cohorts, the average, median, and 90th and 95th percentiles exhibited fair to good reproducibility. The 99th percentile showed fair to good reproducibility and poor reproducibility among the North Carolina and Boston women, respectively, and the maximum demonstrated poor reproducibility among both cohorts. The magnitude of the ICCs were similar between both short- and long-term temporal variability analyses, except that there was a 65% decrease in the ICC for the long-term maximum (Boston cohort) relative to the short-term maximum (North Carolina cohort). These relationships were qualitatively observable in Figures 7 and 8, where the temporal variability in the daily personal magnetic exposure metrics is plotted for 10 randomly selected participants for both cohorts. In particular, the peak personal magnetic field exposure metrics towards the upper tail of the distribution (i.e., 99^{th} percentile and maximum) demonstrated greater intra-individual variability than the other personal magnetic field exposure metrics for these women.

Table 2 shows the predictive ability of a single-day personal magnetic field exposure metric to classify a participant into high or low exposure categories based on a short-term (North Carolina cohort) or long-term (Boston cohort) personal magnetic field exposure metric. In our assessment of sensitivity among the North Carolina cohort, the proportion of women that had an elevated short-term personal magnetic field exposure and that would be classified as such using a single-day personal magnetic field exposure metric ranged from 0.51-0.76 for the average; 0.58-0.83 for the median; 0.62-0.68 for the 90^{th} percentile; 0.43-0.67 for the 95^{th} percentile; 0.26-0.62 for the 99^{th} percentile; and 0.20-0.54 for the maximum. Specificities increased with increasing personal magnetic field exposure thresholds. Similar relationships were also observed among the Boston cohort, except that the sensitivities and specificities were slightly higher relative to those of the North Carolina cohort.

As shown in Tables 1 and 2, modeling the Boston cohort data with a 60-second sampling frequency did not substantially affect the estimated ICCs, sensitivities, or specificities.

Discussion

The temporal variability of continuous and categorical daily personal magnetic field exposure metrics was examined over short- and long-term durations among cohorts of women from North Carolina and Boston. Central tendency metrics demonstrated greater within-subject stability over both durations relative to peak metrics, especially the maximum. When modeling personal magnetic field exposure as a continuous variable, the results suggest it may be possible to characterize personal magnetic field exposures using one day of measurement for reproductive health epidemiology studies that concern both short- (e.g., implantation failure) and long-term (e.g., miscarriage) outcomes when measures of central tendency (e.g., average or median) are of interest. On the other hand, the use of a single-day peak personal magnetic field exposure metric, especially the maximum, will likely result in appreciable measurement error and misclassification of exposure. The same was concluded for categorical personal magnetic field exposure metrics, but temporal variability when modeling exposure in this manner appears to be dictated by the exposure threshold, with decreasing stability over time with increasing exposure threshold.

In comparison to the limited number of previous studies that have examined the temporal variability of continuous measures of personal magnetic field exposure (Lee et al., 2002; Mezei et al., 2006), the present ICC analysis was more robust because it included personal magnetic field exposure data for up to seven repeated measurement periods among individual over both short- and long-term intervals, as opposed to two measurement periods per participant ranging from about 1-2 days in duration separated by several weeks. Our derived personal magnetic field exposure metrics were based on data collected inside and outside the home, which provided a more valid estimate of exposure than exposure metrics based on data collected inside the home only, which was performed by Mezei et al. (2006). Activities performed outside the home, such as work and travel, are important contributors to daily magnetic field exposure (Zaffanella and Kalton, 1998) and failure to include associated exposures in derived personal exposure metrics may introduce bias. Nevertheless, the results from our analysis are consistent with the analyses conducted by Lee et al. (2002) and Mezei et al. (2006) and suggest that, as continuous variables, daily central tendency metrics associated with personal magnetic field exposures exhibit greater temporal stability compared with daily peak metrics. Our findings also indicate that it may be possible to characterize personal magnetic field exposures in epidemiology studies with central tendency exposure metrics derived from a single measurement day. However, epidemiology studies that characterize personal magnetic field exposure with a continuous peak exposure metric, especially the maximum, based on a single measurement day will likely result in a large degree of exposure misclassification. For example, as demonstrated by Eq. 5 (White et al., 2008), in order for the maximum to be as stable as the average (i.e., exposure assessment strategy would provide the same degree of measurement error), it is estimated that three days of sampling versus one day of sampling and 12 days of sampling versus one day of sampling for short- (days) and long-term (weeks) durations, respectively, would be necessary. Eq. 5 is as follows:

$$k = \frac{\rho_{TA}^2\left(1-\rho_{x_1x_2}\right)}{\rho_{x_1x_2}\left(1-\rho_{TA}^2\right)} \qquad \text{(Eq. 5)}$$

where k denotes the number of parallel measures per subject, ρ_{TA} denotes the desired validity coefficient (i.e., derived based on the desired reliability, which is that of the median value in this example, and calculated as $\sqrt{\rho_{x_1x_2}}$), and $\rho_{x_1x_2}$ denotes the reliability coefficient.

Lee et al. (2002) has been the only other study to report on the intra-individual temporal variability of categorical personal magnetic field exposure metrics in adults. This sensitivity and specificity analysis was limited to the average and maximum for the threshold corresponding to the median across the studied population for that metric. The findings of their sensitivity analysis were comparable for these two metrics at this threshold for women in both the North Carolina and Boston cohorts. However, relative to the North Carolina cohort, the specificity was much lower for the average and much higher for the maximum, whereas, relative to the Boston cohort, the specificity was comparable for the average and much higher for the maximum. Contrary to Lee et al. (2002), the current analysis estimated sensitivities and specificities for the average and maximum, as well as other central tendency and peak personal magnetic field exposure metrics, at several different exposure thresholds and durations. In particular, using the 16.0 mG threshold (approximately the 70th percentile of the daily personal magnetic field exposure maximums in the North Carolina cohort) for the maximum reported by Li et al. (2002) may lead to substantial exposure misclassification. On examining this magnetic field exposure threshold further, it was found that the percentage of women with at least one daily maximum $\geq$16 mG increased with each additional sampling day over the course of the week (32-79%), which suggests that most women at some point will likely experience a personal magnetic field exposure $\geq$16.0 mG and, as a result, the validity of this exposure threshold proposed by Li et al. (2002) is questionable.

In addition, the categorical exposure analysis demonstrated that sensitivity decreases with increasing exposure threshold, whereas specificity increases with increasing exposure threshold, which suggests that the selection of the exposure threshold may dictate how stable the exposure metric is over time. These trends are expected due to the distribution of daily personal magnetic field exposure metrics and where the threshold falls in the distribution. The closer the threshold is to the upper tail of the distribution, the lesser number of daily exposures above that threshold. Thus, in the event that a participant has an observed exposure (i.e., across all of the measurement days) above the threshold, she is more likely to have an exposure on any given day below rather than above that threshold as the threshold approaches the upper tail of the distribution, leading to a lesser number of women that are correctly classified as highly exposed (i.e., sensitivity). On the other hand, as the exposure threshold increases, the greater the number of daily exposures below that threshold and, as a result, a greater probability for a woman having a surrogate and observed exposure below the threshold, resulting in a greater number that are correctly classified as being underexposed (i.e., specificity).

Lastly, there does not appear to be much effect of duration, whether short- or long-term, on the estimated ICCs for all personal magnetic field exposure metrics, except for the maximum, which appears to be much less stable over long relative to short durations. It is possible that this relationship could result from decreasing consistency in mobility patterns over time, resulting in a greater probability of encountering different magnetic field sources with differential intensities. Although the categorical measures analysis largely demonstrated the opposite (i.e., less stability over short relative to long durations), the estimated sensitivities and specificities for the Boston cohort might be somewhat overestimated as the predicted values were included in the calculation of the observed values, and, as a result, the predicted and observed values were not independent of each other (Meeker et al., 2005). Thus, the estimated sensitivities and specificities are likely much lower than the values presented in the current analyses. In addition, sampling frequency does not appear to affect the estimates of temporal variability for both continuous and categorical metrics of personal magnetic field exposure, suggesting that the 60-second sampling frequency employed in the North Carolina exposure assessment strategy did not bias the current analyses.

CHAPTER IV – AIM 2 (INFLUENCE OF PHYSICAL ACTIVITY ON MAGNETIC FIELD EXPOSURE IN WOMEN)

Study Participants

Aim 2 focused on data that was associated with the Boston cohort (female only), which allowed for analyses concerning the relationship between physical activity (modeled using both the accelerometer and time-activity diary data) and personal magnetic field exposure.

Statistical Methods

Although the ActiGraph provides an objective measure of overall physical activity, it does not necessarily characterize movement between environments, which may provide a more relevant metric for understanding the potential relationship between physical activity level and personal magnetic field exposure as hypothesized by Savitz (2002). To address this limitation of the ActiGraph, we used the time-activity diary to quantify the daily total number of changes in environments experienced per measurement day using the seven locations described previously. For example, if a woman over the course the day started inside the home, then went outside the home, and finally returned inside the home for the remainder of the day, her daily total number of changes in environments experienced would be two.

Statistical analyses were performed using SAS version 9.3 for Windows (SAS Institute, Cary, NC, USA). Prior to conducting any statistical analyses, non-wear time data was removed from each data set (Buchowski et al., 2009; Jilcott et al., 2007; Savitz et al., 2006). For the Boston cohort, non-wear time periods were identified using the participants' time-activity diaries. For each participant, daily central tendency (average and median) and peak (90^{th}, 95^{th}, and 99^{th} percentiles, and maximum) personal magnetic field exposure metrics, average counts, and total number of changes in environments experienced were estimated. Distributions of personal magnetic field exposure metrics and average counts were estimated for the entire sampling day and by environment because we additionally hypothesized that personal magnetic field exposure and physical activity profiles may differ between settings.

We modeled physical activity (predictor variable) in this analysis as both daily average counts and total number of changes in environments experienced, and assessed their respective associations with daily central tendency and peak personal magnetic field exposure metrics (outcome variable) in linear mixed models with only one random effect as the random intercept for each subject to account for the correlation of personal magnetic field exposure measurements within a woman. Physical activity level was separately modeled as both continuous (Eq. 6) and categorical (Eq. 7) variables, resulting in four separate models: 1) average counts, 2) tertiles of average counts, 3) total number of changes in environments experienced, and 4) categories of total number of changes in environments experienced. The statistical models employed in this analysis were as follows:

$$log(MF)_{ti} = \beta_0 + \beta_1 PA_{ti} + \ b_{0i} + \varepsilon_{ti} \qquad \text{(Eq. 6)}$$

where MF_{ti} denotes the daily personal magnetic field exposure metric (mG) for the *t*th sampling day and *i*th subject, which was log-transformed to address issues concerning non-normality, β_0 denotes the overall intercept, β_1 denotes the fixed effect for physical activity, which was expressed as an IQR increase to improve the interpretation of the effect estimates, PA_{ti} denotes the physical activity, which was modeled as average counts or total number of changes in environments experienced, for *t*th sampling day and the *i*th subject, b_{0i} denotes the random deviation from the overall intercept for subject i, and ε_{ti}denotes the random error for the *t*th sampling day and the *i*th subject, and

$$log(MF)_{ti} = \beta_0 + \beta_1 PA2_{ti} + \ \beta_2 PA3_{ti} + b_{0i} + \varepsilon_{ti} \qquad \text{(Eq. 7)}$$

where MF_{ti} denotes the daily personal magnetic field exposure metric (mG) for the *t*th sampling day and *i*th subject, which was log-transformed, β_0 denotes the overall intercept, β_1 and $\beta_2$denote the fixed effects for physical activity pertaining to groups 2 and 3 (referent: group 1), respectively, $PA2_{ti}$ denotes the physical activity level for the second tertile of average counts or second category of total number of changes in environments experienced, for *t*th sampling day and *i*th subject, $PA3_{ti}$ denotes the physical activity level for the third tertile of average counts or third category of total number of changes in environments experienced, for *t*th sampling day and *i*th subject, b_{0i} denotes the random deviation from the overall intercept for subject i, and ε_{ti}denotes the random error for the *t*th sampling day and the *i*th subject. The *p*-values associated with the trend lines for these models were also calculated. We defined statistical significance as a $p \leq 0.05$.

Results

Table 3 shows the 50th percentile of the personal magnetic field exposure averages and maximums and average counts stratified on environment. Across environments, magnetic field exposure averages were relatively similar (0.7-1.8 mG), whereas maximums varied widely, with the highest and lowest maximums experienced on average were in transit (23.7 mG) and outside at home (6.5 mG), respectively. Participants tended to be most active while outside somewhere else, followed by outside at home, outside at work or school, in transit, inside somewhere else, inside at home, and inside at work or school. Higher physical activity within the environments examined did not necessarily lead to higher maximum personal magnetic field exposures.

Figure 9 is illustrative and shows the personal magnetic field exposure data across two 24-hour sampling periods for two participants with low and high average counts, respectively. Qualitatively there appears to be a positive association between physical activity and personal magnetic field exposure level, where the probability of experiencing an elevated magnetic field exposure was greater among more active compared to less active women.

Table 4 shows the associations between daily physical activity, modeled as both average counts and total number of changes in environments experienced, and daily personal magnetic field exposure metrics. There were statistically significant positive associations between average counts and the 99th percentile and maximum magnetic field exposure and between total number of changes in environments experienced and the 90th, 95th, and 99th percentile and the maximum magnetic field exposure.

As shown in Table 5, when physical activity was modeled as a categorical variable, there was a statistically significant positive association between tertiles of average counts and the 99th percentile and maximum magnetic field exposure, whereas there was a statistically significant positive association between categories of total number of changes in environments experienced and the 95th and 99th percentiles and the maximum magnetic field exposure. Relationships with personal magnetic field exposure were slightly attenuated when modeling physical activity as tertiles of average counts relative to categories of total changes in environments experienced.

Discussion

The influence of physical activity on personal magnetic field exposure was assessed with data from women from the Boston cohort. Among the women, there were differences in physical activity and personal magnetic field exposure across the environments, and physical activity was positively associated with the upper percentile and maximum personal magnetic field exposures.

Personal magnetic field exposures differed by environment, which have been reported by others (Zaffanella and Kalton, 1998). These findings suggest environment may be an important determinant in the interaction of women with sources of magnetic field exposure. For example, the opportunity for elevated magnetic field exposures was the greatest while in transit, possibly due to elevated exposures resulting from the use of AC-powered railways or travel near power transmission lines and other sources of high magnetic fields that tend to dominate urban settings. As expected, women tended to be more physically active outdoors relative to indoors. However, higher physical activity within the environments examined did not necessarily lead to elevated maximum personal magnetic field exposures, suggesting that movement between environments and not within the same environment increases one's probability for encountering a high field source. This finding may be helpful for informing how future epidemiology studies characterize physical activity as an accelerometer, although an objective measurement instrument, measures movement of the body, not movement of the body's location, which may be more relevant in the relationship between physical activity and personal magnetic field exposure.

Only one peer-reviewed study has examined the association between physical activity using accelerometer data and personal magnetic field exposure metrics in women. In that study, Savitz et al. (2006) reported that average counts and the maximum, but not the average, personal magnetic field exposure were positively associated with each other. We observed similar results for the maximum and average in this analysis, as well as associations with upper percentiles, but not the median, which were not examined by Savitz et al. Similar to the accelerometer data, we found positive associations between total number of changes in environments experienced and peak magnetic field exposure metrics, but not central tendency metrics. Mezei et al. (2006) also reported that the daily number of activities (e.g., home + work + travel + other) in women from the Kaiser Study was positively associated with the maximum magnetic field. Taken together, our analysis, along with those published previously, suggest that effect estimates associated with epidemiology studies of peak personal magnetic field exposure metrics and miscarriage may be biased. Unmeasured confounding may be present if physical activity was not included in models, as was the case for the studies published by Lee et al. (2002) and Li et al. (2002) that reported an increase in risk of miscarriage from elevated personal maximum magnetic field exposure. While it has yet to be examined whether or not measurement day nausea is related to physical activity, assuming this is true, along with the fact that previous studies have reported that physical activity decreases with increasing gestational age (Evenson et al., 2002; Hatch et al., 1993; Mottola and Campbell, 2002; Savitz et al., 2006), these findings suggest that physical activity is associated with personal magnetic field exposure and mediated by whether or not the mother has a healthy pregnancy. Should daily accelerometer data (ICC: 0.39, estimated based on Eq. 3 and Eq. 4) or frequency of moving between environments based on time-activity diary data (ICC: 0.37) are selected to characterize physical activity, similar to personal magnetic field exposures, more than one sampling day may be necessary to reduce measurement error associated with estimated physical activity.

CHAPTER V – AIM 3 (MAGNETIC FIELD EXPOSURES BETWEEN SEXES AND WITHIN FEMALE-MALE COUPLES)

Study Participants

Aim 3 focused on data from both the North Carolina and Boston cohorts, permitting us to estimate and compare exposure distributions and temporal variability of personal magnetic field exposure metrics between sexes, and estimate the correlation of personal magnetic field exposure metrics within female-male couples.

Statistical Methods

Statistical analyses were performed using SAS version 9.3 for Windows (SAS Institute, Cary, NC, USA). Prior to conducting any statistical analyses, non-wear time data was removed from each data set (Buchowski et al., 2009; Jilcott et al., 2007; Savitz et al., 2006). For the Boston cohort, non-wear time periods were identified using the participants' time-activity diaries. However, because a time-activity diary was not employed in the North Carolina cohort, alternative methods were required to estimate non-wear-time periods. Periods in which the ActiGraph recorded ≥20 minutes of zero counts were defined as non-wear time for both of the monitors, an approach that has been adopted by others (Buchowski et al., 2009; Jilcott et al., 2007; Savitz et al., 2006).

For each participant, daily average, 90^{th} percentile, and maximum personal magnetic field exposures were calculated. Distributions and ICCs (using Eq. 3 and Eq. 4) of these daily exposure metrics were then estimated and compared between study cohorts and sexes (i.e., North Carolina women vs. Boston women vs. Boston men). As ICCs were estimated for women from the North Carolina and Boston cohorts previously (see Chapter III), ICCs were only necessary for the men from the Boston cohort to complete this analysis. The magnitudes of the ICCs were judged using the following criteria: poor reproducibility (ICC <0.40), fair to good reproducibility (0.40≤ ICC <0.75), and excellent reproducibility (ICC ≥0.75) (Rosner, 2000). Consistent with the analysis in Chapter III, we also modeled the Boston data using a 60-second instead of a 4-second sampling rate to evaluate whether or not a decrease in sampling frequency affected the estimated exposure distributions, and, as a result, shed light on the potential bias of the 60-second rate.

As described in Chapter I (see "Identified Data Gaps"), the correlation of magnetic field exposures within female-male couples has yet to be reported in the literature despite the fact that this information would add value to designing and interpreting the results of reproductive health epidemiology studies. We explored this by estimating Spearman's rank correlation coefficients (due to non-normality of the data) for the mean, 90^{th} percentile, and maximum for female-male couples from a subset of the Boston cohort that had data across all three measurement periods and were sampled on the same days. We estimated correlations associated with these exposure metrics for each measurement period, which were then combined to derive an overall average across all three time points. Correlations were estimated across the entire sampling day, and individually for time that was spent inside the home and outside the home as we hypothesized that correlations of these magnetic field exposure metrics are stronger in environments that are more likely to be shared in comparison to environments that may likely not be shared. For example, magnetic field exposures may be highly correlated inside the home as the couple share this environment and time spent in this environment, but exposures may be weakly correlated outside the home as couples may have different mobility patterns, such as working at different places of employment or performing different leisurely activities, leading to interactions with different sources of magnetic fields and, ultimately, variability in the intensity, frequency, and/or duration of exposures between the partners.

Results

Table 6 shows the distributions of the daily personal magnetic field exposure metrics for the women and men associated with the North Carolina and Boston cohorts. Daily averages and 90^{th} percentiles were relatively similar across both cohorts and sexes (range of the median for the average: 0.8-1.1 mG and range of the median for the 90^{th} percentile: 1.6-2.2 mG), but maximums varied widely (range of the median for the maximum: 10.1-33.5 mG). These results also suggest that a lesser sampling frequency may substantially underestimate the maximum, but not the other examined magnetic field exposure metrics.

Table 7 shows the ICCs for daily personal magnetic field exposure metrics for men in the Boston cohort relative to those for women in the North Carolina and Boston cohorts. Among the men, the average and 90^{th} percentile showed fair to good reproducibility, whereas the maximum demonstrated poor reproducibility over a relatively long duration.

Table 8 presents the Spearman's rank correlation coefficients of personal magnetic field exposure metrics between female-male partners from the Boston cohort. For periods of time that were not stratified on environment, the average was the only magnetic field exposure metric that consistently showed a statistically significant, strong, and positive correlation (average across all three measurement periods: 0.78). A similar finding was also observed when only including data that was derived from time periods when inside the home (average across all three measurement periods: 0.87). The average, 90^{th} percentile, and maximum were not consistently well-correlated for time periods when outside the home.

Discussion

Personal magnetic field exposures were compared between sexes and within female-male couples using data associated with the North Carolina and Boston cohorts. Sex, geography, and environment are potential determinants of personal magnetic field exposure.

Large differences were observed in the magnitude of estimated maximum magnetic field exposures between both cohorts and sexes. For example, there was a 15% difference in estimated maximums when comparing the median of the distributions for women and men from the Boston cohort, which is much greater than the difference by sex for the average (0%) and 90^{th} percentile (10%). This finding suggests that although average magnetic field exposures throughout the day may be similar for both sexes in this cohort, the peak level to which they are exposed may differ possibly due to differential mobility patterns and as a result variability in the sources of magnetic fields to which they are exposed. However, the median of the maximums for women in the North Carolina cohort was nearly 70% less than that for women and men from Boston, suggesting that geography may be an important determinant in the interaction of women and men with magnetic field sources. For example, in Boston, which is a population-dense urban environment, there may be greater opportunity for encountering sources of high magnetic fields, such as railways and/or power transmission lines, which tend to dominate urban settings relative non-urban settings, such as the cities in which the participants resided in North Carolina. On the other hand, this difference in the maximums may have little to do with geography, but rather bias that may have resulted from the differential sampling mechanics of the personal magnetic field exposure monitors. The EMDEX LITE used in the Boston study had a 4-second measurement frequency, whereas the EMDEX II used in the North Carolina study had a 60-second sampling frequency. As a sub-analysis using data from our Boston cohort, we demonstrated that a decrease in measurement frequency from 4 to 60 seconds may significantly underestimate the measured maximum magnetic field exposure (around a 40% decrease), a finding that was similarly observed by Mezei et al. (2006). While distributions were similar for the other exposure metrics examined, systematic bias from sampling mechanics may not entirely explain the small differences in the averages and 90th percentiles observed between both cohorts as Mezei et al. (2006) also reported that the distributions for the average and upper percentiles are relatively constant across different sampling frequencies. Thus, geography may still play a role in personal magnetic field exposure nonetheless.

As part of the 1000-Person Survey, the median of the averages measured over a single 24-hour period among women and men from the U.S. population was 0.9 mG (Zaffanella and Kalton, 1998). While this is comparable to the estimated medians of the averages for the North Carolina (0.8 mG) and Boston (1.1 mG) cohorts, even the reported exposure distributions in the 1000-person survey may not be entirely comparable as the EMDEX PAL that was employed in the survey sampled at 0.5-second intervals and accumulated exposure data for 10 minutes prior to calculating summary measures. The only other published study on the distributions of personal magnetic field exposures was that by Bracken (2002) who reported a median of the averages and maximums of 1.1 mG and 26.9 mG, respectively, using data from women recruited in the Kaiser Spontaneous Abortion Study (Lee et al., 2002; Li et al., 2002). Since the EMDEX LITE with a 4-second sampling frequency was also used in this study, these results may be more appropriately compared to data from the Boston cohort. In particular, average exposures were similar, but the maximum level to which women were exposed in the Kaiser study was slightly lower than that of the Boston cohort, suggesting that perhaps geography does indeed play at least a small role in predicting personal magnetic field exposure. Other demographic factors which could influence personal magnetic field exposure, such as differences in employment, may also be important.

We are aware of no previous studies that have examined the reproducibility of personal magnetic field exposure metrics in men. Our findings suggest that more than one measurement of personal magnetic field exposure may be necessary to reduce exposure measurement error in epidemiology studies that focus on male reproductive health. Li et al. (2010) reported that the 90^{th} percentile is perhaps the biologically-relevant metric that corresponds to poor sperm quality. The authors chose the 90^{th} percentile to examine a threshold effect based on their conclusion that this metric is "relatively stable" over the duration of spermatogenesis. However, this conclusion was based on data derived from a residential study, which may not be appropriate as exposures to magnetic fields occur both inside and outside the home. It is no surprise that exposures inside the home are relatively stable, but incorporation of exposure data corresponding to time spent outside the home may reveal that the variability of the daily 90th percentile is much less stable over spermatogenesis as mobility patterns outside the home will result in variable interactions with different magnetic field sources and, as a result, variability in exposures. In addition, given that they relied on data derived from a single, 24-hour measurement period, the effect estimates that were reported in that study were likely biased to some extent, which, if non-differential, towards the null and, therefore, underestimate true risk. On the other hand, there exists temporal ambiguity between personal magnetic field exposure and poor sperm quality resulting from the case-control study design, which significantly limits conclusions of causality.

There is convincing evidence that personal magnetic field exposures collected in women could be used as an exposure surrogate for their respective male partners and vice versa if there is interest in investigating the average as the biologically-relevant metric in reproductive health epidemiology studies. The findings from our correlation analysis suggest that the strong, positive correlation between average exposures within female-male couples is for the most part driven by shared exposures inside the home. Kavet et al. (1992) reported that spot and 24-hour fixed site measurements inside the home are moderately to strongly correlated (Pearson's correlation: 0.68-0.70) with the average personal magnetic field exposure inside the home. Based on these results, one may argue that investigators could rely on an area measurement inside the home instead of personal exposure data if there is interest in the average. However, the generalizability of Kavet et al. is limited as the study was conducted among a relatively small sample size (n=45) of adults from Maine during the summer months. Several factors that could be variable across cohorts, such as mobility, season, and the size of the home, could influence how well area and personal exposure measures are correlated inside the home. Taken together, with the fact that personal monitors can capture variability in exposure over space and time, personal exposure data should still be collected in analyses where the average is hypothesized to be the biologically-relevant metric. In addition, our results suggest that the average as a surrogate measure of exposure may not necessarily be useful if there is only interest in magnetic field exposures that occur outside of the home. This information is not only novel, but it is also useful, especially if it is feasible to recruit men to provide a semen sample, but challenging to recruit men to wear a personal magnetic field exposure monitor relative to their respective female partners. This was case in our Boston cohort where couples were successfully recruited into the overall EARtH study, but male partners were less likely than their partners to additionally participate in the pilot study (the ratio of females to males recruited into the pilot study was 2:1). Our findings also have application retrospectively among fertility cohorts that primarily focused on women, but also have corresponding semen samples from their male partners who never had their magnetic field exposures characterized.

CHAPTER VI – DISCUSSION

Summary of Primary Findings

This dissertation research concerned magnetic fields and is at the interface of exposure science and reproductive health epidemiology. Data from two longitudinal cohorts were used to investigate several novel exposure science issues and evaluate currently accepted methodology with the underlying goal of informing the design of future epidemiology studies. We found that measures of central tendency associated with daily personal magnetic field exposures were more stable over time compared with measures of peak, and that the stability of these exposure metrics was greater over short-term (days) relative to long-term durations (weeks). The data suggest that if there is interest in peak magnetic field exposure metrics, more than one day of measurement is needed over the window of disease susceptibility to minimize exposure measurement error. We also observed a positive association between physical activity and peak magnetic field exposure metrics. This relationship was true when physical activity was modeled using accelerometer data or frequency of movement between environments, which was derived from a time-activity diary. This finding suggests that physical activity could be an important confounder in the relationship between exposure to magnetic fields and miscarriage, and, as a result, should be adjusted for in statistical models to reduce bias. Lastly, we demonstrated that personal magnetic field exposures among women and men are similar, and that there is promise that female magnetic field exposure data could be used as an exposure surrogate for her male partner in the absence of such data and vice versa, especially if there is interest in the average as the hypothesized biologically-relevant metric and personal magnetic field exposures that occur inside the home only.

Strengths and Limitations

Unique strengths of this research were the robustness of the two data sets, which included thousands of data points per day within each individual, the breadth of magnetic field exposure and physical activity metrics examined, and the originality of many of the examined hypotheses. For instance, no previous peer-reviewed studies have reported on the estimated distributions of personal magnetic field exposure metrics within sub-fertile individuals, variability of personal magnetic field exposure metrics in women and men over durations that are relevant to fertility, association between physical activity and personal magnetic field exposure where activity was modeled using both accelerometer data and time-activity diary approaches in the same study, and correlation of magnetic field exposures within female-male couples. The findings of this research may also be informative in the design of development epidemiology studies. For example, recent research suggests that childhood asthma and obesity may be related with prenatal magnetic field exposures (Li et al., 2011, 2012), and perhaps our findings concerning the temporal variability of magnetic field exposures could inform exposure characterization strategies (e.g., added value of collecting more than one days' worth of personal magnetic field exposure data) in future studies that concern the developmental origins of these adverse health conditions. Furthermore, while we found that physical activity is positively correlated with magnetic field exposure, this connection may extend to other physical, chemical, and biological agents as well, which may have important implications for identifying segments of the population where exposure reduction strategies are necessary.

Despite the many strengths of this research, it is not without its limitations. First, while it is commonly accepted practice to refer to power-frequency magnetic fields as “50/60 Hz magnetic fields,” we are in truth exposed to not only the magnetic fields associated with the fundamental, but also the fields from the harmonics or multiples of the fundamental. The magnetic field level within the appropriate range of frequencies is captured by the broadband setting of the EMDEX exposure monitors. However, as we did not employ a detailed spectral analysis of the personal magnetic field exposure data, we were not able to comment on the specific contribution of the fundamental frequency (believed to be the strongest at this frequency) or associated harmonics to the overall magnetic field strength. Given that the biologically-relevant magnetic field exposure metric in reproductive health epidemiology studies remains a subject of debate, there are endless possibilities that could be used to define exposure. We focused on those previously identified as being potentially biologically-relevant (i.e., maximum for women and 90th percentile for men), while at the same time exploring exposure science issues regarding other measures of central tendency and peak that are potential candidates in future epidemiology studies. Thus, there is some aspect to this research that was exploratory in nature. Even though we did not validate our time-activity diary for the Boston cohort, it was derived from a diary that was designed by the U.S. government for a population-based study in pregnant women, and asked participants about recently performed, routine activities over the course of a single day, which likely minimized the potential for reporting bias. One may also argue that our decision to remove non-wear time data prior to conducting subsequent analyses biased our results. While this approach has not been adopted in some previous epidemiology studies, by definition, personal exposures do not include time periods in which the monitors were not worn, thus removal of data associated with these time intervals is relevant to our stated aims. Along the same lines, although the ActiGraph provides an objective measure of activity, the algorithm that was used to define non-wear time was conservative and may have misclassified some intervals, particularly time in sedentary behavior. Regardless, as shown in Appendix A, when non-wear time data was not removed from both data sets and statistical analyses were repeated, our conclusions remained the same. Due to technological limitations of the time, the personal magnetic field exposure monitors for the North Carolina study sampled once every 60 seconds, which may have biased the results generated using this data set. Consistent with Mezei et al. (2006), estimated exposure distributions for the maximum may have been underestimated, but this bias did not appear to affect the temporal variability analysis. While our sample size that was associated with the Boston cohort was somewhat small and precluded examining additional issues relevant to the subject matter at hand (e.g., the influence of pregnancy nausea on physical activity and resultant personal magnetic field exposure), our findings using data from this cohort were similar to those that incorporate data from much larger sample sizes on the temporal variability of personal magnetic field exposure metrics (see Aim 1) and association between physical activity and personal magnetic field exposure (Savitz et al., 2006), lending credibility to our analysis rather than chance findings due to selection bias. It should also be noted that our personal magnetic field exposure estimates do not represent internal dose, but rather conservative estimates of internal dose. Like other physical agents, magnetic field levels reduce as a function of distance from the source. Therefore, because magnetic field levels were measured at the hip level outside of the body, the magnetic field level imparted to the inside of the body at the target tissue/organ of interest may be lower in reality as there is some distance than needs to be covered when going from the surface of the skin to the internals of the body. A final limitation of this research relates to the uncertainty in our ability to generalize the results to other populations, especially children whose interaction with magnetic field sources may differ from adults.

Recommendations for Future Research

Taken together, additional research is greatly needed to explore whether or not magnetic field exposure is associated with miscarriage, poor semen quality, as well as other reproductive health outcomes. A specific challenge concerns the fact that most miscarriages occur early in pregnancy and may not be clinically reported. However, the literature has predominantly dealt with clinical miscarriages, a design that does not account for the full population of failed conceptions (Wilcox et al., 1988). To advance the science, studies are required that enables the acquisition of personal magnetic field exposure and mobility data, while prospectively following a cohort of pregnancies from a period prior to conception to the pregnancies' ultimate outcomes. An epidemiology study of women enrolled in assisted reproductive technology clinics offers this opportunity. Because of their difficulty in conceiving naturally, coupled with technological advances in clinical methods, increasing numbers of women (and men) are seeking treatment in hospital centers specializing in assisted reproductive technology (Missmer et al., 2011). Enrollees may represent a population of women (and men) with differentially greater sensitivity to potentially harmful environmental exposures, such as magnetic fields, which provides for a statistically powerful setting in which to conduct epidemiology studies.

One aspect that has been somewhat limited in exploring the relationship between exposure to magnetic fields and infertility is the approach to characterizing personal magnetic field exposures in study populations. Summary measures, such as average or maximum daily personal magnetic field exposures or total daily exposure or time above select exposure thresholds, have been used exclusively. Because personal exposure monitors can log large numbers of data points over the measurement period, this permits the investigator flexibility to model personal exposure beyond summary measures in an endless number of ways, which is valuable as the biologically-relevant metric is uncertain and, as a result, remains subject of debate. On the other hand, this flexibility also makes the analysis susceptible to "cut point hunting" to support an a priori hypothesis. It is plausible that magnetic fields induce toxicity from the effects of cumulative exposure or an acute exposure event above some particular threshold. For example, cumulative exposure could be estimated by summing all of the logged personal magnetic field exposures over the measurement period, in other words an "area-under-the-curve" approach. While the personal exposure metrics generated by this approach are correlated with summary measures (e.g., daily average) to some degree, they are more sensitive than such summary measures to the variability in personal magnetic field exposures experienced by the participants over the course of the sampling day. By better capturing this variability, this may help revealing small inflection points in the dose-response relationship. Another possibility for estimating instantaneous exposure events is to use person-4-second (EMDEX LITE), person-minute (EMDEX II), or another frequent sampling time frame rather than person-day data. One of the added values of this alternative approaches is that it greatly increases sample size as each participant contributes thousands of data points instead of one data point for the measurement day, which increases the robustness of the model and options for modeling exposure-outcome relationships (this could also increase the statistical power if the random error is also decreased). Alternative estimates of peak exposure events (e.g., based on the duration or frequency of peaks rather than only the magnitude of peaks) and the potential influence of the monitor's response rate on captured peaks should also be explored. In addition, in many of these epidemiology studies, quantiles of exposure were used to examine relationships with outcome of interest, which may be problematic for accurately examining the strength and shape of non-linear (even non-monotonic) dose-response relationships. As an alternative, splines can be easily added to statistical models to observe associations that normally would not be revealed using a quantile analysis. While it may be true that splines are sensitive to the placement of knots, others have argued that quantiles are equally sensitive to the selection of cut points (Bennette and Vickers, 2012). Despite widespread use of splines in peer-reviewed environmental epidemiology studies (Ashley-Martin et al., 2014; Khalil et al., 2014; Kim et al., 2014; Liu et al., 2014; Wang and Choi, 2014), we were only able to locate one application of splines in magnetic fields epidemiology (Greenland et al., 2000).

Conclusions

In conclusion, infertility is a public health priority and many questions remain whether or not exposure to magnetic fields, a ubiquitous environmental agent, may be linked to its etiology. Results of this research are expected to lead to better epidemiology study designs and, as a result, improve our understanding of the potential relationship between exposure to magnetic fields and infertility. In turn, this will potentially reduce the financial and emotional burden of infertility in the U.S. and other areas of the world, and/or quell unfounded fears and anxiety of certain exposure.

TABLES

Table 1. Temporal Variability of Continuous Magnetic Field Exposure Metrics in Women

	Intraclass Correlation Coefficient		
Metric	NC Cohort[a]	B Cohort[b]	B Cohort[b,c]
Average	0.64	0.63	0.62
Median	0.66	0.56	0.57
90th%tile	0.55	0.62	0.61
95th%tile	0.49	0.59	0.59
99th%tile	0.43	0.32	0.30
Maximum	0.37	0.13	0.10

Abbreviations: B, Boston; NC, North Carolina.
[a]Derived from linear mixed models with only one random effect as the random intercept for each subject using 677 sampling days from 100 women.
[b]Derived from linear mixed models with only one random effect as the random intercept for each subject using 74 sampling days from 27 women.
[c]Re-analyzed using a 60-second sampling rate instead of 4-second sampling rate.

Table 2. Temporal Variability of Categorical Magnetic Field Exposure Metrics in Women

	North Carolina Cohort[a]			Boston Cohort[b]			Boston Cohort[b,c]		
Metric	T[d]	SENS	SPEC	T[d]	SENS	SPEC	T[d]	SENS	SPEC
Average	≥0.8	0.76	0.75	≥1.2	0.81	0.94	≥1.2	0.81	0.94
	≥1.3	0.69	0.92	≥1.9	0.76	0.91	≥1.9	0.71	0.91
	≥1.9	0.51	0.95	≥2.7	0.67	0.92	≥2.7	0.67	0.92
Median	≥0.5	0.80	0.81	≥0.7	0.83	0.85	≥0.7	0.83	0.85
	≥0.9	0.83	0.92	≥1.3	0.71	0.91	≥1.3	0.71	0.91
	≥1.5	0.58	0.94	≥2.1	0.67	0.93	≥2.1	0.67	0.93
90th%tile	≥1.6	0.68	0.73	≥2.1	0.78	0.96	≥2.1	0.78	0.96
	≥2.5	0.64	0.88	≥3.6	0.76	0.93	≥3.6	0.71	0.88
	≥3.9	0.62	0.95	≥4.7	0.67	0.98	≥4.7	0.67	0.98
95th%tile	≥2.3	0.67	0.75	≥3.1	0.72	0.86	≥3.0	0.72	0.86
	≥3.4	0.57	0.85	≥4.5	0.70	0.91	≥4.5	0.77	0.92
	≥5.1	0.43	0.94	≥5.8	0.50	0.97	≥5.8	0.50	0.97
99th%tile	≥4.4	0.62	0.72	≥6.9	0.73	0.76	≥6.7	0.71	0.88
	≥6.8	0.41	0.82	≥9.9	0.59	0.96	≥9.9	0.55	0.93
	≥11.3	0.26	0.92	≥13.7	0.50	0.97	≥15.5	0.50	0.94
Maximum	≥10.1	0.54	0.83	≥34.9	0.69	1.00	≥20.6	0.65	1.00
	≥16.0[e]	0.36	0.88	≥55.0	0.46	1.00	≥35.7	0.46	1.00
	≥37.4	0.20	0.95	≥85.4	0.39	1.00	≥66.1	0.40	1.00

Abbreviations: SENS, sensitivity; SPEC, specificity; T, threshold.
[a]677 sampling days from 100 women.
[b]74 sampling days from 27 women.
[c]Re-analyzed using 60-second sampling rate instead of 4-second sampling rate.
[d]50^{th}, 75^{th}, and 90^{th} percentiles of the daily personal magnetic field exposure metrics (mG).
[e]Reported by Li et al. (2002) as the threshold above which there is an increased risk of miscarriage; 16.0 mG is about the 70^{th} percentile of the daily personal magnetic field exposure maximums.

Table 3. Physical Activity and Magnetic Field Exposure Metrics by Environment in Women

	Boston Cohort						
	Personal Magnetic Field Exposure (mG)			Physical Activity (Average Counts)			
Environment	Metric	P50	Rank-Order	Metric	P50	Rank-Order	Relative to Inside the Home
Inside at home[a]	Average Maximum	1.0 15.0	4 5	Average	13.9	6	1.00 x as active
Inside at work or school[b]	Average Maximum	0.7 18.9	5 (lowest) 3	Average	12.7	7 (lowest)	0.91 x as active
Inside somewhere else[c]	Average Maximum	1.2 18.0	3 4	Average	24.9	5	1.79 x as active
Outside at home[d]	Average Maximum	1.0 6.5	4 7 (lowest)	Average	42.8	2	3.08 x as active
Outside at work or school[e]	Average Maximum	1.0 11.2	4 6	Average	36.8	3	2.65 x as active
Outside somewhere else[f]	Average Maximum	1.8 23.6	1 (highest) 2	Average	47.6	1 (highest)	3.42 x as active
In transit[g]	Average Maximum	1.7 23.7	2 1 (highest)	Average	26.8	4	1.93 x as active

Abbreviations: P50, 50th percentile.
[a]89 sampling days from 40 women.
[b]45 sampling days from 23 women.
[c]57 sampling days from 31 women.
[d]22 sampling days from 16 women.
[e]14 sampling days from 11 women.
[f]58 sampling days from 29 women.
[g]72 sampling days from 32 women.

Table 4. Association between Physical Activity (Cont.) and Magnetic Field Exposure in Women

	Boston Cohort					
	Average Counts			Total Number of Changes in Environments Experienced		
Metric	β[a,b]	95% CI	*p*-value	β[a,c]	95% CI	*p*-value
Average	0.07	-0.14, 0.29	0.48	0.12	-0.06, 0.24	0.13
Median	0.13	-0.14, 0.43	0.35	0.06	-0.12, 0.24	0.71
90th%tile	0.07	-0.14, 0.29	0.55	0.18	0.02, 0.36	0.02
95th%tile	0.14	-0.09, 0.43	0.20	0.24	0.12, 0.42	0.0006
99th%tile	0.43	0.10, 0.58	0.007	0.30	0.12, 0.54	0.0008
Maximum	0.43	0.13, 0.72	0.007	0.24	-0.001, 0.48	0.05

Abbreviations: CI, confidence interval.

[a]Each β estimate is from a separate statistical model.

[b]Derived from linear mixed models with only one random effect as the random intercept for each subject and a fixed effect for daily average counts using 77 sampling days from 38 women.

[c]Derived from linear mixed models with only one random effect as the random intercept for each subject and a fixed effect for daily total number of changes in environments experienced using 89 sampling days from 40 women.

Table 5. Association between Physical Activity (Cat.) and Magnetic Field Exposure in Women

	Boston Cohort							
	Average Counts				Total Changes in Environments Experienced			
Metric	Tertiles	β[a]	95% CI	*p*-value	Categories	β[a]	95% CI	*p*-value
Average	Low (referent)[b]	0			<6 (referent)[c]	0		
	Medium[d]	0.01	-0.27, 0.30		6-9[e]	-0.14	-0.49, 0.20	
	High[f]	0.02	-0.30, 0.35		≥10[g]	0.04	-0.32, 0.41	
	Trend			0.90	Trend			0.31
Median	Low (referent)[b]	0			<6 (referent)[c]	0		
	Medium[d]	0.21	-0.14, 0.56		6-9[e]	-0.09	-0.53, 0.34	
	High[f]	0.22	-0.18, 0.61		≥10[g]	-0.02	-0.48, 0.44	
	Trend			0.25	Trend			0.90
90th%tile	Low (referent)[b]	0			<6 (referent)[c]	0		
	Medium[d]	0.14	-0.18, 0.46		6-9[e]	-0.16	-0.53, 0.22	
	High[f]	0.08	-0.29, 0.45		≥10[g]	0.11	-0.29, 0.51	
	Trend			0.63	Trend			0.11
95th%tile	Low (referent)[b]	0			<6 (referent)[c]	0		
	Medium[d]	0.14	-0.17, 0.44		6-9[e]	0.01	-0.34, 0.37	
	High[f]	0.15	-0.19, 0.50		≥10[g]	0.35	-0.03, 0.73	
	Trend			0.37	Trend			0.01
99th%tile	Low (referent)[b]	0			<6 (referent)[c]	0		
	Medium[d]	0.08	-0.36, 0.51		6-9[e]	0.33	-0.09, 0.76	
	High[f]	0.35	-0.11, 0.80		≥10[g]	0.70	0.26, 1.14	
	Trend			0.13	Trend			0.002
Maximum	Low (referent)[b]	0			<6 (referent)[c]	0		
	Medium[d]	0.09	-0.46, 0.64		6-9[e]	0.63	0.11, 1.15	
	High[f]	0.54	-0.002, 1.09		≥10[g]	0.74	0.21, 1.27	
	Trend			0.05	Trend			0.01

[a]Each β estimate is from a separate linear mixed model with only one random effect as the random intercept for each subject and a fixed effect for each tertile of average counts or category of total number of changes in environments experienced.
[b]26 sampling days from 19 women.
[c]21 sampling days from 14 women.
[d]25 sampling days from 20 women.
[e]34 sampling days from 23 women.
[f]26 sampling days from 19 women.
[g]34 sampling days from 21 women.

Table 6. Distributions of Magnetic Field Exposure Metrics in Women and Men

	NC cohort (W)[a]			B cohort (W)[b]			B cohort (W)[b,c]			B cohort (M)[d]		
Metric	P25	P50	P75	P25	P50	P75	P25	P50	P75	P25	P50	P75
Average	0.6	0.8	1.3	0.8	1.1	1.7	0.7	1.1	1.4	0.8	1.1	1.6
90th%tile	1.0	1.6	2.5	1.4	2.0	3.4	1.1	1.8	2.5	1.6	2.2	2.6
Maximum	6.3	10.1	18.7	18.6	33.5	48.9	11.5	19.8	28.9	19.2	28.8	47.0

Abbreviations: B, Boston; M, men; NC, North Carolina; P25, 25th percentile; P50, 50th percentile; P75, 75th percentile; W, women.
[a]677 sampling days from 100 women.
[b]113 sampling days from 40 women.
[c]Re-analyzed using a 60-second sampling rate instead of 4-second sampling rate.
[d]47 sampling days from 20 men.

Table 7. Temporal Variability of Continuous Magnetic Field Exposure Metrics in Men

	Intraclass Correlation Coefficient			
Metric	NC cohort (W)[a]	B cohort (W)[b]	B cohort (W)[b,c]	B cohort (M)[d]
Average	0.64	0.63	0.62	0.60
90th%tile	0.55	0.62	0.61	0.65
Maximum	0.37	0.13	0.10	0.08

Abbreviations: B, Boston; NC, North Carolina.
[a]Derived from linear mixed models with only one random effect as the random intercept for each subject using 677 sampling days from 100 women as shown in Table 1.
[b]Derived from linear mixed models with only one random effect as the random intercept for each subject using 74 sampling days from 27 women as shown in Table 1.
[c]Re-analyzed using a 60-second sampling rate instead of 4-second sampling rate as shown in Table 1.
[d]Derived from linear mixed models with only random effect as the random intercept for each subject using 41 sampling days from 15 men.

Table 8. Correlation of Magnetic Field Exposure Metrics between Partners by Environment

Boston Cohort					
		Spearman's rank correlation coefficient			
Environment	Metric	Day 1	Day 2	Day 3	Average
Inside the home + outside the home[a]	Average	0.76*	0.76*	0.83*	0.78
	90th%tile	0.79*	0.48	0.44	0.57
	Maximum	-0.06	0.64	-0.31	0.09
Inside the home[a]	Average	0.95*	0.71*	0.94*	0.87
	90th%tile	0.97*	0.47	0.65*	0.70
	Maximum	0.28	-0.62	-0.18	-0.17
Outside the home[b]	Average	0.88*	0.59	0.33	0.60
	90th%tile	-0.11	0.12	-0.65*	-0.21
	Maximum	0.10	0.71*	0.48	0.43

[a]Day 1: n = 22 men + women, Day 2: n = 20 men + women, Day 3: n = 22 men + women.
[b]Day 1: n = 22 men + women, Day 2: n = 20 men + women, Day 3: n = 20 men + women.
*p <0.05

FIGURES

Figure 1. Interaction between Magnetic Fields and the Human Body

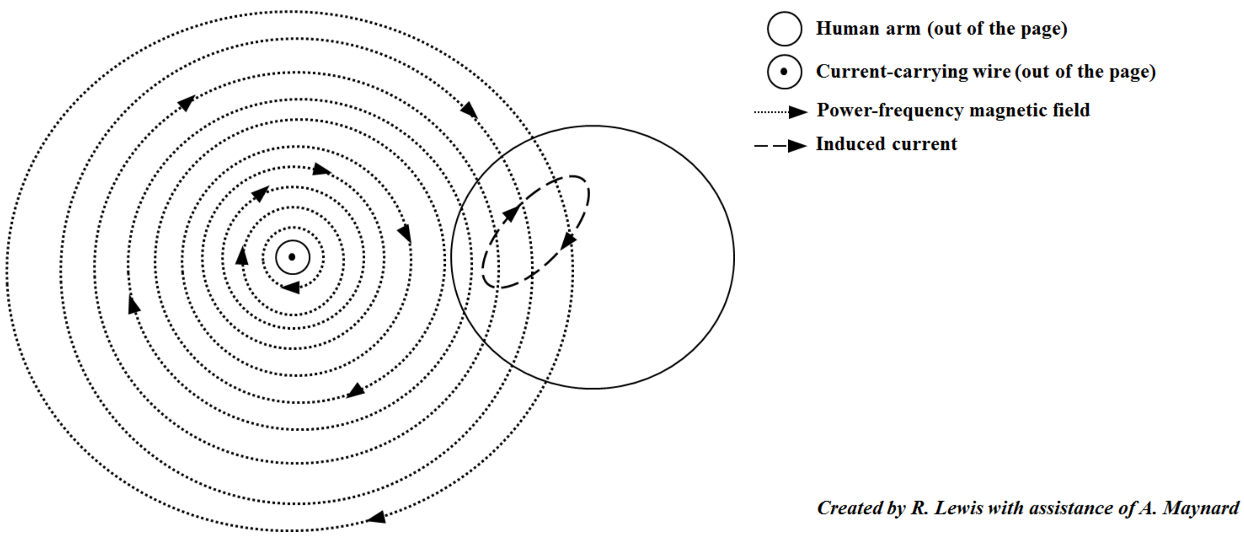


Figure 2. Time-Activity Diary Used by the Women in the Boston Cohort

	Time	Did you have any nausea?	Use any electronics plugged into wall?	Vigorous physical activity	Moderate physical activity	Walking	Sleeping	Activity Description	Inside, at home	Inside, at work or school	Inside, somewhere else	Outside, at home	Outside, at work or school	Outside, somewhere else	In transit
		Activity Columns Mark All that Apply							Place Columns Mark All that Apply						
Morning	12:00 am – 12:29 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	12:30 am – 12:59 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	1:00 am – 1:29 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	1:30 am – 1:59 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	2:00 am – 2:29 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	2:30 am – 2:59 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	3:00 am – 3:29 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	3:30 am – 3:59 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	4:00 am – 4:29 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	4:30 am – 4:59 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	5:00 am – 5:29 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	5:30 am – 5:59 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	6:00 am – 6:29 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	6:30 am – 6:59 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	7:00 am – 7:29 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	7:30 am – 7:59 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	8:00 am – 8:29 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	8:30 am – 8:59 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	9:00 am – 9:29 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	9:30 am – 9:59 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	10:00 am – 10:29 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	10:30 am – 10:59 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	11:00 am – 11:29 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	11:30 am – 11:59 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐

Continues through 24-hour period

Figure 3. Time-Activity Diary Used by the Men in the Boston Cohort

	Time	Did you keep phone in pants pocket?	Use any electronics plugged into wall?	Vigorous physical activity	Moderate physical activity	Walking	Sleeping	Activity Description	Inside, at home	Inside, at work or school	Inside, somewhere else	Outside, at home	Outside, at work or school	Outside, somewhere else	In transit
		Activity Columns Mark All that Apply							Place Columns Mark All that Apply						
Morning	12:00 am – 12:29 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	12:30 am – 12:59 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	1:00 am – 1:29 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	1:30 am – 1:59 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	2:00 am – 2:29 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	2:30 am – 2:59 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	3:00 am – 3:29 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	3:30 am – 3:59 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	4:00 am – 4:29 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	4:30 am – 4:59 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	5:00 am – 5:29 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	5:30 am – 5:59 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	6:00 am – 6:29 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	6:30 am – 6:59 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	7:00 am – 7:29 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	7:30 am – 7:59 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	8:00 am – 8:29 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	8:30 am – 8:59 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	9:00 am – 9:29 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	9:30 am – 9:59 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	10:00 am – 10:29 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	10:30 am – 10:59 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	11:00 am – 11:29 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐
	11:30 am – 11:59 am	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐

Continues through 24-hour period

Figure 4. Eligible Participant Questionnaire Used in the Boston Cohort

Eligible Participant Questionnaire

Date ______________ Participant ID ______________

We would like to receive your feedback on why you did or did not choose to participate in this study.

Please check the boxes that are most appropriate for you.

"I did choose to participate in this study because…"

☐ **This research will be beneficial to me and others.**

☐ **My partner thinks that it is a good idea.**

☐ **I am neutral with respect to my participation.**

☐ **I am interested in the subject matter.**

☐ **I have the time to be involved.**

☐ **I was interested in the extra compensation.**

"I did not choose to participate in this study because…"

☐ **This research will not be beneficial to me and others.**

☐ **My partner does not think that it is a good idea.**

☐ **I am neutral with respect to my participation.**

☐ **I am not interested in the subject matter.**

☐ **I do not have the time to be involved.**

☐ **The compensation offered was not enough.**

Comments:

Figure 5. Post-Participation Questionnaire Used in the Boston Cohort

Participant Questionnaire

Date ______________ **Participant ID ______________**

We would like to receive your feedback on your experience of wearing the two monitors.

Please check the one box that is most appropriate for you.

To what extent do you agree or disagree with the following statements?

1. **"I found participating in this study to be burdensome."**

- ☐ **Totally Agree**
- ☐ **Partially Agree**
- ☐ **Do Not Agree or Disagree**
- ☐ **Partially Disagree**
- ☐ **Totally Disagree**

2. **"I found the two monitors to be burdensome."**

- ☐ **Totally Agree**
- ☐ **Partially Agree**
- ☐ **Do Not Agree or Disagree**
- ☐ **Partially Disagree**
- ☐ **Totally Disagree**

Comments:

Figure 6. Recruiting Brochure Used in the Boston Cohort

FAQ

What are magnetic fields?

Magnetic fields are generated by electricity and are commonly found in and around our homes and workplaces.

How can I be exposed to magnetic fields?

Examples of common sources of magnetic fields include power lines, hair dryers, lamps, televisions, computers, and electric blankets.

How do magnetic fields impact me?

Magnetic fields can penetrate the human body where they may cause health effects.

Where can I get more information on magnetic fields?

Please visit the U.S. National Institutes of Health webpage on electric and magnetic fields and download a copy of *EMF: Electric and Magnetic Fields Associated with the Use of Electric Power*

www.niehs.nih.gov/health/topics/agents/emf

CONTACT US

For more information on the study, please contact your nurse practitioner.

You may also contact the head of the EARtH study directly:

Russ Hauser, MD, ScD, MPH
Harvard School of Public Health

t: 617.432.3326
e: rhauser@hsph.harvard.edu
w: www.hsph.harvard.edu/earth

Environment and Reproductive Health (EARtH) Study

MAGNETIC FIELDS AND FERTILITY

Environment and Reproductive Health (EARtH) Study

PAYING IT FORWARD

Thank you for considering participation in this groundbreaking study. Through your contribution, doctors will learn more about magnetic fields and how they impact fertility. This way we can better help women and men like you who are trying to start a family.

Benefits of Participation

- Opportunity to contribute to pioneering scientific research
- $50 for each 24-hr data collection session ($150 if all three data collection sessions are completed)
- Parking voucher for visits related to research purposes

YOUR PARTICIPATION

Participation in this study is an easy 1 – 2 – 3. Let your nurse practitioner know you would like to participate and we'll get you started.

1. We will send you two monitors, a diary and materials on the study.

2. Wear the two monitors and record your activities in a diary for three 24-hour periods.

3. Mail the materials back to us in the pre-paid, pre-addressed mailer after each three monitoring periods.

PRESTO! You're done!

Rest assured that all information collected will be kept strictly confidential and will not impact the quality of your medical care.

OUR STUDY

There are many reasons for infertility and **previous studies have suggested that exposure to magnetic fields may be one of them.**

However, we don't have enough understanding on the issue and that's why we're investigating this link.

The Environment and Reproductive Health (EARtH) study is led by doctors, nurses and researchers from the Harvard School of Public Heath; Massachusetts General Hospital; and the University of Michigan. We have been studying the effects of environmental factors for over 15 years.

Figure 7. Magnetic Field Exposures for a Subset of 10 Women from the North Carolina Cohort

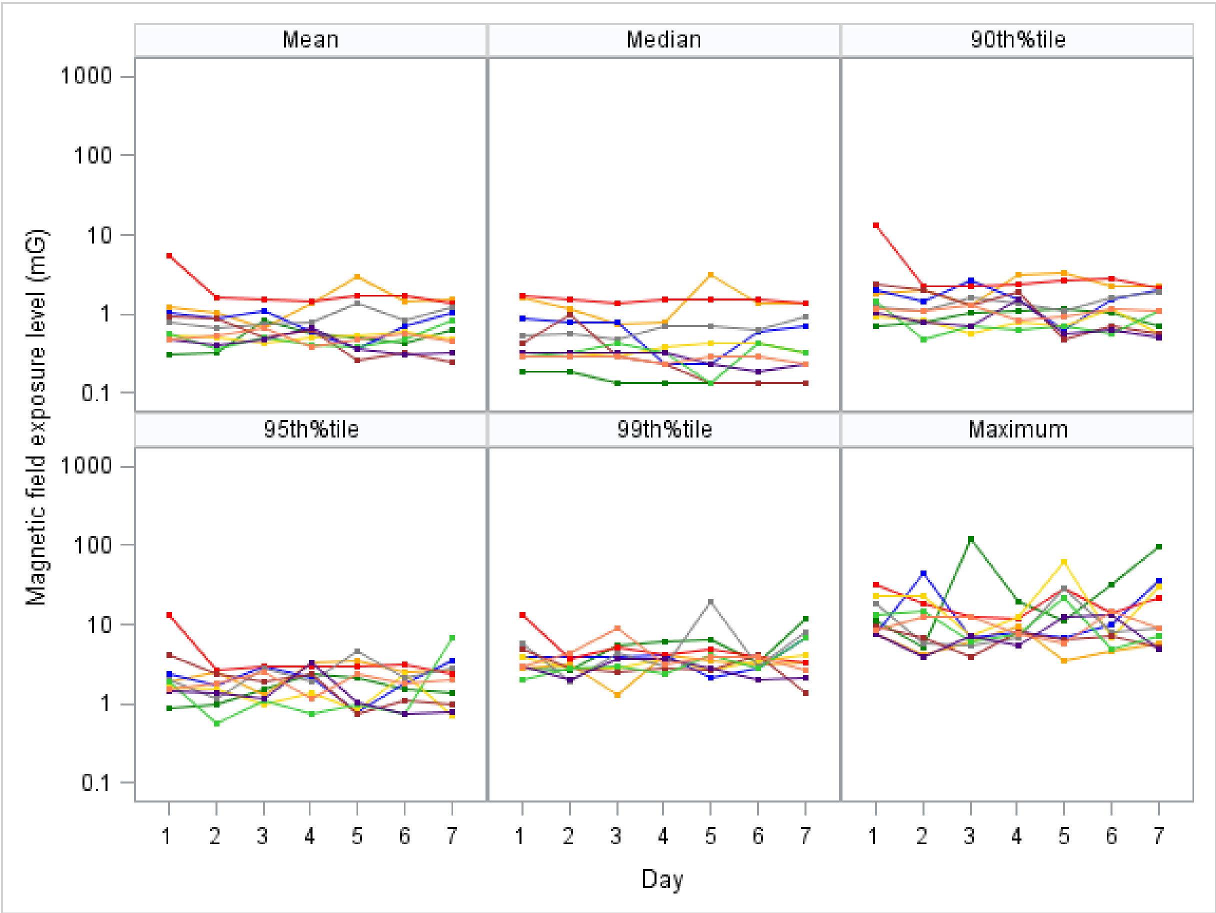


Figure 8. Magnetic Field Exposures for a Subset of 10 Women from the Boston Cohort

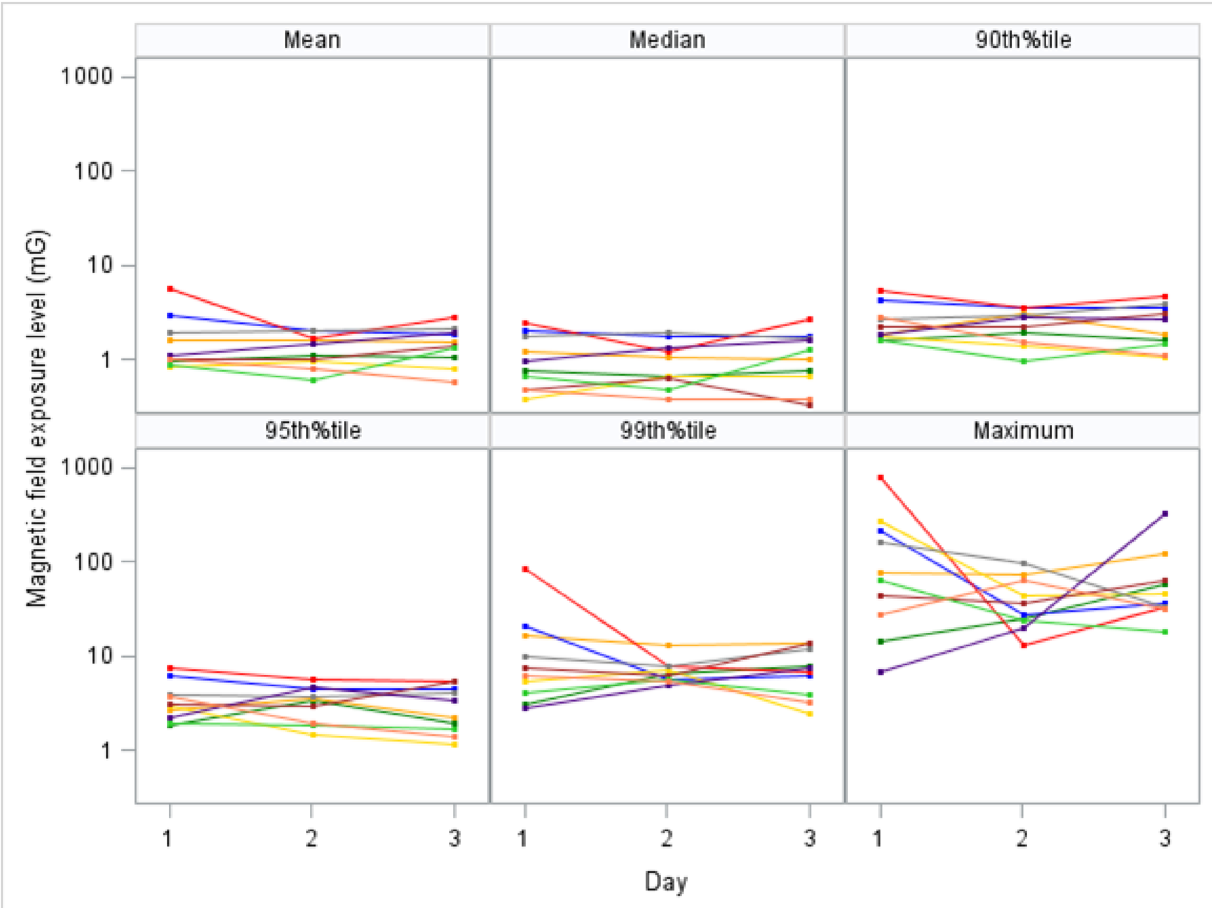
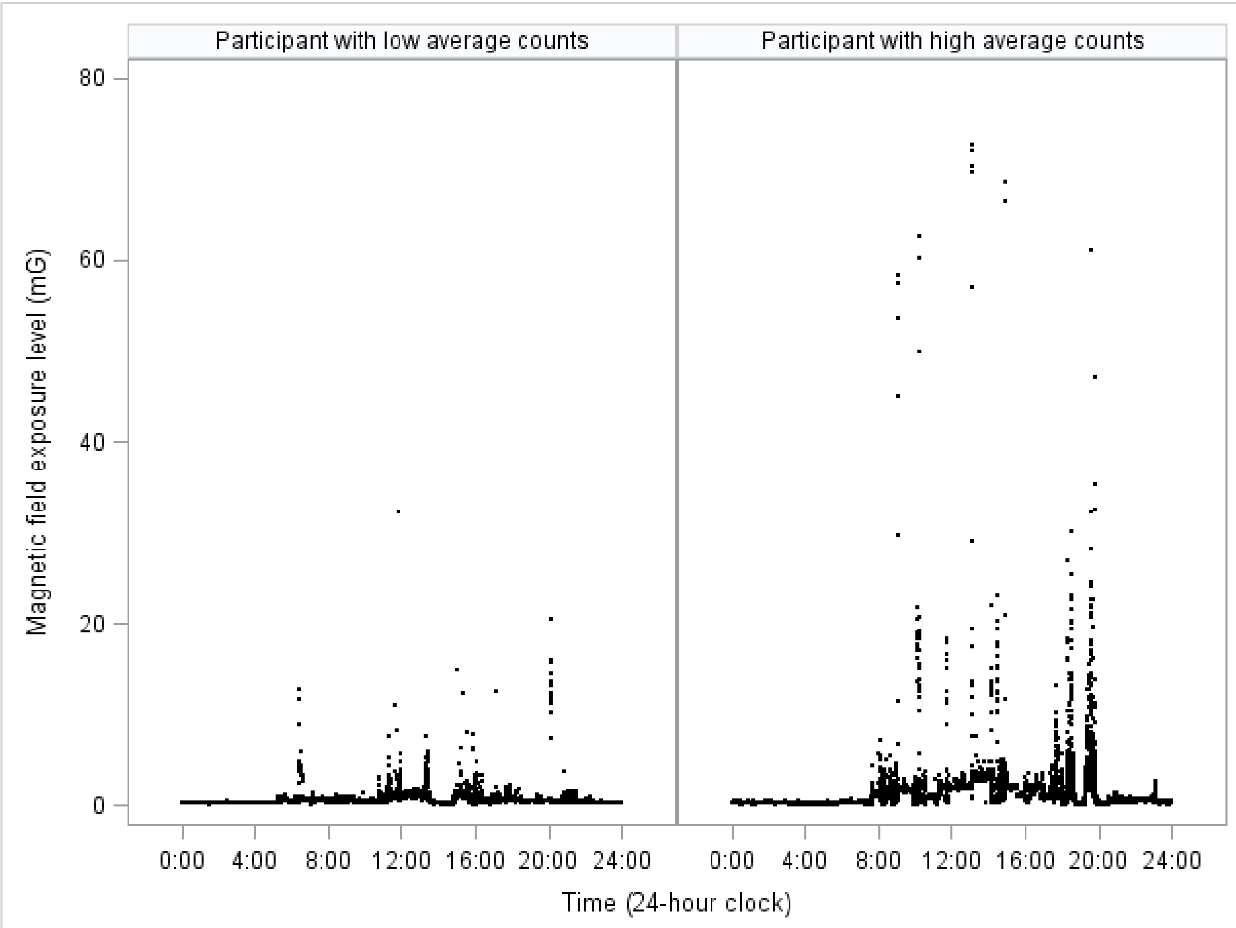


Figure 9. 24-Hour Magnetic Field Exposure Profiles for Two Women from the Boston Cohort



APPENDIX A – INFLUENCE OF NON-WEAR TIME DATA REMOVAL

The primary statistical analyses (Tables 1-8) were re-analyzed without removing data associated with non-wear time intervals (Tables A1-A8) to explore if our handling of non-wear time modified the results. While there is some degree of variability between both sets of results, this alternative approach did not modify our conclusions, suggesting our original methodology for handling non-wear time did not significantly bias the results.

Table A1. Temporal Variability of Continuous Magnetic Field Exposure Metrics in Women

	Intraclass Correlation Coefficient		
Metric	NC Cohort[a]	B Cohort[b]	B Cohort[b,c]
Average	0.67	0.71	0.70
Median	0.75	0.79	0.78
90th%tile	0.59	0.66	0.66
95th%tile	0.54	0.59	0.58
99th%tile	0.46	0.45	0.45
Maximum	0.34	0.09	0.07

Abbreviations: B, Boston; NC, North Carolina.
[a]Derived from linear mixed models with only one random effect as the random intercept for each subject using 677 sampling days from 100 women.
[b]Derived from linear mixed models with only one random effect as the random intercept for each subject using 74 sampling days from 27 women.
[c]Re-analyzed using a 60-second sampling rate instead of 4-second sampling rate.

Table A2. Temporal Variability of Categorical Magnetic Field Exposure Metrics in Women

	North Carolina Cohort[a]			Boston Cohort[b]			Boston Cohort[b,c]		
Metric	T[d]	SENS	SPEC	T[d]	SENS	SPEC	T[d]	SENS	SPEC
Average	≥0.7	0.80	0.81	≥1.1	0.82	0.84	≥1.0	0.86	0.90
	≥1.2	0.75	0.93	≥1.6	0.79	0.95	≥1.5	0.84	0.91
	≥2.1	0.59	0.96	≥2.5	0.67	0.97	≥2.5	0.50	0.97
Median	≥0.4	0.88	0.81	≥0.6	0.90	0.92	≥0.6	0.90	0.91
	≥0.9	0.81	0.92	≥1.1	0.87	0.92	≥1.1	0.87	0.90
	≥1.5	0.81	0.96	≥2.1	1.00	0.93	≥2.1	1.00	0.93
90th%tile	≥1.3	0.76	0.81	≥1.9	0.80	0.89	≥1.8	0.80	0.93
	≥2.3	0.69	0.93	≥3.0	0.84	0.95	≥2.7	0.77	0.94
	≥4.2	0.57	0.96	≥4.2	0.50	0.96	≥4.3	0.50	0.94
95th%tile	≥1.9	0.74	0.78	≥2.4	0.76	0.94	≥2.2	0.80	0.89
	≥3.1	0.65	0.91	≥3.9	0.68	0.93	≥3.7	0.73	0.87
	≥5.7	0.46	0.95	≥4.9	0.64	0.99	≥5.0	0.55	0.98
99th%tile	≥3.7	0.62	0.74	≥5.4	0.80	0.91	≥5.4	0.83	0.88
	≥5.7	0.45	0.86	≥8.1	0.55	0.96	≥7.8	0.62	0.96
	≥9.3	0.32	0.93	≥11.7	0.63	0.97	≥12.2	0.80	0.94
Maximum	≥10.4	0.55	0.88	≥34.9	0.66	1.00	≥20.7	0.67	1.00
	≥16.0[e]	0.37	0.89	≥55.0	0.46	1.00	≥32.6	0.49	1.00
	≥38.7	0.21	0.96	≥85.4	0.39	1.00	≥60.5	0.40	1.00

Abbreviations: SENS, sensitivity; SPEC, specificity; T, threshold.
[a]677 sampling days from 100 women.
[b]74 sampling days from 27 women.
[c]Re-analyzed using 60-second sampling rate instead of 4-second sampling rate.
[d]50^{th}, 75^{th}, and 90^{th} percentiles of the daily personal magnetic field exposure metrics (mG).
[e]Reported by Li et al. (2002) as the threshold above which there is an increased risk of miscarriage; 16.0 mG is about the 70^{th} percentile of the daily personal magnetic field exposure maximums.

Table A3. Physical Activity and Magnetic Field Exposure Metrics by Environment in Women

	Boston Cohort						
	Personal Magnetic Field Exposure (mG)			Physical Activity (Average Counts)			
Environment	Metric	P50	Rank-Order	Metric	P50	Rank-Order	Relative to Inside the Home
Inside at home[a]	Average Maximum	0.8 16.2	5 5	Average	7.1	6	1.00 x as active
Inside at work or school[b]	Average Maximum	0.7 18.9	6 (lowest) 3	Average	12.7	7 (lowest)	1.79 x as active
Inside somewhere else[c]	Average Maximum	1.2 18.0	3 4	Average	24.9	5	3.51 x as active
Outside at home[d]	Average Maximum	1.0 6.5	4 7 (lowest)	Average	42.8	2	6.03 x as active
Outside at work or school[e]	Average Maximum	1.0 11.2	4 6	Average	36.8	3	5.18 x as active
Outside somewhere else[f]	Average Maximum	1.8 23.6	1 (highest) 2	Average	47.6	1 (highest)	6.70 x as active
In transit[g]	Average Maximum	1.7 24.3	2 1 (highest)	Average	26.8	4	3.77 x as active

Abbreviations: P50, 50th percentile.
[a]89 sampling days from 40 women.
[b]45 sampling days from 23 women.
[c]57 sampling days from 31 women.
[d]22 sampling days from 16 women.
[e]14 sampling days from 11 women.
[f]58 sampling days from 29 women.
[g]72 sampling days from 32 women.

Table A4. Association between Physical Activity (Cont.) and Magnetic Field Exp. in Women

	Boston Cohort					
	Average Counts			Total Number of Changes in Environments Experienced		
Metric	β[a,b]	95% CI	*p*-value	β[a,c]	95% CI	*p*-value
Average	-0.02	-0.21, 0.17	0.86	0.03	-0.03, 0.09	0.33
Median	-0.03	-0.24, 0.17	0.74	-0.01	-0.07, 0.05	0.76
90th%tile	0.03	-0.19, 0.25	0.81	0.06	-0.01, 0.13	0.09
95th%tile	0.07	-0.15, 0.30	0.50	0.10	0.03, 0.17	0.006
99th%tile	0.25	-0.00, 0.49	0.05	0.15	0.07, 0.23	0.0004
Maximum	0.37	0.08, 0.66	0.01	0.10	-0.00, 0.20	0.07

Abbreviations: CI, confidence interval.
[a]Each β estimate is from a separate statistical model.
[b]Derived from linear mixed models with only one random effect as the random intercept for each subject and a fixed effect for daily average counts using 77 sampling days from 38 women.
[c]Derived from linear mixed models with only one random effect as the random intercept for each subject and a fixed effect for daily total number of changes in environments experienced using 89 sampling days from 40 women.

Table A5. Association between Physical Activity (Cat.) and Magnetic Field Exposure in Women

	Boston Cohort							
	Average Counts				Total Changes in Environments Experienced			
Metric	Tertiles	β[a]	95% CI	*p*-value	Categories	β[a]	95% CI	*p*-value
Average	Low (referent)[b]	0			<6 (referent)[c]	0		
	Medium[d]	0.24	-2.05, 2.53		6-9[e]	-1.69	-3.62, 0.25	
	High[f]	-0.54	-3.27, 2.20		≥10[g]	-0.70	-2.79, 1.38	
	Trend			0.72	Trend			0.69
Median	Low (referent)[b]	0			<6 (referent)[c]	0		
	Medium[d]	0.08	-2.31, 2.47		6-9[e]	-1.42	-3.57, 0.72	
	High[f]	-0.98	-3.87, 1.91		≥10[g]	-1.14	-3.46, 1.18	
	Trend			0.53	Trend			0.63
90th%tile	Low (referent)[b]	0			<6 (referent)[c]	0		
	Medium[d]	0.69	-2.06, 3.43		6-9[e]	-1.34	-3.66, 0.94	
	High[f]	-0.02	-3.26, 3.21		≥10[g]	0.05	-2.42, 2.52	
	Trend			0.66	Trend			0.26
95th%tile	Low (referent)[b]	0			<6 (referent)[c]	0		
	Medium[d]	1.14	-1.75, 4.04		6-9[e]	-0.14	-2.42, 2.15	
	High[f]	0.66	-2.66, 3.98		≥10[g]	1.94	-0.48, 4.37	
	Trend			0.37	Trend			0.02
99th%tile	Low (referent)[b]	0			<6 (referent)[c]	0		
	Medium[d]	2.04	-1.44, 5.51		6-9[e]	1.72	-0.80, 4.25	
	High[f]	2.82	-0.99, 6.63		≥10[g]	3.99	1.35, 6.63	
	Trend			0.14	Trend			0.002
Maximum	Low (referent)[b]	0			<6 (referent)[c]	0		
	Medium[d]	0.53	-4.13, 5.19		6-9[e]	3.47	0.35, 6.59	
	High[f]	4.31	-0.30, 8.92		≥10[g]	4.15	0.99, 7.31	
	Trend			0.07	Trend			0.02

[a]Each β estimate is from a separate linear mixed model with only one random effect as the random intercept for each subject and a fixed effect for each tertile of average counts or category of total number of changes in environments experienced.
[b]26 sampling days from 20 women.
[c]21 sampling days from 14 women.
[d]25 sampling days from 19 women.
[e]34 sampling days from 23 women.
[f]26 sampling days from 18 women.
[g]34 sampling days from 21 women.

Table A6. Distributions of Magnetic Field Exposure Metrics in Women and Men

	NC cohort (W)[a]			B cohort (W)[b]			B cohort (W)[b,c]			B cohort (M)[d]		
Metric	P25	P50	P75	P25	P50	P75	P25	P50	P75	P25	P50	P75
Average	0.5	0.7	1.2	0.7	1.0	1.4	0.7	1.0	1.4	0.7	0.9	1.4
90th%tile	0.8	1.3	2.3	1.1	1.8	2.5	1.1	1.8	2.5	1.3	1.8	3.1
Maximum	6.8	10.4	18.8	20.5	33.9	48.9	11.5	19.8	28.9	19.6	28.9	47.0

Abbreviations: B, Boston; M, men; NC, North Carolina; P25, 25th percentile; P50, 50th percentile; P75, 75th percentile; W, women.
[a]677 sampling days from 100 women.
[b]113 sampling days from 40 women.
[c]Re-analyzed using a 60-second sampling rate instead of 4-second sampling rate.
[d]47 sampling days from 20 men.

Table A7. Temporal Variability of Continuous Magnetic Field Exposure Metrics in Men

	Intraclass Correlation Coefficient			
Metric	NC cohort (W)[a]	B cohort (W)[b]	B cohort (W)[b,c]	B cohort (M)[d]
Average	0.67	0.71	0.70	0.69
90th%tile	0.59	0.66	0.66	0.68
Maximum	0.34	0.09	0.07	0.15

Abbreviations: B, Boston; NC, North Carolina.
[a]Derived from linear mixed models with only one random effect as the random intercept for each subject using 677 sampling days from 100 women as shown in Table A1.
[b]Derived from linear mixed models with only one random effect as the random intercept for each subject using 74 sampling days from 27 women as shown in Table A1.
[c]Re-analyzed using a 60-second sampling rate instead of 4-second sampling rate as shown in Table A1.
[d]Derived from linear mixed models with only random effect as the random intercept for each subject using 41 sampling days from 15 men.

Table A8. Correlation of Magnetic Field Exposure Metrics between Partners by Environment

Boston Cohort					
		Spearman's rank correlation coefficient			
Environment	Metric	Day 1	Day 2	Day 3	Average
Inside the home + outside the home[a]	Average	0.85*	0.78*	0.80*	0.81
	90th%tile	0.66*	0.57	0.68	0.64
	Maximum	-0.06	0.31	-0.31	-0.02
Inside the home[a]	Average	0.87*	0.88*	0.87*	0.87
	90th%tile	0.93*	0.66*	0.56	0.72
	Maximum	0.33	-0.48	-0.04	-0.06
Outside the home[b]	Average	0.88*	0.59	0.32	0.60
	90th%tile	0.73*	0.48	-0.15	0.35
	Maximum	0.10	0.71*	0.48	0.43

[a]Day 1: n = 22 men + women, Day 2: n = 20 men + women, Day 3: n = 22 men + women.
[b]Day 1: n = 22 men + women, Day 2: n = 20 men + women, Day 3: n = 20 men + women.
*p <0.05.

APPENDIX B – ADDITIONAL ANALYSES NOT RELATED TO RESEARCH AIMS

We investigated several additional issues that were not directly related to the aforementioned research aims, but, nevertheless, added to the state-of-the-science on exposures to magnetic fields in women. These supplemental analyses were conducted using the data from women associated with the North Carolina cohort.

First, we observed moderate to strong positive correlations between all personal magnetic field exposure metric pairs, except for the median and maximum (Table B1). Correlations for all exposure metric pairs were statistically significant. Given that the biologically-relevant personal magnetic field exposure metric remains a subject of debate, there are numerous possibilities that could be used to define exposure. Previous epidemiology studies concerning miscarriage (Lee et al., 2002; Li et al., 2002) have focused on the average and maximum. In our analysis, the average was well correlated with the median and upper percentiles, and, as such, it is plausible that it is a suitable surrogate for these other exposure metrics and vice versa. On the other hand, the average was independent of the maximum as expected. Other studies in adults have also reported that the average is not well correlated with maximum (Lee et al., 2002; Zaffanella and Kalton, 1998).

We also found that personal magnetic field exposures during the week are slightly higher than those that occur on the weekend (Table B2). We are unaware of any other studies that have compared weekday and weekend day personal magnetic field exposures. Our results suggest that there may be differences in the intensity, frequency, and/or duration of magnetic field exposures during these two time periods, which are potentially explained by differences in mobility patterns throughout the week. For example, the environments experienced/activities performed during the week may be different than those during the weekend and, as a result, interaction with magnetic field sources may be different as well. However, because the women did not fill out a diary with information on their locations and activities during the measurement period in the North Carolina cohort, exploration of this hypothesis was not possible.

ICCs for daily personal magnetic field exposure metrics were stratified on tertiles of average counts as it follows that increased physical activity may result in increased variability in daily personal magnetic field exposure metrics over time. Similar to the unstratified analysis, ICCs for central tendency measures were more stable over time than peak measures (Table B3). We demonstrated that higher average counts/minute (indicating higher overall physical activity) was associated with greater within-individual variability in the exposure metrics, which could be explained by the fact that more active women have a greater probability of encountering sources of magnetic fields with a larger range in intensities on any given day than less active individuals.

Lastly, we also investigated whether or not there was an effect of calendar time on the daily personal magnetic field exposure using data from the North Carolina cohort as others have reported non-linear periodic effects of exposure for other environmental agents (for example, polycyclic aromatic hydrocarbons in Wang and Choi, 2014). While there is some degree of variability in magnetic field exposure over time (Figure B1), the variation was not consistent with respect to calendar time, suggesting that it is not time of year that is driving the variability in personal magnetic field exposures.

Table B1. Correlation between Magnetic Field Exposure Metrics in Women

	North Carolina Cohort					
Metric	Average	Median	90th%tile	95th%tile	99th%tile	Maximum
Average						
r_s^1	1.00	0.86	0.90	0.87	0.76	0.53
p-value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Median						
r_s^1		1.00	0.72	0.62	0.48	0.30
p-value			<0.0001	<0.0001	<0.0001	<0.0001
90th%tile						
r_s^1			1.00	0.92	0.71	0.47
p-value				<0.0001	<0.0001	<0.0001
95th%tile						
r_s^1				1.00	0.83	0.54
p-value					<0.0001	<0.0001
99th%tile						
r_s^1					1.00	0.72
p-value						<0.0001
Maximum						
r_s^1						1.00
p-value						

Abbreviations: r_s Spearman's rank-order correlation coefficient.
[a]677 sampling days from 100 women.

Table B2. Distribution of Magnetic Field Exposure Metrics by Part of the Week in Women

North Carolina Cohort				
		Percentiles (mG)		
Part of the week	Metric	25th	50th	75th
Weekdays (Mon.-Fri.)[a]	Average	0.6	0.8	1.3
	Median	0.3	0.5	0.9
	90th%tile	1.0	1.6	2.6
	95th%tile	1.5	2.4	3.5
	99th%tile	3.2	4.5	6.9
	Maximum	6.8	10.2	18.8
Weekend days (Sat.-Sun.)[b]	Average	0.5	0.7	1.2
	Median	0.3	0.4	0.9
	90th%tile	0.9	1.4	2.4
	95th%tile	1.3	2.0	3.1
	99th%tile	2.8	4.4	5.9
	Maximum	5.5	9.9	18.0

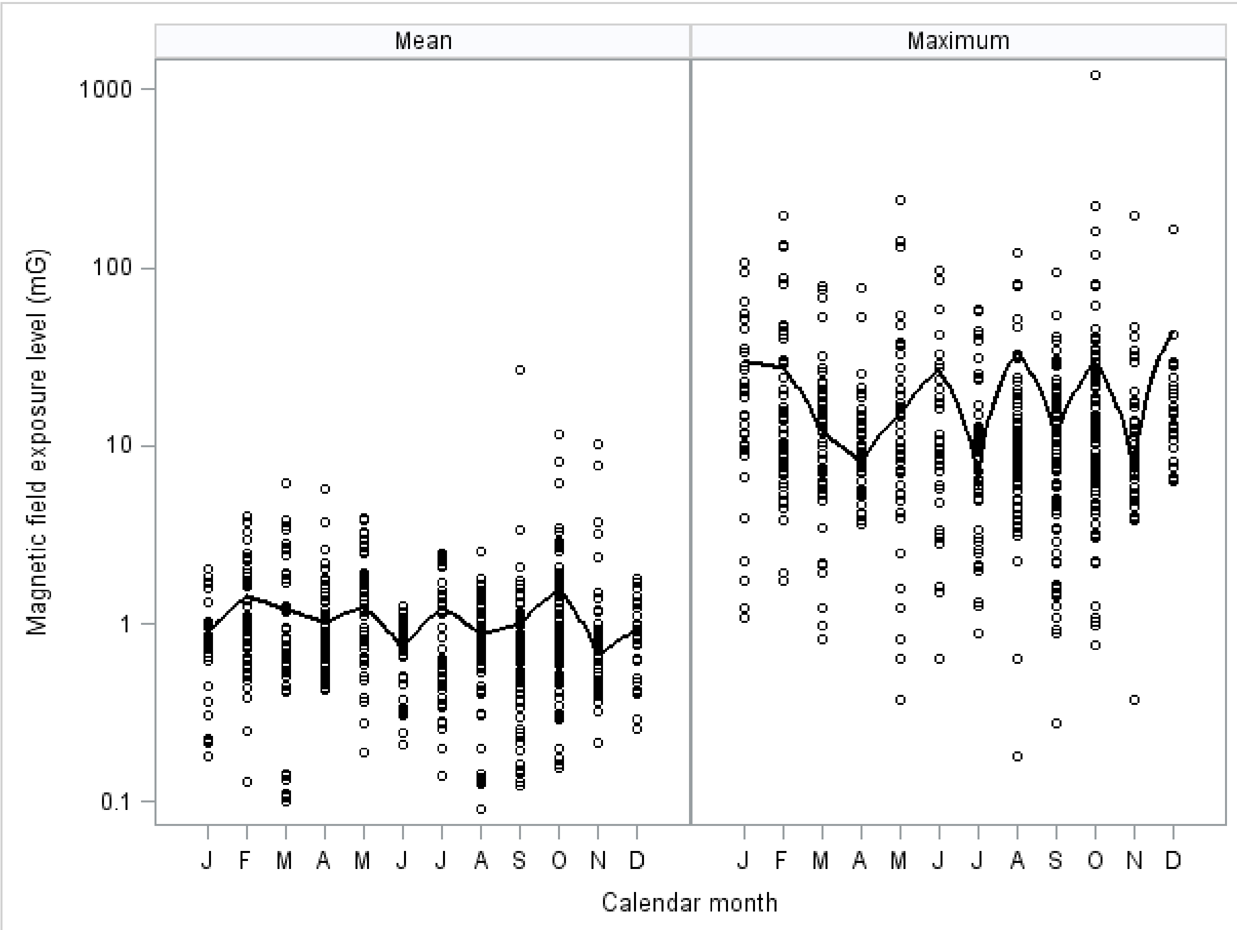
[a]488 sampling days from 100 women.
[b]189 sampling days from 99 women.

Table B3. Temporal Variability of Magnetic Field Exp. Metrics by Activity Level in Women

North Carolina Cohort		
Tertiles of Average Counts	Metric	ICC
Low[a]	Average	0.80
	Median	0.79
	90th%tile	0.74
	95th%tile	0.69
	99th%tile	0.55
	Maximum	0.44
Medium[b]	Average	0.45
	Median	0.48
	90th%tile	0.35
	95th%tile	0.31
	99th%tile	0.25
	Maximum	0.27
High[c]	Average	0.50
	Median	0.60
	90th%tile	0.43
	95th%tile	0.37
	99th%tile	0.40
	Maximum	0.35

Abbreviations: ICC, intraclass correlation coefficient.
[a]215 sampling days from 33 women.
[b]232 sampling days from 34 women.
[c]230 sampling days from 33 women.

Figure B1. Magnetic Field Exposures by Month for Women from the North Carolina Cohort



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