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

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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-glucuronide 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 meters 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 meters or greater, but estimates lacked precision. Our findings suggest that proximity to major roadways may be related to reductions in fecundity. Prospective data from larger populations is warranted to corroborate these findings.

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Graphical abstract

Keywords

infertility; time-to-pregnancy; major roadways; traffic

1.0 Introduction

A recent review of air pollution and fertility⁽¹⁾ 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(2-4), renal function(5) and type 2 diabetes(6).

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(7). 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(8). 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 (NO₂) and PM_{2.5}(9). NO₂ was associated with lower live birth rates and PM_{2.5} with decreased conception rates after in vitro fertilization (IVF),(10) whereas miscarriage rates appeared higher in couples exposed to the highest quartile of PM exposure prior to IVF or embryo transfer(11). In mice, traffic-related pollutant exposures decreased fertility with effects demonstrated for both males and females as well as mating pairs(12;13) and reductions in placental and fetal weight were observed among mice housed near roadways in Brazil(14).

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(15-17) and traffic policemen(18;19). Sperm motility was reduced in relation to particulate matter <2.5 microns (PM_{2.5}) among men presenting for clinical semen analysis or artificial insemination(20). 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(21;22) whereas noise stress *in utero* and postnatally have also been associated with smaller testes (23) as well as decrements in semen quality(24) 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.

2.0 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⁽²⁵⁾. Details of the study sample are provided elsewhere⁽²⁵⁾, 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-glucuronide 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 meter 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 pregnancy, 12 months of trying, or study exit prior to 12 months of follow-up. The FOR is a summary statistic that is below one when the time-to-pregnancy (TTP) is longer and above one for a shorter TTP. We also conducted log-binomial regression with generalized estimating equations to assess infertility status among couples who completed the study protocol (n=401 total and 393 with alpha-amylase data); these groups have 12 months of prospective follow-up without pregnancy or a spontaneous conception during the study period. Couples who completed the protocol were similar to those who withdrew in both study sites with respect to age, education, insurance status, gravidity and parity, while those who withdrew tended to have lower household income⁽²⁵⁾. There were also minor differences in the proportion of American Indian/Alaska Native and the other race group identified between couples who withdrew and those who completed the protocol, but white race was reported by 85% of women and 87% of men⁽²⁵⁾. Few couples (2%) withdrew from the prospective study to enter fertility treatment.

We evaluated potential covariates derived from the baseline in-person interviews at enrollment and biospecimens collected at that visit using non-parametric Wilcoxon Rank-Sum tests for continuous variables and chi-square tests for categorical variables. For each partner in the couple, age, gravidity, parity, parity conditioned on gravidity, body mass index, serum cotinine, race/ethnicity, education, household income, and chronic disease status were assessed but only age (male and female), parity (female) and study site were significantly associated with distance to a major roadway and remained in the model. Considering the correlation between male and female age, we adjust for female age and the difference between her age and the male partner's age. We ran adjusted models with and without parity as a covariate. Because salivary alpha-amylase, a stress biomarker, was previously found to increase infertility in our data⁽²⁶⁾ we also adjusted for alpha-amylase in tertiles in our final models among the cohort with available saliva biomarker data (n=393;

98% of the complete protocol group). In sensitivity analyses, we also included both male and female race/ethnicity, income and education as covariates.

Simulation studies were performed to estimate the power of the proportional odds model and log-binomial model in identifying significant associations between fecundability, infertility and major roadway proximity. These calculations suggest an appropriate sample size for future studies if the effect estimates we observe were correct. We simulated data based on the estimated proportional odds model adjusting for age (female and male) and parity. The covariates and left truncation time were simulated from their empirical distribution in the data set. We considered three sample sizes, $N=500$, 1000 and 2000, with censoring time generated from a Kaplan-Meier estimator of the censoring distribution (which resembles the censoring mechanism in the LIFE study). In addition, with sample size of 500, we also considered an “ideal” follow-up scheme: the censoring time was randomly generated between 12-18 months, i.e., every woman got a follow-up of at least 12 months if she did not get pregnant. For each simulated data set, the FORs were estimated for the distance to major roadway (contrast of each category with the reference category of $>1000\text{m}$), and tested for significance. An overall test of association was constructed based on Wald test. With 1000 simulated data sets, the power was calculated as the percentage of simulations that yielded significant test results. For the log-binomial regression of infertility, we performed a similar simulation by generating data from the estimated log-binomial model with sample sizes $N=400$, 800, and 1600. Compared to the proportional odds model, the sample size attrition is due to the smaller number of couples who completed the study protocol.

3.0 Results

As anticipated, couples who became pregnant during the study were younger and the women had higher parity than those who did not get pregnant or were infertile (Table 1). Fifty-three couples completed the protocol and were categorized as infertile after 12 months of follow-up without becoming pregnant (53/393; 14%). The average distance to major roadways was farther for pregnant couples (841-843 m) compared to those who were not pregnant (735 m) or infertile (689 m) who tended to live closer to major roadways, but these differences were not statistically significant ($p=0.56$ and $p=0.86$, respectively).

Fecundability appeared reduced for all couples who lived < 1000 m from a major roadway in unadjusted models (FOR ranged from 0.86-0.92) but estimates were imprecise (Table 2). Adjustment for couple age, study site and parity made little difference for close distances but tended to strengthen the findings for the 500-1000 meter category (FOR ranged from 0.79-0.80). Results from models without parity as a covariate were similar to the final models (data not shown). Further adjustment for alpha-amylase measures did not change the effect estimates for the complete protocol group. All FOR estimates were below one, suggesting a potential delayed time-to-pregnancy for couples living closer to major roadways; however, we may be underpowered to determine statistical significance.

Examining distance as a continuous measure, couples were 3% more likely to become pregnant for each 200 meters further away their residence was from a major roadway (FOR=1.03, CI=1.01-1.06). However, the lack of a dose-response at close distances in the

categorical analyses suggested a non-linear effect. Adding quadratic distance terms, using a cube root transformation and evaluating the natural spline all suggest that the linear effect is influenced by a shorter time-to-pregnancy at greater than 500 meters (see Supplemental Figure 1) with less precision at close distances.

The risk of infertility among those with 12 months of follow-up appeared elevated (Table 3) at moderate distances (< 1000 m) by 22-31%, but the estimates were not statistically significant. Adjustment for couple age, study site, parity and salivary alpha-amylase all yielded relative risk models with wide confidence intervals. Models without parity had results similar to the unadjusted models, but no significant differences (data not shown). Similarly, continuous measures of distance were not significantly related to infertility (data not shown).

We considered race/ethnicity, education and income as potentially important covariates in sensitivity analyses. Our participants were primarily non-Hispanic White, college-educated with annual incomes over \$100,000 (Supplemental Table 1). Effect estimates were fairly similar although adding these variables to the analyses generally diminished the effect estimates observed and none were significant (Supplemental Tables 2 and 3).

The simulations we conducted showed that with our sample size of 500, the power to observe a significant association in the range of effect size observed in our study was quite low for the proportional odds model (13%) and the log-binomial model had similar power for a sample of 400. Increasing the sample to more than 2000 couples would be needed to increase the power to more than 50%. Exploratory analyses examining the effects associated with the roadway Feature Class Code and the potential interaction between distance to a major roadway and the Feature Class Code were not significant (data not shown).

4.0 Discussion

This is the first study to examine infertility in relation to major roadways using a population-based prospective design with 12 observed months of follow up. Couples who lived farther from major roadways were more likely to become pregnant, particularly if they lived more than 500 meters from a major roadway. Overall, couples who took longer to conceive or were infertile tended to live closer to major roadways in our study, but we lacked statistical power to observe a significant association at close distances or for prospectively measured infertility. These findings are consistent with other investigations showing decrements in fertility rates (8), fecundability (9) and IVF treatment success (10;11) associated with traffic-related pollutant exposures.

Much of the research in this area has examined the impact of traffic on male reproductive health. Exposure to high traffic volumes in occupational settings are related to poor semen quality(16;17) and elevated reproductive hormone levels in men(18;19). Whether proximity to major roadways in a residential setting, such as the LIFE study, can influence semen quality remains to be evaluated but this is one plausible pathway for traffic/roadway exposures to impact fecundity.

Traffic noise can trigger a series of stress responses including sleep disturbances⁽²⁷⁾ and night-time cardiac and sympathetic nervous system hyperactivity⁽²⁸⁾. We measured high-traffic major roadways in proximity to the couple's residence, so even if they are not home during the day, the effects related to sleep and cardiac responsiveness overnight are relevant. Although salivary alpha-amylase, a stress biomarker, was associated with increased risk of infertility in our data⁽²⁶⁾, it did not contribute to traffic models in these analyses. This was unexpected as we assumed a stress pathway would be operating, but perhaps traffic represents a more chronic stressor which might not be reflected by alpha-amylase⁽²⁹⁾.

Major roadway proximity is measured in various units in the literature, for example lower boundaries of 50 meters(3;5;6), 100 meters(4), 200 meters(2) and reference categories in excess of 200 meters(6), 500 meters(3), 1000 meters(2;4;5) have been reported. Distances closer to roadways would presumably carry greater physical disturbance and potential adverse health impact. In our data, only 31 couples lived less than 50 meters from a major roadway, a number too small to support categorical analysis. Our categorization was designed to explore distances commonly used in the literature that were supportable by the distribution in our data. In continuous models, living farther from a major roadway (particularly more than 500 meters) increased the likelihood of pregnancy but we noted the lack of a dose-response at close distances where we may be underpowered to see an effect. We also recognize that dispersion of traffic-related pollutants will occur (30) and our straight-line exposure metric does not control for short-range local variation such as roadside vegetation (31). As with most other studies of roadway proximity, we also lack information on potential mediators of major roadway exposures, such as greenspace (32). We also lack information on neighborhood characteristics or commuting patterns that might influence exposures.

The specific mechanisms that underlie an association between proximity to major roadways and fertility are not clear and are likely to be complex. Traffic exposures are a mix of urban stressors, including noise and air pollutants associated with vehicle exhaust but the literature on fertility-related effects is exceedingly sparse, particularly with respect to female and couple factors. We note that both noise (33) and traffic-related pollutants (34) have been related to coronary heart disease. It is possible that traffic exposure could also be related to vascular factors that might limit fertility, such as implantation failure. Accordingly, renal (5) or metabolic dysfunction (6) associated with traffic exposures could also impair fertility. Several studies suggest a male-mediated pathway, with decrements in semen quality (16;17;20;21) and altered hormone levels (18;19), but investigations of female factors such as ovulation and early pregnancy loss are needed as well as a couple-based approach to examining factors that impact fertility. It is also important for future work to measure social context and other potentially explanatory factors associated with roadway proximity in relation to fertility in a more diverse population.

Our study is notable in that we have a population-based sample of couples attempting pregnancy followed for up to 12 months of trying. Our participants were primarily non-Hispanic White, college educated and their household incomes were generally high. This is potentially a low risk group with respect to traffic exposure and we note that sensitivity analyses adjusting for these factors tended to diminish our effect estimates. Prospectively

measured time-to-pregnancy and infertility avoid the problems associated with recall bias, particularly when the follow-up time is long (35). In our data, we also observed clustering of recalled time-to-pregnancy among women who remained in the study for a second pregnancy attempt after a loss (36). The detailed protocol estimating ovulation and early pregnancy testing (25) provides a gold standard for time-to-pregnancy and infertility that is difficult to obtain in less intensive efforts. On the other hand, our study has a relatively small cohort which limits our precision and statistical power although it is one of the largest population-based prospective pregnancy studies to date.

5.0 Conclusions

We observed an increased likelihood of pregnancy among couples living farther from major roadways but the relationship between distance and fecundability was not as strong at close distances. Infertility risk also appeared elevated at moderate distances from a major roadway (200-1000 m). Overall, our findings suggest that proximity to major roadways may be related to time-to-pregnancy with a 3% increase in the likelihood of pregnancy for each 200 m further from a major roadway, but we lacked statistical power to assess the effect on prospective infertility. This is consistent with emerging research on fertility decrements in relation to traffic-related pollutants and is the first study to report on prospectively-measured time-to-pregnancy and infertility. These suggestive findings warrant further study and corroboration in a larger study with more diverse populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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 meters further from a roadway increased fecundability by 3%.
- Prospectively-measured infertility also appeared higher at moderate distances.

Table 1

Descriptive characteristics of the study sample, LIFE Study 2005-2009.

	Full cohort		Complete protocol *	
	Pregnant n=347	Not Pregnant n=153	Pregnant n=340	Infertile n=53
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age, female (years)	29.8 (3.9)	30.4 (4.6)	29.7 (3.9)	30.6 (4.3)
Age, male (years)	31.6 (4.6)	32.2 (5.6)	31.6 (4.5)	32.4 (5.3)
Parity at baseline	0.7 (0.8)	0.5 (0.9)	0.7 (0.8)	0.2 (0.5)
Proximity to major roadway (meters)	841.1 (1158.1)	734.9 (1089.7)	843.4 (1165.6)	688.8 (747.7)

* Pregnant or prospective 12-months of trying (infertile) with complete data including salivary alpha-amylase.

Table 2

Fecundability odds ratios (FOR) and 95% confidence intervals (CI), comparing time-to-pregnancy in relation to proximity to major roadway, LIFE Study 2005-2009.

	Proximity to major roadway (meters)	Full cohort n=500 FOR (CI) n	Complete protocol n=400 FOR (CI) n	Complete protocol with alpha amylase n=393 FOR (CI) n
Unadjusted	<200	0.87 (0.62, 1.21) 118	0.91 (0.64, 1.29) 93	0.91 (0.65, 1.29) 93
	200 to <500	0.92 (0.66, 1.27) 144	0.90 (0.65, 1.26) 114	0.88 (0.63, 1.23) 110
	500 to <1000	0.86 (0.62, 1.20) 126	0.86 (0.61, 1.21) 99	0.86 (0.61, 1.21) 97
	1000 meters or more	Reference 112	Reference 94	Reference 93
	Continuous per 200 meter increase	1.02 (1.00, 1.04)	1.02 (1.00, 1.05)	1.02 (1.00, 1.05)
Adjusted for couple age* study site and parity	<200	0.85 (0.60, 1.21)	0.91 (0.64, 1.31)	0.92 (0.64, 1.32)
	200 to <500	0.89 (0.64, 1.26)	0.89 (0.63, 1.27)	0.89 (0.62, 1.27)
	500 to <1000	0.79 (0.56, 1.12)	0.79 (0.56, 1.13)	0.80 (0.56, 1.14)
	1000 meters or more	Reference	Reference	Reference
	Continuous per 200 meter increase	1.03 (1.00, 1.05)	1.03 (1.01, 1.06)	1.03 (1.01, 1.06)
Adjusted for couple age, study site, parity and salivary alpha-amylase	<200			0.92 (0.64, 1.33)
	200 to <500			0.89 (0.62, 1.28)
	500 to <1000			0.80 (0.56, 1.14)
	1000 meters or more			Reference
	Continuous per 200 meter increase			1.03 (1.01, 1.06)

* Female age and the difference between her age and the male partner's age.

Table 3

Prospectively-measured infertility in relation to proximity to major roadways, LIFE Study 2005-2009.

	Proximity to major roadways (meters)	Complete protocol with alpha amylase n=393 RR (CI)
Unadjusted	<200	1.00 (0.46, 2.19)
	200 to <500	1.31 (0.64, 2.65)
	500 to <1000	1.22 (0.58, 2.55)
	1000 meters or more	Reference
Adjusted for couple age * study site and parity	<200	0.86 (0.40, 1.87)
	200 to <500	1.29 (0.61, 2.76)
	500 to <1000	1.14 (0.56, 2.32)
	1000 meters or more	Reference
Adjusted for couple age, study site, parity and salivary alpha-amylase	<200	0.89 (0.39, 2.02)
	200 to <500	1.30 (0.57, 2.95)
	500 to <1000	1.23 (0.57, 2.65)
	1000 meters or more	Reference

Number of couples infertile in the <200 m = 11/93 total; 200 to <500 = 17/110 total; 500 to <1000 = 14/97 total; and 1000 m or greater = 11/93 total.

* Female age and the difference between her age and the male partner's age.