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# Proximity to major roadways and prospectively-measured time-to-pregnancy and infertility

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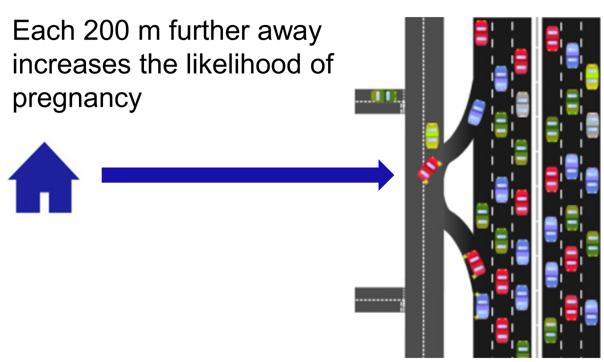
## HIGHLIGHTS

- Traffic-related air pollutants and noise may decrease fertility.
- Couples conceived more quickly when their home was farther from a major roadway.
- Each 200 m further from a roadway increased fecundability by 3%.
- Prospectively-measured infertility also appeared higher at moderate distances.

## GRAPHICAL ABSTRACT

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## ABSTRACT

We aimed to study the potential impact of proximity to major roadways on time-to-pregnancy and infertility in couples attempting pregnancy in the Longitudinal Investigation of Fertility and Environment (LIFE) study (2005–2009), a population-based, prospective cohort study. Couples attempting pregnancy (n = 500) were enrolled and followed prospectively until pregnancy or 12 months of trying and 393 couples (78%) had complete data and full follow-up. Time-to-pregnancy was based on a standard protocol using fertility monitors, tracking estrone-3-glucuonide and luteinizing hormone, and pregnancy test kits to detect human chorionic gonadotropin (hCG). The fecundability odds ratio (FOR) and 95% confidence interval (CI) were estimated using proportional odds models. Infertility was defined as 12 months of trying to conceive without an hCG pregnancy and the relative risk (RR) and 95% CI were estimated with log-binomial regression. Final models were adjusted for age, parity, study site, and salivary alpha-amylase, a stress marker. Infertile couples (53/393; 14%) tended to live closer to major roadways on average than fertile couples (689 m vs. 843 m, respectively) but the difference was not statistically significant. The likelihood of pregnancy was increased 3% for every 200 m further away the couples residence was from a major roadway (FOR = 1.03; CI = 1.01–1.06). Infertility also appeared elevated at moderate distances compared to 1000 m or greater, but estimates lacked precision. Our findings suggest that proximity to

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major roadways may be related to reductions in fecundity. Prospective data from larger populations is warranted to corroborate these findings.



## 1. Introduction

A recent review of air pollution and fertility (Frutos et al., 2015) suggested a significant impact of air pollution, including traffic-related pollutants, on indicators of fertility such as miscarriage and live birth rates in both animal and human studies with few prospective human studies noted as an important limitation in the extant literature. Traffic exposures represent an interesting mixture of urban stressors. In addition to commonly measured air pollutants, major roadways are a source of noise and exposure to other compounds such as diesel exhaust and metal particles. Proximity to major roadways has been associated with cardiovascular events (Maheswaran and Elliott, 2003; Hart et al., 2014; Rosenbloom et al., 2012), renal function (Lue et al., 2013) and type 2 diabetes (Puett et al., 2011).

The few available human and animal studies suggest a potential effect of traffic and traffic-related pollutants on fecundity. A prospective cohort of pregnant women from a pre-paid health plan in California observed an increased risk of spontaneous abortion associated with the highest traffic counts (≥90th percentile) within 50 m of a residence among African-Americans or non-smokers (Green et al., 2009). The only population-based study of fertility and traffic-related air pollutant exposure found a 13% reduction in fertility rates among women aged 15–44 years in Barcelona, Spain in 2011–2012 associated with coarse particles using a land-use regression model and vital statistics data (Nieuwenhuijsen et al., 2014). Couple-based fecundability was assessed in Teplice, where pregnancy in the first month of unprotected intercourse was less likely when couples were exposed to higher levels of nitrogen dioxide ($NO_2$) and $PM_{2.5}$ (Slama et al., 2013). $NO_2$ was associated with lower live birth rates and $PM_{2.5}$ with decreased conception rates after in vitro fertilization (IVF) (Legro et al., 2010), whereas miscarriage rates appeared higher in couples exposed to the highest quartile of PM exposure prior to IVF or embryo transfer (Perin et al., 2010). In mice, traffic-related pollutant exposures decreased fertility with effects demonstrated for both males and females as well as mating pairs (Veras et al., 2009; Mohallem et al., 2005) and reductions in placental and fetal weight were observed among mice housed near roadways in Brazil (Rocha et al., 2008).

Prior work on traffic-related male reproductive health effects also tends to suggest potential decrements in fecundity. Adverse effects of traffic exposure on men have been demonstrated in small studies of tollgate workers (De et al., 2003; Calogero et al., 2011; Guven et al., 2008) and traffic policemen (Tomei et al., 2007, 2009). Sperm motility was reduced in relation to particulate matter <2.5 μm ($PM_{2.5}$) among men presenting for clinical semen analysis or artificial insemination (Hammoud et al., 2010). Poor semen quality and DNA fragmentation in sperm has been associated with episodic high air pollution from burning coal in studies in Teplice, Czech Republic, in the mid-1990′s (Selevan et al., 2000; Rubes et al., 2005) whereas noise stress in utero and postnatally have also been associated with smaller testes (Jalali et al., 2013) as well as decrements in semen quality (Jalali et al., 2012) in rodents.

Our objective was to evaluate prospectively-measured time-to-pregnancy and infertility among couples attempting pregnancy in relation to their residential proximity to a major roadway in a contemporary US cohort.

## 2. Material and methods

The Longitudinal Investigation of Fertility and the Environment (LIFE) Study was a prospective cohort study that enrolled couples planning pregnancy from two sites (Texas and Michigan) using population-based sampling frameworks designed to study environmental exposures (Buck Louis et al., 2011). Details of the study sample are provided elsewhere (Buck Louis et al., 2011), but briefly, two sampling frameworks (fish/wildlife license registry and a direct marketing database) were used to identify participants from 16 counties with presumed exposure to persistent organochlorine chemicals, since there is no established sampling framework or registry available to identify couples planning pregnancy. Both sites used the same recruitment strategy (i.e., mailed introductory letters followed by telephone screening calls and enrollment in the couples' home). Couples who had been told by a physician that they could not achieve pregnancy without assistance were ineligible. Couples were recruited preconception from 2005 to 2009 (n = 501) and provided with home pregnancy test kits and fertility monitors that tracked estrone-3-glucuonide and luteinizing hormone. Couples were followed daily for up to 12 months of trying or until they had a positive pregnancy test (sensitive to detect 25 mIU human chorionic gonadotropin (hCG)). Full institutional review board approval was obtained at all collaborating institutions and all participating couples gave written informed consent.

Proximity to the nearest major roadway was measured using ArcGIS and the residential address of the couple at enrollment (www.ArcGIS.com). One residence could not be geocoded, leaving 500 couples in the analysis. The latitude and longitude of each residence was determined and the shortest straight line distance from the geocoded residence to a Class A major roadway was calculated. The original recruitment sites in Texas and Michigan hold the address data and used the ESRI desktop software package (ArcGIS) to geocode the street addresses. The software integrated the data using an address-based approach with residential and commercial US addresses from the Tele Atlas Address Points database (www.tele-mart.com). The Tele Atlas database at that time relied on data from multiple sources including local agency data, TIGER data, and their own data derived from GPS equipped cars and remote sensing (2005–2006 data). The data were cleaned and then merged together into a single dataset. The ESRI software used this database as well as the major roads shape file to generate geo-coordinates, the straight-line distance, and Feature Class Codes (FCC) for each address.

Participants from Texas (n = 397, 79% of the cohort) also had a 2010 address available. Of these, 132 (33%) had moved at some point between their enrollment and the end of the study, but most moves resulted in nominal changes in distance to a major roadway (mean difference: 141 m; median difference: 28 m) and for 12 couples (3%) one partner stayed at the original address while the second had moved.

Distance to major roadway was evaluated as a linear variable and categorized as <200 m; 200 to <500 m; 500 to <1000 m; with the reference category set at 1000 m or greater given the distribution of residence proximity. We considered the roadway Feature Class Code based on the Census TIGER files (Class A 15–35, which includes major interstate, US and state highways, excluding local, neighborhood or rural roads; http://www.census.gov/geo/maps-data/data/tiger.html) as an independent indicator as well as examining the interactions between distance and road type. We also evaluated distance as a continuous measure based on 200 m increments and examined the robustness of the linear relationship using quadratic terms, cube root transformation and a natural spline.

Cox's proportional odds model for discrete survival were used to estimate fecundability odds ratios (FOR) with time to pregnancy subject to left truncation to account for couples who had started trying prior to their enrollment (1–2 months) and right censoring at hCG-detected