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Proximity To Nearest Major Road And Time To Pregnancy In The Early Pregnancy Study

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Abstract

Purpose: Current literature suggests that air pollution may affect reproductive outcomes, but little research has evaluated the association between air pollution and fertility. Our aim is to further examine the relationship between distance to major roadway, a proxy for traffic-related air pollution, and fecundability.

Methods: Our analysis was conducted within the North Carolina Early Pregnancy Study (n=221). Our outcome was pregnancy attempt time, an estimate of fecundability, or the per cycle probability of conception. Our primary definition of conception included early pregnancy loss, spontaneous miscarriage, ectopic and molar pregnancy, and singleton or twin pregnancies. In a secondary analysis, we defined conception as clinical pregnancy, which excluded early pregnancy loss. Residential proximity to nearest major road was calculated for each participant. We used general linear regression models to estimate fecundability ratios (FR) according to road proximity. We also used a logistic regression to estimate odds ratios (OR) for the risk of early loss within our proximity metrics. We adjusted for male and female age, education, occupation, and income.

Results: In our primary analysis of all conceptions, fecundability may be slightly improved for couples living near a major road (FR range: 1.11 – 1.42). When we evaluated only clinical pregnancies, results were attenuated, suggesting that proximity to nearest major road is not associated with fecundability. In the analysis of early loss, there appeared to be a slightly increased of early loss in women who live less than 200 meters away from a major road (OR: 2.08, 95%CI: 0.85, 5.09) and in women who live between 200 - <500 meters away from a major road (OR: 1.82, 95%CI: 0.78, 4.24).

Conclusion: We found some evidence that living near a major road may be associated with increased fecundability but there was no clear dose-response pattern. The slight increase in fecundability reflect an increased risk of early losses for participants who live closer to major roads. Further study of this association is warranted.

Introduction & Background

Subfertility affects up to 12.1% of women aged 15-44 in the United States, and 6.7% are infertile (Centers for Disease Control and Prevention, 2015). Infertility is defined as inability to conceive within 12 months and fecundability is the probability of pregnancy in one cycle, measured by time to pregnancy. Despite the prevalence of infertility, relatively little is known of the cause. The current literature shows the potential effect of the environment, particularly air pollution, on various reproductive outcomes including fertility (Frutos et al., 2015). Studying air pollution and fertility is challenging. Exposure metrics to measure air pollution vary by study and the methods to measure the outcome also vary depending on study design. The best study design for this research is through using a prospective preconception cohort. Using a preconception cohort allows researchers to more accurately know when the outcome of a pregnancy occurs, how much time a couple tried before becoming pregnant, as well as accurately measure exposures and covariates in the preconception window.

Air pollution and reproductive outcomes

Air pollution and fertility

While there has been much work on the effect of air pollution on respiratory and cardiovascular systems as well as birth outcomes, there is little research on air pollution and fertility. Air pollutants have been shown to affect hormonal activity, creating a potential risk to fertility (Carré, Gatimel, Moreau, Parinaud, & Léandri, 2017; Mahalingaiah et al., 2016; Perin, Maluf, Czeresnia, Nicolosi Foltran Januário, & Nascimento Saldiva, 2010). To our knowledge, only four studies have examined the association between exposure to air pollution and fertility. Mendola et al (2017) investigated residential proximity to a major roadway in relation to time to pregnancy among couples in a preconception prospective cohort. They found that a 200 meter increase in the distance between their residence and a major road was associated with a 3% decrease in time to pregnancy (fecundability odds ratio (FOR) of 1.03 (CI: 1.01-1.06)) (Mendola et al., 2017). In the Nurses' Health Study II, Mahalingaiah et al found an increased risk of infertility for those living closer to a major roadway, however exact time to pregnancy data were not collected (Mahalingaiah et al., 2016). In a third study, increased ambient levels of PM2.5 and NO_2 during the preconception period were associated with a decrease in fecundability, however the study was based on a post-partum cohort and time to pregnancy was collected retrospectively (Slama et al., 2013). Finally, in a population-based study using country wide fertility rates from census data and air pollution metrics of ambient air monitor data and land use regression models, Nieuwenhuijsen et al found that an increase in traffic-related pollution levels was associated with a decrease in fertility rates (Nieuwenhuijsen et al., 2014).

Air Pollution and Adverse Birth Outcomes and Miscarriage

With respect to adverse birth outcomes and miscarriage, Wilhelm and Ritz used residential proximity to major roads to look for an association with adverse birth outcomes and found a 10-20% increase in risk of low birth weight and preterm birth for women who lived closer than 220 meters to heavily trafficked roads (Wilhelm & Ritz, 2003). Kioumourtzoglou et al found that higher NO_2 exposure during the 15th gestational week was associated with an increased risk of pregnancy loss (Kioumourtzoglou et al., 2019). Green et al found that exposure to high traffic within 50m of residential location was associated with increased miscarriage (Green et al., 2009). In a case crossover study, Leiser et al found that greater exposure to NO_2 increased odds of spontaneous abortion (OR=1.16, 95%CI: 1.01 – 1.33) (Leiser et al., 2019).

Air Pollution and IVF Outcomes

Several studies have looked at air pollution in relation to IVF outcomes. Legro et al found a complex relationship between ambient air pollution measurements and IVF outcome (Legro et al., 2010). Increased

NO_2 was associated with lower rates of IVF pregnancy and live birth, but increasing ozone concentration during IVF was associated with an increased live birth rate (Legro et al., 2010). Perin et al found that women exposed to an increase in particulate matter during the follicular phase of IVF treatment were at an increased risk of miscarriage following IVF (Perin et al., 2010). Gaskins et al found a reduced probability of IVF implantation for women that lived close to a major roadway (Gaskins et al., 2018).

Air Pollution and Men's Fertility

Finally, research has suggested that air pollution adversely affects men's fertility. In a study of tollgate workers, an increased concentration of biomarkers and measured environmental pollutants was associated with lower sperm quality (De Rosa et al., 2003). In looking at residential proximity to a major road, the relationship is less clear. Nassan et al found that residential proximity to nearest major roadway was not associated with the semen volume and quantity (Nassan et al., 2018).

Our Aim

Each of the above papers shows the potential for an association between exposure to air pollution and reproductive outcomes. Only four papers look directly at exposure to air pollution in relation to fertility and fecundability, and only one of these papers used a preconception cohort (Mendola et al., 2017). Our aim for this study is to further examine the relationship between distance to major roadway and fecundability. We will improve on previous literature by including a preconception cohort with detailed time to pregnancy data and urinary hormonal data for the assessment of conception and early pregnancy loss.

Materials & Methods

Study Population

Our analysis was conducted within the National Institute of Environmental Health Sciences (NIEHS) North Carolina Early Pregnancy Study, a prospective preconception cohort study designed to examine risk factors for early pregnancy loss (Wilcox et al., 1988). The cohort included 221 women with no history of infertility living in the Raleigh, Durham, and Chapel Hill areas of North Carolina who were enrolled between 1982 and 1986 when they discontinued use of birth control and were planning to become pregnant (Jukic, McConnaughey, Weinberg, Wilcox, & Baird, 2016). Women were enrolled through community advertisements and flyers posted in local clinicians' offices (Wilcox et al., 1988).

Outcome Assessment

Daily urine samples were collected until the occurrence of a participant-recognized clinical pregnancy, or for six months of trying if she did not observe a pregnancy (Wilcox et al., 1988). Urine samples were analyzed for human chorionic gonadotropin (hCG). Bleeding information recorded in daily diaries was used to quantify the number of menstrual cycles until the first of three events occurred: 1) the participant withdrew from the study, 2) the participant observed a pregnancy verified by a physician or pregnancy test, or 3) six months had passed (Jukic, Calafat, et al., 2016). This pregnancy attempt time, or time to conception, was the outcome of interest for this analysis. Pregnancy attempt time is an estimator of fecundability, or the per cycle probability of conception. Pregnancy attempt time was defined as the number of menstrual cycles until a urinary hCG level of at least 0.025 ng/mL was sustained for three days, signifying conception (Jukic, Calafat, et al., 2016; Wilcox et al., 1988). Our primary definition of conception included early pregnancy loss, spontaneous miscarriage, ectopic and molar pregnancy, and singleton or twin pregnancies. Early pregnancy loss was defined as a subsequent decline in hCG level with the occurrence of menstrual bleeding, following this three day elevated 0.025 ng/mL hCG measurement

(Wilcox et al., 1988). We also performed a secondary analysis where we defined conception as clinical pregnancy. Clinical pregnancy was defined as a conception based on a positive home pregnancy test or a pregnancy confirmed by a physician, which included all singleton and twin pregnancies, spontaneous miscarriages, and ectopic and molar pregnancies.

Exposure Assessment

Geocoding Methodology

Residential addresses were collected at enrollment for each participant, as researchers picked up urine samples each week at the home of each participant. Cleaned addresses were imported into ArcGIS using a WGS84 projection and geocoded using the geocoding tool in ArcGIS and the ESRI DATA 2013 address locator. A total of 170 addresses (77%) were geocoded (with a match score of above 80), and 51 were not able to be geocoded using the automated program (23%) due to incomplete addresses, homes located on historic rural roads unrecognized in the 2013 geolocator dataset, or because researchers used driving directions rather than an address to annotate the participants residential location. The 51 unmatched addresses were manually geocoded using ancillary information from the participant files. For two participants, the driving directions were uncertain (i.e. the old road was minimally developed, and directions didn't account for the plethora of newly built houses), or the residence no longer existed (i.e. the trailer community no longer exists). In these cases, the midpoint of the road was taken for the participant.

During the study, 8 of the participants moved residences. Their second addresses were geocoded using ArcGIS. Six of the second addresses (75%) were geocoded, with a match score of above 80. Two remained not geocoded due to incomplete addresses (25%). These two participants remained in the analysis with their initial address used.

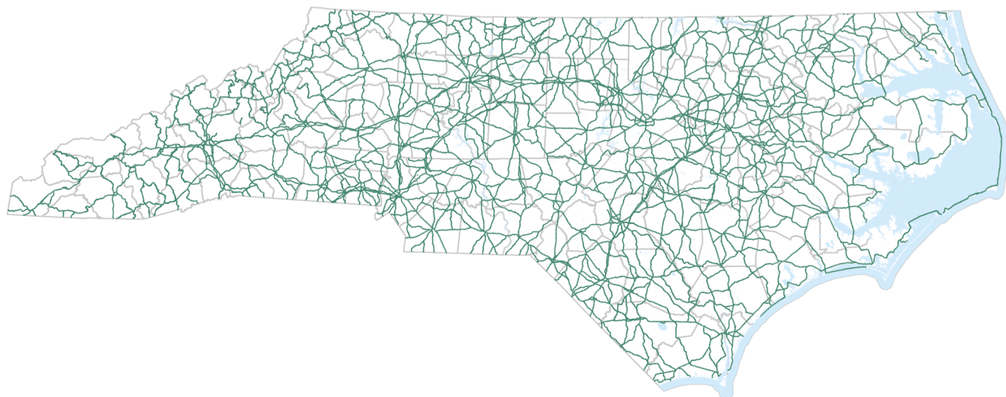
Following the above methods, we were able to geocode 218 of the participants' first residences, leaving 3 participants (1.3%) unlocated. These 3 participants were dropped from further analysis.

Road Data for Proximity Measurement

To calculate residential proximity to major roads, we obtained roadway location information from the US Census. The earliest spatially accurate GIS road data for North Carolina is from 1995, later than the EPS study period of 1982-1986. The road data used for this analysis were 1995 Census Class A Roads in North Carolina, published by the U.S. Census Bureau in 1996 (U.S. Census Bureau, 1996). We selected all A1, A2, and A3 major roads for our analysis, as detailed by the U.S. Census feature class codes (ESRI, 2016). A1 roads include primary roads with limited access, such as interstate highways that have distinct exits and access ramps. A2 roads include primary roads without limited access such as US and state highways that connect cities. A3 roads include secondary roads such as state and county highways and numbered routes. We assessed the integrity of the 1995 road data in two steps.

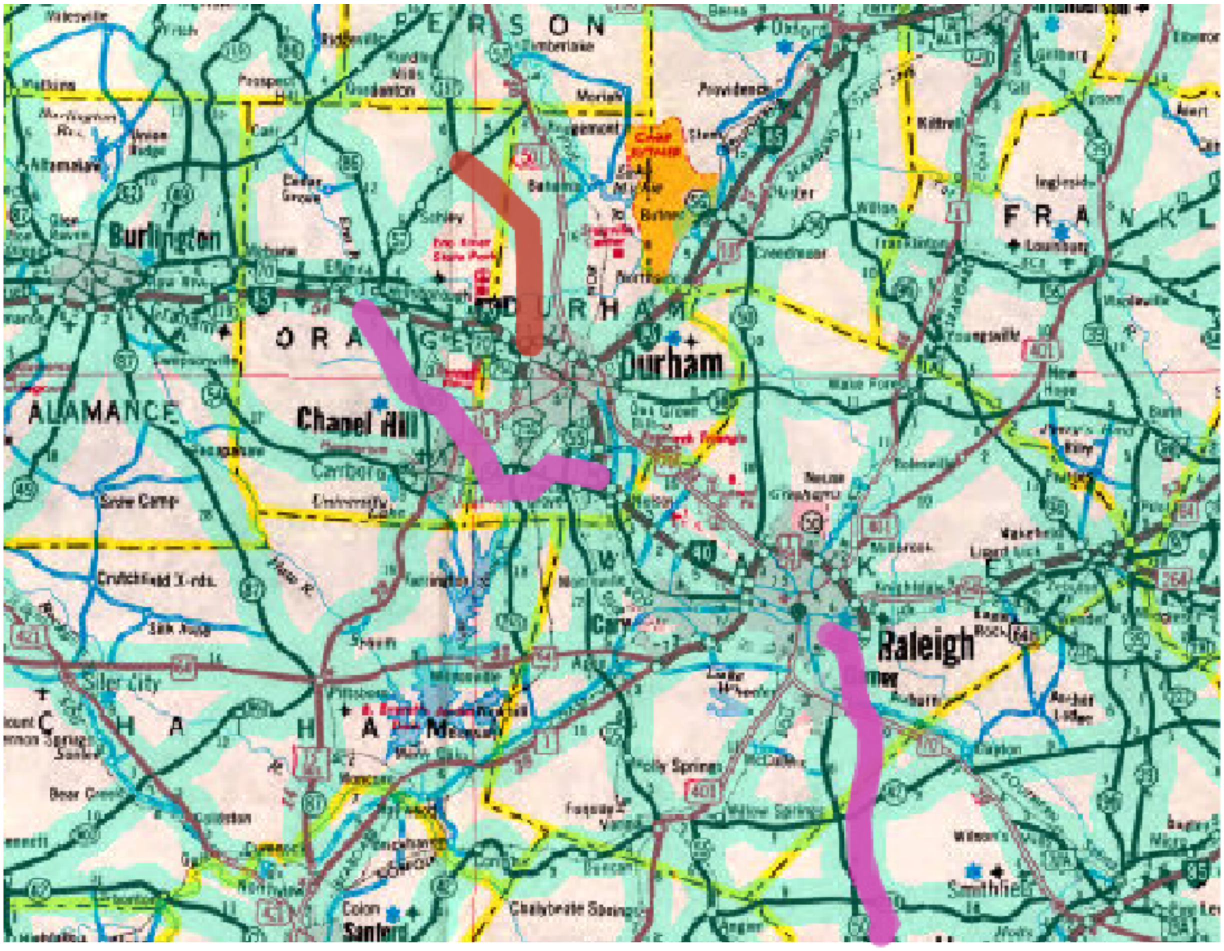
First, we looked at the spatial accuracy of the 1995 road data. In order to understand the spatial accuracy of the 1995 road data, the data was compared to the most recent 2018 TIGER/Line data from the U.S. Census Bureau (U.S. Census Bureau, 2018). Spatial accuracy was assessed by testing how well the 1995 data overlapped with the highly accurate 2018 data. Using a 500-mile overlap buffer (i.e. did the 1995 road location overlap the 2018 road location within 500 miles?), the percentage that the 1995 data overlapped was 97.8%. Using a 200-mile buffer, the percentage that the 1995 data overlapped was 96.8%, and using a 100-mile buffer the percentage that the 1995 data overlapped was 94.1%. Though not 100% spatially accurate, we considered the high degree of overlap to suggest that the 1995 data are fit for this analysis.

Figure 1. Major road network in North Carolina – 1995 (U.S. Census Bureau, 1996)



Second, because the EPS cohort data was collected during 1982-1986, we needed to understand the change in roads between 1986 and 1995, the year our road data was collected. We visually compared the 1995 road data with a 1980 North Carolina Official Highway Map by the North Carolina Department of Transportation (North Carolina Department of Transportation, 1980). The 1980 map was georeferenced to the ESRI base map and 1995 road data, and this overlap was visually inspected. The major road, I-40, was extended south of Raleigh from 1986 to 1990, and south of Burlington to north of Raleigh in 1988, and therefore, was removed from our 1995 road data set in order to reduce exposure misclassification (highlighted in purple in Figure 2) (Prince, 2013). Route 157 was extended at Route 57 to north of Durham during 1988, and was removed from our 1995 road data set (highlighted in red in Figure 2) (Prince, 2013). Visual inspection after these deletions suggests that few other roads major were built between 1986 and 1995 in our study area. Figure 2 depicts the 1995 roads in transparent blue, above the georeferenced 1980 North Carolina Map (North Carolina Department of Transportation, 1980; U.S. Census Bureau, 1996).

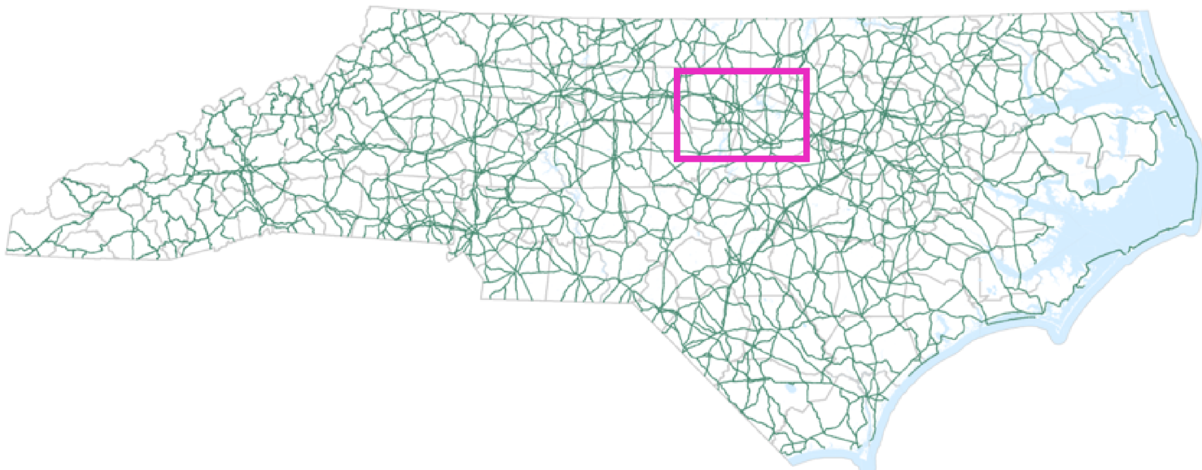
Figure 2. 1995 roads (transparent blue) visual comparison to the 1980 major road map. I-40 is highlighted in purple. Rt-157 is highlighted in red (North Carolina Department of Transportation, 1980; U.S. Census Bureau, 1996)



Proximity Analysis

Both the participants' residential longitude and latitude as well as the edited 1995 road data were imported into ArcGIS projected with NAD 1983 State Plane of North Carolina, and the shortest distance to the residence and the nearest major road was calculated in meters. For the participants who moved during the study period, two proximity measures were taken. Half of the person-time was ascribed to the first proximity, and the other half was ascribed to the second proximity measure. The median proximity to nearest major road for the participants (n=218) was 661.3 meters.

Figure 3. Study Population area in North Carolina, 1995 roads
(residential points not shown for participant confidentiality) (U.S. Census Bureau, 1996)



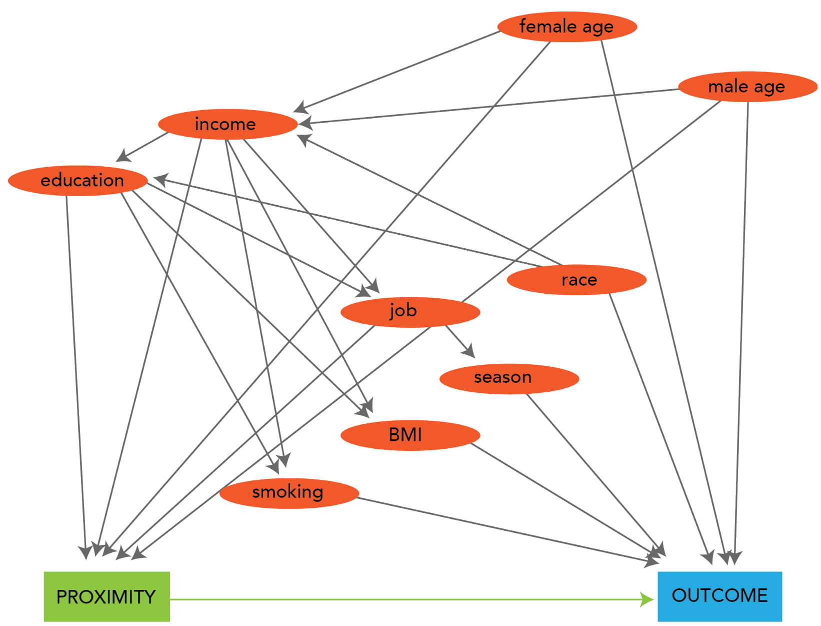
The Health Effects Institute report on Traffic-Related Air Pollution notes that traffic related air pollutants decay within 300 meters to 500 meters of a major road; in other words, the exposure zone affected by traffic related air pollutants is within 300 to within 500 meters of a road (Health Effects Institute Panel, 2010). Considering air pollutant dispersion patterns, the shape of our proximity to nearest major road data and the outlier groups and thresholds within it, as well as previous methods for assessing exposure to traffic related air pollutants in relation to time to pregnancy from Mendola et al (2013), we evaluated the exposure metric of proximity to nearest major road in the following ways:

- *Metric 1:* Proximity as a continuous measure in 100-meter increments
- *Metric 2:* Proximity in four categories: <200 meters, 200 - <500 meters, 500 - <1000 meters, and 1000 meters or more (1000 meters or more as the reference)

Additional Covariates

We determined several additional covariates *a priori* to analyze. This list was informed by creating a directed acyclic graph (DAG) (Figure 4) as well as through a literature review on risk factors that related to both infertility and proximity to nearest road. We evaluated female age (A. Wesselink et al., 2017), male age (Kidd, Eskenazi, & Wyrobek, 2001), age at menarche (Gulbrandsen et al., 2014; A. Wesselink et al., 2016), SES variables (income, education, occupation, race, body mass index (BMI)) (Law, Maclehose, & Longnecker, 2007), season, smoking (ever, never) (A. K. Wesselink et al., 2018). We ran sensitivity analyses to test parity, water source, and race. In the final model, we adjusted for male and female age, education, occupation, and income.

Figure 4. Directed Acyclic Graph to understand covariates and confounders

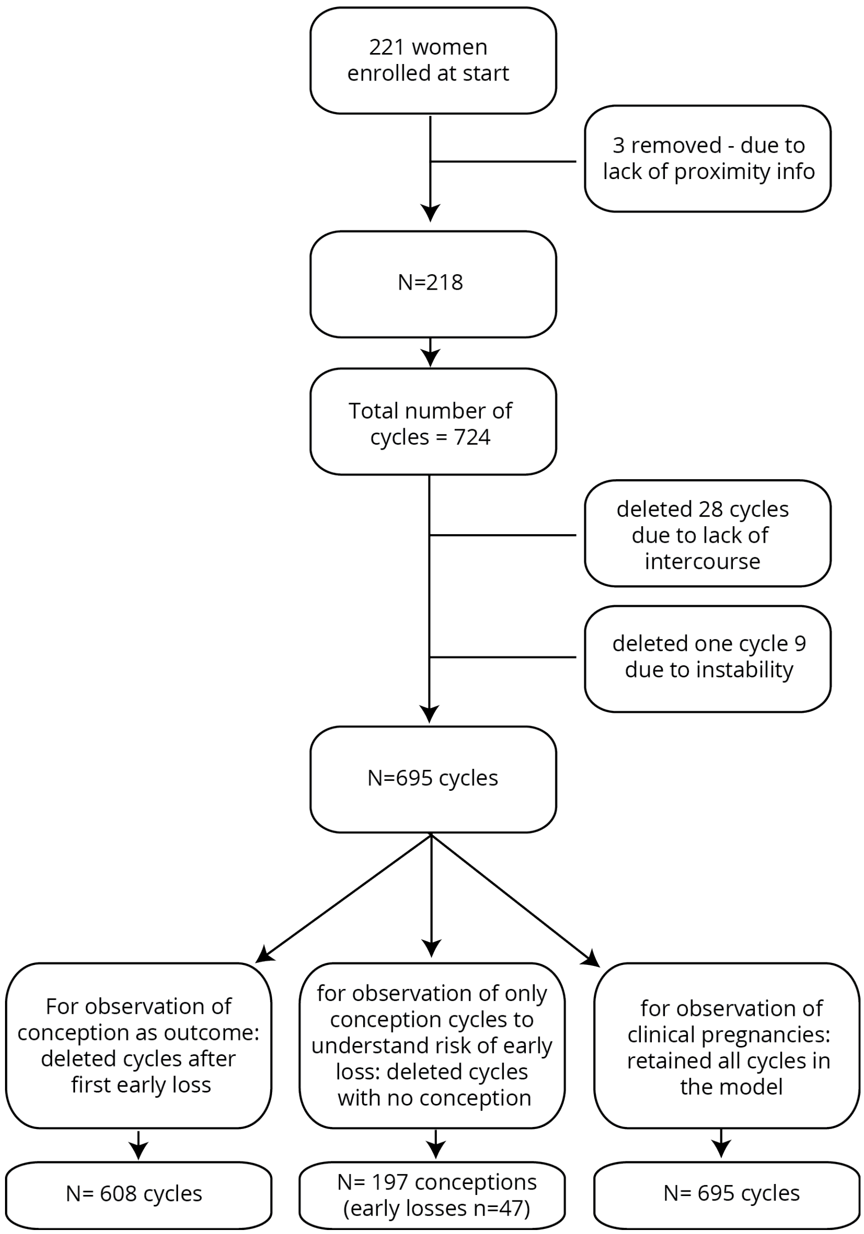


Statistical Analysis

Sample Size

As noted above, we excluded three participants lacking proximity information from the analysis. After exclusion, there were 218 participants in the study with 724 ovulatory cycles. We excluded one cycle that was the 9th cycle for a participant, due to instability in the final model. We also excluded 28 cycles for which there was no unprotected intercourse during the fertile window (Jukic, Calafat, et al., 2016; Wilcox, Weinberg, & Baird, 1995). For our primary analysis looking at fecundability of conception, we excluded 87 cycles that came after a participant had an early loss recognized by urine analysis, because we are including early losses as a conception outcome in our analysis, which left 608 cycles (Figure 5). In secondary analysis looking at the risk of early loss in relation to proximity, we took a subset of all conceptions leaving 197 conceptions in the data set (Figure 5). In further secondary analyses, in assessing fecundability to clinical pregnancy, all cycles until a clinical pregnancy remained in the analysis (n=695) (Figure 5).

Figure 5. N flow through study



Analysis

To examine the association between proximity to nearest road and fecundability in looking at conceptions, assessed by time to pregnancy, we ran log transformed general linear regression models for the two proximity metrics determined *a priori*, to estimate fecundability ratios (FR). A fecundability ratio is the probability of conception per menstrual cycle comparing exposed with unexposed women; an FR of >1 indicates the exposure is related to an improved fecundability or reduced time to pregnancy (Mckinnon et al., 2016). Covariates were analyzed *a priori* using the DAG in Figure 5. We analyzed the correlation between each covariate with proximity (Table 1) as well as the outcome of pregnancy (Table 2) to assess confounding. In our final model, we controlled for female age, male age, education, income, and occupation. We present adjusted and unadjusted model results.

As a secondary analysis, we examined the association between proximity to nearest road and risk of early pregnancy loss, as we included early pregnancy loss in our conception outcome. To analyze this, we took a subset of cycles for which there was a conception (197 cycles) (Figure 5). In an assessment of early loss and proximity to nearest road, we adjusted for female age, male age, education, income, and occupation. We used a logistic regression to understand this relationship and estimate odds ratios (OR).

After examining this relationship, we assessed the association between proximity to nearest major road and fecundability in looking at clinical pregnancy as an outcome. Clinical pregnancy includes single and twin pregnancies, spontaneous abortions, and ectopic pregnancy, and excludes early losses. We ran a log transformed general linear model regression for the two proximity metrics to estimate fecundability ratios in regard to clinical pregnancy. We controlled for female age, male age, education, income, and occupation in our final model.

Ethical Approval

Ethical approval (number 2000024380) was obtained from the Yale School of Public Health as well as from NIEHS. Material Data Transfer was obtained by Yale School of Public Health and NIEHS.

Results

Baseline characteristics of EPS participants can be found in Table 1. A total of 15.6% of participants lived within 200 meters of a major road, 40.8% of the participants lived within 500 meters of a major road, and 64.2% of participants lived within 1000 meters of the nearest major road. The median proximity to nearest road was 661.3 meters (range: 3.67m to 7444.23m). The majority of the participants had a conception within 6 months (n = 170, 78%). Most participants were white (95.9%), did not smoke (69.7%), and had a college education or more (71.6%). The average age of participants was 28.9 years (standard deviation = 3.77) and the average BMI was 21.5 (standard deviation=3.39). The average age of the male partners was 30.5 years (standard deviation=3.99). 170 participants conceived at least once within 6 months and 48 participants did not conceive within 6 months.

Table 1. Baseline Characteristics of EPS Participants based on Proximity to Nearest Major Road (meters) [n %] (n=total pop)

	n	<200m	200m to <500m	500m to <1000m	>1000m
		34	55	51	78
Pregnant before 6 mo					
no	*48*	5 (10.4)	13 (27.1)	11 (22.9)	19 (39.6)
yes	*170*	29 (17.1)	42 (24.7)	40 (23.5)	59 (34.7)
Participant Age					
<=25	*32*	5 (15.6)	11 (34.4)	8 (25.0)	8 (25.0)
25-29	*98*	13 (13.3)	25 (26.5)	23 (23.5)	37 (37.8)
>=30	*88*	16 (18.2)	19 (21.6)	20 (22.7)	33 (37.5)
Partner Age					
<=25	*18*	3 (16.7)	5 (27.8)	7 (38.9)	3 (16.7)
25-29	*75*	14 (18.8)	19 (25.3)	16 (21.3)	26 (34.7)
>=30	*125*	17 (13.6)	31 (24.8)	28 (22.4)	49 (39.2)
BMI					
<20	*80*	12 (15.0)	22 (27.5)	20 (25.0)	26 (32.5)
20-25	*113*	20 (17.7)	26 (23.0)	29 (25.7)	38 (33.6)
>25	*25*	2 (8.0)	7 (28.0)	2 (8.0)	14 (56.0)
Income					
<20,000	*65*	14 (21.5)	17 (26.2)	17 (26.2)	17 (26.2)
20,000-29,000	*71*	13 (18.3)	20 (28.2)	13 (18.31)	25 (35.2)
>29,000	*82*	7 (8.5)	18 (22.0)	21 (25.6)	36 (43.9)
Race					
Nonwhite	*9*	0 (0.0)	2 (22.2)	2 (22.2)	5 (55.6)
White	*209*	34 (16.7)	53 (25.7)	49 (23.4)	73 (34.9)
Smoking					
Never	*152*	24 (15.8)	37 (24.3)	38 (25.0)	53 (34.9)
Ever	*66*	10 (15.2)	18 (27.3)	13 (19.7)	25 (37.9)
Parity					
Null	*105*	20 (19.0)	31 (29.5)	27 (25.7)	27 (25.7)
Parous	*113*	14 (12.4)	24 (21.2)	24 (21.2)	51 (45.1)
Education					
Some college <16 yr	*62*	7 (11.3)	14 (22.6)	11 (17.7)	30 (48.4)
Grad. college = 16 yr	*83*	14 (16.9)	26 (31.3)	19 (22.9)	24 (28.9)
Above college >16 yr	*73*	13 (17.8)	15 (20.6)	21 (28.8)	24 (32.9)
Job					
Not assigned	*11*	1 (9.1)	3 (27.3)	3 (27.3)	4 (36.4)
Teaching / Office	*71*	11 (15.5)	24 (33.8)	16 (22.5)	20 (28.2)
Medical / Health	*80*	15 (18.8)	15 (18.8)	20 (25.0)	30 (37.5)
Mgmt. / White Collar	*37*	6 (16.2)	6 (16.2)	7 (18.9)	18 (48.7)
Sales / Service	*19*	1 (5.26)	7 (36.8)	5 (26.3)	6 (31.6)
Season of Conception/Ovulation					
Spring	*50*	7 (14.0)	13 (26.0)	13 (26.0)	17 (34.0)
Summer	*55*	10 (18.2)	14 (25.5)	12 (21.8)	19(34.6)
Fall	*55*	8 (14.6)	15 (27.3)	11 (20.0)	21 (38.2)
Winter	*45*	8 (17.8)	11 (24.5)	13 (28.9)	13 (28.9)
Missing	*13*				
City Water					
No	*40*	10 (25.0)	6 (15.0)	6 (15.0)	18 (45.0)
Yes	*130*	18 (13.8)	38 (29.2)	36 (27.7)	38 (29.23)
Missing/Other	*48*				

*proximities taken from participants 1st address in the case of 8 that moved during the study

Table 2. Baseline Characteristics of EPS population by Outcome [n %]

	n	Conception within 6 months	No Conception within 6 months
		170	48
Proximity (meters)			
<200	*34*	29 (85.3)	5 (14.7)
200 - <500	*55*	42 (76.4)	13 (23.6)
500 - <1000	*51*	40 (78.4)	11 (21.6)
>1000	*78*	59 (75.6)	19 (24.4)
Participant Age			
<=25	*32*	24 (75.0)	8 (25.0)
25-29	*98*	78 (79.6)	20 (20.4)
>=30	*88*	68 (77.3)	20 (22.7)
Partner Age			
<=25	*18*	13 (72.2)	5 (27.8
25-29	*75*	61 (81.3)	14 (18.7)
>=30	*125*	96 (76.8)	29 (23.2)
BMI			
<20	*80*	63 (78.8)	17 (21.3)
20-25	*113*	92 (81.4)	21 (18.6)
>25	*25*	15 (60.0)	10 (40.0)
Income			
<20,000	*65*	50 (76.9)	15 (23.1)
20,000-29,000	*71*	55 (77.5)	16 (22.5)
>29,000	*82*	65 (79.3)	17 (20.7)
Race			
Nonwhite	*9*	8 (88.9)	1 (11.1)
White	*209*	162 (77.5)	47 (22.5)
Smoking			
Never	*152*	115 (75.7)	37 (24.3)
Ever	*66*	55 (83.3)	11 (16.7)
Parity			
Null	*105*	78 (74.3)	27 (25.7)
Parous	*113*	92 (81.4)	21 (18.6)
Education			
Some college <16 yr	*62*	47 (75.8)	15 (24.2)
Grad. college = 16 yr	*83*	67 (80.7)	16 (19.3)
Above college >16 yr	*73*	56 (76.7)	17 (23.3)
Job			
Not assigned	*11*	6 (54.6)	5 (45.4)
Teaching / Office	*71*	56 (78.9)	15 (21.1)
Medical / Health	*80*	67 (83.8)	13 (16.2)
Mgmt. / White Collar	*37*	27 (73.0)	10 (27.0)
Sales / Service	*19*	14 (73.7)	5 (26.3)
Season		*of conception*	*of last ovulation cyc.*
Spring	*50*	40 (80.0)	10 (20.0)
Summer	*55*	44 (80.0)	11 (20.0)
Fall	*55*	43 (78.2)	12 (21.8)
Winter	*45*	36 (80.0)	9 (20.0)
Missing	*13*		
City Water			
No	*40*	32 (80.0)	8 (20.0)
Yes	*130*	102 (79.2)	27 (20.8)
Missing/Other	*48*		

*proximities taken from participants 1st address in the case of 8 that moved during the study

*conception includes: early losses, singletons, twins, spontaneous abortions, ectopic/molar pregnancies

None of the roadway proximity metrics were associated with time to pregnancy (Table 3). We hypothesized that water source (city or well water), parity, and race may be confounders, but adjustment did not alter point estimates (see Table 4 in Appendix 1). Contrary to our hypothesis, fecundability may be improved for couples that live closer to a major road. In looking at proximity as a continuous measure in 100m intervals, the association is null; fecundability may decrease very slightly the with greater distance to a major road (FR: 0.99, 95%CI: 0.98, 1.01). In metric 2, testing four proximity categories, for proximities below 200 meters, the fecundability ratio (FR) was 1.42 (95% CI: 0.98, 2.14), for proximities between 200 and 500 meters, the FR was 1.11 (95%CI: 0.77, 1.60), and for proximities between 500 and 1000, the FR was 1.18 (95%CI: 0.83, 1.67). All fecundability ratios in the four proximity model were greater than 1.00, suggesting that participants living nearer to major roads may have improved fecundability.

Table 3. Fecundability ratios for proximity to nearest major road (meters)

	cycles	*Unadjusted*		*Adjusted**	
	n	**FR**	**95%CI**	**FR**	**95%CI**
Metric 1: Continuous Proximity per 100m increase	608	0.99	(0.98, 1.01)	0.99	(0.98, 1.01)
Metric 2: Four Categories					
<200	79	1.40	(0.97, 2.02)	1.42	(0.94, 2.14)
200 - <500	157	1.09	(0.77, 1.53)	1.11	(0.77, 1.60)
500 - <1000	137	1.20	(0.86, 1.68)	1.18	(0.83, 1.67)
1000>	235	ref	ref	ref	ref

*adjusted for: education, income, job, female age, male age
outcome of conception (including: early losses, singletons, twins, spontaneous abortions, ectopic/molar pregnancies)

In secondary analysis, we evaluated the association between proximity to nearest major road and early pregnancy loss. We found there may be a slightly increased risk in early loss in women who live less than 200 meters away from a major road (OR: 2.08, 95%CI: 0.85, 5.09) as well as women who live between 200 - <500 meters away from a major road (OR: 1.82, 95%CI: 0.78, 4.24), yet these results are not precise. In our continuous metric by 100m intervals, the association is null; odds of early loss may be very slightly reduced with the greater distance to a major road (OR: 0.98, 95%CI: 0.94, 1.01). These results suggest there may be an increased risk of early loss for participants living nearer to major roads as compared to participants living farther from a major road (Table 5).

Table 5. Proximity vs. Early Loss (subset of cycles with conceptions)

	Conceptions (losses)	*Unadjusted*		*Adjusted**	
	n	**OR**	**95%CI**	**OR**	**95%CI**
Metric 1: Continuous Proximity per 100m increase	*197 (47)*	0.98	(0.94, 1.01)	0.98	(0.94, 1.01)
Metric 2: Four Categories					
<200	*33 (9)*	2.14	(0.78, 5.85)	2.08	(0.85, 5.09)
200 - <500	*48 (15)*	2.48	(1.00, 6.16)	1.82	(0.78, 4.24)
500 - <1000	*50 (11)*	1.29	(0.50, 3.35)	1.06	(0.45, 2.49)
1000>	*66 (12)*	ref	ref	ref	ref

*adjusted for: education, income, job, female age, male age

In our secondary analysis of proximity to major road and fecundability with a clinical pregnancy outcome, we presented these results alongside the conception results in Table 6, both unadjusted and adjusted. As noted previously, when we analyzed the data defining the outcome as all conceptions, fecundability may be improved for couples who lived closer to a major road. In looking only at clinical pregnancies (excludes early pregnancy loss), the relationship is more variable and less precise (FR range: 0.80 – 1.10). The results suggest that proximity to nearest major road is not associated with fecundability for clinical pregnancies. The data suggests there may be slightly reduced fecundability in terms of clinical pregnancy for participants living between 200 and 500 meters away from a major road (FR: 0.80, 95%CI: 0.55, 1.21).

Table 6. Fecundability Ratios for Conception vs. Clinical Pregnancy Outcome

	Conception[1]					***Clinical Pregnancy[2]***				
	yes (n) 170 cycles no (n) 438 cycles					yes (n) 150 cycles no (n) 545 cycles				
	cycles	*Unadjusted*		*Adjusted**		*cycles*	*Unadjusted*		*Adjusted**	
	n	**FR**	**95%CI**	**FR**	**95%CI**	***n***	**FR**	**95%CI**	**FR**	**95%CI**
Metric 1: Continuous Proximity per 100m increase	*608*	0.99	(0.98, 1.01)	0.99	(0.98, 1.01)	*695*	1.00	(0.99, 1.01)	1.00	(0.99, 1.02)
Metric 2: Four Categories										
<200	*81*	1.40	(0.97, 2.02)	1.42	(0.94, 2.14)	*97*	1.16	(0.76, 1.76)	1.07	(0.68, 1.68)
200 - <500	*166*	1.09	(0.77, 1.53)	1.11	(0.77, 1.60)	*188*	0.84	(0.57, 1.24)	0.80	(0.53, 1.21)
500 - <1000	*145*	1.20	(0.86, 1.68)	1.18	(0.83, 1.67)	*155*	1.15	(0.80, 1.64)	1.10	(0.76, 1.59)
1000>	*216*	ref	ref	ref	ref	*255*	ref	ref	ref	ref

*adjusted for: education, income, job, female age, male age
1. Conception outcome includes : early pregnancy losses, singletons, twins, spontaneous abortions, ectopic/molar pregnancies
2. Clinical pregnancy outcome includes: singletons, twins, spontaneous abortions, ectopic/molar pregnancies

Discussion

Our analysis shows no consistent association between proximity to nearest road and fecundability in terms of conception or clinical pregnancy. For fecundability in terms of conception, contrary to our initial hypothesis, our analysis suggests there may be a modest protective effect of living closer to a major road with regard to fecundability. In other words, women who live closer to a major road tended to become pregnant more quickly. In looking only at the risk of early loss, our analysis shows that there may be an increased risk of early loss for women living closer to major roads. In looking at only fecundability in terms of clinical pregnancy, excluding early loss, our analysis shows there may be reduced fecundability for participants living within 500 meters of a major road as compared to those living farther away, but this association is variable and not precise. In conclusion, this analysis suggests that the possible slight increase in fecundability for participants living close to major roads in our conception outcome, could be due to the fact that participants who live closer to major roads may be having increased early losses, as opposed to participants that live further from a major road.

The strengths of our study include the use of a preconception prospective cohort with little missing data. In this unique study design, hormonal data was collected to monitor ovulation patterns as well as accurately predict pregnancy and early loss by specific cycle.

This study also has limitations. Because our cohort was from the 1980s, the addresses that we geocoded were old. Although we were as accurate as possible in this process, some error likely occurred in using the 2013 geolocator. Furthermore, the road data used for the proximity analysis was from 1995. Though we were as accurate as possible in our visual analysis of the changes to major roads from the 1980 roadmap, it is possible that there were more minor changes to roads that were not apparent or could not be detected. This may have caused some exposure misclassification. Further, the spatial accuracy of the 1995 road data was not 100% accurate to today's ArcGIS standards. This positional accuracy could cause further exposure misclassification. The proximity to nearest road measure as a proxy for traffic related air pollution has become less frequently used as better air pollution exposure methods are available, but proximity to nearest road is a valid measurement for understanding traffic related air pollution (Van Roosbroeck et al., 2007). To strengthen the proximity measure, it is best used in conjunction with understanding traffic density patterns and air pollution monitoring information. Our analysis did not look at ambient air quality or traffic density data, which would bolster our proximity metric and give a better overall picture of air pollution exposure for each participant. We were also unable to assess how much time a participant spent within and outside of their house, which the residential proximity to nearest road metric cannot capture or assess. Finally, living closer to major roads may have benefits that we were unable to account for in our study. Some of these factors could be greater social connectedness, better access to health care facilities, and better access to healthy food.

Conclusion

We found some evidence that living near a major road may be associated with increased fecundability but there was no clear dose-response pattern. The slight increase in fecundability reflect an increased risk of early losses for participants who live closer to major roads. There also may be unmeasured confounding. Further study of this association is warranted.

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Appendix: All Tables

Table 1. Baseline Characteristics of EPS Participants based on Proximity to Nearest Major Road (meters) [n %] (n=total pop)					
		<200m	**200m to <500m**	**500m to <1000m**	**>1000m**
	n	34	55	51	78
Pregnant before 6 mo					
no	*48*	5 (10.4)	13 (27.1)	11 (22.9)	19 (39.6)
yes	*170*	29 (17.1)	42 (24.7)	40 (23.5)	59 (34.7)
Participant Age					
<=25	*32*	5 (15.6)	11 (34.4)	8 (25.0)	8 (25.0)
25-29	*98*	13 (13.3)	25 (26.5)	23 (23.5)	37 (37.8)
>=30	*88*	16 (18.2)	19 (21.6)	20 (22.7)	33 (37.5)
Partner Age					
<=25	*18*	3 (16.7)	5 (27.8)	7 (38.9)	3 (16.7)
25-29	*75*	14 (18.8)	19 (25.3)	16 (21.3)	26 (34.7)
>=30	*125*	17 (13.6)	31 (24.8)	28 (22.4)	49 (39.2)
BMI					
<20	*80*	12 (15.0)	22 (27.5)	20 (25.0)	26 (32.5)
20-25	*113*	20 (17.7)	26 (23.0)	29 (25.7)	38 (33.6)
>25	*25*	2 (8.0)	7 (28.0)	2 (8.0)	14 (56.0)
Income					
<20,000	*65*	14 (21.5)	17 (26.2)	17 (26.2)	17 (26.2)
20,000-29,000	*71*	13 (18.3)	20 (28.2)	13 (18.31)	25 (35.2)
>29,000	*82*	7 (8.5)	18 (22.0)	21 (25.6)	36 (43.9)
Race					
Nonwhite	*9*	0 (0.0)	2 (22.2)	2 (22.2)	5 (55.6)
White	*209*	34 (16.7)	53 (25.7)	49 (23.4)	73 (34.9)
Smoking					
Never	*152*	24 (15.8)	37 (24.3)	38 (25.0)	53 (34.9)
Ever	*66*	10 (15.2)	18 (27.3)	13 (19.7)	25 (37.9)
Parity					
Null	*105*	20 (19.0)	31 (29.5)	27 (25.7)	27 (25.7)
Parous	*113*	14 (12.4)	24 (21.2)	24 (21.2)	51 (45.1)
Education					
Some college <16 yr	*62*	7 (11.3)	14 (22.6)	11 (17.7)	30 (48.4)
Grad. college = 16 yr	*83*	14 (16.9)	26 (31.3)	19 (22.9)	24 (28.9)
Above college >16 yr	*73*	13 (17.8)	15 (20.6)	21 (28.8)	24 (32.9)
Job					
Not assigned	*11*	1 (9.1)	3 (27.3)	3 (27.3)	4 (36.4)
Teaching / Office	*71*	11 (15.5)	24 (33.8)	16 (22.5)	20 (28.2)
Medical / Health	*80*	15 (18.8)	15 (18.8)	20 (25.0)	30 (37.5)
Mgmt. / White Collar	*37*	6 (16.2)	6 (16.2)	7 (18.9)	18 (48.7)
Sales / Service	*19*	1 (5.26)	7 (36.8)	5 (26.3)	6 (31.6)
Season of Conception/Ovulation					
Spring	*50*	7 (14.0)	13 (26.0)	13 (26.0)	17 (34.0)
Summer	*55*	10 (18.2)	14 (25.5)	12 (21.8)	19(34.6)
Fall	*55*	8 (14.6)	15 (27.3)	11 (20.0)	21 (38.2)
Winter	*45*	8 (17.8)	11 (24.5)	13 (28.9)	13 (28.9)
Missing	*13*				
City Water					
No	*40*	10 (25.0)	6 (15.0)	6 (15.0)	18 (45.0)
Yes	*130*	18 (13.8)	38 (29.2)	36 (27.7)	38 (29.23)
Missing/Other	*48*				

*proximities taken from participants 1st address in the case of 8 that moved during the study

Table 2. Baseline Characteristics of EPS population by Outcome [n %]			
		Conception within 6 months	**No Conception within 6 months**
	n	170	48
Proximity (meters)			
<200	*34*	29 (85.3)	5 (14.7)
200 - <500	*55*	42 (76.4)	13 (23.6)
500 - <1000	*51*	40 (78.4)	11 (21.6)
>1000	*78*	59 (75.6)	19 (24.4)
Participant Age			
<=25	*32*	24 (75.0)	8 (25.0)
25-29	*98*	78 (79.6)	20 (20.4)
>=30	*88*	68 (77.3)	20 (22.7)
Partner Age			
<=25	*18*	13 (72.2)	5 (27.8
25-29	*75*	61 (81.3)	14 (18.7)
>=30	*125*	96 (76.8)	29 (23.2)
BMI			
<20	*80*	63 (78.8)	17 (21.3)
20-25	*113*	92 (81.4)	21 (18.6)
>25	*25*	15 (60.0)	10 (40.0)
Income			
<20,000	*65*	50 (76.9)	15 (23.1)
20,000-29,000	*71*	55 (77.5)	16 (22.5)
>29,000	*82*	65 (79.3)	17 (20.7)
Race			
Nonwhite	*9*	8 (88.9)	1 (11.1)
White	*209*	162 (77.5)	47 (22.5)
Smoking			
Never	*152*	115 (75.7)	37 (24.3)
Ever	*66*	55 (83.3)	11 (16.7)
Parity			
Null	*105*	78 (74.3)	27 (25.7)
Parous	*113*	92 (81.4)	21 (18.6)
Education			
Some college <16 yr	*62*	47 (75.8)	15 (24.2)
Grad. college = 16 yr	*83*	67 (80.7)	16 (19.3)
Above college >16 yr	*73*	56 (76.7)	17 (23.3)
Job			
Not assigned	*11*	6 (54.6)	5 (45.4)
Teaching / Office	*71*	56 (78.9)	15 (21.1)
Medical / Health	*80*	67 (83.8)	13 (16.2)
Mgmt. / White Collar	*37*	27 (73.0)	10 (27.0)
Sales / Service	*19*	14 (73.7)	5 (26.3)
Season		*of conception*	*of last ovulation cyc.*
Spring	*50*	40 (80.0)	10 (20.0)
Summer	*55*	44 (80.0)	11 (20.0)
Fall	*55*	43 (78.2)	12 (21.8)
Winter	*45*	36 (80.0)	9 (20.0)
Missing	*13*		
City Water			
No	*40*	32 (80.0)	8 (20.0)
Yes	*130*	102 (79.2)	27 (20.8)
Missing/Other	*48*		

*proximities taken from participants 1st address in the case of 8 that moved during the study
*conception includes: early losses, singletons, twins, spontaneous abortions, ectopic/molar pregnancies

Table 3. Fecundability ratios for proximity to nearest major road (meters)

	cycles	*Unadjusted*		*Adjusted**	
	n	**FR**	**95%CI**	**FR**	**95%CI**
Metric 1: Continuous Proximity per 100m increase	608	0.99	(0.98, 1.01)	0.99	(0.98, 1.01)
Metric 2: Four Categories					
<200	79	1.40	(0.97, 2.02)	1.42	(0.94, 2.14)
200 - <500	157	1.09	(0.77, 1.53)	1.11	(0.77, 1.60)
500 - <1000	137	1.20	(0.86, 1.68)	1.18	(0.83, 1.67)
1000>	235	ref	ref	ref	ref

*adjusted for: education, income, job, female age, male age
outcome of conception (including: early losses, singletons, twins, spontaneous abortions, ectopic/molar pregnancies)

Table 4. Fecundability ratios for proximity to nearest major road (meters) with various adjustments

	cycles	*Unadjusted*		*Adjusted 1*		*Adjusted 2*		*Adjusted 3*		*Adjusted 4*	
	n	**FR**	**95%CI**	**FR**	**95%CI**	**FR**	**95%CI**	**FR**	**95%CI**	**FR**	**95%CI**
Metric 1: Continuous Proximity per 100m increase	*608*	1.00	(0.98, 1.01)	0.99	(0.98, 1.01)	0.99	(0.98, 1.01)	1.01	(0.98, 1.02)	0.99	(0.98, 1.01)
Metric 2: Four Categories											
<200	*79*	1.41	(0.98, 2.04)	1.42	(0.94, 2.14)	1.41	(0.94, 2.12)	1.32	(0.83, 2.10)	1.47	(0.98, 2.23)
200 - <500	*157*	1.10	(0.78, 1.55)	1.11	(0.77, 1.60)	1.15	(0.80, 1.64)	1.05	(0.69, 1.60)	1.14	(0.79, 1.63)
500 - <1000	*137*	1.17	(0.83, 1.64)	1.18	(0.83, 1.67)	1.24	(0.87, 1.76)	1.12	(0.75, 1.66)	1.23	(0.86, 1.75)
1000>	*235*	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref

1 adjusted for: education, income, job, female age, male age
2 adjusted for: education, income, job, female age, male age, parity
3 adjusted for: education, income, job, female age, male age, water source
4 adjusted for: education, income, job, female age, male age, race
outcome of conception (including: early losses, singletons, twins, spontaneous abortions, ectopic/molar pregnancies)

Table 5. Proximity vs. Early Loss (subset of cycles with conceptions)

	Conceptions (losses)	*Unadjusted*		*Adjusted**	
	n	**OR**	**95%CI**	**OR**	**95%CI**
Metric 1: Continuous Proximity per 100m increase	*197 (47)*	0.98	(0.94, 1.01)	0.98	(0.94, 1.01)
Metric 2: Four Categories					
<200	*33 (9)*	2.14	(0.78, 5.85)	2.08	(0.85, 5.09)
200 - <500	*48 (15)*	2.48	(1.00, 6.16)	1.82	(0.78, 4.24)
500 - <1000	*50 (11)*	1.29	(0.50, 3.35)	1.06	(0.45, 2.49)
1000>	*66 (12)*	ref	ref	ref	ref

*adjusted for: education, income, job, female age, male age

Table 6. Fecundability Ratios for Conception vs. Clinical Pregnancy Outcome

	Conception[1]					***Clinical Pregnancy[2]***				
	yes (n) 170 cycles no (n) 438 cycles					yes (n) 150 cycles no (n) 545 cycles				
	cycles	*Unadjusted*		*Adjusted**		*cycles*	*Unadjusted*		*Adjusted**	
	n	**FR**	**95%CI**	**FR**	**95%CI**	***n***	**FR**	**95%CI**	**FR**	**95%CI**
Metric 1: Continuous Proximity per 100m increase	*608*	0.99	(0.98, 1.01)	0.99	(0.98, 1.01)	*695*	1.00	(0.99, 1.01)	1.00	(0.99, 1.02)
Metric 2: Four Categories										
<200	*81*	1.40	(0.97, 2.02)	1.42	(0.94, 2.14)	*97*	1.16	(0.76, 1.76)	1.07	(0.68, 1.68)
200 - <500	*166*	1.09	(0.77, 1.53)	1.11	(0.77, 1.60)	*188*	0.84	(0.57, 1.24)	0.80	(0.53, 1.21)
500 - <1000	*145*	1.20	(0.86, 1.68)	1.18	(0.83, 1.67)	*155*	1.15	(0.80, 1.64)	1.10	(0.76, 1.59)
1000>	*216*	ref	ref	ref	ref	*255*	ref	ref	ref	ref

*adjusted for: education, income, job, female age, male age
1. Conception outcome includes : early pregnancy losses, singletons, twins, spontaneous abortions, ectopic/molar pregnancies
2. Clinical pregnancy outcome includes: singletons, twins, spontaneous abortions, ectopic/molar pregnancies