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Application of Spatial Methods to Explore the Association between Environmental Exposures and Pregnancy Outcomes

DISSERTATION

submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in Environmental Health Sciences

by

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Dissertation Committee:
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DEDICATION

To

Carson and Rosalane Tang
My parents, my foundation, and my source of unwavering support

My sister, my family, and my friends
For their unconditional love, laughs, and inspiration

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ABSTRACT OF DISSERTATION

Application of Spatial Methods to Explore the Association between Environmental Exposures and Pregnancy Outcomes

By

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Spatial methods can be used to assess environmental contaminants and analyze their effect on pregnancy outcomes. When considering space, current methods in selecting controls in case-control studies may not be adequate in selecting a geographically diverse sample of participants, particularly when the exposure varies across a study area. Unmatched spatially stratified random sampling (SSRS) designs may improve study efficiency compared to simple random samples (SRS) in studies that require controls across the study area. Typically, SRS selects controls from data dense areas, and may not sufficiently select controls along the edges or where environmental exposures may occur. In a simulation study, SSRS selected controls from evenly sized strata was found to have lower mean squared error across simulations and along edges of the study area where SRS naturally may not select controls.

The SSRS method was applied to a case-control study of Texas birth defects from 1999 to 2011 examining the relationship between exposure to unconventional natural gas developments (UNGD) and birth defects. Birth defects are multifaceted diseases that can affect multiple organs throughout the body and their etiology are poorly understood. In-utero exposure to environmental contaminants, such as UNGD, may contribute to risk of birth defects in Texas, where UNGDs are spatially distributed in shales across the state. Exposure was a density

measure evaluated as the number of UNGD wells within 1, 3, and 7.5km of maternal address for congenital heart defects (CHD), neural tube defects (NTD), orofacial defects, and gastroschisis. UNGD exposure was associated with some CHDs, NTDs, and some gastroschisis, particularly within 1km of maternal address.

Spatial methods were also used to investigate birth defect risk factors in nested models to produce maps indicating high and low risk. Birth defects were significantly associated with maternal address location, and high-risk areas substantially decreased after adjusting for maternal, environmental and community variables. However, birth defect risk remained high in areas around North and South Texas and warrant further investigation of potential chemical exposures. This research has demonstrated the effective use of a novel control selection method to investigate spatial risk factors. Additionally, despite limitations in the research, exposure to UNGD chemicals may increase the risk of birth defects and more studies are needed to understand and prevent birth defects.

INTRODUCTION

Over the years, spatial methods have been used to further our understanding of diseases, especially with poorly understood etiologies such as pregnancy outcomes [1,2]. Still, further research in methodology is necessary to address known limitations and elucidate the risk factors related to place and disease. This work uses novel spatial methods to explore the relationship between location, prenatal environmental factors, and pregnancy outcomes in three chapters using data from two state-wide birth registries. Specifically, new sampling methods based on spatial strata can improve study efficiency, particularly for large datasets with geographically dispersed populations. This approach is evaluated in one data set and then applied to another for analysis. Birth defect etiology is complex and thought to be explained partly by environmental factors. Using spatial methods for control selection, exposure assessment, and disease mapping, the objective of this dissertation was to investigate the association between birth defects in Texas and widespread exposure to unconventional natural gas developments (UNGD), while accounting for maternal and community risk factors. Data from the Massachusetts Birth Registry, Texas Birth Defects Registry, and Center for Health Statistics at the Texas Department of State Health Services were analyzed for these studies.

Overview of Dissertation

The first chapter examines potential gains in efficiency by using unmatched spatially stratified random sampling (SSRS) designs to select a spatially-diverse set of controls using Massachusetts (MA) live births and pre-term births in 2004. This study develops SSRS methods with a simulation study to address known limitations related to simple random sampling (SRS) of controls in a simulation study and uses measures of fitness to compare the efficiency between using a specific sampling design in spatial analyses.

The second chapter investigates the association between unconventional natural gas developments (UNGD) and major structural birth defects using exposure density measures. A growing body of evidence suggests exposure to UNGD-related teratogens may induce birth defects, a group of diseases that are multifactorial and the causes are still being investigated. This association was investigated using Texas birth defects and live births born between 1999 and 2011 across the state. Current work has utilized inconsistent exposure modeling methods and yielded heterogeneous results and UNGD developments have only increased in the past decade. Controls for this analysis were sampled using the SSRS design evaluated in Chapter 1.

The third chapter attempts to further understand risk factors for birth defects that may differ by location by using generalized additive models to map risk. Identifying areas of high or low risk may provide insight on geographic-specific risk factors that may be previously unknown, even after accounting for important confounding variables. This chapter uses the same Texas birth data and UNGD exposure as Chapter 2 and examines the effect of maternal and environmental factors in nested analyses with generalized additive models, a novel spatial method that smooths over location. Few studies have investigated large datasets using spatial methods and often are limited by the use of aggregated data.

Both Chapter 2 and Chapter 3 employ the sampling method from Chapter 1 to select controls across the state of Texas. These studies apply new techniques in sampling and mapping risk for disease and explore potential unknown risk factors in Texas that may vary spatially, thereby potentially making important contributions to the field of spatial and environmental epidemiology.

Selecting Controls for Spatial Analyses

Considerations in study design is integral to analyzing health associations in epidemiology. Epidemiological studies often analyze subsets of people as investigating the entire population may be impractical.[3] Population sampling can be based on either probability and non-probability sampling, and each sampling design has its strengths and weaknesses.[4] In case-control studies, controls must represent the population base that gave rise to the cases and the most common way to ensure controls are representative of cases is to conduct a probabilistic simple random sample (SRS) design among a larger population.[5,6] This allows every individual to have the same probability of being selected into the study. However, SRS methods may not be appropriate when conducting spatial analyses because the SRS design tends to select controls in data-dense areas, leaving geographic areas with low population less likely to be represented in the sample.[7] A lack of controls in less geographically dense areas from SRS designs may lead to decreases in precision and study efficiency, especially if there are cases in a rural region and no nearby controls selected[3]. In addition, "edge effects" may occur where data ceases because of the study area boundary.[8–10] Data sparsity from SRS designs may compound these edge effects near the study boundary and lead to distortions in model estimations. Therefore, Chapter 1 aims to explore the use of unmatched spatially stratified sampling as an alternative method of selecting controls by forcing selection of controls evenly distributed across the study area.

Etiology of Birth Defects

Birth defects are a leading cause of infant mortality and life-long disability, affecting 3-5% of births in Texas.[11,12] Infants born with birth defects may face further health consequences later in life and many die within the first year of life. The estimated annual cost of birth defects from hospitalizations is $22.9 billion, accounting for 5.2% of total hospital costs.[13] Causes of birth defects by teratogens account for an estimated 5-10% of all birth defects and are commonly

attributed to maternal illness, maternal nutrition, and drug/alcohol use.[12,14] However, common multifactorial birth defects are of unknown origin and may be caused by environmental factors. These include congenital heart defects (CHD) that affect the blood flow through the heart and 25% of CHDs are considered critical, requiring medical attention within the first year of life, neural tube defects (NTD) that are structural malformations along the neuroaxis, usually from the improper closure of the neural tube, orofacial defects that refer to abnormal structuring of the facial palate or lip, and gastroschisis which are described as having the intestines outside of the body due to abdominal wall malformations.[15–18] These birth defects are not always diagnosed at birth and at least some of these birth defects are attributed to maternal behaviors such as smoking, medication, infections, and supplements[12].

UNGDs and Birth Defects

Over the last decade, unconventional natural gas developments (UNGD) have been used to extract gas using hydraulic fracturing methods and made up approximately two-thirds of the US natural gas production in 2018.[19] This method of gas extraction injects millions of liters of hydraulic fracturing fluid to create fissures within "hard-to-reach" shales by first drilling vertically, and then horizontally.[20] A single well typically uses 15-30 million liters of fluid, and 1-2% of the fluid consists of chemical additives.[21] An estimated 1,000 chemicals have been identified within the fluid and about 10% were identified to be reproductive or developmental toxicants[3]. In addition, air pollutants such as benzene, toluene, ethylbenzene, xylene (BTEX), hydrogen sulfide, methane, nitrogen oxides, sulfur oxides, polyaromatic hydrocarbons (PAH), volatile organic compounds (VOC), particulate matter 2.5 (PM2.5), and ozone are either directly emitted or are secondary-formed chemicals as a result of drilling, transportation, and diesel engines.[22–29]

Some animal case studies have documented animal death and adverse reproductive outcomes after exposure to fracturing fluid.[30] A growing body of evidence have observed an increase in risk of preterm birth and potentially low birth weight, but few observational studies have been conducted examining the effect of living near UNGDs and birth defects.[31–35] In addition, there are limited studies measuring direct emissions from UNGDs, and the majority of epidemiological studies have used proximity to UNGDs as their exposure. Cohort studies in Colorado have observed associations between living near intense oil and gas activity with CHDs and possibly NTDs; another study based in Oklahoma observed imprecise elevated risk with NTDs only.[34–36] One other study in Pennsylvania that accounted for secular trends before and after UNGD developments did not observe any effect on birth defects.[37] Associations between UNGD and birth defects have been inconsistent, as has been the methodology. To date, more than 10% of people live within 1.6 km of an active oil or gas well, and most self-reported health outcomes are reported within 1km of a UNGD and many of these studies have extended their radius of exposure from maternal address to 16km while using inverse-distance weighting.[38] Given that many people live closer to wells, a large radius may be subject to residual confounding and may bias associations. Chapter 2 investigates the role of distance to UNGD exposure with three different radii and multiple birth defect groups born between 1999 and 2011 in Texas.

Spatial Epidemiology of Birth Defects

Location plays an important role in understanding environmental contexts that may affect a mother. Clusters of severe birth defects often raise community concerns of potentially harmful exposures. Spatial methods can be useful in mapping and observing potential disease patterns.[1,39] Previously, clusters were detected using aggregated data bound by artificial boundaries,

potentially leading to known problems such as the modifiable areal unit problem, and the uncertain geographic context problem.[40–44] The use of individual-level data has become increasingly common and avoids limitations related to geographic boundaries and allows for use of unique biomarkers or covariates. One method is the use of generalized additive models (GAM) which includes a locally weighted smoother that averages locations locally and simultaneously. The product is a map indicating areas of high and low risk and statistical significance of the outcome of interest.

There are limited studies on the clustering of CHDs. Two studies in China observed significant clustering and suggested exposure to environmental factors may be a possible cause, while a temporal study in New York found non-significant elevation of CHD cases and controls, attributing the excess cases to possible infectious diseases.[37,45,46] Clustering of NTDs have also been observed in China and Texas, and some investigators have also suggested social and environmental factors as potential causes.[47–49] Gastroschisis is also a major birth defect that affects the abdominal wall, and is described as having the intestines outside of the body. Both orofacial defects and gastroschisis have been found in clusters around the world, including Texas.[50–54] There have only been a few large-scale spatial analyses on birth defects, with the majority of them in China. Many of these studies use aggregated data and are unable to adjust for potential confounding variables. Chapter 3 uses GAMs to spatially analyze birth defects across Texas in order to investigate risk factors that may be distributed geographically.

Innovation

This research will contribute to our understanding of environmental risk factors for birth defects and evaluates a novel approach to case-control analyses in spatial epidemiology. Literature on control selection for case-control studies was largely settled back in the 1980s to

1990s, and it became common practice to select approximately 3 to 4 controls per case to maximize statistical power.[5] Sampling methods have further been expanded to include matching, cluster sampling, or stratified sampling. However, newer studies on control selection have essentially come to a halt, especially within spatial epidemiology. Simple random sample is the most common method to select controls that are representative of the population from which cases arise, but it has limitations in spatial studies. Stratified sampling is effective in selecting controls when the population is not uniform which is commonly the case with populations. Unmatched spatially stratified random sampling selects controls that are geographically diverse and provides better spatial effect estimation in studies relevant to location in a simulation study. This method particularly may be effective when costs of collecting data on controls are high and when using all non-cases is computationally intensive.

The etiology of birth defects is still incomplete, and some evidence implicates environmental factors. The presented research adds to the sparse literature on the association between UNGDs and multiple birth defect subtypes using a state-wide sample of cases and controls from the Texas Birth Defects Registry (TBDR). Texas is one of the largest producers of natural gas in four main oil/gas shales, and therefore provides a highly variable exposure to UNGD across the entire state. Prior studies have implemented a radius of 16km using inverse-distance weighting or inverse-distance weighting squared to weigh wells less the farther away they are from the centroid of the radius. Smaller distances within 1km were only examined as sensitivity analyses. The exposure assessment in Chapter 2 utilizes three different radii within 7.5km, and therefore compared how wells within a distance affected birth defects, particularly since some studies examining different birth outcomes have observed positive associations at 1km. The use of three different radii also provides insight on potential exposure pathways to

pollutants closer to mother's address or farther away. This may aid in understanding potential water and air pollution emissions from UNGDs. UNGD exposure was also evaluated as a continuous variable to understand whether UNGD risk is homogeneous across the three radii. In addition, there is only one prior temporal analysis investigating the effect of UNGD over time.[37] This analysis provided much needed information on time trends for associations with UNGD. For birth defects with larger case counts, analyses are stratified by time to allow for observation of temporal trends.

Spatial analyses often include Moran's I using aggregated data, or scan statistics. This research also utilized the spatial method of generalized additive models (GAM) to map the risk of different birth defect subgroups. GAMs are comparable to individual-level scan-statistics, but they have an added advantage of smoothing over location rather than a predetermined shape.[55] The majority of spatial analyses have been only able to identify clusters. However, GAMs can be utilized to investigate how covariates contribute to the effect of location on a birth defect group and use novel sampling of controls to identify areas of increased and decreased risk. Therefore, this dissertation used three nested models to investigate how different variables affect birth defects: a crude model with just location (Model 1), an adjusted model with location and individual-level maternal characteristics (Model 2), and a fully adjusted model that includes location, individual-level, and environmental and community factors (Model 3). With the addition of each group of covariates, differences in the risk pattern were observed to identify areas where there may be spatial confounding and prompt further research in potential environmental exposures that contribute to birth defect risk.

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CHAPTER 1

Unmatched Spatially Stratified Controls: A simulation study examining efficiency and precision using spatially-diverse controls and generalized additive models

BACKGROUND AND AIM: A simple random sample (SRS) of non-cases selects the majority of controls from densely-populated areas and may not be an ideal approach for spatial case-control studies. An unmatched spatially stratified random sample (SSRS) of non-cases is a useful alternative that selects geographically balanced controls, and the sampling design is facilitated by the MapGAM package in R.

METHODS: Using preterm birth in Massachusetts as a case study, we divided the study area into non-overlapping spatial strata and randomly selected controls from among all non-cases within each stratum. We compared results for SSRS or SRS designs to the model with all non-cases in a simulation study using 500 separate iterations of randomly selected controls per design. For SSRS we selected 1-3 controls per stratum to observe if efficiency changed, and we compared mean squared error (MSE), bias, relative efficiency (RE), and statistically significantly map areas across sampling designs. Generalized additive models with inverse-probability weights were used to analyze the association between location and preterm birth.

RESULTS: We analyzed 4389 preterm births in crude and adjusted models with approximately 8778 controls using SSRS or SRS to select from among 64,785 non-cases. SSRS designs had lower average MSE (range: 0.0042-0.0044) and higher RE (range: 77-80%) across simulations compared to SRS designs (MSE: 0.0072-0.0073; RE for all SRS designs: 71%). SSRS also provided better estimates along the map edges. All SRS and SSRS designs detected areas of high risk, but SSRS results were more consistent across simulations and identified areas of statistically significant low risk more reliably than SRS designs.

CONCLUSIONS: The SSRS approach improved efficiency by selecting controls geographically distributed across the study area, particularly in low population density areas and

map edges, compared to the SRS approach. This method should be considered when sampling controls for spatial case-control studies.

Introduction

Control selection for case-control studies requires careful consideration to effectively estimate associations between exposures and health outcomes. Ideally, controls are chosen from a cohort or study base representative of cases to minimize the impact of confounding and selection bias, and are assessed in the same way as cases in order to improve study efficiency and precision, and to minimize bias.[1–3] The most common method to achieve these principles is to select a simple random sample (SRS) of controls from the population that gave rise to the cases, where each individual is independently sampled and has the same probability of selection into the study. Other methods to provide adequate controls include matching controls based on one or more confounding variables, counter-matching on exposure or an exposure surrogate, or stratified sampling.[2,4] Because cases are typically rarer than controls, and sometimes much rarer, many case-control studies include all available cases.

Spatial analyses have emerged as a powerful tool to investigate diseases using geographic information systems. Maps often display areas of high or low incidence and identify clusters which may generate hypotheses on potentially unknown risk factors.[5] Spatial studies using individual-level data can be powerful in avoiding known issues with aggregated data, such as the modifiable areal unit problem, and the uncertain geographic context problem.[6–10] The application of SRS controls in individual-level spatial analyses is common in epidemiological studies, even when data for all non-cases are potentially available, for many reasons, including computational demands of working with large datasets, statistical independence, and the potential need to collect additional measurements for selected controls. However, SRS generally yields low efficiency in spatial analyses due to the preponderance of controls in data-dense areas such as major cities.[11] Consequently, spatial studies using SRS may be more prone to "edge effects,"

which occur when data ceases at the study area boundary and may lead to distortions of the estimates.[12–14] Generally, widening the geographic study area in traditional case-control studies may increase precision in comparison to selecting more controls as there are diminishing returns from selecting more than 3 random controls per case.[2,15] Spatial studies often resort to cluster sampling or stratified sampling, which may be more efficient when collecting survey data.[16–19]

An unmatched spatially stratified random sample (SSRS) design can select controls from the geographic extent of the population that gave rise to the cases. This allows for not only a spatially representative control sample, but also ensures that controls are selected in low data-dense areas, especially along the study area boundaries where edge effects may occur in SRS designs. A geographically diverse cohort, such as a birth registry, can be used to select controls by spatially stratifying the population into non-overlapping regions across a study area.[20–22] The objective of this study was to examine the potential improvements in efficiency and bias using controls selected with an SSRS design compared with an SRS design in a simulation study. The simulation scenario was a case-control study of the association between location and preterm births, using repeated iterations of SRS or SSRS designs for control selection from a statewide birth registry.

Methods

Study Population

Our study obtained information on all live births in 2004 from the Massachusetts (MA) state birth registry. Cases of preterm births were defined as live births that occurred before 37 weeks of gestation and non-cases were live births born to term. For this study, we refer to all non-cases as all eligible non-preterm births in the registry, which are potentially available for

selection by the study sampling designs; controls refer to the non-cases that were actually selected by a sampling design. Some risk factors, such as overall maternal health, parity, smoking status, age, race/ethnicity, and social determinants of health, are available from the birth registry and may cause regional clustering of preterm birth cases.[23–25] We restricted our analysis to singleton births due to the association between plurality and preterm births.[26–28] In addition, we excluded births that were missing residential location (4.8%) and covariates of interest (season of birth, race/ethnicity, education status, parity, alcohol use, cigarette use, marital status, prenatal care, maternal age, and average census tract-level median income; <1.0%s total) for a total of 4,389 preterm cases and 64,785 non-cases born in 2004.

Spatially Stratified Controls

To obtain a spatially distributed sample of controls, we used unmatched spatially stratified random sampling (SSRS) to select from non-cases with the *sampcont* function in the *MapGAM* (Version 1.2-6) package using R (Version 3.6.2). The R code for *sampcont* can be found in Appendix A. The goal was to select approximately a 1:2 case to control ratio (8778 controls) using this method. SSRS divides the study area extent into non-overlapping spatial strata and then randomly selects controls from the non-cases that fall within each spatial stratum.

Inverse-probability weights were calculated for each selected control based on the proportion of selected controls to the total non-cases with each spatial stratum to account for the non-random selection of controls without replacement due to spatial stratification. As a result, controls in rural areas are sampled with higher probability, e.g. 100% if they are the only control in the stratum. Controls are sampled with lower probability in urban areas where there are more non-cases to select from. Thus, the controls selected within a stratum represent themselves and all other non-sampled units within the stratum.[29] This method of sampling selects a more even

spatial distribution of controls compared to a SRS sample (Figure 1.1), providing more stability and efficiency for spatial effect estimates.

The size of the spatial strata is determined in the *sampcont* function by dividing the study area into regions based on the number of columns and rows specified by the user. This essentially overlays a grid on the study area, and each stratum is a cell in the grid. The maximum number of controls to be sampled from each stratum is also passed through the function, and the total number of controls across the study area is arrived at iteratively by adjusting the columns and rows that are specified and thus the size of the strata. In our simulation study, we compared results using a random sample model to stratified sample models with 1,2, and 3 controls selected per stratum. We optimized the number of rows and columns for each SSRS design so that the total number of controls across the study area approximated our target of 8778 controls (about 14% of eligible non-cases, for an overall 1:2 case to control ratio). We also evaluated a sampling design with multiple stratification: by spatial location and by an important covariate. Prenatal care (PNC) was chosen as an additional stratification variable within the SSRS design due to the high imbalance of those who did not receive adequate prenatal care (measured by the Adequacy of Prenatal Care Utilization Index) which may result in spatial disparities. Therefore, within each spatial stratum, *sampcont* selects one non-case with prenatal care and one non-case without prenatal care into the control sample, when they are available. Inverse-probability weights for this design reflect the fraction of selected controls to the total non-cases within each stratum defined by both spatial location and whether or not the mother received prenatal care.

Because some stratum did not include any eligible non-cases, the number of controls selected with the SSRS does not exactly sum to 8778. We therefore evaluated additional SRS control sampling designs selecting an identical number of SRS controls to each respective SSRS

design. For example, using SSRS to select up to 1 control per stratum, 8787 controls were selected; the additional SRS sampling design matched the SSRS sample size exactly, also with 8787 controls. These additional evaluations ensured that model estimators did not perform better for SSRS than SRS simply because there were a few additional controls. All sampling designs conducted for this simulation study are summarized in Table 1.1. We refer to the sampling designs as N=1, N=2, N=3 and N=1+PNC to indicate the number of controls selected per stratum for the SSRS designs and corresponding SRS designs. The SRS design with exactly 1:2 ratio of cases controls was also included in this study. We compare results for these sampling designs to results for the model fit to all non-cases (ANC, n=64,785), which we refer to as the ANC Model. Figure 1.2 compares the geographic distribution of control selection for SSRS and SRS N=1 models in areas with high and low population density using the SSRS N=1 sample design grid as an example.

Spatial Analysis

We utilized generalized additive models (GAM) to analyze the spatial association between location and preterm births (MapGAM package). GAMs use individual-level location to predict the log odds of an outcome by applying a locally weighted straight line smoother (LOESS). This smoother fits local regressions to the data within a spatial area based on a span size, and without the smooth, the GAM reduces to a generalized linear model. The optimal LOESS span size of 0.10 (or 10% of the data) was determined by minimizing the Akaike Information Criterion and held constant across all models in this study.[10,30–32] A larger span size fits a larger proportion of the data and creates a smoother, more generalizable surface, while a smaller span size results in more spatial variation, reflecting local spatial effects. Thus, the

LOESS adapts to changes in population density, which is important for individual-level spatial analyses. The GAM is expressed as:

$\text{Logit}[p(X_1,X_2)] = S(X_1,X_2) + \alpha;\ \ \alpha = \beta_0 + \beta_1 z_1 + \beta_2 z_2 + \ldots + \beta_j Z_j$

where the left side of the equation is the log disease odds at location (X_1,X_2), and on the right side, $S(X_1,X_2)$ is the bivariate smoother and α represents covariates and their respective beta coefficients. A benefit of using a LOESS smoother is the ability to account for unmeasured risk factors that may vary spatially. Therefore, GAMs can be effective in examining multifactorial or poorly understood diseases for which not all predictors are known or measured. For models with SSRS controls, GAMs included the inverse-probability weights. We then generate maps of odds ratios by predicting the models' log odds at evenly spaced grid points throughout the contiguous state, with the median odds of the entire study area as referent. For this study, we refer to the map grid points as "map points" of log-odds. Areas of low and high odds of disease are indicated by blue and red colors, respectively, on our GAM maps. Maps also account for statistically significant areas by using standard errors to produce 95% confidence intervals (CI), as indicated by contour lines (areas that exclude an OR of 1).

Spatial patterns for preterm births were assessed in crude and adjusted models. Crude models include only the smoothing term to predict the odds of preterm birth at a location. Adjusted models account for season of birth (Winter, Spring, Summer, Fall), and the following maternal variables: race/ethnicity (White, Black, Hispanic, Asian/ Pacific Islander, and Other), education status (less than high school, high school, and more than high school), parity (no siblings, 1 sibling, 2-10 siblings), alcohol use (no drinking, at least 1 drink during pregnancy), cigarette usage (no cigarette, at least 1 cigarette during pregnancy), marital status (married, unmarried), prenatal care (fewer than 8 visits of prenatal care, at least 8 visits of prenatal care),

maternal age (≤19, 20-24, 25-29, 30-34, 35-40, 40+), and average census tract-level median income (continuous). If covariates are significant predictors of spatial risk, then we would expect patterns of spatial risk to change with adjustment and areas of statistical significance may become null.

Simulations

Differences in the GAM estimator (spatial log-odds) between SSRS and SRS controls naturally occur because of specific spatially significant selected controls that can affect model predictions. The addition or removal of a single control in a less-dense area, which can occur with SRS models, may produce heterogeneous results for each model iteration. Therefore, we repeated each SSRS N=1, N=2, N=3, N=1+PNC design, and their corresponding SRS design, fitting crude and adjusted GAMs in 500 iterations. All cases were included in each model, and a new set of controls were selected in each simulation with each SSRS or SRS method. Within each simulation, we averaged the mean squared error (MSE) and bias across all map points in our study area, relative to the ANC model. Study designs with low bias and low MSE are preferable. In addition, we calculated the theoretical standard error (SE) and the relative gain in efficiency (ratio of the ANC model SE and the specific model SE) for each model. Theoretical SEs assume that cases are resampled from a larger population, but this study holds the cases fixed for each iteration, resulting in less variability for all sampling designs than the theoretical standard errors would suggest. Maps displaying the odds ratios for preterm birth by location are also presented.

The known effect of aggregation of controls using random sampling in data-dense areas may also decrease efficiency along the edges of the study area and compound existing edge effects due to sparse data or geographic barriers such as oceans being more common at map

edges. Therefore, we also examined the estimation of log-odds of points along the edge of the study area border compared to interior points further inside of the study area. We classified edge points as those within 6 km of the border (approximately 3 grid points) and interior points as all other points inside the map boundaries (Figure 1.3).

Results

Our entire data set included 4,389 preterm birth cases and 64,785 non-case births born between January 1st to December 31st, 2004. Births were located throughout Massachusetts, and clustered in densely populated areas (Figure 1.1). Cases were composed of a higher proportion of mothers who were Black or Hispanic/Latino, without education beyond high school, nulliparous, and unmarried, compared to non-cases. In addition, mothers of cases were more likely to have smoked during pregnancy, not have adequate prenatal care, be younger than age 20 or age 40 years or older, and have a lower median income compared to mothers of non-case births (Table 1.2). Overall, the case characteristics were expected based on known risk factors for preterm birth.

Across our simulations, differences in model fit were observed between SRS controls and SSRS controls (Figure 1.4). Average MSE in our SSRS models for both crude (range: 0.0037-0.0039) and adjusted (range: 0.0042-0.0044) models were considerably lower than SRS models (crude range: 0.0066-0.0069, adjusted range: 0.0072-0.0073; Figure 1.4a). The theoretical standard errors were also lower among SSRS models for crude and adjusted models, and the relative efficiency was 15-17% higher for crude models, and 6-9% higher for adjusted models compared to SRS (Table 1.3). Although bias was small for all sampling designs (Figure 1.4b), average bias for crude models across 500 iterations for SSRS N=1 and SSRS N=1+ PNC was

notably closer to 0 (-0.0007 and -0.0010 respectively), compared to other SRS and SSRS models (range: -0.0029 to -0.0066). Adjusted bias for SSRS models was higher (range: 0.0071-0.0089) in contrast to SRS models (range 0.0027-0.0047).

MSE along the edge of the study area also differed among SSRS and SRS models. Average MSE along edge points in SSRS models ranged from 0.0052 to 0.0053 compared to SRS models which ranged around 0.010 (Figure 1.5). For interior points, SSRS MSE was also lower (range: 0.0036-0.0040) compared to SRS models (range: 0.0057-0.0060).

We present maps of model fits for 5 iterations of each SSRS design and the SRS (N=1+PNC) design, which had the highest number of controls among the SRS models. SSRS models were highly consistent in crude map outputs across all models (Figure 1.6), with SSRS N=2 and SSRS N=3 correctly identifying the area of low statistical significance in the center of MA. In comparison, SRS model maps were more variable across simulations. All models were able to detect areas of high risk in the West and East of MA which have higher population density. Maps for adjusted models were heterogeneous across the different sampling techniques (Figure 1.7). SSRS models consistently observed one of the two cold spots in the center and center-east of MA four out of five simulations, but SSRS N=1+PNC detected the cold spot in all five simulations, although the magnitude of the cold spot was smaller than other SSRS models. Maps for the first five simulations for SRS 1:2, N=1, N=2, and N=3 also displayed a high amount of variation (Figure 1.6-1.7).

Discussion

SSRS designs yielded a more spatially diverse set of controls than SRS designs. The use of spatial strata allowed for the selection of controls with sufficient coverage of the geographic

distribution of the population that gave rise to the cases, including rural or less-densely populated areas such as Western MA (Figure 1.1-1.2). In contrast, SRS designs predominately selected controls in metropolitan areas, leaving low-density areas vulnerable to imprecise estimation. This is supported by our analysis comparing points at the border of the study area to interior points, for which SSRS models had lower MSE for edge points compared to SRS models (Figure 1.5), and in our identification of hotspots, for which SRS models did not consistently identify areas of significantly different risk of preterm birth in rural western MA. Among the mapped results of five iterations for each design, more heterogeneity of identified significant areas occurred with SRS compared with SSRS designs. The selection of more controls per strata (SSRS N=2, N=3) in rural areas provided more stable identification of significant areas in rural locations, perhaps because it increased the proportion of strata for which all available non-cases were included in the model. All sampling designs appeared to reliably identify hot spots in data-dense areas of MA.

SSRS controls improved the efficiency of estimator prediction compared with SRS designs using the same total number of controls. The relative efficiency among crude SSRS models ranged from 86% to 88%, with SSRS N=2 performing the best among crude models, indicating that a spatially stratified sample of only 14% of non-cases was nearly as precise as using all non-cases. Interestingly, although SSRS designs also outperformed SRS designs for the adjusted models, albeit by less of a difference than for the crude models, SSRS N=1+PNC had the highest relative efficiency (80%; Table 1.3). This demonstrates the potential benefits of using multiple stratification on spatial location and one or more covariates when selecting controls, particularly when the covariate is highly unbalanced between cases and controls and varies spatially (e.g., when the covariate is a strong confounder). This multiple stratification sampling

approach, with spatial location and other covariate(s), should be considered when expecting one or more strong confounders in a spatial analysis. Differences in average MSE were markedly lower for SSRS designs compared to SRS designs, and SSRS (N=1+PNC) performed the best for crude and adjusted models, followed by SSRS N=2 and N=1 with only minor differences in MSE. SSRS N=3 crude and adjusted MSE were similar to each other (both were 0.0043), and both models had the lowest efficiency compared to other SSRS models. This may be due to oversampling of rural and less-densely populated areas using larger grid sizes. For this simulation study, grids were approximately square after accounting for the curvature of the state projection. We additionally performed simulations using a rectangular grid and observed nearly identical results as the current study (data not shown).

The use of SSRS controls could increase study efficiencies in terms of cost and efforts.[2] By using a simulation study with repeated sampling using the same SRSS and SRS designs, we were able to observe increases in efficiency that were unlikely due to chance. In earlier studies, we used SRSS designs with GAMs and inverse-probability weights to compare multiple birth defect subtypes to controls from the largest sample of cases in a birth defect group in Texas. [21,22] Hoffman et al. 2017 also utilized this method to select controls for autism spectrum disorder cases that accounted for the use of spatial clustering from familial similarities across the United States.[20] In epidemiology studies with large data sets, using all available non-cases can be too computationally intensive, potentially making it impractical. In addition, using a subset of spatially representative controls can have additional applications when developing new cohorts or enrolling new participants using other study designs, linking existing data sets with increasing costs or effort for adding each record, or collecting new information from selected controls that is not available for all non-cases. For example, one practical use of SSRS is to efficiently select

controls for linkage to a biorepository, in order to select stored blood samples that have not yet been analyzed for a particular exposure or confounder. It is typically expensive and time-consuming to perform laboratory analyses on biological samples, and SSRS can help select more efficient controls for biorepository sample analysis. Moreover, researchers may be interested in collecting additional data from a spatially diverse control set, following up with additional biosamples, questionnaires, and/or other measurements from those study participants. These potential applications, along with its high relative efficiency, suggests SSRS is an underutilized method for selecting controls, particularly in spatial epidemiological case-control studies.

There are a few limitations to consider when using SSRS. When a fixed total number of controls is desired, strata selection is an iterative process and requires testing different numbers of columns and rows forming the grids to achieve the desired number of controls. In addition, SSRS performs effectively if there is a large, representative data set with known case status and spatial location, or if those two variables can easily be ascertained before or upon enrollment of new controls. This method oversamples controls from some regions, but this oversampling is accounted for by including inverse-probability weights. The average bias across simulations (Figure 1.8, Table 1.4) in crude and adjusted models was close to 0, but it was statistically significant in all of our simulation results except SSRS N=1 and N=1+PNC. This is likely due to having so few study participants in rural regions of the study area. There is also some evidence that maximum likelihood estimators (MLE) in logistic regression may be biased in specific settings, which may also apply here.[33,34] However, the median point-wise bias in our simulations was less than 1% and would likely be viewed as negligible in most epidemiologic analyses. We also chose to use GAM as our method to map individual-level data, but GAM smoothers are also vulnerable to edge effects due to sparse data. Although SSRS appears to mitigate some edge

effects by selecting controls in low data areas, more research may be needed to develop approaches to effectively address edge effects in spatial analyses.

Conclusions

We observed lower average MSE, lower theoretical standard error, and lower bias across 500 simulations over the entire study area and near its edges when using SSRS compared to SRS. SSRS designs provided both lower MSE than SRS and only a minor loss in efficiency compared to ANC, despite using only 14% of all-non cases. Overall, selecting 1 or 2 controls per strata (SRS N=2 and SRS N=1+PNC) while holding the total number of controls approximately constant yielded the highest relative efficiency when considering map points, but SSRS designs with more controls per strata produced maps that more reliably identified low-risk areas that other sampling designs could not. SRRS designs effectively select controls more evenly distributed across a study area and ensures sampling in low-density areas, improving map estimation. Therefore, SSRS should be considered more often in spatial case-control studies. Additional studies of the performance of alternative sampling designs in spatial studies is needed, particularly using realistic participant locations and map shapes with edge effects from sparse data and geography.

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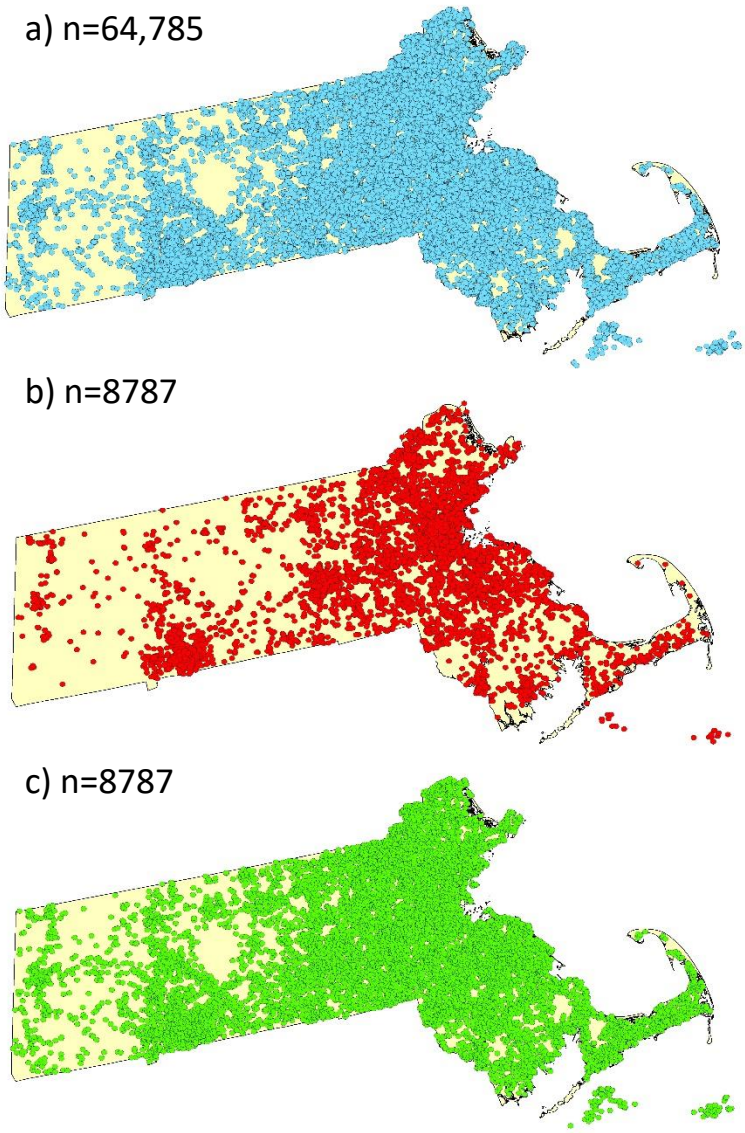

Figure 1.1: Comparison of the distribution of 4,389 cases of preterm birth and sampling designs with a) all non-cases (n=64,785), b) a simple random sample (SRS) design to select 8787 controls, and c) a spatially stratified random sample (SSRS) design to select 8787 controls (1 control per strata) in Massachusetts, 2004. SSRS selects a geographically representative set of controls relative to all non-cases. Locations have been altered to preserve confidentiality

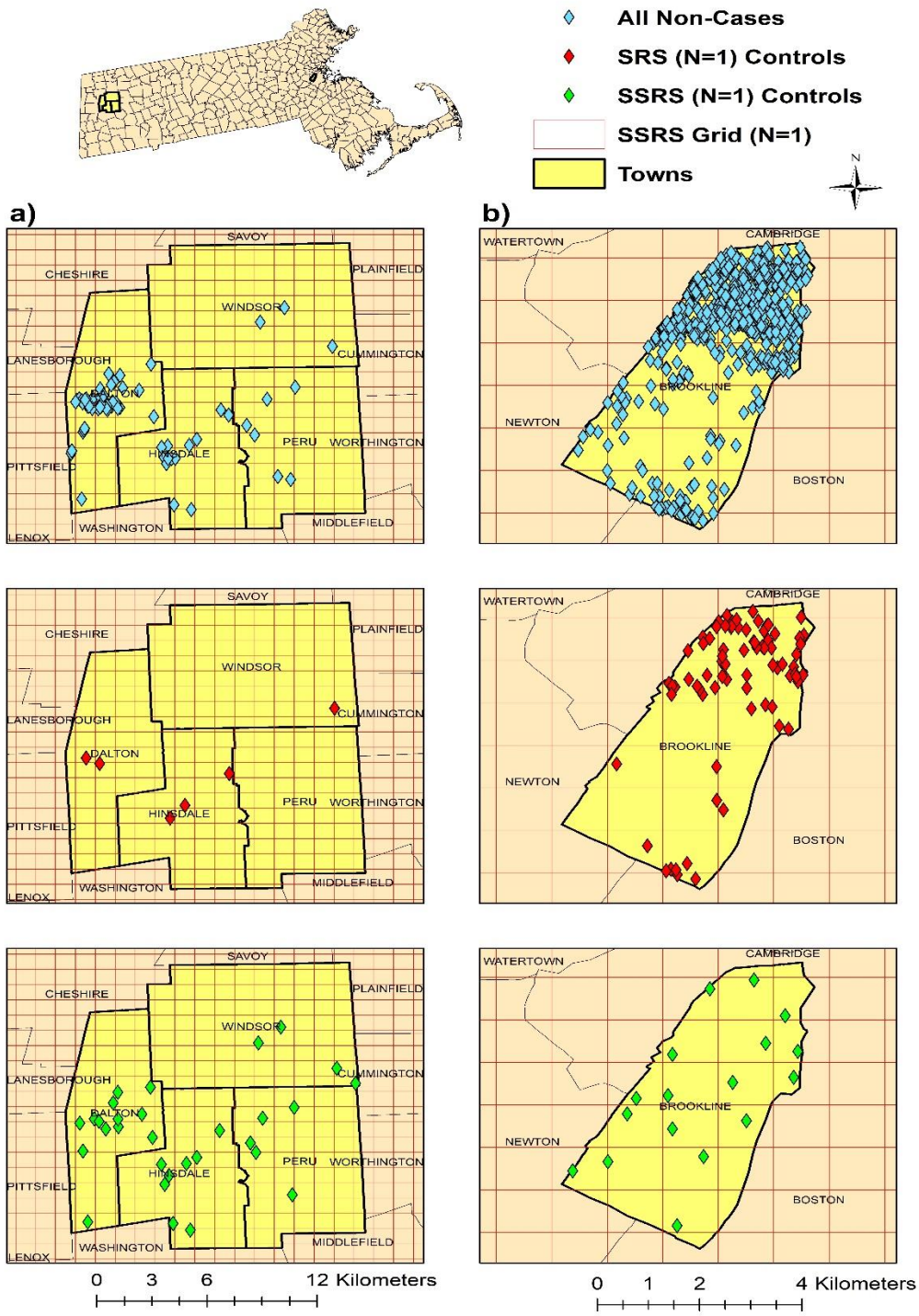

Figure 1.2: Selection of controls using simple random sample (SRS) design compared to spatially stratified random sample (SSRS) design compared to all non-cases using spatially stratified grids in a) a less densely populated area, and b) a more densely populated area, Massachusetts Towns, 2004. SSRS selects a geographically representative control group compared to SRS. Grid size shown is for the SSRS N=1 sampling design using 162 rows and 281 columns. Locations have been altered to preserve confidentiality.

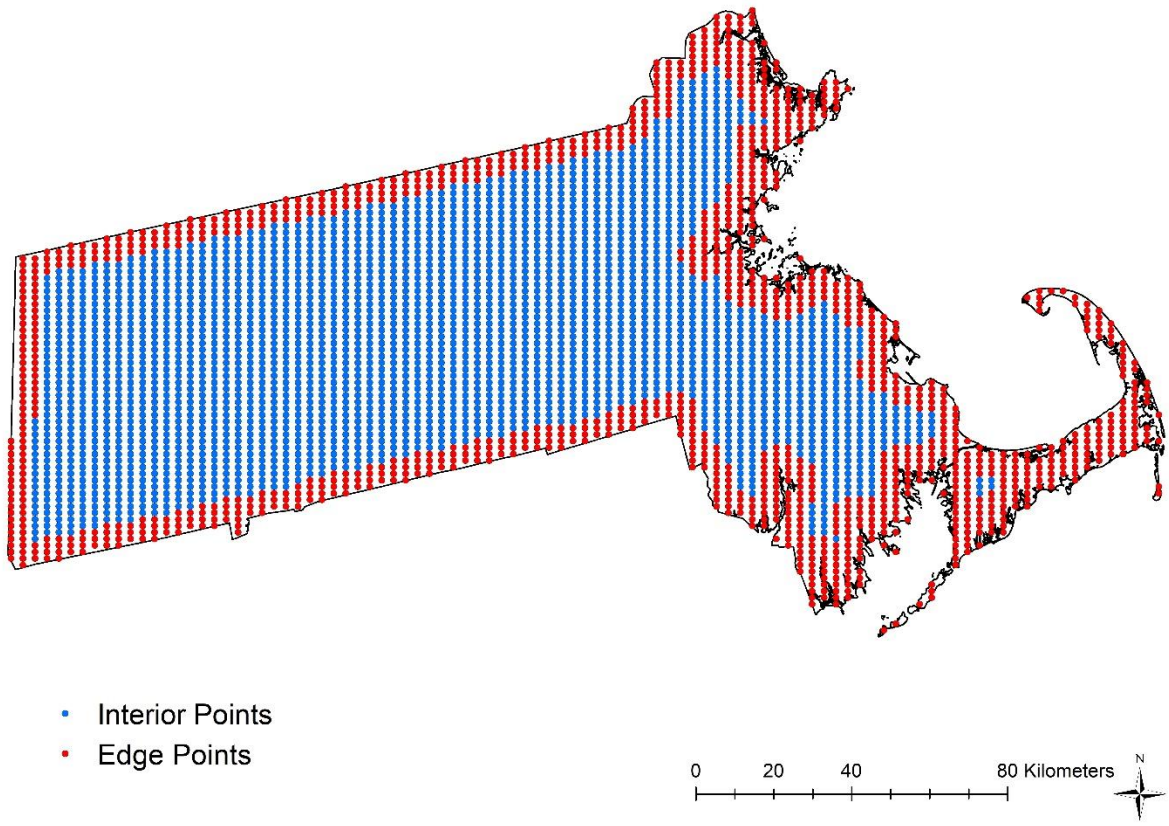

Figure 1.3: Edge map points (red) within 6km of the Massachusetts border and interior points (blue) that exclude edge map points in Massachusetts.

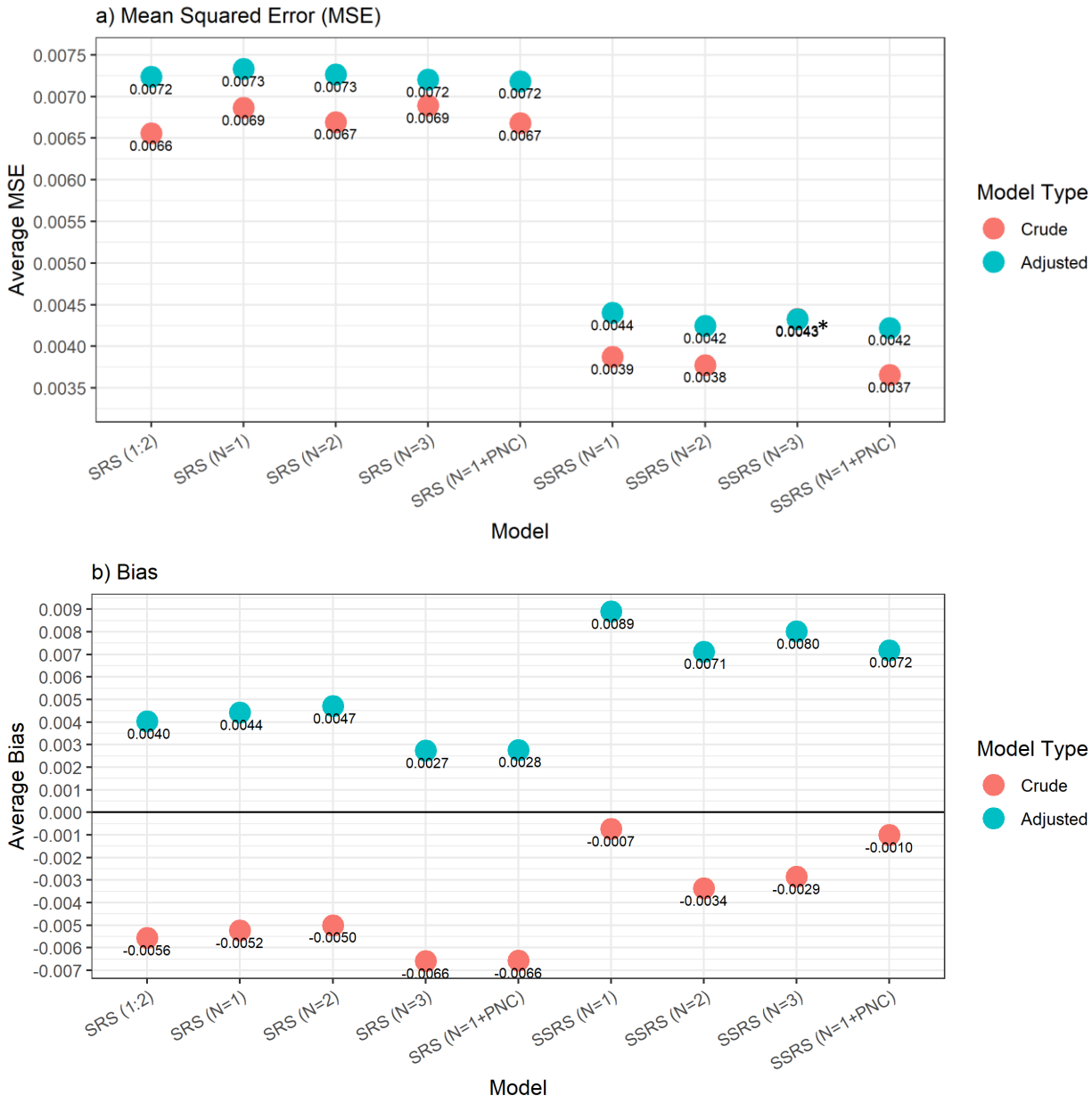

Figure 1.4: Comparing a) mean Squared Error (MSE), and b) average bias of crude and adjusted models for simple random sample (SRS) designs and spatially stratified random sample (SSRS) designs across 500 iterations; N=1,2,3 represents the number of controls per strata for SSRS designs; * SSRS (N=3) crude and adjusted are the same value

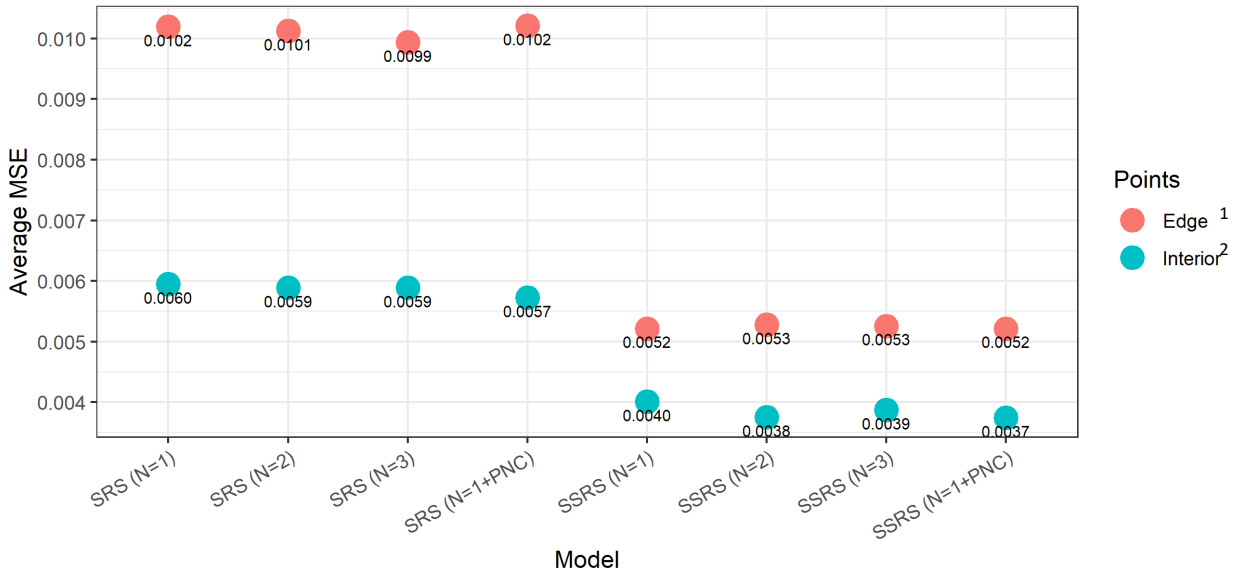

Figure 1.5: Lower averaged mean squared error (MSE) between interior and edge map points among crude and adjusted models for simple random sample (SRS) designs compared to spatially stratified random sample (SSRS) designs across 500 iterations; N=1,2,3 represents the number of controls per strata for SSRS designs.

[1] Edge points were classified as map points within 6 km of the Massachusetts border.

[2] Interior points were classified as map points that excluded map points within 6km of the Massachusetts Border.

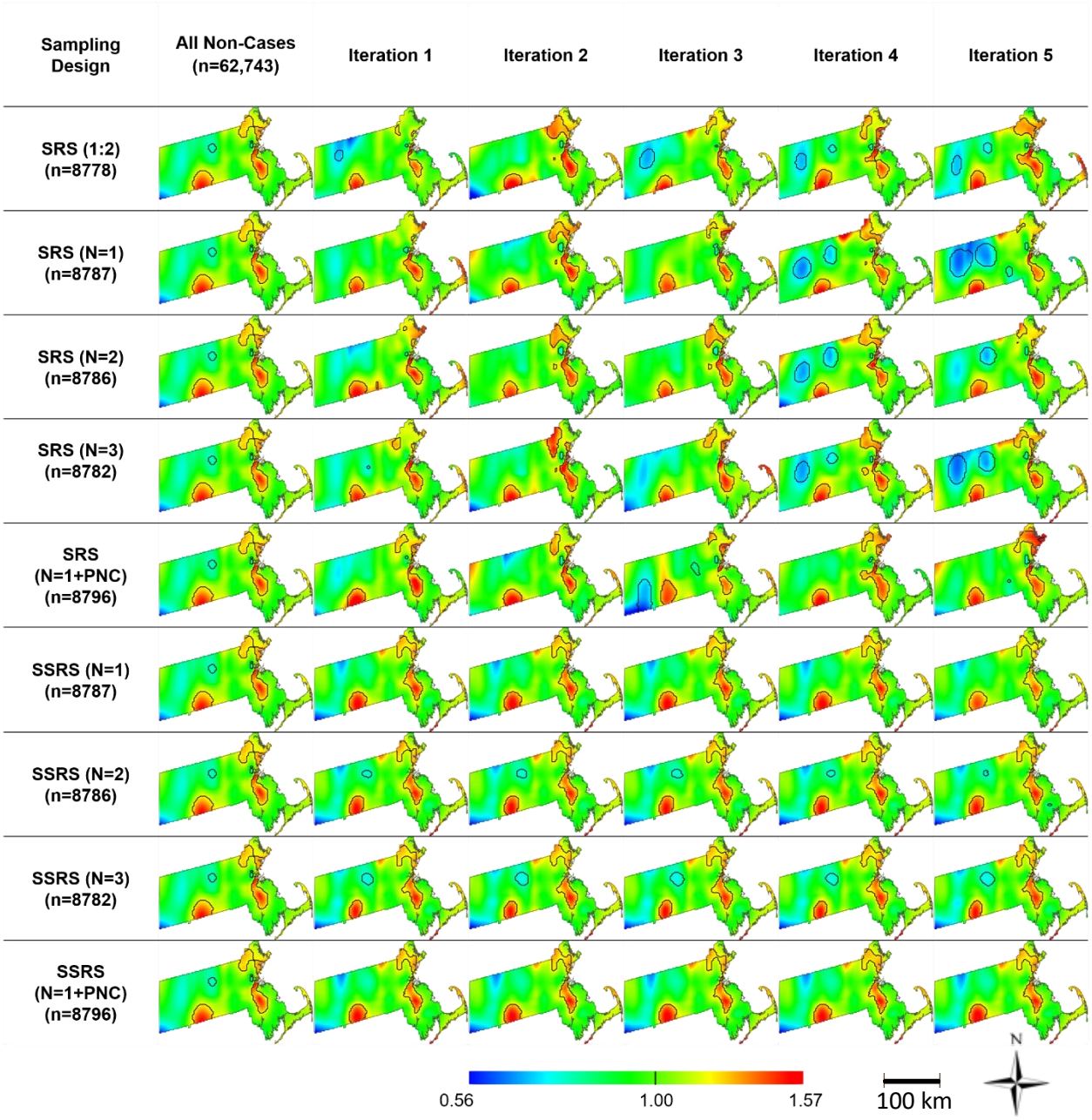

Figure 1.6: Simulated geographic patterns of crude odds ratios for preterm birth using simple random sample (SRS) and spatially stratified random sample (SSRS) designs compared to the model with all non-cases in Massachusetts, 2004. Black contour lines indicate statistically significant areas of increased or decreased risks. Maps share odds ratio scale for comparability.

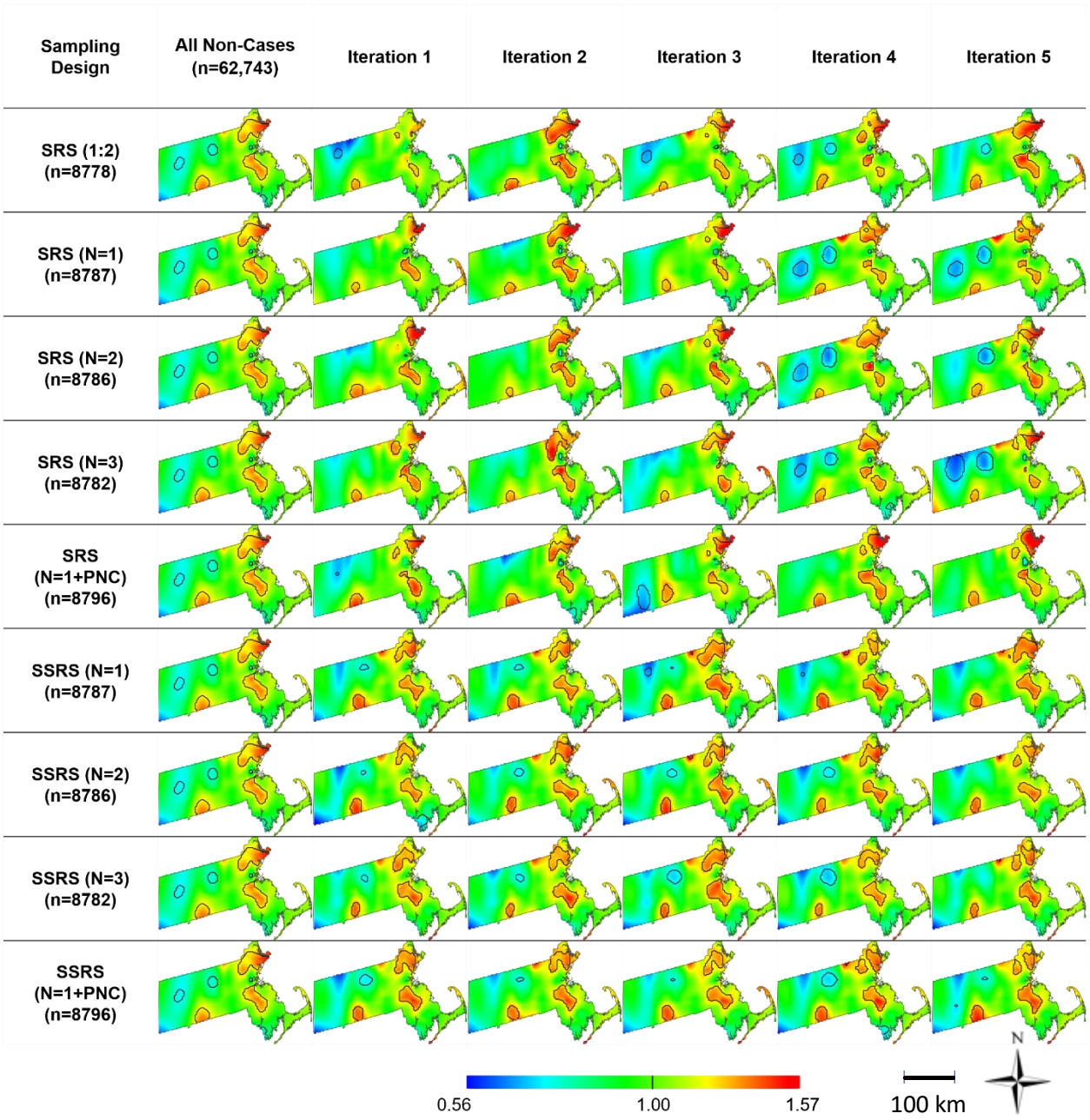

Figure 1.7: Simulated geographic patterns of adjusted odds ratios for preterm birth using simple random sample (SRS) and spatially stratified random sample (SSRS) designs compared to the model with all non-cases in Massachusetts, 2004. Black contour lines indicate statistically significant areas of increased or decreased risks. Maps share odds ratio scale for comparability.

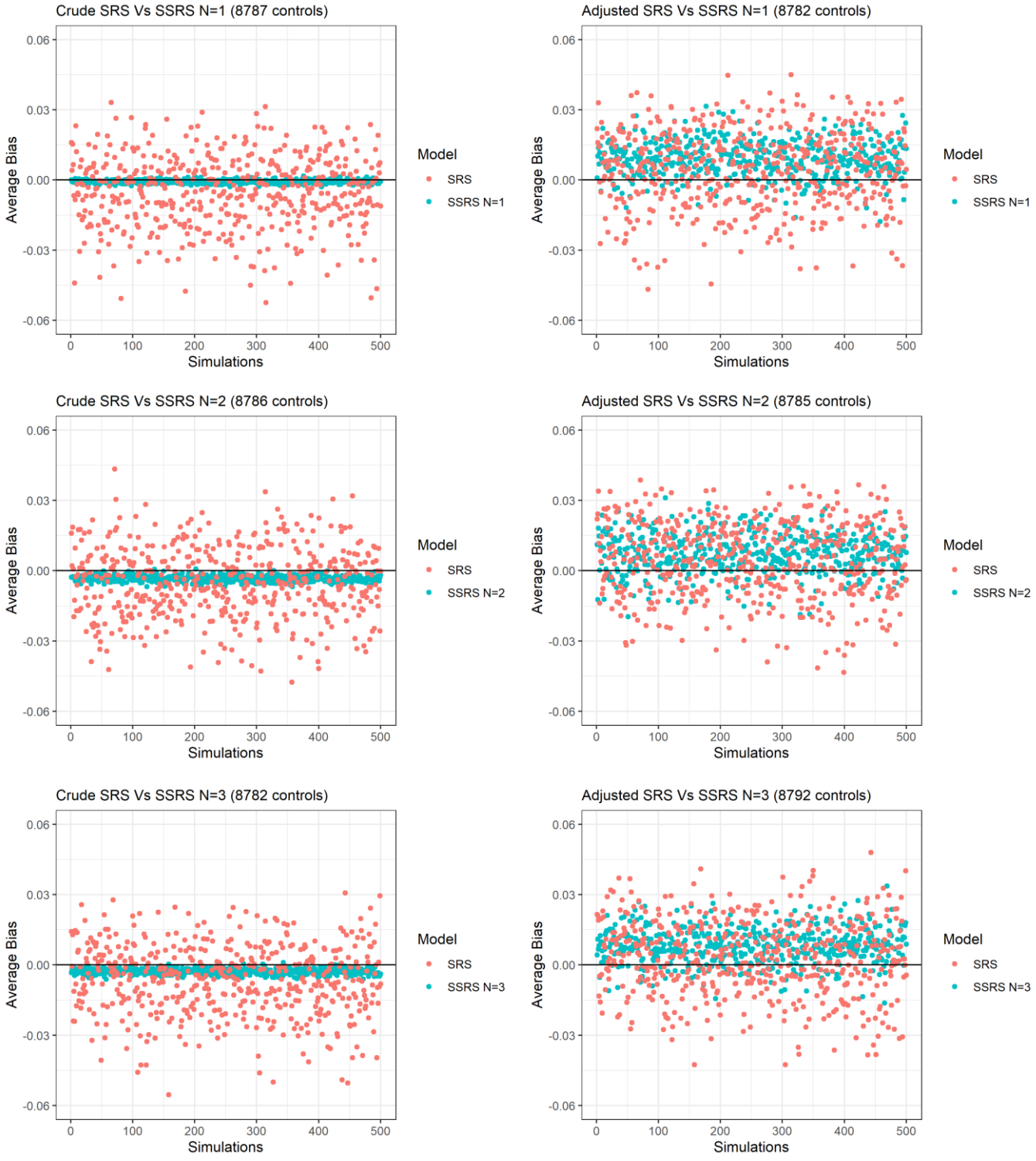
Crude SRS Vs SSRS N=1 (8787 controls)
Adjusted SRS Vs SSRS N=1 (8782 controls)
Crude SRS Vs SSRS N=2 (8786 controls)
Adjusted SRS Vs SSRS N=2 (8785 controls)
Crude SRS Vs SSRS N=3 (8782 controls)
Adjusted SRS Vs SSRS N=3 (8792 controls)
Average Bias
Simulations
Model
SRS
SSRS N=1
SSRS N=2
SSRS N=3

Figure 1.8: Comparison of average bias across 500 iterations for simple random sample (SRS) and spatially stratified random sample (SSRS) designs

Table 1.1. Sampling designs, grid sizes, and respective numbers of controls for the simulations. Simple random sampling (SRS) designs selected controls equivalent to spatially stratified random sampling (SSRS) models to ensure efficiency was not due to the addition of new controls.

All non-cases + Spatially Stratified Designs	Spatially Stratified Grid Size (row x col)	Simple Random Sample (SRS) Designs	Number of Controls
All non-cases	-	-	64,785
-	-	Random Sample (SRS 1:2 Ratio)	8778
Stratified 1 control per grid (SSRS N=1)	162x281	Random Sample (SRS N=1)	8787
Stratified 2 control per grid (SSRS N=2)	103x179	Random Sample (SRS N=2)	8786
Stratified 3 control per grid (SSRS N=3)	80x141	Random Sample (SRS N=3)	8782
Stratified 1 control per grid, stratified by prenatal care (SSRS N=1+PNC)	140x239	Random Sample (SRS N=1+PNC)	8796

Table 1.2. Characteristics of Massachusetts preterm birth cases and non-cases born in 2004.

	Non-cases (n=64,785)	Cases (n=4389)
Sex, n(%)		
Female	31,725 (48.97)	2009 (45.77)
Male	33,060 (51.03)	2380 (54.23)
Race/ethnicity, n(%)		
White	45,441 (70.14)	2866 (65.30)
Black	4795 (7.40)	525 (11.96)
Hispanic/ Latino	8370 (12.92)	642 (14.63)
Asian/PI	4775 (7.37)	248 (5.65)
Other	1404 (2.17)	108 (2.46)
Education, n(%)		
Less than HS	6882 (10.62)	565 (12.87)
HS	15,876 (24.51)	1219 (27.77)
More than HS	42,027 (64.87)	2605 (59.35)
Siblings, n(%)		
No siblings	29,044 (44.83)	2234 (50.90)
1 sib	22,454 (34.66)	1256 (28.62)
2-10 sibs	13,287 (20.51)	899 (20.48)
Alcohol usage during pregnancy, n(%)		
No drinking	63,462 (97.96)	4316 (98.34)
at least 1 drink	1323 (2.04)	73 (1.66)
Cigarette usage during Pregnancy, n(%)		
No cigarette	59,940 (92.52)	3949 (89.97)
at least 1 cigarette	4845 (7.48)	440 (10.03)
Marriage Status, n(%)		
Married	46,110 (71.17)	2786 (63.48)
Unmarried	18,675 (28.83)	1603 (36.52)
Season of Birth, n(%)		
Winter	15,488 (23.91)	1116 (25.43)
Spring	16,477 (25.43)	1075 (24.49)
Summer	17,091 (26.38)	1120 (25.52)
Fall	15,729 (24.28)	1078 (24.56)
Prenatal Care Status, n(%)		
No Prenatal	3452 (5.33)	792 (18.05)

Prenatal Care	61,333 (94.67)	3597 (81.95)
Maternal Age, n(%)		
≤19	3855 (5.95)	360 (8.20)
20-24	9917 (15.31)	693 (15.79)
25-29	15,031 (23.20)	935 (21.30)
30-34	21,237 (32.78)	1314 (29.94)
35-40	12,103 (18.68)	827 (18.84)
40+	2642 (4.08)	260 (5.92)
Average Median Income (mean ± sd)	$70,544 ± 34,785	$66,232 ± 33,508

Table 1.3. Theoretical standard errors of crude and adjusted spatial models for preterm birth using simple random sample (SRS) and spatially stratified random sampling (SSRS) designs across 500 iterations among Massachusetts births, 2004.

		Theoretical Standard Error (SE)			
Sampling designs	Number of controls	Crude	Adjusted	Crude Relative Efficiency *	Adjusted Relative Efficiency *
All non-cases	64,785	1.89 e-02	2.14 e-02	-	-
SRS (1:2 Ratio)	8778	2.65 e-02	3.01 e-02	71%	71%
SRS (N=1)	8787	2.65 e-02	3.00 e-02	71%	71%
SRS (N=2)	8786	2.65 e-02	3.01 e-02	71%	71%
SRS (N=3)	8782	2.65 e-02	3.01 e-02	71%	71%
SRS (N=1+PNC)	8796	2.65 e-02	3.01 e-02	71%	71%
SSRS (N=1)	8787	2.16 e-02	2.75 e-02	87%	78%
SSRS (N=2)	8786	2.15 e-02	2.75 e-02	88%	78%
SSRS (N=3)	8782	2.20 e-02	2.79 e-02	86%	77%
SSRS (N=1+PNC)	8796	2.19 e-02	2.67 e-02	86%	80%

*Relative Efficiency = SE of model with all non-cases divided by SE of simulated model

Table 1.4: P-values for the T-test of average grid-point bias in crude and adjusted models of preterm birth with simple random sample (SRS) and spatially stratified random sample (SSRS) designs across 500 iterations among Massachusetts births, 2004. The null hypothesis is that the average bias at a grid point is zero.

Model	Crude	Adjusted
SRS 1:2	<0.001	<0.001
SRS N=1	<0.001	<0.001
SRS N=2	<0.001	<0.001
SRS N=3	<0.001	<0.001
SRS N=1+PNC	<0.001	<0.001
SSRS N=1	0.44	<0.001
SSRS N=2	<0.001	<0.001
SSRS N=3	<0.001	<0.001
SSRS N=1+PNC	0.28	<0.001

CHAPTER 2

Birth Defects and Unconventional Natural Gas Developments in Texas, 1999-2011

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Background: Unconventional natural gas developments (UNGD) may release air and water pollutants into the environment, potentially increasing the risk of birth defects.

Objectives: We conducted a case-control study to investigate the relationship between UNGD exposure and the risk of gastroschisis, congenital heart defects (CHD), neural tube defects (NTDs), and orofacial clefts in Texas.

Methods: We evaluated 52,955 cases with birth defects and 642,399 controls born between 1999 to 2011. We calculated UNGD densities (number of UNGDs per area) within 1, 3, and 7.5 km of maternal address at birth and categorized exposure by density tertiles, continuously, and as a percentile range difference. For CHD subtypes with large case numbers, we also performed time-stratified analyses to examine temporal trends. We calculated adjusted odds ratios (aOR) and 95% confidence intervals (CI) for the association with UNGD exposure, accounting for maternal characteristics and neighborhood factors. We also included a bivariable smooth of geocoded maternal location in an additive model to account for unmeasured spatially varying risk factors.

Results: Positive associations were observed between the highest tertile of UNGD density within 1 km of maternal address and risk of anencephaly (aOR: 2.44, 95% CI: 1.55, 3.86), spina bifida (aOR: 2.09, 95% CI: 1.47, 2.99), gastroschisis among older mothers (aOR: 3.19, 95% CI: 1.77, 5.73), aortic valve stenosis (aOR: 1.90, 95% CI: 1.33, 2.71), hypoplastic left heart syndrome (aOR: 2.00, 95% CI: 1.39, 2.86), and pulmonary valve atresia or stenosis (aOR: 1.36, 95% CI: 1.10, 1.66). For CHD subtypes, results did not differ substantially by distance from maternal address or when residual confounding was considered, except for atrial septal defects. We did not observe associations with orofacial clefts.

Discussion: Our results suggest that UNGDs were associated with some CHDs and possibly NTDs. In addition, we identified temporal trends and observed presence of spatial residual confounding for some CHDs.

Introduction

Birth defects are serious and costly medical conditions, affecting approximately 3-4% of births in Texas and are a leading cause of infant mortality.[1,2] Risk factors for birth defects are complex and multifactorial, and environmental teratogens may contribute to additive risks for neural tube defects (NTDs), congenital heart defects (CHDs), gastroschisis and orofacial clefts.[3–5] As the causes of most birth defects are unknown, further investigation of environmental risk factors may contribute to our understanding of their etiology.[6,7]

Technology has advanced the ability to extract shale gas using unconventional methods such as horizontal drilling and hydraulic fracturing. Unconventional natural gas developments (UNGDs) made up approximately two-thirds of US natural gas production in 2018 and continues to grow.[8] With the continued growth in gas production is the potential increase in exposures to various pollutants throughout the drilling process. Air pollution emissions from diesel-powered equipment and trucks contribute to emissions of volatile organic compounds (VOCs) sulfur dioxide, BTEX (benzene, toluene, ethylebenzene, xylene), hydrogen sulfide, poly aromatic hydrocarbons (PAHs) and ozone.[9–19] UNGDs using hydraulic fracturing methods inject millions of liters of fracturing fluid made up of water, proppant, and more than 1,000 other chemicals, including a combination of methane, heavy metals, PAHs, BTEX, and solvents.[14,20–24] Residents living near wells can be exposed to these chemicals during transport of hydraulic fracturing fluid, deterioration of well casings, or leakage from wastewater pits.[14]

There have been efforts to understand the potential reproductive implications of living near UNGDs.[14,15,23,25–28] Case studies have described the release of fracturing fluid into animal enclosures leading to death and adverse reproductive outcomes, including birth defects.[20,29] There are only a few observational studies that have evaluated the association between UNGDs

and birth defects in humans.[30–33] McKenzie et al. (2014) and Janitz et al. (2019) used retrospective cohort studies in Colorado and Oklahoma respectively, while McKenzie et al. (2019) employed a nested case-control study design based on the same Colorado retrospective cohort to investigate associations between birth defects and intensity of oil and gas activity.[30,32,33] Ma et al. (2016) used a time series approach to analyze birth certificate data in Pennsylvania while accounting for secular trends before and after UNGDs.[31] These studies suggest that there may be potential elevated risks between some birth defects and UNGDs, but results were inconsistent. McKenzie et al. (2014, 2019) and Janitz et al. (2019) used inverse distance weighting (IDW) at a radius of approximately 16 kilometers from maternal address, but the authors stated a need for more precise exposure estimates at smaller radii.[30,32,33]

The objective of this study is to investigate the association between local UNGD density within varying distances of maternal residential location and risk of NTDs, CHDs, gastroschisis, and orofacial clefts among deliveries in Texas from 1999 to 2011. UNGDs are located in shales across Texas, allowing us to investigate associations with UNGD density (Figure 2.1) in the highest natural gas producing state.[8] Our study addresses the limitations of previous work related to UNGDs by examining the relationship with birth defects throughout Texas with a much larger number of births and with exposure measures closer to maternal address at birth.

Methods

Study Population

We conducted a case-control analysis using data obtained from the Texas Birth Defects Registry (TBDR) at the Texas Department of State Health Services. The TBDR regularly identifies birth defects through an active state-wide surveillance system. TBDR staff regularly

access medical charts from all Texas facilities where affected children are delivered or treated. Staff abstract relevant data and enter it into a web-based registry database. The data then go through several data quality steps including review by other staff, and roughly 50% meet criteria for review by clinical geneticists. The TBDR classifies birth defects using the *British Pediatric Association* (BPA) coding system (1979), derived from the *International Classification of Disease*, Ninth Revision, Clinical Modification (ICD- 9CM) codes, and further modified by CDC and the TBDR; additional digits allow for greater distinction between similar birth defects.

For this study, we used cases from all pregnancy outcomes (live births, spontaneous fetal deaths, and pregnancy terminations) delivered between January 1, 1999 through December 31, 2011, with a confirmed diagnosis of a birth defect made prenatally or within one year after delivery. We analyzed selected NTDs, CHDs, and orofacial clefts primarily as individual birth defects, and stratified gastroschisis cases by maternal age at birth. For NTDs, we analyzed spina bifida (BPA code: 741.000-741.990) and anencephaly (740.000-740.080) separately. Among CHDs, we analyzed transposition of the great vessels (TGV) (745.100-745.190), tetralogy of Fallot (TOF) (745.200,746.840), ventricular septal defects (VSD) (745.400-745.490), atrial septal defects (ASD) (745.510-745.590), endocardial cushion defects (ECD) (745.600-745.690), pulmonary valve atresia or stenosis (PVAS) (746.000-746.010), tricuspid valve atresia or stenosis (TVAS) (746.100, 746.106), aortic valve stenosis (AVS) (746.300), and hypoplastic left heart syndrome (HLHS) (746.700). Cleft defects were separated into cleft palate only (749.00-749.090) and cleft lip with or without cleft palate (749.100-749.220). Finally, we stratified gastroschisis (756.710) analyses by maternal age (less than 25 years, 25 years and older) given the critical importance of age as a risk factor, as well as its recognition as an effect measure modifier.[34–37]

Controls were live births during the study period that had no structural or chromosomal birth defects. Data were obtained from the Center for Health Statistics at the Texas Department of State Health Services. In our analyses, we used unmatched spatially stratified sampling with a 1:2 ratio of cases to controls.[38] The study area was divided into evenly sized grid areas, such that if we divided the study area into 100 evenly sized grids, each grid area would be 14,761 km^2; from within those areas, all cases were selected. Using the total number of non-cases in each grid area, we calculated inverse probability weights for the sampled controls. These weights were then used in all analyses to account for the non-random control selection. This probability sampling approach assures selection of controls from rural areas and reduces data sparseness in regions of the state with low population density; a simple random sample across the state would have selected the majority of controls from densely populated areas. For CHDs, we used the same controls calculated from our PVAS sample for ECD, HLHS, TGV, TOF, and TVAS while anencephaly controls were based on the spina bifida sample. All other defects had controls calculated with grid sizes that maintained a 1:2 ratio. Cases and controls were excluded if the maternal address could not be successfully geocoded (8.0% and 9.0% respectively). The institutional review boards of the University of California, Irvine (2012-8930) and Texas Department of State Health Services (14-006) approved this research.

Exposure Assessment

We considered UNGD density at a mother's residence for the year of birth as a surrogate measure of exposure from potential contaminants in the surrounding air and water based on prior literature.[22,26,30,32,39–42] We obtained from the Railroad Commission of Texas (RRC) the longitudes and latitudes of UNGD wells and the dates they were completed, shut-in, or plugged.[43] More than 10% of Texans live within 1.6 km of a UNGD well and there is some

evidence that residents have more self-reported exposure-related symptoms when they live within 1 km of a UNGD, although previous studies have also used larger distances.[30,32,44–47] We calculated UNGD well densities defined as the number of yearly-active wells in a geographic area, using areas of three different radii: within 1, 3, and 7.5 km of maternal address at year of birth. Thus, we refer to 1 km UNGD exposure as the number of UNGDs within a 1 km radius, 3 km UNGD exposure as the number of UNGDs within a 3 km radius, and 7.5 km UNGD exposure as the number of UNGDs within 7.5 km radius of maternal address. Our objective was to capture the effect of potential exposures near residential homes, so we restricted our analyses to UNGDs within 7.5 km. We used geographic information system software (ArcGIS, version 10.7; ESRI) to calculate annual density surface maps with a resolution of 200 meters and assigned the density measures to maternal addresses. Mothers living within 7.5 km of at least one UNGD well were categorized into tertiles of UNGD densities based on the distribution among control mothers (Table 2.2).

Statistical Analysis

Our primary analysis modeled UNGD density categorically by tertiles, based on the distribution of nonzero values among controls; zero UNGD exposure as the referent group. The number of wells in each tertile varied across the three different radii. We used logistic regression models to calculate crude and adjusted odds ratios (aORs) and 95% confidence intervals (CI) for the association between each birth defect outcome group and UNGD exposure for a given radius, controlling for maternal characteristics and neighborhood factors (listed below). In additional analyses, we used generalized additive models that included a bivariate smooth term for a mother's geocoded location, thereby accounting for any unmeasured confounding variables that may be distributed spatially such as socioeconomic status and access to prenatal care.

We also conducted secondary analyses with UNGD density modeled continuously to compare equivalent density measures (number of wells per area) across the three radii. Effect estimates for continuous UNGD density are presented for an increase in density of one well per km^2 area. This equates to 1 UNGD within a 1km radius, 9 UNGD within a 3km radius, and 56 UNGD within a 7.5km radius. For ASDs and VSDs, CHD subtypes with large numbers of cases, we also performed time-stratified analyses using our continuous measure which allowed us to examine temporal trends. Births were stratified by year of delivery in overlapping three-year time intervals (i.e. 1999-2001, 2000-2002) across the entire study period.

We selected covariates a priori based on previous literature. Maternal characteristics included smoking status (yes/no), plurality of birth (1 fetus, 2 or more fetuses), maternal age (<19, 20-24, 25-29, 30-34, 35-39, 40+ years), race/ethnicity (white non-Hispanic, black non-Hispanic, Hispanic, other non-Hispanic), and education status (less than high school, high school, greater than high school). Only births with complete data were included in each analysis; missingness for the covariates was less than 1%. Neighborhood factors included median household income at maternal address block group, urbanicity in 2010, and average daily vehicle miles traveled (DVMT) for all trucks by county. We obtained median household income and urbanicity data from the U.S. Census American Community Survey.[48] Household incomes from the 2000 census and 2010 census were averaged for each block group to calculate an average measure that was included in the model as a continuous variable. We created a binary urbanicity indicator based on the spatial location of mothers living in urban clusters or urban areas, which are defined as regions with populations greater than 2,500 people and 50,000 people, respectively. Average DVMT was available from the Texas Department of Transportation for

2005 through 2011 and data for all the years were averaged for a single county-level measure.[49] Effect estimates for these covariates within each buffer radii model is reported in Appendix B.

Results were also presented using a continuous analysis for UNGD for a difference between the 5th to 95th percentile range (PR) to evaluate how groups of risk factors may affect the association between birth defects and continuous UNGD exposure in nested models. Model 1 included a GAM model with the smoothing term and UNGD, Model 2 included the adjusted model with the smooth term, UNGD density, and maternal characteristics, and Model 3 included a fully adjusted model with the smooth term, UNGD density, maternal characteristics, and community factors. With these models, we can observe the effect of these variables on the potential risk of UNGD density and birth defect groups.

We conducted several post-hoc sensitivity analyses to observe if additional county-level risk factors from the Centers for Disease Control and Prevention (CDC) were related to UNGD and birth defects. Percent of women with diabetes, rate of opioid prescription, and percent of the population that were uninsured were included in the model for anencephaly, hypoplastic left heart syndrome, aortic valve stenosis, pulmonary valve atresia/stenosis, and atrial septal defects in 2007-2009[50–57]. These defects were chosen based on their relationship with UNGDs. Race and ethnicity, as well as socioeconomic status, are important risk factors and were analyzed within stratified analyses among all birth defects to provide insight on risk for vulnerable populations.

Results

There were 2,157 NTDS, 42,445 CHDs, 6,174 orofacial clefts, and 2,179 gastroschisis cases with isolated or multiple birth defects. The majority of mothers did not smoke, had a singleton birth, gave birth at age 20-29 years, were Hispanic, and lived in an urban area (Table

2.1). However, mothers of gastroschisis cases were younger than controls (83.9% were <25 years old) and had less than high school education (40.6%). Under 10% of mothers lived within 1 km of a UNGD well at time of their child's delivery. This proportion increased with increasing radius from maternal address; about half the mothers lived within 7.5 km of at least one well. Adjusted ORs and corresponding 95% CIs for each tertile exposure group within a radius of 1, 3, and 7.5 km are presented in Figure 2.2. The associated number of cases and controls for each birth defect subtype within each tertile by buffer radii distance is described in Table 2.2. Mothers with the highest tertile of exposure within 1 km of maternal address had significantly increased odds for anencephaly (1km aOR: 2.94, 95% CI: 1.83, 4.75) and spina bifida (aOR: 2.09, 95% CI: 1.47, 2.99) compared to mothers without any exposure. Further, odds associated with the highest exposure tertile decreased with increasing radius from maternal address. We also observed elevated odds for total gastroschisis cases in the highest tertile of exposure across all buffer radius distances. While gastroschisis is more common among younger mothers, the highest ORs were observed for older mothers with the highest exposure tertile within 1km of maternal address (1km aOR: 3.19, 95% CI: 1.77, 5.73). Adjusted ORs for cleft palate only and cleft lip with/ without palate were generally null or suggestive of an inverse association, and associations were inconsistent across tertiles of exposure and distances from maternal address.

We also observed elevated risks among CHD subtypes for the second and third tertiles of exposure (Figure 2.2), although results did not differ substantially by distance from maternal address. The exception was ASD, which showed an obvious increase in ORs with increasing distance (3rd tertile, 1km aOR: 1.66, 95% CI: 1.54, 1.79; 3km aOR: 2.03, 95% CI: 1.90, 2.15; 7.5km aOR: 2.62, 95% CI: 2.48, 2.77). In addition, risk was generally elevated for the third

tertile among AVS, HLHS, PVAS, and VSD. Results for ECD, TGV, TOF, and TVAS defects included the null and the direction of effects were inconsistent across tertiles.

Results from analyses of UNGD density modeled as a continuous exposure (Figure 2.3) were similar to our categorical exposure results. For anencephaly and spina bifida, risks were highest for the 1km distance, and null associations were observed for cleft palate and cleft lip. There was a slight increase in risk of CHDs with increasing distance from maternal address, but confidence intervals overlapped substantially for all subtypes except PVAS.

In the secondary time-stratified analysis for ASDs using a continuous exposure variable (Figure 2.4), we observed consistently elevated aORs that increased with buffer radii. Risks appeared generally consistent over time, with 95% CIs shrinking as case counts increased. We observed a decrease in VSD aORs (Figure 2.5) in the earlier time periods followed by an increase from 2005 to 2009. ORs were generally similar across buffer radii, with slightly higher ORs observed for 1km in the earlier years and slightly higher ORs observed for 7.5km in the later years. Effect estimates and associated confidence intervals from GAM results overlapped with the continuous exposure model results (Figure 2.1 and 2.5) except for ASDs (Figure 2.4), suggesting that adjustment for maternal location attenuated the effect estimates for UNGD density in later years for ASDs.

We also conducted an analysis comparing models with different risk factors that may contribute to birth defects and potentially explain away the association between continuous UNGD exposure and birth defects. No substantial differences between Model 1, 2, and 3 were noted among all birth defects on the effect estimates of continuous UNGD (Figure 2.6-Figure 2.8), and the confidence intervals for the effect of UNGD from the 5^{th} to 95^{th} PR overlapped

across distances. Therefore, the risk factors we chose, although sometimes significant, were not attenuating the risk of exposure to UNGDs.

Although inclusion of risk factors did not attenuate UNGD risk, birth defect risk for specific race/ethnicities and socioeconomic statuses (SES) were found to be differentiated when evaluated in stratified analyses. Mothers who are Hispanic or living below or equal to block-level median household income had an increased risk for NTDs and some CHDs when separated by UNGD tertiles (Table 2.3). ORs were elevated in the highest tertile across all buffer radii for Hispanic mothers. However, SES appeared to be dependent on the type of birth defect and therefore suggestive of effect modification.

Discussion

Our analysis examined the relationship between UNGD density and anatomical groupings of NTDs, CHDs, orofacial, and gastroschisis defects. We were able to analyze UNGD density within three distances of maternal address at birth to account for the effect of pollutants associated with UNGDs closer to maternal residence. We observed elevated ORs for NTDs and gastroschisis associated with increased UNGD density within 1 km of maternal address and significant positive associations for CHDs at all three distances.

Density of UNGDs was used as a proxy measure for environmental exposures associated with the hydraulic fracturing process. Air quality is a concern partly due to diesel-powered equipment; an average of 1,200 trucks are used to develop a well in a Texas shale.[58,59] In addition, multiple pollutants potentially emitted from UNGDs, such as chlorinated solvents NO_2, ozone, PM, and benzene, may increase the risk of CHDs.[39,60–68] Although the mechanism of birth defect malformation during organogenesis is still unknown, there is some evidence that that

PAHs can cross the placenta and form PAH-DNA adducts in the embryo.[69] Benzene and PM may also induce oxidative stress to the fetus, causing teratogenesis during the critical period in which the neural crest is developing.[66,70,71]

Risk of NTDs in our study was associated with UNGD density within 1 km of maternal address and decreased with increased radius suggesting that living closer to UNGDs increased risk. Thus, NTDs may be more susceptible to acute, frequent, and concentrated airborne and water exposures from high-intensity UNGD production. A potential pathway of acute airborne exposure is flaring, where intentional combustion of gas during the extraction process can emit pollutants and was association with increased preterm birth.[72] Our results were similar to McKenzie et al. 2014 who found associations between NTDs and the highest tertile of UNGD exposure, but our estimates were contrary to Janitz et al. 2019 in their subtype analysis for spina bifida and anencephaly, even though our buffer of 3 km was comparable to their 3.2 km (2-mile) distance.[30,32] These two previous studies had small samples and used IDW densities which may explain the inconsistencies with our results. Although our results are suggestive of increased risks associated with living closer to UNGDs, we were unable to account for the protective nature of folic acid consumption or for fetal loss caused by NTDs.[73]

We did not observe a significant association between UNGD density and orofacial clefts, which is consistent with prior studies of UNGDs and air pollution that also reported null results.[30,32,63,68,74,75] Gastroschisis was only associated with UNGDs in the highest tertiles. When stratified by age, older mothers in the highest tertile of 1km exposure to UNGDs had the highest risk of gastroschisis. While Padula et al. (2013) also did not find any association between pollutants and gastroschisis in California, other studies have observed elevated risk associated with some air exposures (Van Dorp et al. 2010; Wang et al. 2019) and water pollutants (Brender

and Weyer 2016; Mattix et al. 2007), although these studies did not stratify their analysis by age.[60,76–79]

Overall, the effect of the highest tertile of UNGD exposure on CHD risk was fairly consistent across the three different distances from maternal address. This suggests that the UNGD exposure associated with CHDs might not be proximity dependent; a plausible scenario is groundwater contamination of a public supply that services an extended geographic area.[22] Organic hydraulic fracturing contaminants travel through the groundwater at different rates depending on their chemical properties.[20] Inorganic chemicals associated with UNGDs are also found to be persistent in the environment and can potentially contaminate drinking water.[80] In addition, an estimated 0.4 to 12.2 spills occur for every 100 UNGD wells nationally, and spills in Texas have increased over time.[20,81,82] Thus, maternal consumption of drinking water contaminated with UNGD-related chemicals may be a possible exposure pathway for CHDs across all distance radii.

Our results support work by Janitz et al. (2019), and McKenzie et al. (2014, 2019) who observed elevated risk for PVAS, TVAS, and VSDs.[30,32,33] Although we observed elevated risk of VSDs, our time stratified analyses often included the null from 2000 to 2005 and fluctuated in direction over time, suggesting that VSDs may not have a clear temporal trend during our study period. ASD was the one CHD that did show a consistent pattern across the various analyses, with higher risk at greater distances from maternal address that increased over time. Our time-stratified analyses of VSD and ASD suggest risks may have increased over time as fracturing well numbers began to grow around the state.[83]

Our study was limited by several factors. We were unable to analyze the effect of UNGDs on fetuses with the most severe defects that did not survive and may have been

spontaneously aborted early in the pregnancy, which likely led to an underestimation of our results. Furthermore, certain birth defects (particularly internal defects like ASDs and VSDs) are subject to diagnostic variability and may be differentially ascertained in different areas.[84,85] Additionally, the birth records data only provide maternal address at time of birth. An estimated 30% of mothers in Texas change residence between conception and delivery, especially if the mother is young, lower income, and non-Hispanic white.[86] Thus, we may have misclassified exposure during the first trimester of pregnancy, which is the most critical period. However, a study of benzene and birth defects in Texas observed short distance mobility by mothers, and there was little difference between benzene exposures and mobility among case and control mothers.[87] Furthermore, our UNGD densities were only annual estimates as we do not have precise exposures for specific trimesters. However, one study conducted a sensitivity analysis and observed little difference between annual and first trimester estimates of UNGDs.[30] This misclassification is expected to be non-differential and will result in bias toward the null, as observed in a study of ambient benzene exposure and birth defects.[88]

Risk factors included in this analysis were complex and differed for each birth defect subtype. Our sensitivity analysis observed some relationships between diabetes, and uninsured rates by county, but these variables did not attenuate the relationship between UNGD and birth defects in the adjusted models (Appendix B).

Our primary analysis incorporated sixteen birth defect subgroups and three UNGD density distances for a total of 48 models. We did not include an analysis to test for multiple comparisons. However, of our models, we observed 30 (62.5%) significant associations between different UNGD densities and birth defects. GLMs and GAMs in our secondary analysis consisted of 228 models, of those, 107 (46.9%) models were significant. In total, we had 137

(49.6%) significant models across both of our analyses, exceeding the 5% type 1 error rate that would be expected under independent null hypotheses and it is reasonable to rule out spuriousness among models.

Since a mother's residence is a proxy for location of exposure, we may also overestimate exposure if the mothers do not spend the majority of their time at or near their home. Intensity and timing of UNGD production is also a limitation in our study since we were not able to assign exposure at date of conception, and because pollutants differ by stage of production. This is expected to be non-differential as the same UNGD densities will be applied to cases and controls.[89] Furthermore, pollutants from UNGDs may vary due to geological, meteorological, and physicochemical properties that affect the directionality and mobility of pollutants. Our inability to measure UNGD exposure directly or model related contamination limits our understanding of the mechanism in which UNGD density may be associated with birth defects. Despite these limitations, our study included several strengths that addressed many of the weaknesses in previous birth defects studies of UNGDs. We were able to investigate birth defect subtypes given our large numbers of cases and controls so that we maintained statistical power to detect smaller effect sizes across our models. In addition, our spatially stratified control selection provided a geographically representative sample of births. Texas is a highly diverse state with a significant UNGD presence, providing large variability in our density measures and sociodemographic predictors. Our density measures of UNGD were calculated within three distances of maternal address at birth that captured the effect of proximity to UNGDs at a resolution of 200 meters. We were able to observe effect estimates for different radius distances using both categorical, continuous, and percent difference exposure measures. Pollutants associated with UNGDs likely affect different birth defects at different distances, as observed

most strongly with NTDs and ASD. Our analyses of different exposure distances may inform future exposure assessments of UNGD pollutants that vary spatially. Furthermore, we were able to account for unmeasured confounding by spatially-varying factors using GAMs. Our study also included a time-stratified analysis to better understand the related risks of VSDs and ASDs over time, as well as identified potential effect modification of race/ethnicity and socio-economic status.

Conclusions

We observed an increase in risk of CHDs among infants whose mothers lived in areas with higher UNGD well densities in Texas. While there was a suggestive association between NTDs, gastroschisis, and certain CHD subtypes with the highest UNGD exposure category within 1 km of maternal address at time of birth, there did not appear to be an association between UNGD density and orofacial clefts. Our study supports prior research examining UNGDs and birth defects. In addition, we were able to investigate temporal trends in the effects of UNGD exposures within specific distances of maternal address and consider residual confounding based on location. Further research is needed to understand the risks of UNGDs with NTDs and CHDs, specifically within a smaller distance from maternal address, and to better understand the mechanisms of UNGD exposure.

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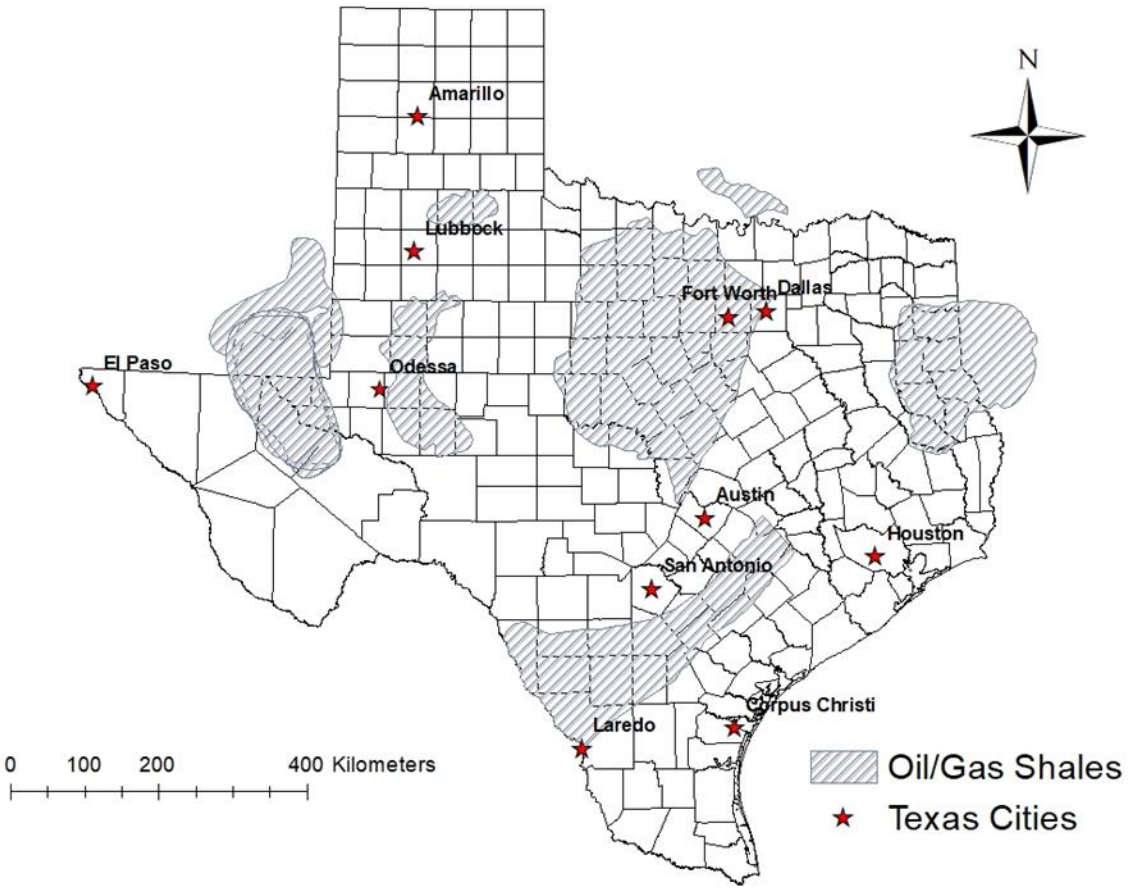

Figure 2.1: Map of Texas cities and oil and gas shales

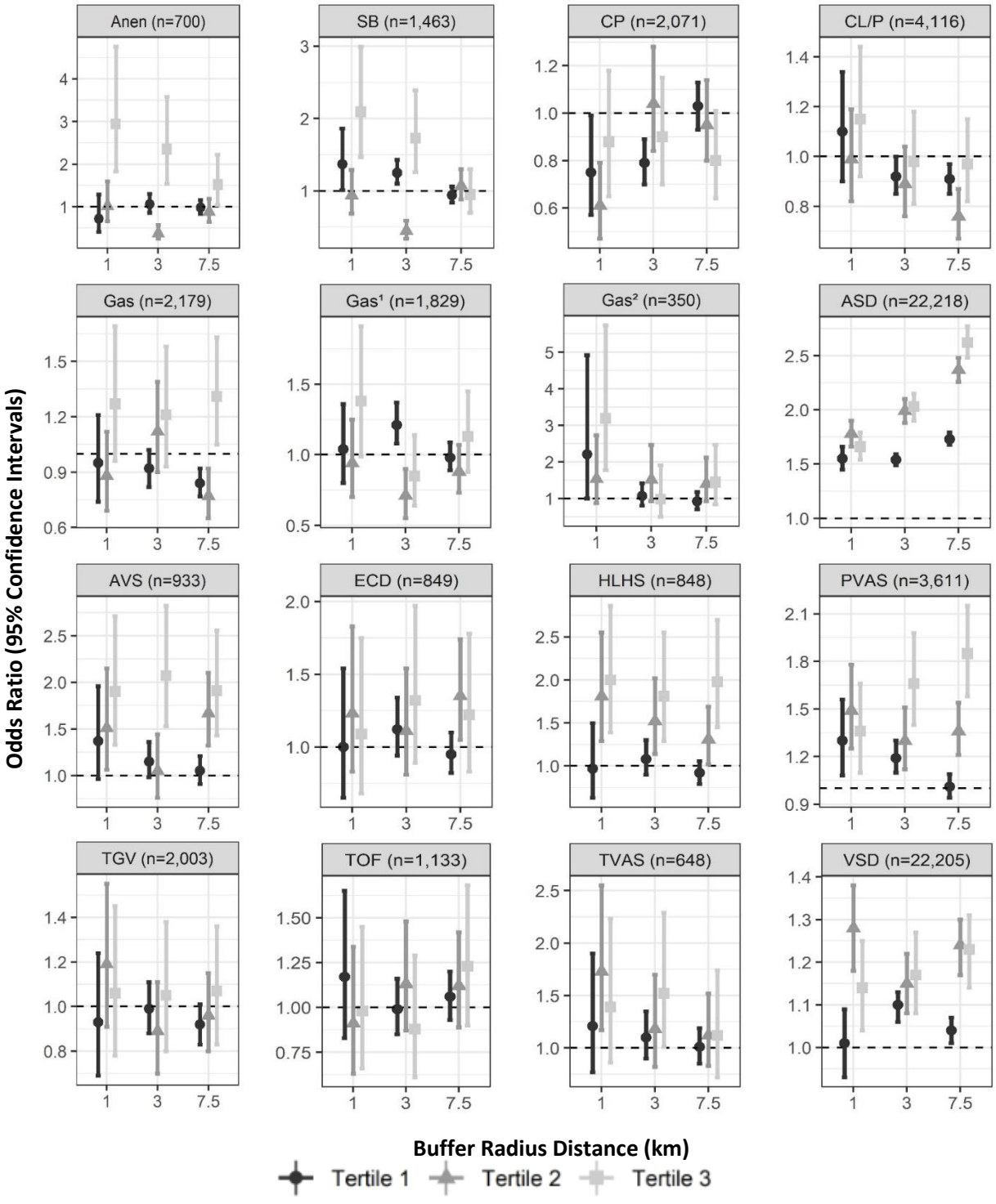

Figure 2.2: Adjusted odds ratios (95% confidence intervals) for the association between birth defects and exposure to unconventional natural gas development (UNGD) density, Texas, 1999-2011. UNGD density separated by tertiles based on the all non-case data set within buffer radii of 1, 3, and 7.5km of maternal address at birth, Texas, 1999-2011. SB=Spina Bifida, Anen=Anencephaly, CL=Cleft Lip with/without Palate, CP=Cleft Palate Only,

Gas=Gastroschisis, Gas^1=Gastroschisis (Age≤24), Gas^2=Gastroschisis (Age>24), AVS=Aortic Valve

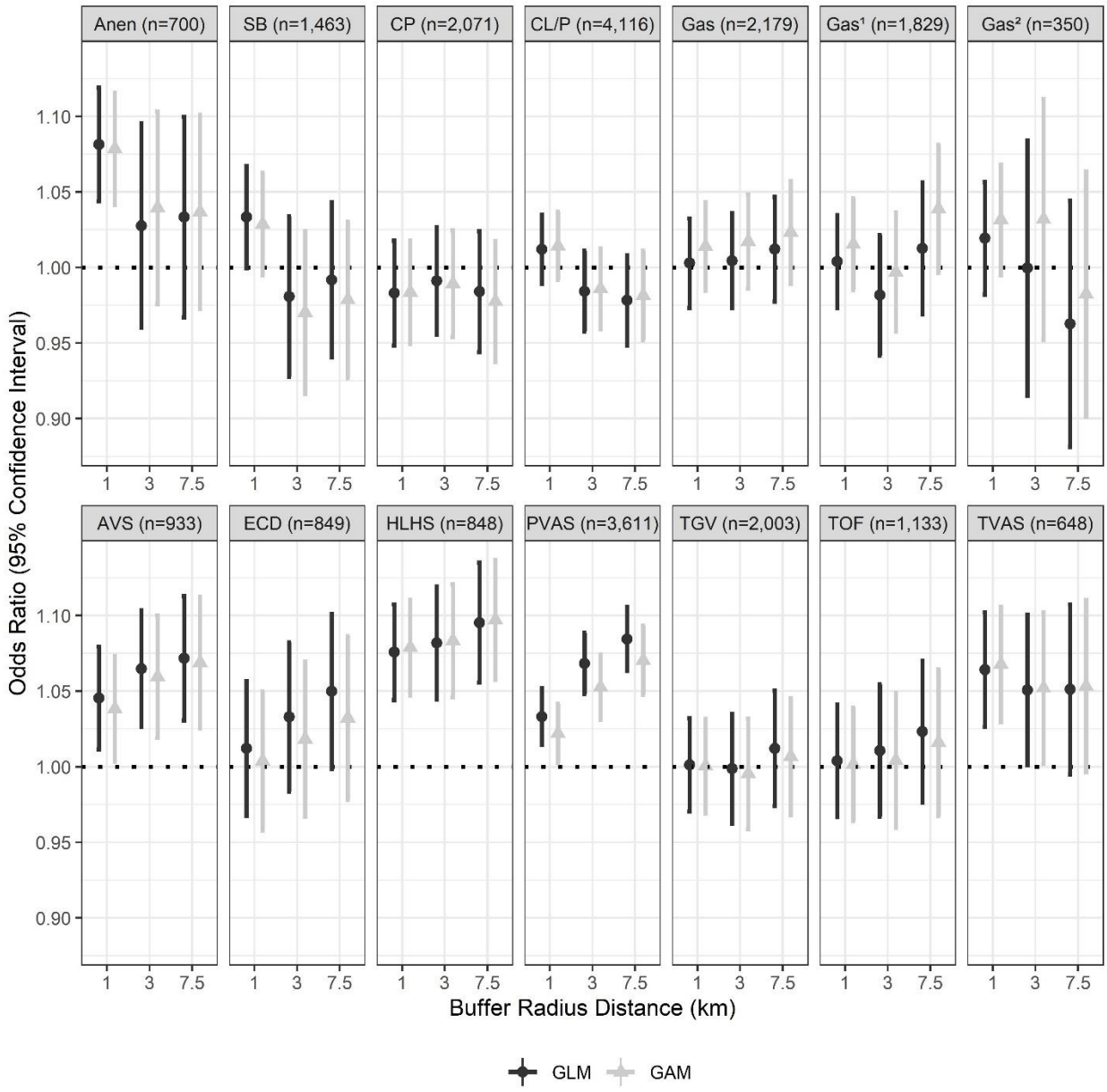

Figure 2.3: Adjusted odds ratios (95% confidence intervals) for the association between birth defects and an increase in unconventional natural gas developments (UNGD) density, Texas, 1999-2011. Models are separated by generalized linear models (GLM) and generalized additive models (GAM). Odds ratios indicate an increase of 1 well per km^2 area (measured on a continuous scale), equating to 1, 9, and 56 UNGD wells per buffer radii of 1, 3, and 7.5km of maternal address at birth. SB=Spina Bifida, Anen=Anencephaly, CL=Cleft Lip with/without Palate, CP=Cleft Palate Only, Gas=Gastroschisis, Gas1=Gastroschisis (Age≤24), Gas2=Gastroschisis (Age>24), AVS=Aortic Valve Stenosis, ECD=Endocardial Cushion Defect, HLHS=Hypoplastic Left Heart Syndrome, PVAS=Pulmonary Valve Atresia/Stenosis, TGV=Transposition of Great Vessels, TOF=Tetralogy of Fallot, TVAS=Tricuspid Valve Atresia/Stenosis

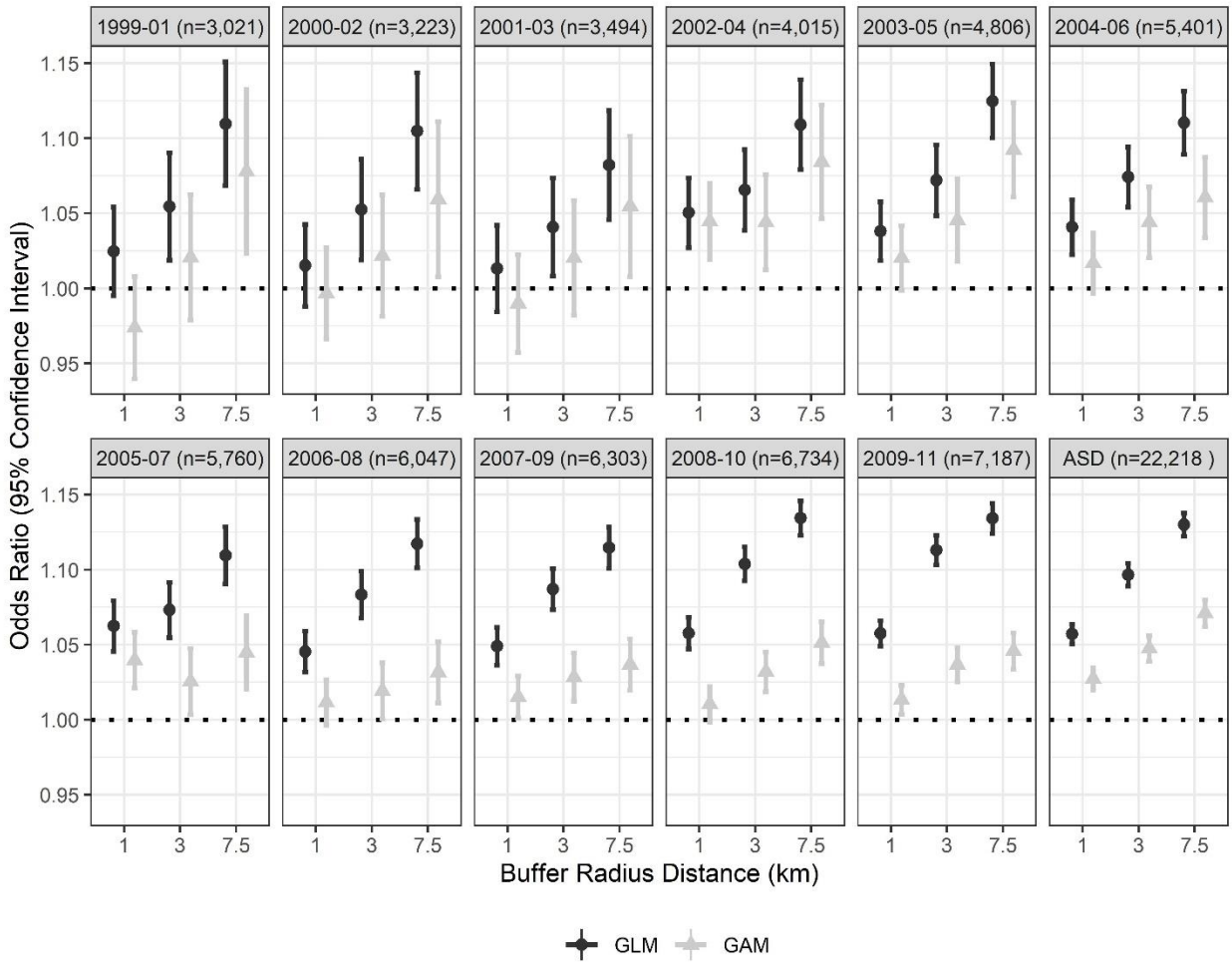

Figure 2.4: Adjusted odds ratios (95% confidence intervals) of time-stratified analyses for the association between atrial septal defects (ASD) and an increase in unconventional natural gas developments (UNGD) density, Texas, 1999-2011. Models are separated by generalized linear models (GLM) and generalized additive models (GAM). Odds ratios indicate an increase of 1 well per km^2 area (measured on a continuous scale), equating to 1, 9, and 56 UNGD wells per buffer radii of 1, 3, and 7.5km of maternal address at birth. SB=Spina Bifida, Anen=Anencephaly, CL=Cleft Lip with/without Palate, CP=Cleft Palate Only, Gas=Gastroschisis, Gas1=Gastroschisis (Age≤24), Gas2=Gastroschisis (Age>24), AVS=Aortic Valve Stenosis, ECD=Endocardial Cushion Defect, HLHS=Hypoplastic Left Heart Syndrome, PVAS=Pulmonary Valve Atresia/Stenosis, TGV=Transposition of Great Vessels, TOF=Tetralogy of Fallot, TVAS=Tricuspid Valve Atresia/Stenosis

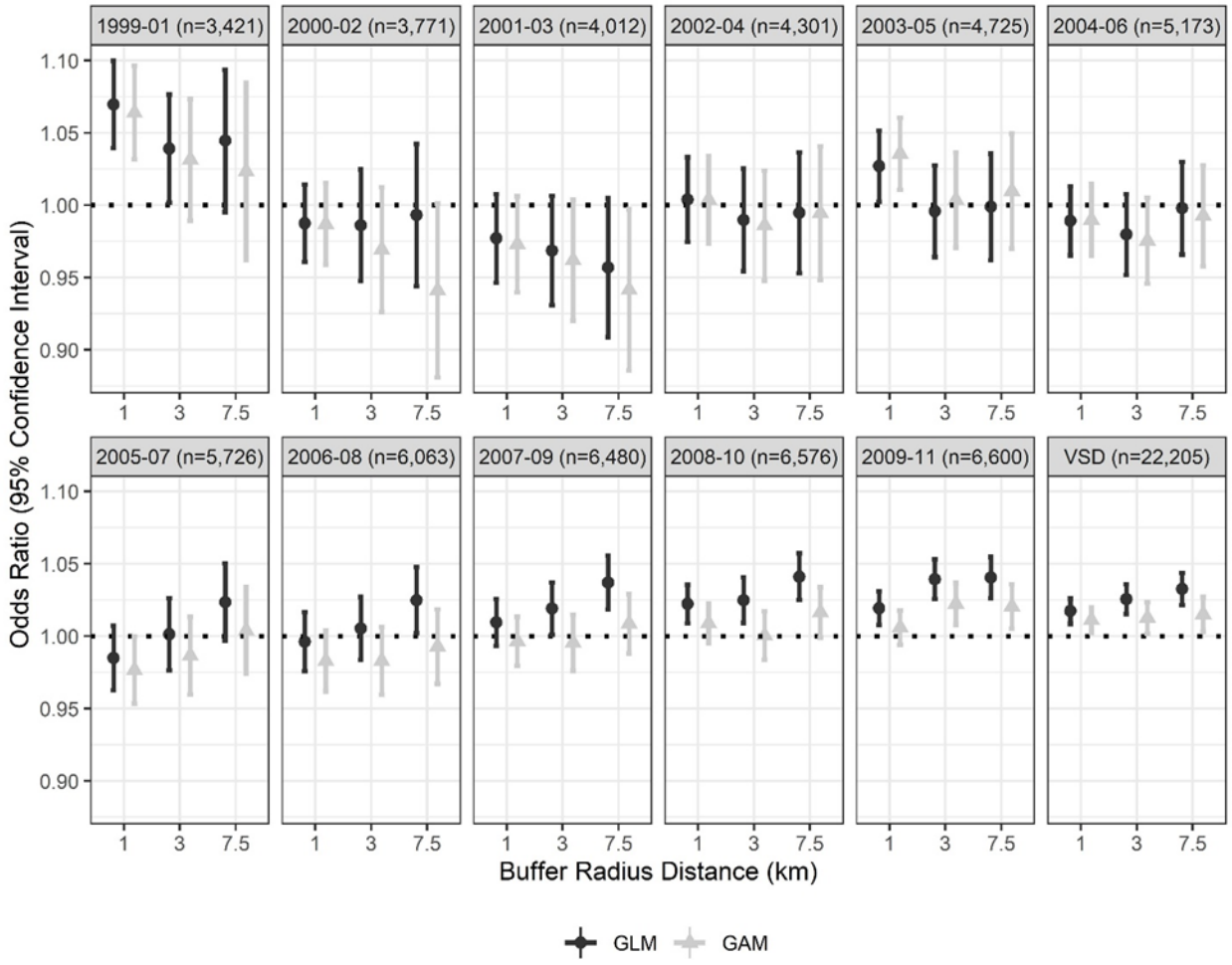

Figure 2.5: Adjusted odds ratios (95% confidence intervals) of time-stratified analyses for the association between ventricular septal defects (VSD) and an increase in unconventional natural gas developments (UNGD) density, Texas, 1999-2011. Models are separated by generalized linear models (GLM) and generalized additive models (GAM). Odds ratios indicate an increase of 1 well per km^2 area (measured on a continuous scale), equating to 1, 9, and 56 UNGD wells per buffer radii of 1, 3, and 7.5km of maternal address at birth. SB=Spina Bifida, Anen=Anencephaly, CL=Cleft Lip with/without Palate, CP=Cleft Palate Only, Gas=Gastroschisis, Gas1=Gastroschisis (Age≤24), Gas2=Gastroschisis (Age>24), AVS=Aortic Valve Stenosis, ECD=Endocardial Cushion Defect, HLHS=Hypoplastic Left Heart Syndrome, PVAS=Pulmonary Valve Atresia/Stenosis, TGV=Transposition of Great Vessels, TOF=Tetralogy of Fallot, TVAS=Tricuspid Valve Atresia/Stenosis

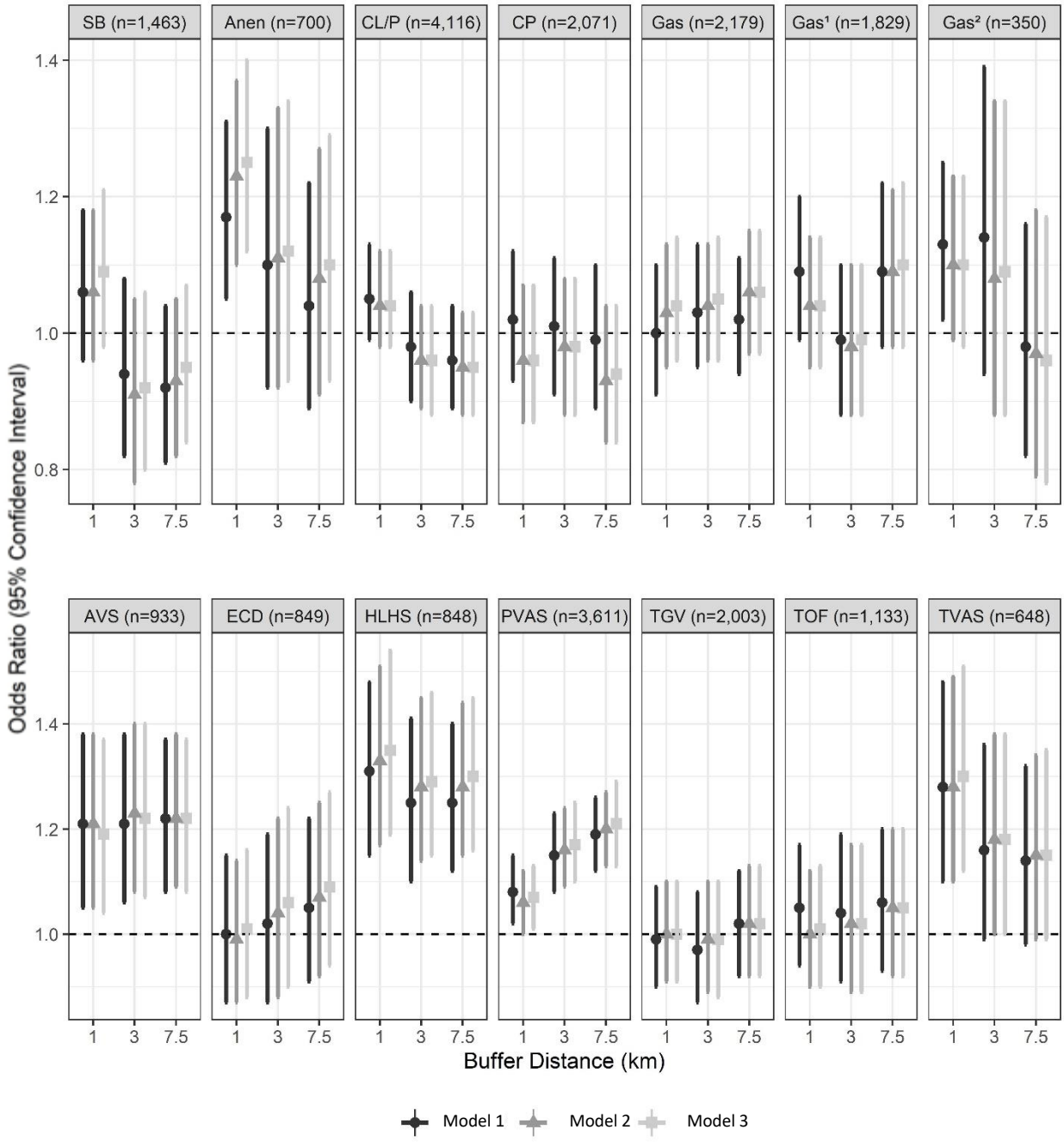

Figure 2.6: Odds ratios (95% confidence intervals) for the association between birth defects and an increase in unconventional natural gas developments (UNGD) density, Texas, 1999-2011. UNGD density was evaluated as 5th to 95th percentile range increase using generalized additive models (GAM) for 1, 3, and 7.5km buffer radii. Nested models were used to observe effects from risk factors. Model 1 only adjusted for UNGD density, Model 2 (maternal characteristics) adjusted for UNGD density, maternal smoking, plurality, maternal age, race/ethnicity, and education status, and Model 3 adjusted for adjusted for UNGD density, maternal characteristics, median income, urban indicator, and average daily vehicle miles

traveled for trucks by county. Gas=Gastroschisis, Gas1=Gastroschisis (Age≤24), Gas2=Gastroschisis (Age>24), AVS=Aortic Valve Stenosis, ECD=Endocardial Cushion Defect, HLHS=Hypoplastic Left Heart Syndrome, PVAS=Pulmonary Valve Atresia/Stenosis, TGV=Transposition of Great Vessels, TOF=Tetralogy of Fallot, TVAS=Tricuspid Valve Atresia/Stenosis

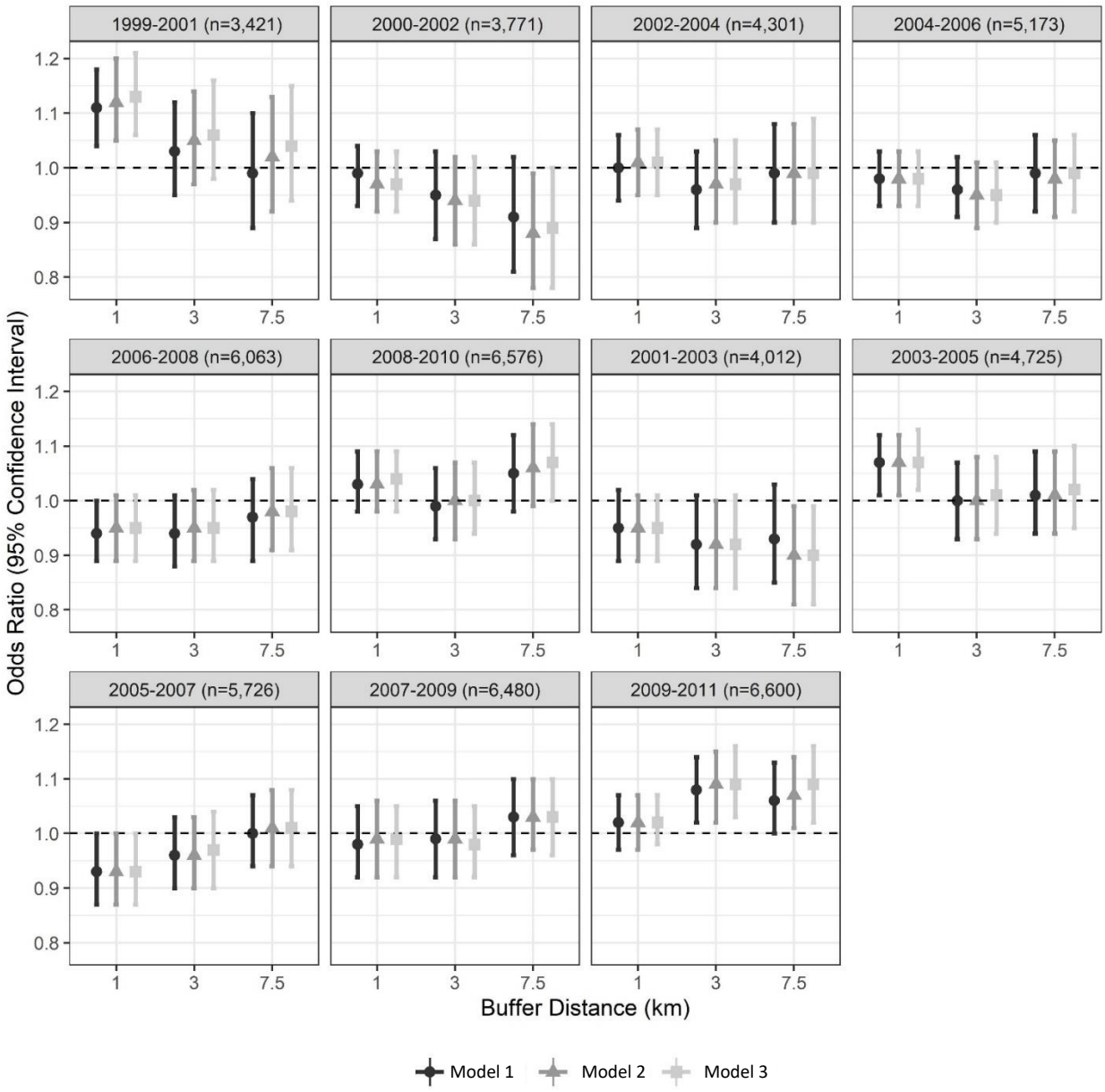

Figure 2.7: Odds ratios (95% confidence intervals) for the association between ventricular septal defects (VSD) and an increase in unconventional natural gas developments (UNGD) density, Texas, 1999-2011. UNGD density was evaluated as 5th to 95th percentile range increase using generalized additive models (GAM) for 1, 3, and 7.5km buffer radii. Nested models were used to observe effects from risk factors. Model 1 only adjusted for UNGD density, Model 2 (maternal characteristics) adjusted for UNGD density, maternal smoking, plurality, maternal age, race/ethnicity, and education status, and Model 3 adjusted for adjusted for UNGD density, maternal characteristics, median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Gas=Gastroschisis, Gas1=Gastroschisis (Age≤24), Gas2=Gastroschisis (Age>24), AVS=Aortic Valve Stenosis, ECD=Endocardial Cushion Defect, HLHS=Hypoplastic Left Heart Syndrome, PVAS=Pulmonary Valve Atresia/Stenosis,

TGV=Transposition of Great Vessels, TOF=Tetralogy of Fallot, TVAS=Tricuspid Valve Atresia/Stenosis

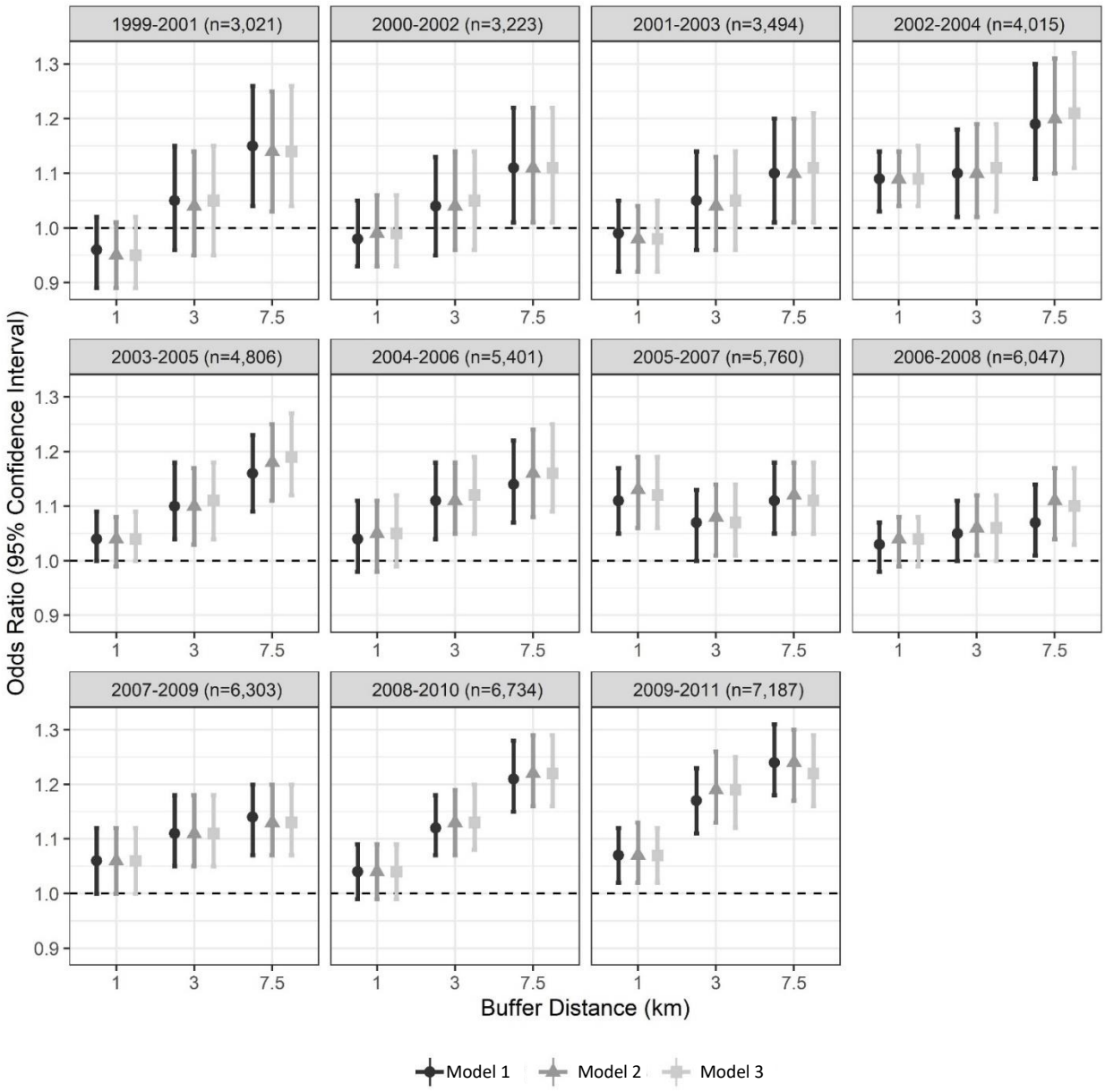

Figure 2.8: Odds ratios (95% confidence intervals) for the association between atrial septal defects (ASD) and an increase in unconventional natural gas developments (UNGD) density, Texas, 1999-2011. UNGD density was evaluated as 5th to 95th percentile range increase using generalized additive models (GAM) for 1, 3, and 7.5km buffer radii. Nested models were used to observe effects from risk factors. Model 1 only adjusted for UNGD density, Model 2 (maternal characteristics) adjusted for UNGD density, maternal smoking, plurality, maternal age, race/ethnicity, and education status, and Model 3 adjusted for adjusted for UNGD density, maternal characteristics, median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Gas=Gastroschisis, Gas1=Gastroschisis (Age≤24), Gas2=Gastroschisis (Age>24), AVS=Aortic Valve Stenosis, ECD=Endocardial Cushion Defect, HLHS=Hypoplastic Left Heart Syndrome, PVAS=Pulmonary Valve Atresia/Stenosis,

TGV=Transposition of Great Vessels, TOF=Tetralogy of Fallot, TVAS=Tricuspid Valve Atresia/Stenosis

Table 2.1: Characteristics of Texas birth defect cases and controls, n (%), born in 1999-2011

Maternal and Environmental Characteristics	Neural Tube (n=2,157)	Congenital Heart (n=42,445)	Orofacial Clefts (n=6,174)	Gastroschisis (n=2,179)	Controls (n=642,399)
Infant Sex					
Male	1,072 (49.7)	21,010 (49.5)	3,425 (55.5)	1,134 (52.0)	325,422 (50.7)
Female	1,081 (50.1)	21,435 (50.5)	2,749 (44.5)	1,045 (48.0)	316,977 (49.3)
Unknown	4 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Maternal Age					
11-19	314 (14.6)	5,397 (12.7)	863 (14.0)	934 (42.9)	85,578 (13.3)
20-24	601 (27.9)	11,176 (26.3)	1,739 (28.2)	895 (41.1)	175,452 (27.3)
25-29	587 (27.2)	11,230 (26.5)	1,609 (26.1)	251 (11.5)	174,373 (27.1)
30-34	445 (20.6)	8,912 (21.0)	1,239 (20.1)	72 (3.3)	133,203 (20.7)
35-39	173 (8.0)	4,625 (10.9)	568 (9.2)	23 (1.1)	60,830 (9.5)
40-58	37 (1.7)	1,105 (2.6)	156 (2.5)	4 (0.2)	12,963 (2.0)
Smoke During Pregnancy					
Yes	98 (4.5)	2,467 (5.8)	463 (7.5)	179 (8.2)	35,110 (5.5)
No	2,059 (95.5)	39,978 (94.2)	5,711 (92.5)	2,000 (91.8)	607,289 (94.5)
Plurality of Pregnancy					
Singleton	2,061 (95.5)	39,412 (92.9)	5,972 (96.7)	2,143 (98.3)	623,568 (97.1)
Two or more fetuses	96 (4.5)	3,033 (7.1)	202 (3.3)	36 (1.7)	18,831 (2.9)
Race/ Ethnicity					
White non-Hispanic	670 (31.1)	14,695 (34.6)	2,411 (39.1)	774 (35.5)	228,171 (35.5)
Black non-Hispanic	183 (8.5)	4,647 (10.9)	465 (7.5)	153 (7.0)	74,332 (11.6)
Hispanic	1,260 (58.4)	21,649 (51.0)	3,012 (48.8)	1206 (55.3)	312,065 (48.6)
Other non-Hispanic	44 (2.0)	1,454 (3.4)	286 (4.6)	46 (2.1)	27,831 (4.3)
Education Completed					
< High School	793 (36.8)	12,858 (30.3)	1,968 (31.9)	884 (40.6)	186,858 (29.1)

High School Graduate	630 (29.2)	12,382 (29.2)	1,862 (30.2)	772 (35.4)	180,747 (28.1)
>High School	734 (34.0)	17,205 (40.5)	2,344 (38.0)	523 (24.0)	274,794 (42.8)
Urbanization					
Rural	168 (7.8)	3,368 (7.9)	593 (9.6)	224 (10.3)	55,213 (8.6)
Urban	1,989 (92.2)	39,077 (92.1)	5,581 (90.4)	1,955 (89.7)	587,186 (91.4)
Average Truck Daily Vehicle Miles Traveled (DVMT), mean ± SD	2,061,198 ± 1,765,104	1,967,701 ± 1,726,739	2,025,038 ± 1,782,341	1,938,612 ± 1,747,816	2,127,171 ±1,822,098
Household Median Income ($1000), median ± SD	37.4 ± 20.6	39.0 ± 24.2	39.4 ± 24.3	36.8 ± 17.5	40.5 ± 24.6

Table 2.2: Number of cases and controls by birth defect within 1, 3, and 7.5km of maternal address at birth, Texas, 1999-2011.

Buffer Size	1 KM				3 KM				7.5 KM			
Category	**Ref**	**Tertile 1**	**Tertile 2**	**Tertile 3**	**Ref**	**Tertile 1**	**Tertile 2**	**Tertile 3**	**Ref**	**Tertile 1**	**Tertile 2**	**Tertile 3**
Number of Wells	0	1	2-4	5-40	0	1-12	13-30	31-226	0	1-57	58-136	136-1189
Anencephaly (Cases=700; Controls=2,956)												
Number of cases / controls *	648 / 2,548	12 / 148	21 / 155	19 / 105	532 / 1,967	118 / 682	26 / 185	24 / 122	348 / 1,282	270 / 1,226	51 / 281	31 / 167
UNGD OR (CI)	-	0.72 (0.41, 1.29)	1.02 (0.66, 1.59)	2.94 (1.83, 4.75)	-	1.06 (0.86, 1.30)	0.38 (0.25, 0.57)	2.35 (1.54, 3.58)	-	0.98 (0.83, 1.16)	0.88 (0.65, 1.19)	1.52 (1.04, 2.22)
Spina Bifida (Cases=1,463; Controls=2,956)												
Number of cases / controls *	1,344 / 2,548	45 / 148	41 / 155	33 / 105	1,083 / 1,967	283 / 682	57 / 185	40 / 122	719 / 1,282	573 / 1,226	126 / 281	45 / 167
UNGD OR (CI)	-	1.37 (1.01, 1.86)	0.94 (0.69, 1.29)	2.09 (1.47, 2.99)	-	1.25 (1.10, 1.43)	0.45 (0.34, 0.59)	1.73 (1.26, 2.39)	-	0.94 (0.84, 1.06)	1.07 (0.88, 1.30)	0.95 (0.70, 1.3)
Cleft Palate Only (Case=2,071; Control=5,664)												
Number of cases / controls *	1,917/ 4,833	52/310	57/311	45/210	1,576/ 3,723	335/ 1,326	95/363	65/252	1,027 / 2,416	821/ 2,367	142/535	81/346
UNGD	-	0.75	0.61	0.88	-	0.79	1.04	0.90		1.03	0.95	0.80

OR (CI)		(0.57, 0.99)	(0.47, 0.79)	(0.65, 1.18)		(0.70, 0.89)	(0.84, 1.28)	(0.70, 1.15)		(0.93, 1.13)	(0.80, 1.14)	(0.64, 1.01)
Cleft Lip With/Without Palate (Case=4,116; Control= 8,567)												
Number of cases / controls *	3,821/ 7,295	104/458	112/490	79/324	3,158/ 5,618	679/ 1,969	164/553	115/427	2,119 / 3,680	1,586/ 3,566	263/755	148/566
UNGD OR (CI)	-	1.10 (0.90, 1.34)	0.99 (0.82, 1.19)	1.15 (0.92, 1.44)	-	0.92 (0.85, 1.00)	0.89 (0.76, 1.04)	0.98 (0.81, 1.18)	-	0.91 (0.85, 0.97)	0.76 (0.67, 0.87)	0.97 (0.82, 1.15)
Gastroschisis (Case=2,179; Control= 4,583)												
Number of cases / controls *	1,996/ 3,959	65/230	67/242	51/152	1,627/ 3,025	402/ 1,076	90/286	60/196	1,098 / 1,984	845/ 1,913	147/433	89/253
UNGD OR (CI)	-	0.95 (0.74, 1.21)	0.88 (0.69, 1.12)	1.27 (0.96, 1.69)	-	0.92 (0.82, 1.02)	1.12 (0.90, 1.39)	1.21 (0.93, 1.58)	-	0.84 (0.77, 0.92)	0.77 (0.65, 0.92)	1.31 (1.05, 1.63)
Gastroschisis (Age≤24) (Case=1,829; Control= 3,827)												
Number of cases / controls *	1,683/ 3,274	58/203	50/219	38/141	1,376/ 2,530	334/88 2	71/244	48/181	930/ 1,618	713/ 1,662	116/329	70/228
UNGD OR (CI)	-	1.04 (0.80, 1.36)	0.94 (0.70, 1.25)	1.38 (0.99, 1.91)	-	1.21 (1.08, 1.37)	0.71 (0.55, 0.90)	0.85 (0.64, 1.14)	-	0.98 (0.89, 1.09)	0.88 (0.73, 1.07)	1.13 (0.88, 1.45)
Gastroschisis (Age>24) (Case=350; Control= 704)												
Number of cases	313/ 613	7/28	17/40	13/23	251/ 473	68/152	19/50	12/29	168/ 319	132/281	31/67	19/37

/ controls *												
UNGD OR (CI)	-	2.21 (1.00, 4.92)	1.54 (0.87, 2.73)	3.19 (1.77, 5.73)	-	1.07 (0.81, 1.41)	1.52 (0.93, 2.46)	0.98 (0.50, 1.91)	-	0.92 (0.71, 1.18)	1.40 (0.93, 2.12)	1.45 (0.85, 2.47)
Atrial Septal Defects (Case=22,218; Control= 44,586)												
Number of cases / controls *	19,536/ 38,639	922/ 2,030	1,018/ 2,165	742/ 1,752	14,256/30,283	5,179/ 9,557	1,609/ 2,528	1,174/ 2,217	7,755/ 20,070	10,286/ 18,106	2,533/ 3,576	1,644/ 2,834
UNGD OR (CI)	-	1.55 (1.45, 1.66)	1.78 (1.66, 1.90)	1.66 (1.54, 1.79)	-	1.54 (1.49, 1.59)	1.99 (1.88, 2.10)	2.03 (1.90, 2.15)	-	1.73 (1.68, 1.79)	2.37 (2.26, 2.48)	2.62 (2.48, 2.77)
Aortic Valve Stenosis (Case=933; Control=7,245)												
Number of cases / controls *	835/ 6,180	32/384	33/378	33/303	675/ 4,739	173/ 1,680	40/473	45/353	424/ 3,091	368/ 3,033	88/669	53/452
UNGD OR (CI)	-	1.37 (0.96, 1.96)	1.51 (1.06, 2.15)	1.90 (1.33, 2.71)	-	1.15 (0.98, 1.36)	1.05 (0.76, 1.44)	2.07 (1.53, 2.82)	-	1.05 (0.91, 1.21)	1.67 (1.32, 2.10)	1.91 (1.43, 2.56)
Endocardial Cushion Defect (Case=849; Control= 7,245)												
Number of cases / controls *	783/ 6,180	22/384	26/378	18/303	627/ 4,739	156/ 1,680	40/473	26/353	412/ 3,091	333/ 3,033	75/669	29/452
UNGD OR (CI)	-	1.00	1.23	1.09	-	1.12	1.11	1.32	-	0.95	1.35	1.22

		(0.65, 1.54)	(0.83, 1.83)	(0.68, 1.75)		(0.94, 1.34)	(0.81, 1.54)	(0.89, 1.97)		(0.82, 1.1)	(1.05, 1.74)	(0.83, 1.78)
Hypoplastic Left Heart Syndrome (Case=848; Control= 7,245)												
Number of cases / controls *	406/ 3,091	321/ 3,033	74/669	47/452	612/ 4,739	148/ 1,680	52/473	36/353	406/ 3,091	321/ 3,033	74/669	47/452
UNGD OR (CI)	-	0.97 (0.63, 1.50)	1.81 (1.29, 2.55)	2.00 (1.39, 2.86)	-	1.08 (0.90, 1.30)	1.52 (1.14, 2.02)	1.81 (1.29, 2.55)	-	0.92 (0.79, 1.06)	1.31 (1.02, 1.69)	1.98 (1.45, 2.70)
Pulmonary Valve Atresia/Stenosis (Case=3,611; Control=7,245)												
Number of cases / controls *	3,260/ 6,180	118/384	135/378	98/303	2,589/ 4,739	688/ 1,680	195/473	139/353	1,696 / 3,091	1,413/ 3,033	313/669	189/452
UNGD OR (CI)	-	1.30 (1.08, 1.56)	1.49 (1.25, 1.78)	1.36 (1.10, 1.66)	-	1.19 (1.10, 1.30)	1.30 (1.12, 1.51)	1.66 (1.40, 1.98)	-	1.01 (0.94, 1.09)	1.36 (1.21, 1.54)	1.85 (1.58, 2.15)
Transposition of Great Vessels (Case=2,003 Control=7,245)												
Number of cases / controls *	1,855/ 6,180	47/384	58/378	43/303	1,529/ 4,739	341/ 1,680	78/473	55/353	1,000 / 3,091	803/ 3,033	130/669	70/452
UNGD OR (CI)	-	0.93 (0.69, 1.24)	1.19 (0.91, 1.55)	1.06 (0.78, 1.45)	-	0.99 (0.88, 1.11)	0.89 (0.70, 1.11)	1.05 (0.80, 1.38)	-	0.92 (0.83, 1.01)	0.96 (0.80, 1.15)	1.07 (0.83, 1.36)
Tetralogy of Fallot (Case=1,133; Control=7,245)												
Number of cases	1,045/ 6,180	34/384	28/378	26/303	854/ 4,739	191/ 1,680	59/473	29/353	531/ 3,091	475/ 3,033	83/669	44/452

/ controls *												
UNGD OR (CI)	-	1.17 (0.83, 1.65)	0.91 (0.63, 1.34)	0.98 (0.66, 1.45)	-	0.99 (0.85, 1.16)	1.13 (0.87, 1.48)	0.88 (0.61, 1.29)	-	1.06 (0.93, 1.20)	1.12 (0.89, 1.42)	1.23 (0.90, 1.68)
Tricuspid Valve Atresia/Stenosis (Case=648, Control= 7,245)												
Number of cases / controls *	582/ 6,180	20/384	28/378	18/303	474/ 4,739	117/ 1,680	32/473	25/353	308/ 3,091	268/ 3,033	50/669	22/452
UNGD OR (CI)	-	1.21 (0.77, 1.90)	1.73 (1.17, 2.55)	1.39 (0.86, 2.23)	-	1.10 (0.90, 1.35)	1.18 (0.82, 1.70)	1.52 (1.01, 2.29)	-	1.01 (0.85, 1.19)	1.12 (0.83, 1.52)	1.12 (0.72, 1.74)
Ventricular Septal Defects (Case=22,205, Control= 44,586)												
Number of cases / controls *	20,391/ 38,666	622/ 2,035	693/ 2,167	499/ 1,718	16,239/30,281	4,171/ 9,539	1,086/ 2,566	709/ 2,199	10,51/ 20,036	8,947/ 18,147	1,834/ 3,588	909/ 2,815
UNGD OR (CI)	-	1.01 (0.93, 1.09)	1.28 (1.18, 1.38)	1.14 (1.04, 1.25)	-	1.10 (1.06, 1.13)	1.15 (1.08, 1.22)	1.17 (1.08, 1.27)	-	1.04 (1.01, 1.07)	1.24 (1.17, 1.30)	1.23 (1.14, 1.31)

Table 2.3. Stratified models of unconventional natural gas developments (UNGD) odds ratios (95% confidence intervals) by race/ethnicity (Hispanic/non-Hispanic) and socioeconomic status (block median household income)

Buffer Radius		1km			3km			7.5km		
Tertile	n	Tertile 1	Tertile 2	Tertile 3	Tertile 1	Tertile 2	Tertile 3	Tertile 1	Tertile 2	Tertile 3
Anencephaly (Cases=700; Controls=2,956)										
Hispanic	424	0.54 (0.22, 1.31)	1.31 (0.74, 2.32)	6.09 (3.22, 11.52)	1.14 (0.87, 1.51)	0.19 (0.11, 0.32)	4.04 (2.36, 6.93)	0.85 (0.68, 1.07)	0.55 (0.36, 0.84)	3.41 (2.05, 5.69)
Non-Hispanic	276	0.94 (0.43, 2.07)	0.79 (0.39, 1.61)	1.61 (0.75, 3.47)	0.84 (0.62, 1.15)	1.05 (0.51, 2.16)	1.22 (0.62, 2.40)	1.01 (0.77, 1.32)	1.01 (0.60, 1.69)	0.86 (0.49, 1.51)
Below or equal to median Income	419	0.28 (0.07, 1.14)	1.33 (0.74, 2.37)	5.13 (2.64, 9.99)	1.23 (0.92, 1.65)	0.32 (0.20, 0.53)	3.31 (1.89, 5.80)	0.96 (0.77, 1.20)	1.22 (0.80, 1.87)	1.62 (0.98, 2.65)
Above median income	281	1.00 (0.51, 1.97)	0.76 (0.37, 1.55)	1.96 (0.94, 4.09)	0.92 (0.67, 1.26)	0.31 (0.14, 0.67)	1.80 (0.92, 3.53)	1.00 (0.76, 1.31)	0.68 (0.41, 1.14)	0.96 (0.51, 1.81)
Spina Bifida (Cases=1,463; Controls=2,956)										
Hispanic	839	1.31 (0.87, 1.97)	1.02 (0.64, 1.60)	3.94 (2.49, 6.23)	1.63 (1.36, 1.95)	0.23 (0.16, 0.35)	3.50 (2.31, 5.30)	1.02 (0.87, 1.19)	0.89 (0.67, 1.17)	2.44 (1.60, 3.73)
Non-Hispanic	624	1.57 (0.98, 2.52)	0.84 (0.54, 1.31)	1.14 (0.62, 2.08)	0.83 (0.67, 1.01)	1.31 (0.87, 1.98)	0.90 (0.53, 1.51)	0.85 (0.71, 1.02)	1.19 (0.88, 1.61)	0.50 (0.32, 0.78)
Below or equal to median Income	796	0.70 (0.37, 1.33)	0.59 (0.28, 1.26)	1.36 (0.59, 3.11)	0.88 (0.64, 1.21)	0.50 (0.27, 0.92)	1.13 (0.53, 2.39)	0.87 (0.65, 1.15)	1.09 (0.69, 1.71)	0.70 (0.37, 1.35)

Above median income	667	1.39 (0.69, 2.81)	0.86 (0.48, 1.57)	0.57 (0.27, 1.18)	1.11 (0.80, 1.52)	1.01 (0.56, 1.81)	0.57 (0.28, 1.13)	0.79 (0.60, 1.03)	1.26 (0.79, 2.03)	0.50 (0.26, 0.93)
Cleft Palate Only (Case=2,071; Control=5,664)										
Hispanic	922	0.68 (0.45, 1.04)	0.85 (0.56, 1.28)	0.55 (0.32, 0.94)	0.65 (0.53, 0.78)	1.30 (0.96, 1.76)	1.39 (0.92, 2.09)	0.96 (0.83, 1.10)	0.78 (0.60, 1.01)	1.23 (0.83, 1.84)
Non-Hispanic	1,149	0.76 (0.52, 1.12)	0.51 (0.36, 0.72)	1.12 (0.78, 1.61)	0.79 (0.67, 0.92)	0.90 (0.67, 1.21)	0.80 (0.58, 1.10)	1.04 (0.92, 1.18)	1.01 (0.78, 1.30)	0.72 (0.54, 0.95)
Below or equal to median Income	1,060	0.50 (0.32, 0.77)	0.78 (0.53, 1.14)	0.86 (0.55, 1.32)	0.92 (0.77, 1.09)	0.89 (0.67, 1.19)	1.03 (0.71, 1.48)	0.90 (0.78, 1.03)	1.06 (0.83, 1.34)	1.09 (0.79, 1.50)
Above median income	1,011	1.14 (0.79, 1.65)	0.45 (0.31, 0.67)	0.86 (0.56, 1.31)	0.70 (0.59, 0.83)	1.27 (0.93, 1.74)	0.83 (0.58, 1.18)	1.18 (1.03, 1.35)	0.87 (0.66, 1.14)	0.65 (0.47, 0.91)
Cleft Lip With/Without Palate (Case=4,116; Control= 8,567)										
Hispanic	2,097	0.68 (0.44, 1.05)	0.72 (0.46, 1.12)	0.64 (0.36, 1.13)	0.64 (0.52, 0.78)	0.72 (0.50, 1.05)	0.60 (0.37, 0.95)	0.68 (0.58, 0.80)	0.62 (0.46, 0.84)	0.63 (0.42, 0.96)
Non-Hispanic	2,019	0.79 (0.56, 1.13)	0.69 (0.50, 0.97)	0.74 (0.51, 1.08)	0.81 (0.68, 0.95)	0.65 (0.48, 0.89)	0.76 (0.55, 1.06)	0.85 (0.74, 0.98)	0.72 (0.55, 0.93)	0.69 (0.52, 0.92)
Below or equal to median Income	2,334	0.68 (0.47, 1.00)	0.75 (0.51, 1.11)	0.55 (0.33, 0.94)	0.62 (0.52, 0.75)	0.76 (0.55, 1.06)	0.55 (0.36, 0.85)	0.70 (0.60, 0.81)	0.72 (0.56, 0.94)	0.57 (0.39, 0.82)
Above median income	1,782	0.83 (0.55, 1.25)	0.69 (0.48, 0.99)	0.84 (0.56, 1.26)	0.87 (0.72, 1.04)	0.62 (0.44, 0.88)	0.84 (0.60, 1.19)	0.86 (0.74, 1.01)	0.63 (0.46, 0.84)	0.78 (0.57, 1.06)
Gastroschisis (Case=2,179; Control= 4,583)										

Hispanic	1,206	0.93 (0.52, 1.66)	0.45 (0.25, 0.82)	2.01 (1.03, 3.92)	0.83 (0.62, 1.10)	0.74 (0.44, 1.25)	1.10 (0.57, 2.12)	0.68 (0.54, 0.87)	0.73 (0.48, 1.12)	0.87 (0.47, 1.59)
Non-Hispanic	973	0.60 (0.35, 1.03)	1.52 (0.97, 2.39)	0.76 (0.43, 1.34)	0.77 (0.60, 0.98)	1.09 (0.70, 1.70)	0.90 (0.56, 1.44)	0.86 (0.70, 1.06)	0.95 (0.65, 1.37)	1.19 (0.79, 1.77)
Below or equal to median Income	1,246	0.76 (0.45, 1.28)	0.96 (0.56, 1.64)	1.51 (0.80, 2.84)	0.75 (0.58, 0.97)	0.75 (0.46, 1.24)	1.20 (0.66, 2.15)	0.62 (0.50, 0.78)	0.71 (0.48, 1.05)	1.23 (0.74, 2.06)
Above median income	933	0.75 (0.42, 1.32)	0.94 (0.56, 1.56)	0.86 (0.49, 1.53)	0.88 (0.68, 1.14)	1.17 (0.73, 1.88)	0.83 (0.50, 1.38)	0.98 (0.78, 1.22)	1.02 (0.68, 1.51)	0.99 (0.64, 1.55)
Gastroschisis (Age≤24) (Case=1,829; Control= 3,827)										
Hispanic	1,056	1.06 (0.60, 1.88)	0.73 (0.39, 1.39)	1.30 (0.62, 2.73)	0.83 (0.63, 1.10)	0.50 (0.30, 0.84)	0.94 (0.46, 1.93)	0.65 (0.52, 0.83)	0.46 (0.30, 0.69)	1.09 (0.56, 2.12)
Non-Hispanic	773	0.76 (0.44, 1.30)	0.85 (0.52, 1.39)	0.75 (0.40, 1.39)	0.87 (0.67, 1.12)	0.72 (0.45, 1.17)	0.87 (0.52, 1.45)	0.80 (0.64, 1.00)	1.00 (0.67, 1.50)	1.03 (0.66, 1.59)
Below or equal to median Income	1,108	1.03 (0.59, 1.78)	0.92 (0.54, 1.59)	1.31 (0.68, 2.51)	0.75 (0.58, 0.98)	0.46 (0.28, 0.75)	1.32 (0.71, 2.46)	0.59 (0.47, 0.73)	0.62 (0.42, 0.92)	1.23 (0.71, 2.10)
Above median income	721	0.74 (0.42, 1.30)	0.69 (0.39, 1.23)	0.65 (0.33, 1.29)	1.06 (0.81, 1.39)	0.81 (0.49, 1.32)	0.66 (0.37, 1.18)	0.99 (0.79, 1.26)	0.78 (0.50, 1.21)	0.95 (0.58, 1.55)
Gastroschisis (Age>24) (Case=350; Control= 704)										
Hispanic	150	1.69 (0.37, 7.66)	1.74 (0.49, 6.27)	2.55 (0.78, 8.33)	0.89 (0.45, 1.75)	1.82 (0.57, 5.79)	1.10 (0.30, 4.01)	0.57 (0.31, 1.04)	1.00 (0.40, 2.55)	1.08 (0.33, 3.58)

Non-Hispanic	200	0.97 (0.23, 4.07)	1.77 (0.73, 4.31)	1.63 (0.46, 5.76)	0.91 (0.51, 1.62)	1.47 (0.61, 3.55)	1.04 (0.36, 3.01)	0.84 (0.51, 1.37)	1.66 (0.75, 3.65)	1.70 (0.67, 4.30)
Below or equal to median Income	153	1.15 (0.29, 4.55)	2.29 (0.77, 6.85)	1.98 (0.62, 6.38)	1.06 (0.54, 2.07)	1.32 (0.44, 3.94)	1.18 (0.36, 3.80)	0.61 (0.34, 1.11)	1.05 (0.43, 2.56)	1.16 (0.37, 3.60)
Above median income	197	1.69 (0.36, 7.91)	1.38 (0.52, 3.61)	2.54 (0.72, 8.95)	0.78 (0.44, 1.40)	1.87 (0.73, 4.79)	1.05 (0.34, 3.24)	0.78 (0.47, 1.30)	1.69 (0.73, 3.94)	1.71 (0.66, 4.43)
Atrial Septal Defects (Case=22,218; Control= 44,586)										
Hispanic	10,960	1.30 (1.14, 1.49)	1.24 (1.08, 1.43)	1.25 (1.06, 1.47)	1.43 (1.34, 1.53)	1.86 (1.65, 2.09)	1.80 (1.56, 2.08)	1.69 (1.59, 1.80)	2.42 (2.19, 2.67)	2.72 (2.38, 3.12)
Non-Hispanic	11,258	0.97 (0.85, 1.10)	1.22 (1.09, 1.37)	0.98 (0.87, 1.11)	1.09 (1.03, 1.16)	1.40 (1.26, 1.55)	1.23 (1.11, 1.37)	1.19 (1.13, 1.26)	1.60 (1.46, 1.75)	1.52 (1.38, 1.67)
Below or equal to median Income	13,346	1.10 (0.97, 1.25)	0.99 (0.85, 1.14)	1.08 (0.99, 1.19)	1.56 (1.40, 1.73)	1.44 (1.27, 1.63)	1.07 (0.98, 1.18)	2.08 (1.90, 2.27)	1.78 (1.59, 2.00)	1.07 (0.97, 1.18)
Above median income	8,872	1.17 (1.02, 1.35)	1.46 (1.29, 1.65)	1.18 (1.03, 1.36)	1.30 (1.22, 1.39)	1.75 (1.57, 1.96)	1.45 (1.29, 1.63)	1.52 (1.44, 1.62)	1.97 (1.79, 2.18)	2.07 (1.86, 2.29)
Aortic Valve Stenosis (Case=933; Control=7,245)										
Hispanic	443	1.56 (0.87, 2.77)	1.41 (0.79, 2.50)	2.94 (1.78, 4.87)	0.99 (0.76, 1.28)	1.21 (0.75, 1.92)	3.55 (2.32, 5.43)	0.98 (0.80, 1.20)	1.22 (0.85, 1.75)	1.98 (1.25, 3.13)
Non-Hispanic	490	1.19 (0.73, 1.95)	1.40 (0.89, 2.21)	1.24 (0.75, 2.05)	1.24 (0.99, 1.56)	0.97 (0.62, 1.51)	1.26 (0.81, 1.98)	1.11 (0.91, 1.36)	1.95 (1.43, 2.66)	2.01 (1.37, 2.95)

Below or equal to median Income	496	1.14 (0.66, 1.98)	1.54 (0.91, 2.61)	3.84 (2.34, 6.31)	1.02 (0.80, 1.30)	1.59 (1.01, 2.52)	2.50 (1.65, 3.78)	1.06 (0.87, 1.28)	1.35 (0.97, 1.87)	2.44 (1.60, 3.72)
Above median income	437	1.65 (1.01, 2.68)	1.54 (0.95, 2.49)	1.34 (0.80, 2.24)	1.23 (0.97, 1.57)	0.77 (0.49, 1.23)	1.70 (1.07, 2.70)	0.94 (0.75, 1.17)	1.98 (1.42, 2.78)	1.52 (1.01, 2.30)
Endocardial Cushion Defect (Case=849; Control= 7,245)										
Hispanic	391	0.71 (0.32, 1.58)	1.38 (0.68, 2.81)	1.88 (0.98, 3.59)	0.93 (0.70, 1.23)	1.58 (1.01, 2.45)	1.89 (0.99, 3.58)	0.77 (0.62, 0.96)	1.41 (0.99, 2.01)	1.15 (0.60, 2.22)
Non-Hispanic	458	1.11 (0.66, 1.86)	1.23 (0.76, 1.98)	0.65 (0.32, 1.31)	1.27 (1.01, 1.60)	0.82 (0.51, 1.32)	1.12 (0.67, 1.85)	1.11 (0.91, 1.36)	1.27 (0.90, 1.81)	1.33 (0.83, 2.15)
Below or equal to median Income	485	0.95 (0.55, 1.65)	1.02 (0.55, 1.91)	2.63 (1.49, 4.64)	1.09 (0.86, 1.39)	1.81 (1.17, 2.80)	1.69 (1.02, 2.77)	0.88 (0.72, 1.07)	1.27 (0.92, 1.75)	1.88 (1.14, 3.08)
Above median income	364	0.89 (0.44, 1.82)	1.48 (0.88, 2.50)	0.43 (0.18, 1.05)	1.11 (0.84, 1.45)	0.69 (0.42, 1.14)	0.91 (0.46, 1.78)	0.93 (0.74, 1.18)	1.35 (0.90, 2.03)	0.75 (0.41, 1.40)
Hypoplastic Left Heart Syndrome (Case=848; Control= 7,245)										
Hispanic	368	1.97 (1.06, 3.67)	2.29 (1.26, 4.14)	2.49 (1.40, 4.43)	0.98 (0.73, 1.31)	1.94 (1.29, 2.93)	2.90 (1.64, 5.12)	0.79 (0.63, 0.99)	1.13 (0.76, 1.69)	2.97 (1.84, 4.78)
Non-Hispanic	480	0.60 (0.31, 1.16)	1.58 (1.04, 2.40)	1.56 (0.98, 2.49)	1.14 (0.90, 1.44)	1.25 (0.83, 1.87)	1.41 (0.92, 2.17)	1.03 (0.84, 1.26)	1.42 (1.03, 1.97)	1.65 (1.09, 2.49)
Below or equal to median Income	454	1.01 (0.56, 1.82)	2.22 (1.39, 3.57)	3.76 (2.28, 6.21)	0.93 (0.72, 1.20)	2.58 (1.75, 3.80)	1.61 (0.97, 2.70)	0.97 (0.79, 1.19)	1.06 (0.75, 1.52)	2.78 (1.79, 4.32)

Above median income	394	0.98 (0.50, 1.91)	1.56 (0.94, 2.60)	1.50 (0.88, 2.55)	1.26 (0.97, 1.64)	0.96 (0.62, 1.49)	2.12 (1.33, 3.38)	0.77 (0.61, 0.98)	1.62 (1.13, 2.32)	1.47 (0.94, 2.28)
Pulmonary Valve Atresia/Stenosis (Case=3,611; Control=7,245)										
Hispanic	1,819	1.05 (0.68, 1.62)	1.13 (0.72, 1.77)	1.05 (0.62, 1.75)	1.00 (0.81, 1.23)	1.09 (0.77, 1.54)	1.16 (0.70, 1.92)	0.92 (0.76, 1.10)	1.12 (0.83, 1.53)	1.03 (0.68, 1.58)
Non-Hispanic	1,792	0.87 (0.59, 1.29)	1.05 (0.74, 1.50)	0.70 (0.47, 1.04)	0.87 (0.73, 1.05)	0.77 (0.55, 1.09)	0.91 (0.66, 1.27)	0.74 (0.63, 0.86)	0.99 (0.75, 1.31)	1.00 (0.74, 1.35)
Below or equal to median Income	2,055	0.85 (0.58, 1.26)	0.94 (0.63, 1.38)	0.87 (0.56, 1.37)	0.93 (0.77, 1.12)	0.95 (0.69, 1.31)	0.96 (0.62, 1.47)	0.82 (0.69, 0.97)	1.04 (0.79, 1.37)	1.02 (0.70, 1.48)
Above median income	1,556	1.12 (0.74, 1.71)	1.29 (0.87, 1.92)	0.80 (0.52, 1.22)	0.96 (0.79, 1.18)	0.92 (0.64, 1.32)	1.05 (0.73, 1.50)	0.83 (0.70, 0.99)	1.15 (0.84, 1.57)	1.08 (0.78, 1.49)
Transposition of Great Vessels (Case=2,003 Control=7,245)										
Hispanic	1,001	1.03 (0.65, 1.62)	1.34 (0.87, 2.06)	1.51 (0.98, 2.33)	1.01 (0.85, 1.20)	1.04 (0.76, 1.43)	1.24 (0.78, 1.98)	0.82 (0.72, 0.94)	1.13 (0.89, 1.44)	1.10 (0.75, 1.63)
Non-Hispanic	1,002	0.86 (0.58, 1.28)	1.09 (0.78, 1.53)	0.78 (0.50, 1.20)	0.97 (0.82, 1.15)	0.76 (0.55, 1.06)	1.01 (0.72, 1.42)	1.02 (0.89, 1.16)	0.79 (0.60, 1.06)	1.14 (0.82, 1.56)
Below or equal to median Income	1,092	0.75 (0.49, 1.15)	1.10 (0.73, 1.67)	1.99 (1.30, 3.04)	0.97 (0.83, 1.15)	1.55 (1.14, 2.12)	0.91 (0.60, 1.38)	0.90 (0.79, 1.02)	0.90 (0.71, 1.15)	1.17 (0.80, 1.72)
Above median income	911	1.16 (0.77, 1.74)	1.28 (0.90, 1.81)	0.74 (0.47, 1.16)	0.95 (0.80, 1.14)	0.54 (0.38, 0.77)	1.21 (0.85, 1.74)	0.85 (0.73, 0.99)	0.94 (0.70, 1.26)	0.98 (0.71, 1.35)
Tetralogy of Fallot (Case=1,133; Control=7,245)										

Hispanic	477	1.69 (1.00, 2.86)	1.79 (1.06, 3.04)	1.91 (1.08, 3.37)	0.88 (0.68, 1.14)	1.64 (1.12, 2.40)	1.95 (1.15, 3.31)	1.03 (0.85, 1.26)	1.59 (1.15, 2.20)	1.33 (0.79, 2.25)
Non-Hispanic	656	0.77 (0.47, 1.26)	0.58 (0.33, 1.01)	0.64 (0.37, 1.11)	1.00 (0.81, 1.22)	0.89 (0.61, 1.30)	0.54 (0.31, 0.92)	1.03 (0.87, 1.22)	0.80 (0.57, 1.12)	1.18 (0.80, 1.75)
Below or equal to median Income	584	1.09 (0.68, 1.74)	1.24 (0.76, 2.02)	1.62 (0.88, 2.97)	0.94 (0.75, 1.17)	1.92 (1.33, 2.78)	0.94 (0.54, 1.61)	1.00 (0.84, 1.20)	1.19 (0.88, 1.61)	1.26 (0.76, 2.09)
Above median income	549	1.17 (0.69, 1.98)	0.60 (0.32, 1.14)	0.81 (0.48, 1.37)	0.92 (0.73, 1.16)	0.68 (0.46, 1.01)	0.90 (0.53, 1.52)	0.93 (0.77, 1.13)	0.87 (0.59, 1.29)	1.19 (0.79, 1.78)
Tricuspid Valve Atresia/Stenosis (Case=648, Control= 7,245)										
Hispanic	314	2.01 (1.08, 3.76)	2.76 (1.58, 4.80)	0.94 (0.34, 2.54)	1.07 (0.79, 1.44)	1.61 (0.99, 2.63)	1.47 (0.69, 3.15)	1.05 (0.83, 1.33)	1.35 (0.89, 2.04)	0.26 (0.06, 1.05)
Non-Hispanic	334	0.76 (0.37, 1.53)	1.28 (0.74, 2.20)	1.57 (0.91, 2.70)	1.12 (0.84, 1.49)	0.93 (0.54, 1.60)	1.45 (0.89, 2.36)	0.99 (0.78, 1.26)	0.93 (0.59, 1.45)	1.74 (1.08, 2.81)
Below or equal to median Income	364	1.33 (0.75, 2.35)	2.37 (1.42, 3.95)	1.07 (0.44, 2.63)	0.99 (0.75, 1.32)	2.09 (1.29, 3.37)	1.39 (0.75, 2.57)	1.01 (0.81, 1.26)	1.10 (0.75, 1.61)	1.00 (0.46, 2.15)
Above median income	284	1.10 (0.51, 2.37)	1.30 (0.70, 2.38)	1.35 (0.76, 2.39)	1.24 (0.91, 1.68)	0.69 (0.39, 1.22)	1.72 (0.99, 3.00)	0.92 (0.70, 1.19)	1.03 (0.62, 1.69)	1.23 (0.71, 2.12)
Ventricular Septal Defects (Case=22,205, Control= 44,586)										
Hispanic	12,099	0.88 (0.75, 1.02)	0.87 (0.73, 1.03)	0.87 (0.71, 1.07)	1.10 (0.97, 1.25)	0.97 (0.83, 1.14)	0.87 (0.71, 1.07)	1.20 (1.08, 1.33)	0.98 (0.85, 1.14)	0.86 (0.70, 1.06)

Non-Hispanic	10,106	0.72 (0.62, 0.84)	0.75 (0.65, 0.86)	0.62 (0.53, 0.72)	0.86 (0.80, 0.92)	0.87 (0.77, 0.98)	0.69 (0.61, 0.79)	0.87 (0.83, 0.92)	0.82 (0.74, 0.91)	0.78 (0.70, 0.88)
Below or equal to median Income	12,987	0.78 (0.67, 0.89)	0.76 (0.66, 0.88)	0.78 (0.67, 0.92)	0.83 (0.78, 0.89)	1.01 (0.90, 1.14)	0.82 (0.71, 0.95)	0.81 (0.76, 0.85)	1.08 (0.98, 1.19)	0.85 (0.75, 0.98)
Above median income	9,218	0.84 (0.72, 0.98)	0.90 (0.78, 1.04)	0.66 (0.56, 0.77)	0.94 (0.88, 1.00)	1.00 (0.88, 1.13)	0.79 (0.69, 0.90)	0.95 (0.90, 1.01)	0.98 (0.88, 1.09)	0.88 (0.78, 1.00)

CHAPTER 3

A Spatial Analysis of Birth Defects in Texas, 1999-2011

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ABSTRACT

Background: The etiologies of major birth defects are still unclear and few spatial analyses have been conducted in the United States. Spatial analyses of individual-level data can help elucidate environmental and social risk factors.

Methods: We used generalized additive models (GAM) to analyze 52,955 deduplicated cases of neural tube defects (NTD), congenital heart defects (CHD), gastroschisis, and orofacial cleft defects, and 642,399 controls born between 1999 and 2011 in Texas. The effect of geographic location was measured using a bivariable smooth term of geocoded birth address within a logistic regression framework. We calculated and mapped odds ratios (ORs) and 95% confidence intervals (CIs) for birth defects subtypes across Texas, and adjusted for maternal characteristics, environmental indicators, and community-level covariates. We also performed time-stratified spatiotemporal analyses for more prevalent birth defects.

Results: Location was significantly associated with crude odds of all birth defects except for hypoplastic left heart syndrome. After adjusting for maternal characteristics, environmental indicators, and community-level factors, ORs in many geographic areas were no longer statistically significant for most defects, especially CHDs. However, areas of significant and insignificant elevated risk remained for defects in all groups in North and South Texas, with ORs for ventricular septal defects increasing over time. Low risk of birth defects was often present in the northern part of East Texas.

Conclusion: Significant spatial patterns of birth defects were identified and varied depending on adjustment of different categories of covariates. Further investigation of areas with increased risks may aid in our understanding of birth defects.

Introduction

Spatial methods have been used to map and observe disease patterns. Studying disease distributions using geographic information systems can be a powerful tool for identifying spatial patterns and understanding the etiology of diseases where cases appear close together in space.[1–3]. Risk assessments based on spatially varying neighborhood risk factors, such as pollution, green space, and access to health care, may provide insight to the context for which diseases appear.[2,4] The use of individual-level data has become more common in spatial epidemiology and often addresses issues related to aggregated data, specifically that of artificial boundaries which is subject to the modifiable areal unit problem.[2,3,5–7]

Novel spatial methods can be utilized to better understand the largely unknown etiology of birth defects which affect 4-5% of births in Texas.[8] Predictors of birth defects are likely to be multifactorial and may include environmental and genetic factors.[9] Some spatial analyses have observed non-random geographic patterns of birth defects, and many studies in China identified environmental risk factors as possible teratogens.[10–16] Social factors such as insurance and socioeconomic status may also contribute to birth defect risk.[17–23] Studies have identified spatial variation of gastroschisis in Texas and other states, but to our knowledge there have been few large-scale US spatial studies on other birth defects.[12,24,25]

The objective of this study was to explore the spatial association between maternal residential location at time of birth and risk of neural tube defects (NTD), congenital heart defects (CHD), gastroschisis, and orofacial defects among deliveries in Texas from 1999 to 2011. We examined location at the individual-level to avoid known issues related to aggregated data and small sample sizes. Birth defects were separated into subtypes and we considered maternal characteristics, environmental indicators, and community-level factors within our

models. By comparing results of models adjusted for maternal predictors to results from models including environmental and social indicators, we aimed to disentangle the impacts from individual and community risk factors. With this approach, our study has the potential to generate new hypotheses for spatial factors associated with the observed patterns of different birth defect groups and guide further research on risk assessment.

Methods

Study Population

Data on cases of birth defects were obtained from the Texas Birth Defects Registry (TBDR), an active state-wide birth defects surveillance system at the Texas Department of Health of State Health Services (TDSHS). Cases included all pregnancy outcomes (live births, spontaneous fetal deaths, and pregnancy terminations) with a confirmed diagnosis of a birth defect prenatally or within one year after delivery between January 1, 1999 through December 31, 2011. The TBDR classifies birth defects using 6-digit codes originally derived from the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9CM) as modified by the British Pediatric Association (BPA, 1979), Centers for Disease Control and Prevention, and TBDR. Controls were selected from live births in Texas with no structural or chromosomal birth defects that were born in the same time period as cases, and were obtained from the Center for Health Statistics, also at the TDSHS.

We analyzed individual birth defect subtypes of NTDs, CHDs, and orofacial clefts. Among NTDs, we separately analyzed spina bifida (BPA code: 741.000-741.990) and anencephaly (740.000-740.080). CHDs were independently analyzed as transposition of the great vessels (TGV) (745.100-745.190), tetralogy of Fallot (TOF) (745.200, 746.840), ventricular

septal defects (VSD) (745.400-745.490), atrial septal defects (ASD) (745.510-745.590), endocardial cushion defects (ECD) (745.600-745.690), pulmonary valve atresia or stenosis (PVAS) (746.000-746.010), tricuspid valve atresia or stenosis (TVAS) (746.100, 746.106), aortic valve stenosis (AVS) (746.300), and hypoplastic left heart syndrome (HLHS) (746.700). Orofacial defects were separated into cleft palate only (749.00-749.090) and cleft lip with or without cleft palate (749.100-749.220). We stratified gastroschisis cases by maternal age (younger than 25 years, and 25 years and older) due to the critical importance of age as a risk factor.[12,26,27] If a child or fetus had more than one of the above birth defects, they were included in each relevant analysis.

We used unmatched spatially stratified sampling to select controls among births with no defects born between 1999-2011 in Texas.[28] Unlike taking a random sample across Texas which results in more control births included from densely populated areas and data sparseness in rural areas, we sampled a uniform distribution of controls. To do this, the study area was divided into equally sized grids and the number of controls in each grid was summed. Inverse probability weights were calculated for each selected control based on the ratio of selected controls to total controls in the relevant grid and used in the statistical analysis to account for the non-random sampling. The benefit of this control sampling approach is that data are distributed throughout the study area for providing stable effect estimates in the spatial analyses.

We applied a 1:2 ratio of cases to controls for defects. For CHDs, we used the same controls selected from the PVAS sample for ECD, HLHS, TGV, TOF, and TVAS. For NTDs, we used the same controls selected from the spina bifida sample for the anencephaly analysis. All other defects had controls individually selected based on the number of cases for that defect.

Cases and controls were excluded from the spatial analysis if the maternal address at delivery could not be successfully geocoded (8.0% and 9.0% respectively).

Statistical Analysis

Generalized additive models (GAMs) with inverse probability weighting were used to analyze the spatial association between location, our proxy for potential environmental or community risk factors, and each birth defect subtype (MapGAM package Version 1.2-5 in R Version 3.4.3). GAMs apply a smoothing regression based on locally weighted averages to predict the log odds of the birth defect associated with the geocoded X and Y coordinates for maternal location. We used a locally weighted straight line smoother (LOESS) for maternal location and determined the optimal span for each model by minimizing the Akaike Information Criterion.[7,29–31] Smaller spans result in a surface with more variation that reflect local spatial effects while larger spans create a smoother surface. These surfaces indicate geographic areas of higher or lower log odds on a two-dimensional plane. We calculated global p-values using a chi-square test to assess the significance of locations across the entire study area; the null hypothesis is that risk of birth defects case is not dependent on the location of the mother's residence at time of delivery.[32] We used the following GAM equation:

$$\text{Logit}[p(X_1,X_2)] = S(X_1,X_2) + \alpha;\ \ \alpha = \beta_0 + \beta_1 z_1 + \beta_2 z_2 + \ldots + \beta_j Z_j$$

where $\text{Logit}[p(X_1,X_2)]$ is the log disease odds at location (X_1,X_2), $S(X_1,X_2)$ is the bivariable smoothing function of location, and α consists of different covariates and their respective coefficients ($\beta_j Z_j$). Odds ratios (ORs) for the effect of location were calculated using the median log odds of the entire state as the reference, and 95% confidence intervals (CIs) were calculated using model standard errors. Contour lines indicate geographic areas where the 95% CIs exclude an OR of one.

We assessed the spatial patterns of birth defects with three nested models: a crude model with only the smooth term for location (Model 1), an adjusted model with the smooth term and individual-level maternal characteristics (Model 2), and a fully adjusted model with the smooth term, maternal characteristics, environmental indicators, and community-level factors (Model 3). When we begin with the crude model (Model 1), we expect to see spatial patterns given what we know about the distribution of risk factors for birth defects (i.e. spatial clustering of older mothers). As we add risk factors to the model, more of those spatial patterns should be explained. If the combination of risk factors adequately explains the patterns of birth defect risk, then the resulting smooth term in the fully adjusted model will display no spatial variation when mapped. If variation does exist, then the pattern may provide new insight into factors that contribute to the risk of birth defects in those Texas communities.

Model 2 includes maternal characteristics available from the TBDR and vital records that have been previously associated with birth defects in other studies: smoking (checked off in the vital record vs not checked), plurality of birth (1 fetus, 2 or more fetuses), maternal age (≤19, 20-24, 25-29, 30-34, 35-39, 40≥ years), race/ethnicity (White non-Hispanic, Black non-Hispanic, Hispanic, other non-Hispanic), and education group (less than high school, high school, greater than high school.[22,23,27,33–39] Only deliveries with complete data were included in each analysis; missingness for the selected covariates were less than 1%. Model 2 accounts for individual predictors that may contribute to spatial patterns if clustered in non-random patterns (e.g., an area of Texas with a higher proportion of black non-Hispanics).

Model 3 includes environmental indicators and community-level factors in addition to the maternal characteristics. Unconventional natural gas developments (UNGD) risk with birth defects was evaluated in Chapter 2 of this work and have been associated with birth defects in

Texas and other states. However, we evaluated each buffer radii density (1,3, and 7.5km) within our spatial analysis (Appendix C) but did not observe significant associations and therefore included density of UNGD wells within 1km radius of maternal address as a potential environmental exposure that might be contributing to spatial patterns in the final model.[40–46] We included average daily vehicle miles traveled (DVMT) for trucks by county as a measure of traffic-related air pollution; DVMT data were collected from the Texas Department of Transportation for 2005 through 2011 and data for all the years were averaged for a single county-level measure.[47] Lastly, we calculated toxic release inventory (TRI) densities, defined as the number of releases within 1km of maternal address at year of delivery.[48–51]

In Model 3, we also considered community-level factors that may contribute to the spatial variation of birth defects: median household income at maternal address block group, urbanicity in 2010, percent uninsured, and percent of women with diabetes averaged from 2009-2011. We obtained median household income, percent uninsured, and urbanicity data from the U.S. Census American Community Survey. Household incomes from the 2000 Census and 2010 Census were averaged for each block group to calculate an average measure that was included in the model as a continuous variable. Percent uninsured by county in 1999 was used as a proxy measure for prenatal care, and we used county-level age-adjusted percentage of diabetes averaged between 2009-2011 from the Centers for Disease Control and Prevention (CDC) given the significant birth defect risk observed in Chapter 2 sensitivity analyses and subsequent exploratory spatial analyses (Appendix C).[17,18,52–56] We created a binary urbanicity indicator based on the spatial location of mothers living in urban clusters or urban areas. These urban clusters or urban areas were defined as regions with populations greater than 2,500 people and 50,000 people respectively, by the 2010 US Census.[57]

For ASDs and VSDs (CHD subtypes with large numbers of cases), we performed time-stratified analyses to examine spatiotemporal trends. Birth deliveries were stratified by year of delivery in overlapping three-year time intervals (e.g., 1999-2001, 2000-2002) over the entire study period. Spatial analyses were then conducted for each data subset as described above using a common a priori selected span size of 0.20, or 20% of the data, to identify regional variation in ORs.[58] By using overlapping time periods, the analyses essentially provide a smoothed effect of time when compared spatially.

Results

There were 2,157 infants/fetuses (deduplicated cases) with NTDS, 42,445 with CHDs, 6,174 with orofacial defects, and 2,179 with gastroschisis. As expected, the number of births were highest in and around major Texas cities (Figure 3.1- 3.2). Among controls and the four case groups, most mothers did not smoke, delivered at age 20-29, were Hispanic, and lived in an urban area (Table 3.1). However, mothers of gastroschisis cases were significantly younger (83.9% for <25) and had less than high school education (40.6%). The distributions of control mothers living in areas with UNGD, TRI, DVMT, median household income, percent diabetes, and percent uninsured were similar to mothers in case groups.

We used GAMS to identify significant associations between geographic location of maternal residence at delivery and birth defects. We use modified TDSHS Public Health Region names when referring to geographic areas in Texas (Figure 3.1). In Table 3.2, we summarized regions that included at least one entire county within an area of statistically significant increased or decreased risk, as indicated by black contour lines. Location was statistically significant in the crude model (Model 1) for all defects except for HLHS. For Model 1, East Texas and Upper

Gulf Coast were consistently associated with areas of significant decreased ORs for nearly all of the defects except for cleft palate only, and ECD, respectively, and the Panhandle was significantly elevated for cleft lip with/without palate, ECD, gastroschisis, and TVAS (Table 3.2). In addition, statistically significant PVAS risk was not completely attenuated after full adjustment, but the area of statistical significance did reduce in size as indicated by the contour lines. For the majority of birth defects, areas of statistical significance were no longer present after accounting for maternal, environmental and community variables (Model 3).

Spatial risk patterns varied by defect throughout our analysis, and we present map odds ratios in Table 3.3. We present birth defects with considerable local spatial variation in the results. Risk for spina bifida (Figure 3.3a) was attenuated in South Texas after adjustment for maternal characteristics (Model 2), but elevated risk in North/Central Texas remained after adjustment for environmental and community factors (Model 3). For cleft palate only (Figure 3.3b), the significant protective effect of location in South Texas became null after Model 3 adjustment, but other significant areas in North, South-Central, Central and some parts of East Texas that also became null did not change substantially in risk patterns. Spatial patterns for anencephaly (Figure 3.4a) and cleft lip with/without palate (Figure 3.4b) were predominantly attributable to maternal characteristics and did not change after full adjustment. Maximum crude map ORs were similar among NTDs and orofacial defects ranging from 1.20 to 1.52.

ORs for all gastroschisis cases (Figure 3.5) and ORs among the larger subset of younger mothers (<25 years) (Figure 3.6a) were higher in West, Central, and eastern regions of South and South-Central Texas, but were lower in East Texas. After Model 3 adjustment, areas of decreased ORs were still present in East Texas and the magnitude of risk increased in the south. For older mothers (≥25 years) (Figure 3.6b), the spatial pattern of gastroschisis ORs was highest

(max cOR=3.49) in the northern Panhandle and lowest along the upper North Texas border. Although ORs in North/Central Texas were attenuated and no longer statistically significant, Model 3 adjustment did not meaningfully change the spatial patterns.

We identified areas of the highest ORs for AVS (max cOR=1.66) (Figure 3.7a) and PVAS (max cOR=3.49) (Figure 3.7b) in South Texas and the lowest ORs in East Texas. The spatial pattern for ECD risk (Figure 3.7c) was notably different, with increased ORs (max cOR=2.14) in the Panhandle and the southeastern border of Texas. Lower ORs were present in West and South-Central Texas. For all three heart defects, ORs were elevated near Fort Worth in North Texas even after Model 3 adjustment, though not always statistically significant. In contrast, risk in southern regions were generally attenuated after adjustment for environmental indicators and community-level factors (Model 3 compared to Model 2). Risk patterns for HLHS (Figure 3.8a), TGV (Figure 3.8b), TOF (Figure 3.8c), and TVAS (Figure 3.8d) did not change appreciably with Model 2 and Model 3 adjustment and were notably higher for TVAS (max cOR=1.98) compared to the later three defects (max cOR=1.32). East Texas was consistently associated with lower risks for all CHDs except for ECD (Figure 3.7c), and of note, this region became statistically significant for HLHS after full adjustment.

Fully adjusted VSD risk (Model 3) varied spatially and temporally, with areas of significant increased ORs consistently in South Texas (Figure 3.9). Over time, ORs decreased in the Panhandle and increased in the South. Spatial patterns were also observed across each time period for ASDs, with significant increased ORs in Upper Gulf Coast, North, South, and South-Central Texas that were attenuated over time (Model 3, Figure 3.10). Conversely, significant areas of decreased risk appeared over time in the Panhandle and were consistently present in East and Central Texas. Maximum crude ORs in Model 3 maps were similar (adjusted OR range=

2.24-3.80) for VSDs across the three-year intervals, but ASD maximum Model 3 ORs varied noticeably by interval (aOR range= 2.93-10.80) (Table 3.4-3.5). Spatial patterns of ASD and VSD ORs did not vary appreciably across the three models (data not shown).

Discussion

We analyzed the relationship between maternal location and selected birth defects across Texas while considering specific confounding variables. Location was significantly associated with most defects, with multiple birth defects sharing distinct geographic areas of increased risk in North, South, and South-Central Texas. Adjusting for maternal characteristics (Model 2) attenuated risks attributed to location, especially for stratified gastroschisis, AVS, and HLHS. Conversely, Model 2 adjustment also substantially increased the risk of birth defects associated with location for spina bifida (Figure 3.3a), anencephaly (Figure 3.4a), gastroschisis (Figure 3.5), TGV (Figure 3.8b), and TOF (Figure 3.8c). These are indicative of spatial confounding, an occurrence in which risk factors such as race/ethnicity, age, and education status are not evenly distributed across a study area and likely impact the effect of location. Spatial confounding was also observed after adjustment for Model 3 variables, and one area of Texas often decreases in risk while another area increases in risk, as observed with spina bifida, gastroschisis, gastroschisis (age<25), PVAS, and ECD. Notably, Model 3 variables appear to attenuate ORs in the southern regions for these defects. In contrast, AVS and HLHS risk decreased across the state after adjusting for Model 3 variables. These changing spatial patterns highlight the complex and multifactorial etiology of birth defects.

Elevated crude risk was present for all selected birth defects except HLHS, which was not associated with location and risk was reduced after adjustment in Model 2. Our results were similar to a Massachusetts study in which spatial patterns for HLHS were no longer present after

adjustment for maternal characteristics and $PM_{2.5}$, and ASD risk did not change substantially after adjustment.[59] Furthermore, our results support other studies that observed regional variation of risks for CHDs and NTDs using a variety of spatial statistics which attributed possible environmental exposures as potential explanations.[14–16] Although we did not model specific pollutants, we were able to adjust for UNGD operations, toxic release inventory sites, and heavy truck traffic. Increased presence of these modifiable risk factors, such as UNGDs in oil and gas shales, polluted areas, or highly uninsured areas, may explain some of the spatial confounding that we observed across defects. For many of our birth defects, spatial associations were no longer significant after the inclusion of these variables. Nevertheless, areas of residual increased risk after adjustment for these variables suggests that unmeasured or inadequately measured social or environmental risk factors still may be present.

Increased risks for birth defects were apparent in North Texas. Our time-stratified analyses for ASD and VSDs observed increased risk around this area beginning in 2003, and risk began to diminish after 2007. Studies on water quality in the area west of Fort Worth in North Texas detected a variety of chemicals such as BTEX, VOCs and heavy metals.[60,61] In addition, counties within North Texas varied from each other in percent uninsured, percent diabetic, and median income. However, maternal factors for cases and controls were not different in this area.

Southern Texas has been of public interest, particularly with gastroschisis around Corpus Christi and neural tube defects south of Corpus Christi.[12,24,62] Our study observed a slight increase in risk of gastroschisis for mothers younger than 25 years in the area from Austin south to Corpus Christi and was consistent with prior studies of gastroschisis clusters that also observed similar increases in risk throughout central Texas, extending south to Corpus Christi, and decreased risk near Houston.[12,24] Nine superfund sites in the surrounding counties, including

a row of photochemical facilities, also known as "Refinery Row" in Corpus Christi, have been associated with VSD and other anomalies of the aorta in prior studies although that was limited to the county containing Corpus Christi.[63] We observed significant ASD ORs of 10.80, the maximum Model 3 map OR in 1999-2001, in this same region (Table 3.5).

There are some limitations of the data that must be considered when interpreting our results. We were not able to consider deliveries of fetuses that were terminated or spontaneously aborted early in gestation, possibly resulting in an underestimation of our results since we could not include infants/fetuses with very severe defects that did not survive. Under-ascertainment of cases and diagnostic variability may also bias the association between location and Texas birth defects. The spatial variation of ASD and VSDs, for example, may be due to variability in coding and diagnosis of birth defects by physicians.[64,65] The area of decreased risk in the southern part of East Texas/eastern part of the Upper Gulf Coast may be due to identified under-ascertainment of birth defects in this region, which has also been observed in New Jersey and New York.[66,67]

Birth records also only provided maternal address at time of delivery and may be subject to misclassification if the mother moved during pregnancy. One study in Texas observed residential mobility among 30% of pregnant mothers between conception and delivery; the risk of mobility increased if a mother was young, lower income, and was White non-Hispanic.[37] This brings up the possibility of misclassifying the exposure to our environmental indicators during the first trimester of pregnancy, which is the most critical period. This misclassification is expected to be non-differential and to result in bias toward the null, as observed in a study of ambient benzene exposure and birth defects.[68] Birth records were also limited in the covariates available for inclusion in our analyses. To address this to some extent, we used community-level

data for important risk factors (e.g., percent uninsured as a proxy variable for prenatal care), but we were unable to adjust for consumption of important supplements such as folic acid which has some protective effects for NTDs and possibly other defects, and maternal drug use.[69] We also used proximity to UNGD, TRI, and county-truck traffic to estimate air pollutants and therefore were not able to assess the effects of specific pollutants on our birth defects, and we averaged our community-level data based on availability.

Our study had several advantages that allowed for the observation of areas of low and high risks among selected birth defects. We were able to assess the spatial variability of birth defects using individual-level data that created a smoother surface, not bound by administrative boundaries. Texas is also a highly diverse state, providing variation in our demographic predictors. Further adjustment of environmental and community variables allowed us to capture the spatial variability of confounders within our model that were not available at the individual-level. The large number of cases and controls allowed for substantial statistical power and spatially stratified control selection provided sufficient data availability across Texas. We were also able to investigate spatial-temporal changes with some CHDs with large case numbers to better understand the patterns of risk over time.

Conclusions

We identified areas of increased and decreased risks of specific birth defect subtypes across the entire state of Texas. Areas of elevated risk persisted in North and South Texas after adjustment of covariates for neural tube defects, cleft palate, gastroschisis, and some CHDs. Our findings suggest that some birth defect risks are consistently higher in some areas. We observed risk of defects after adjustment of maternal factors, such as age, race/ethnicity, and education group were impacted by the addition of community and environmental factors, such as insurance

status, urbanicity, median income, UNGD density, and TRI density. Residual risk remained, suggesting the presence of unaccounted risk factors and warranting further investigation of social, environmental, and genetic factors in these areas to improve our understanding of these birth defects.

Acknowledgement

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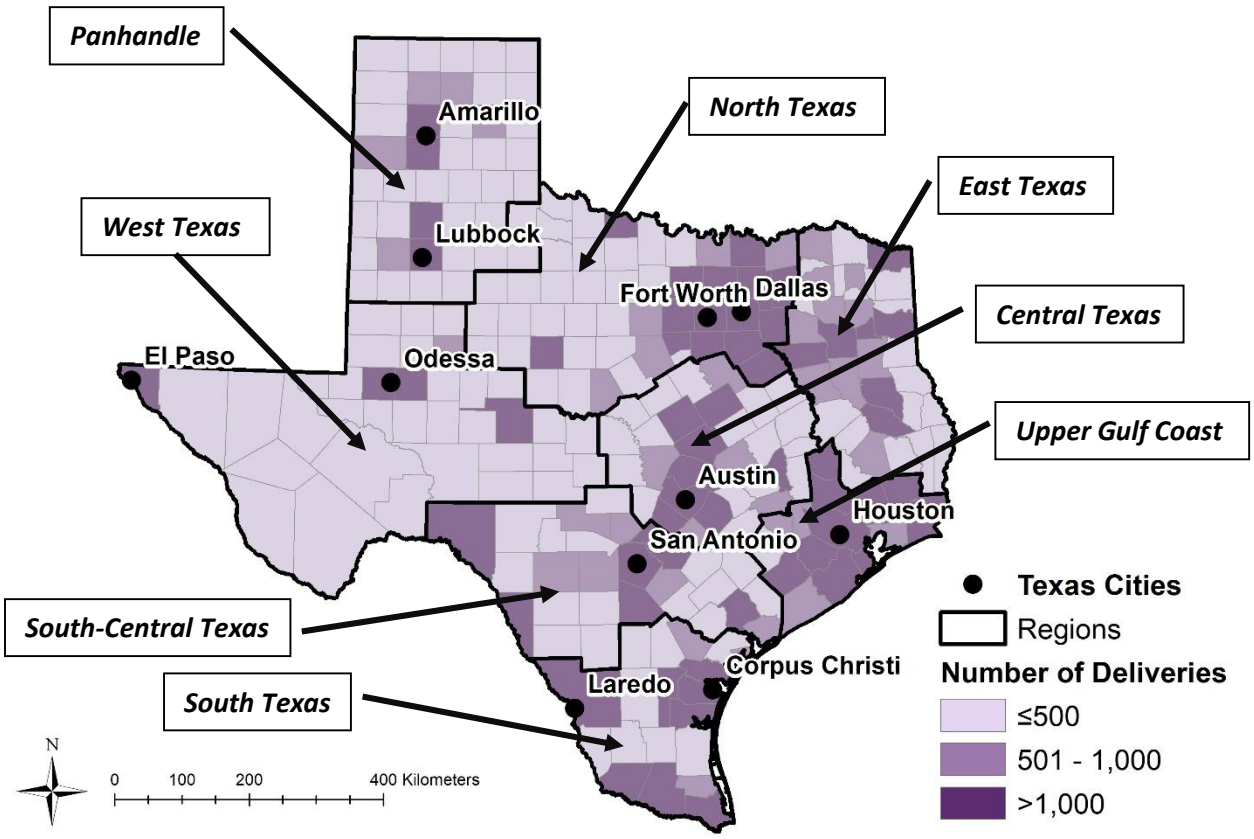


Figure 3.1: Distribution of total deliveries (deduplicated cases and controls) by Texas counties, 1999-2011

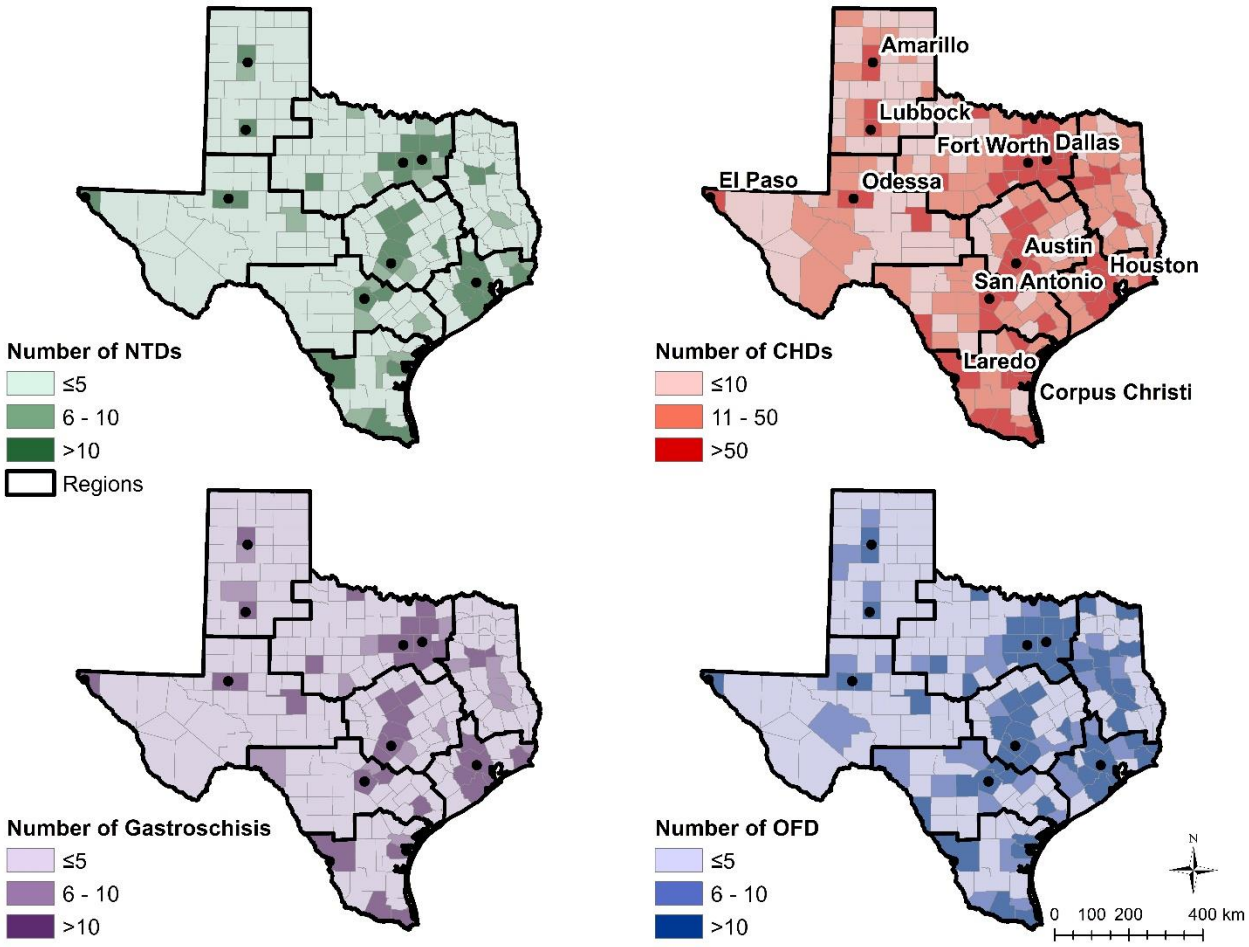


Figure 3.2: Distribution of cases by birth defect group in Texas Counties, 1999-2011. CHD= Congenital Heart Defect; NTD= Neural Tube Defect; OFD= Orofacial Defect

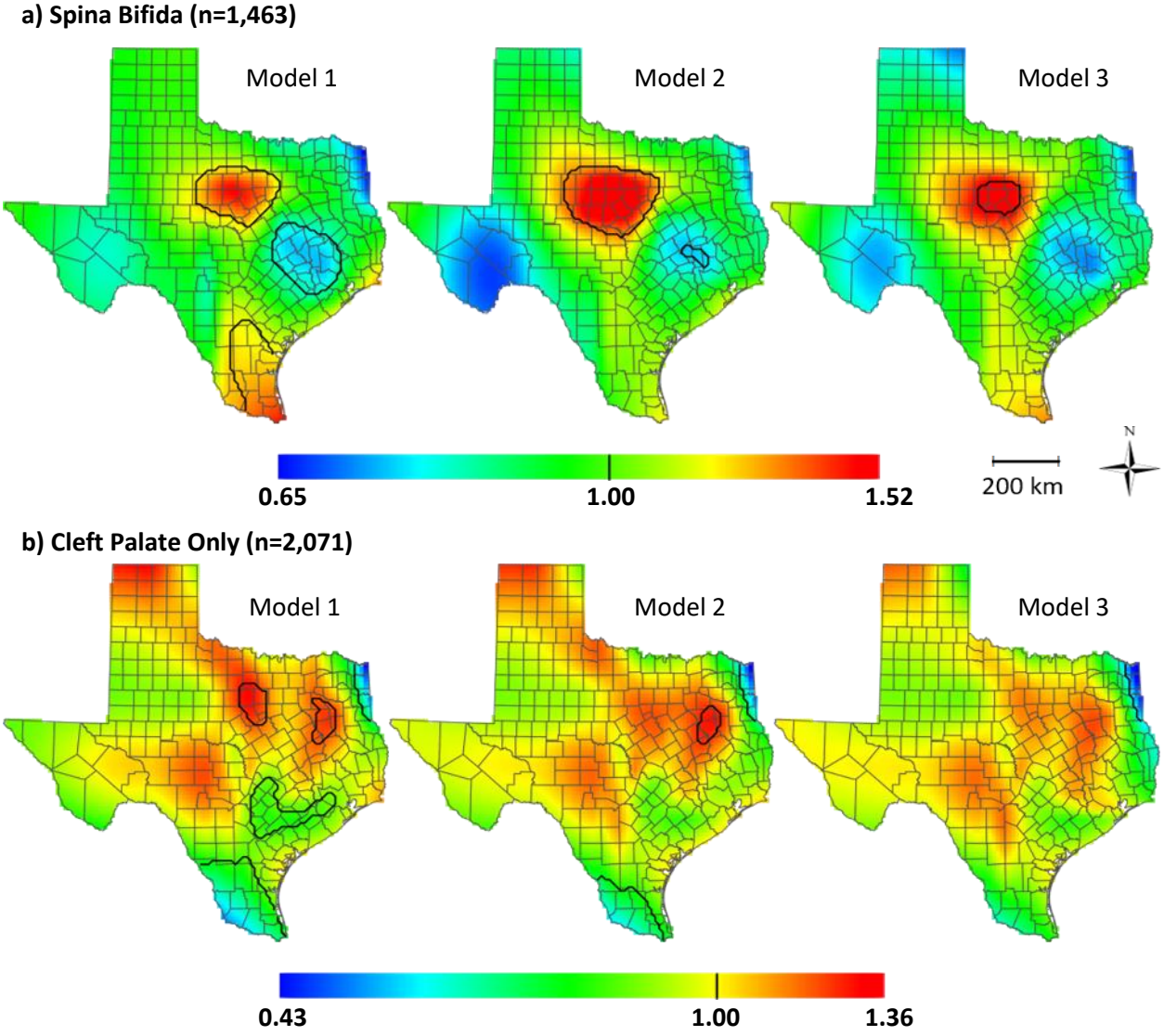


Figure 3.3: Geographic patterns of odds ratios for selected neural tube and orofacial birth defects among Texas deliveries, 1999-2011. Model 1: crude model with only location and birth defects; **Model 2**: adjusted model with maternal smoking status, plurality, age group, race/ethnicity, and education status; **Model 3**: fully adjusted model that includes Model 2 variables, as well as median income, urban indicator, average daily vehicle miles traveled for trucks by county, percent age-adjusted diabetes among women, percent uninsured, TRI facility density, and UNGD density. Black contour lines indicate statistically significant areas of increased or decreased risks. Odds ratio scale uses the prediction range for Model 1.

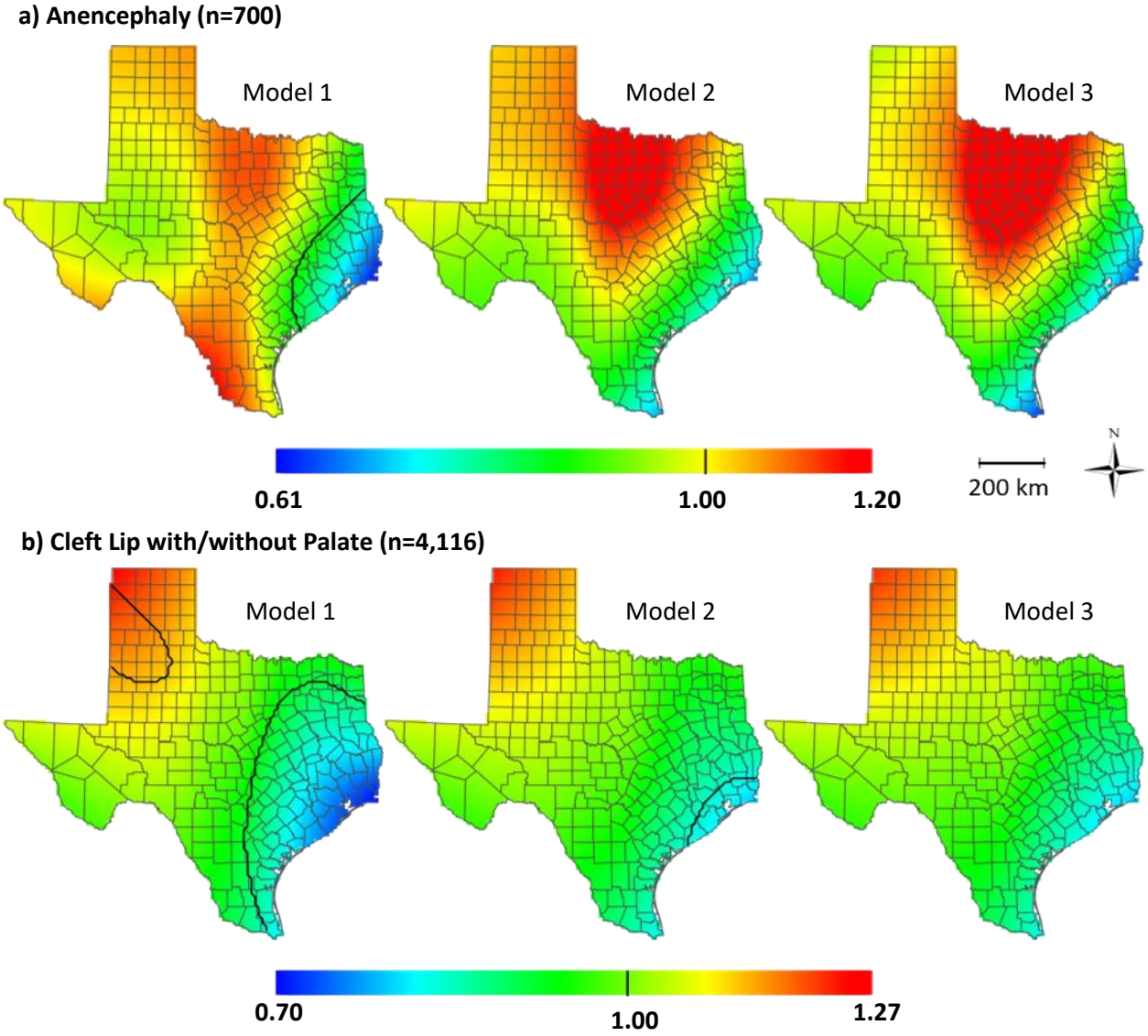


Figure 3.4: Geographic patterns of odds ratios for selected birth defects among Texas deliveries, 1999-2011. Model 1: crude model with only location and birth defects; **Model 2**: adjusted model with maternal smoking status, plurality, age group, race/ethnicity, and education status; **Model 3**: fully adjusted model that includes Model 2 variables, as well as median income, urban indicator, average daily vehicle miles traveled for trucks by county, percent age-adjusted diabetes among women, percent uninsured, TRI facility density, and UNGD density. Black contour lines indicate statistically significant areas of increased or decreased risks. Odds ratio scale uses the prediction range for Model 1.

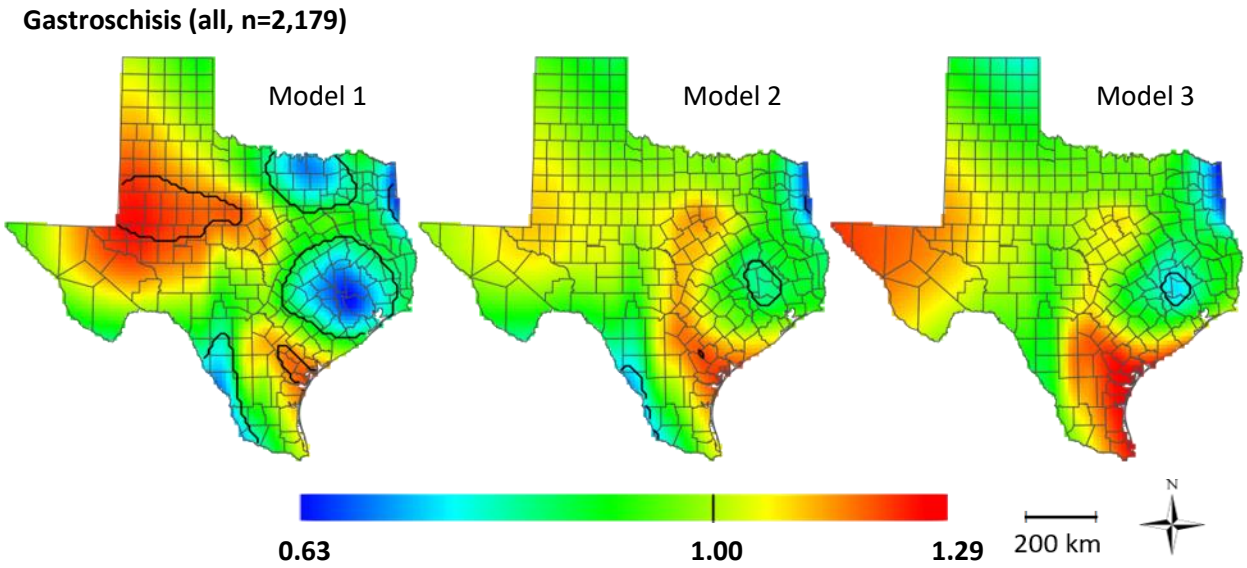


Figure 3.5: Geographic patterns of odds ratios for gastroschisis defects among Texas deliveries, 1999-2011. Model 1: crude model with only location and birth defects; **Model 2**: adjusted model with maternal smoking status, plurality, age group, race/ethnicity, and education status; **Model 3**: fully adjusted model that includes Model 2 variables, as well as median income, urban indicator, average daily vehicle miles traveled for trucks by county, percent age-adjusted diabetes among women, percent uninsured, TRI facility density, and UNGD density. Black contour lines indicate statistically significant areas of increased or decreased risks. Odds ratio scale uses the prediction range for Model 1.

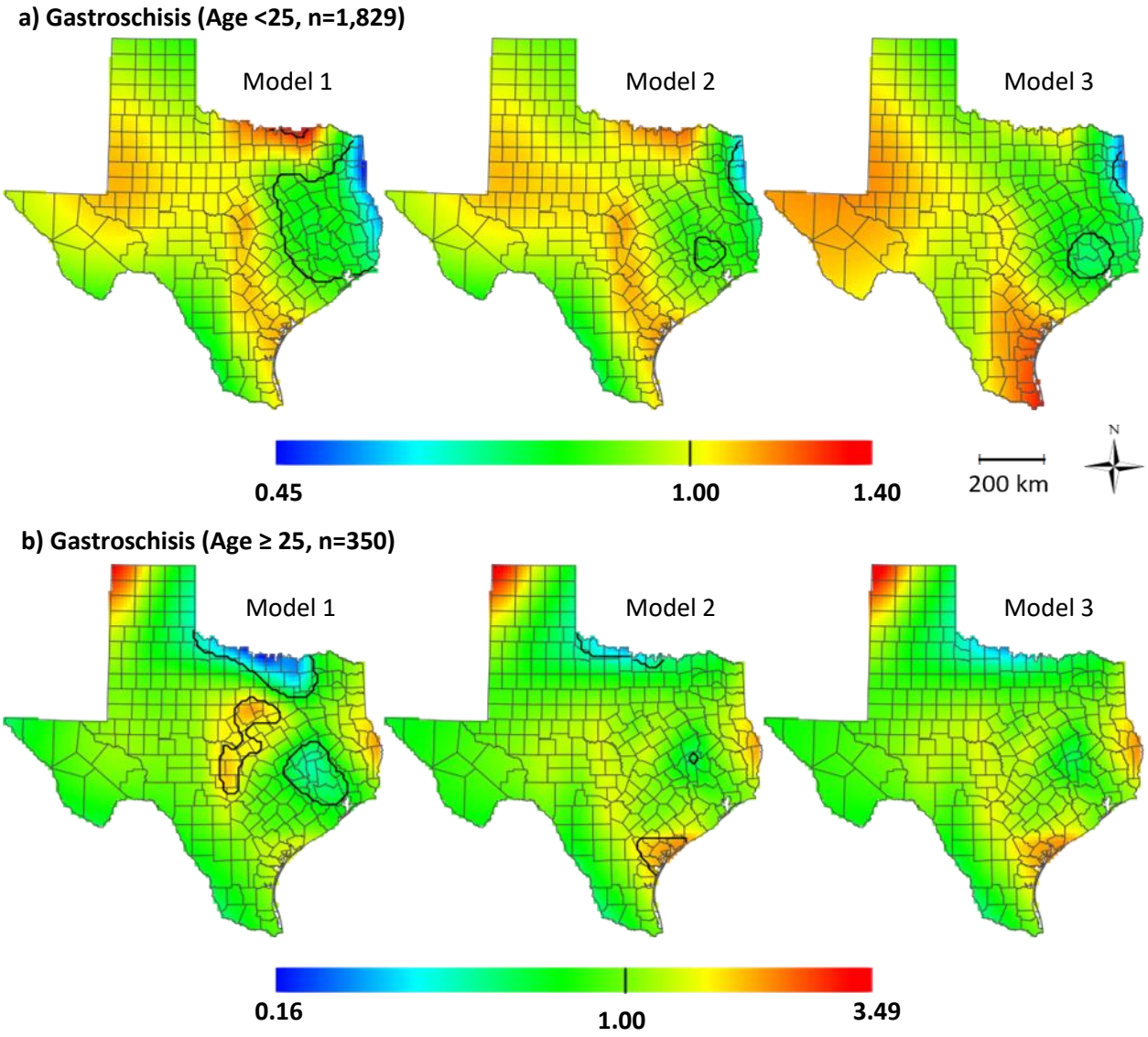
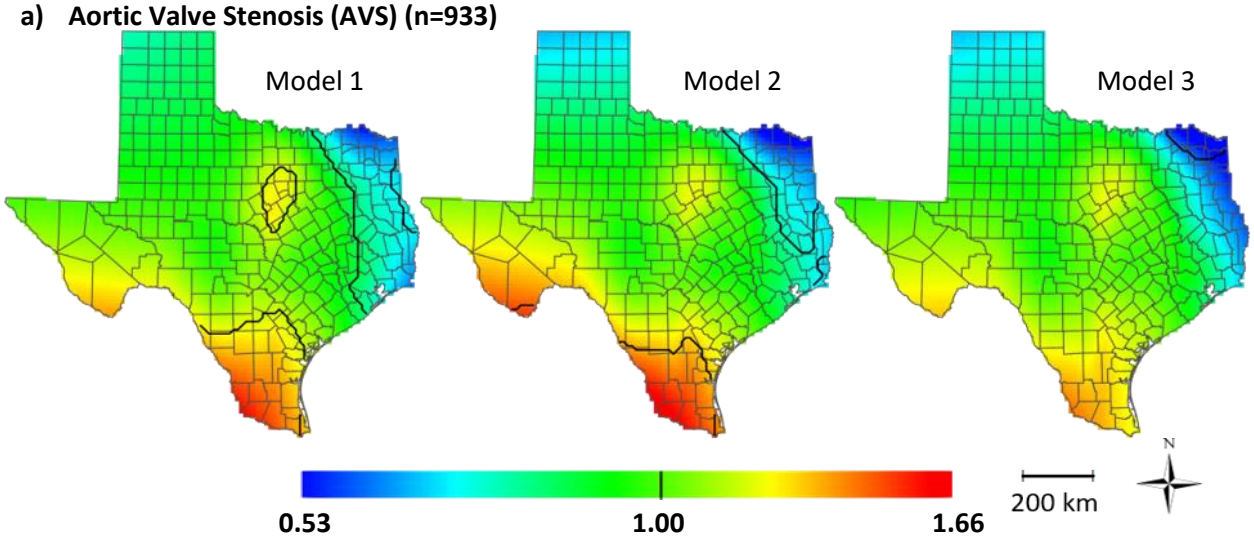
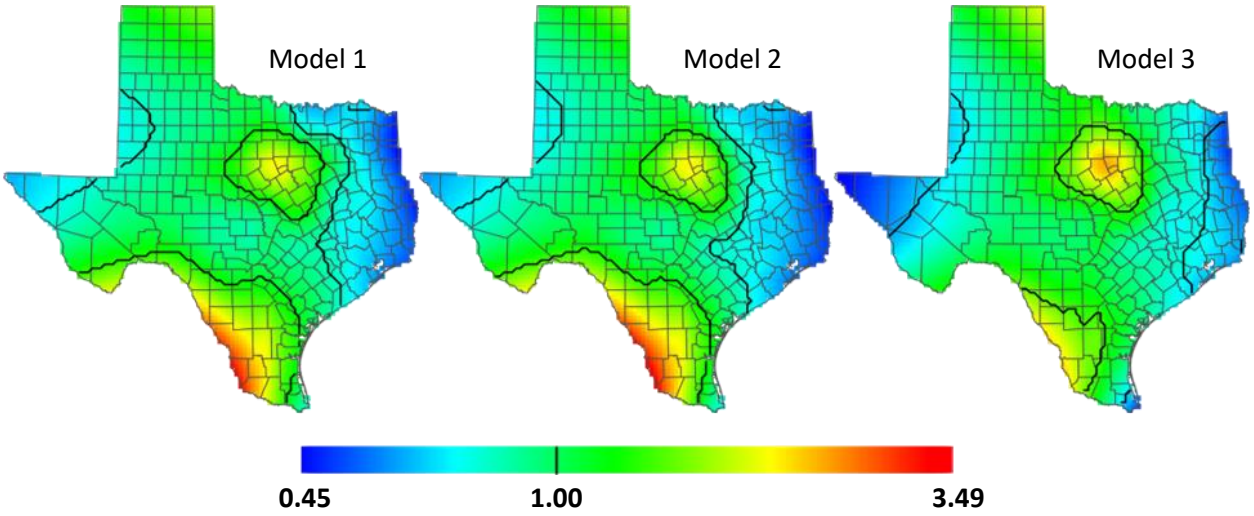


Figure 3.6: Geographic patterns of odds ratios for stratified gastroschisis among Texas deliveries, 1999-2011.Model 1: crude model with only location and birth defects; **Model 2**: adjusted model with maternal smoking status, plurality, age group, race/ethnicity, and education status; **Model 3**: fully adjusted model that includes Model 2 variables, as well as median income, urban indicator, average daily vehicle miles traveled for trucks by county, percent age-adjusted diabetes among women, percent uninsured, TRI facility density, and UNGD density. Black contour lines indicate statistically significant areas of increased or decreased risks. Odds ratio scale uses the prediction range for Model 1.

a) Aortic Valve Stenosis (AVS) (n=933)



b) Pulmonary Valve Atresia/Stenosis (PVAS) (n=3,611)



c) Endocardial Cushion Defects (ECD) (n=849)

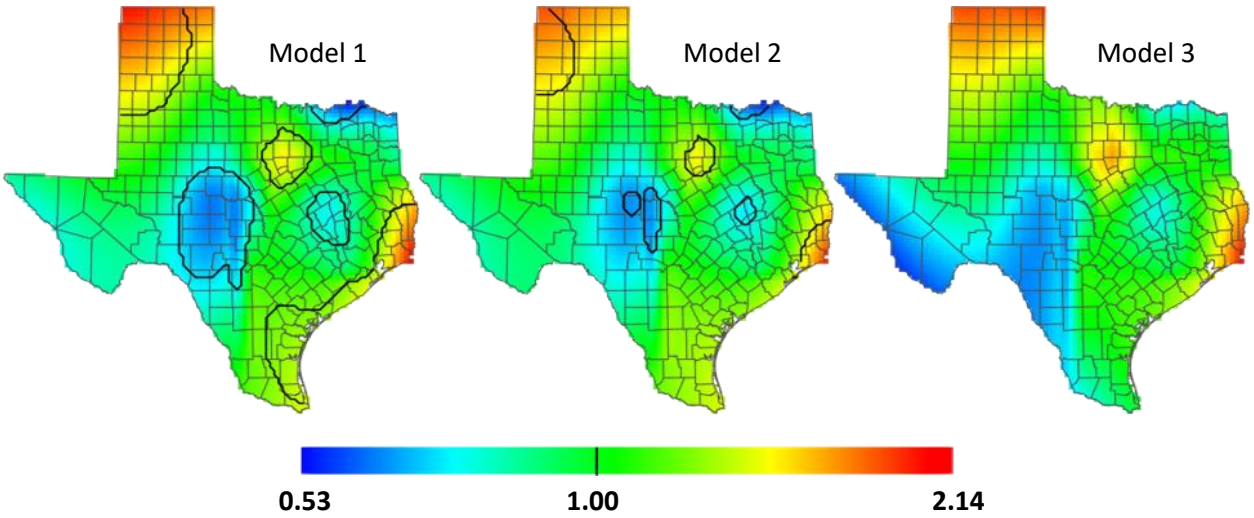
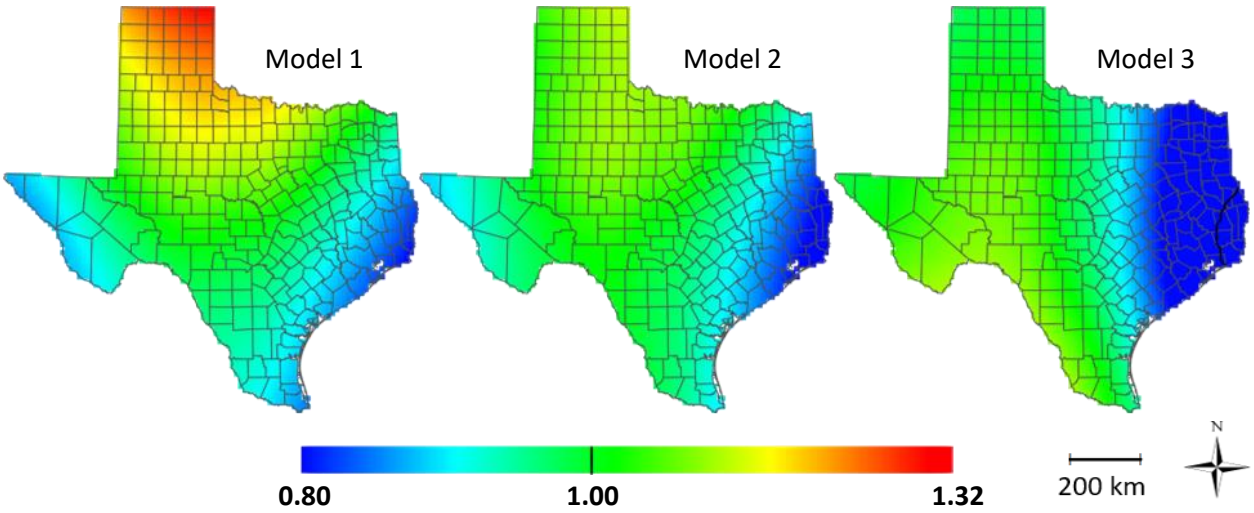
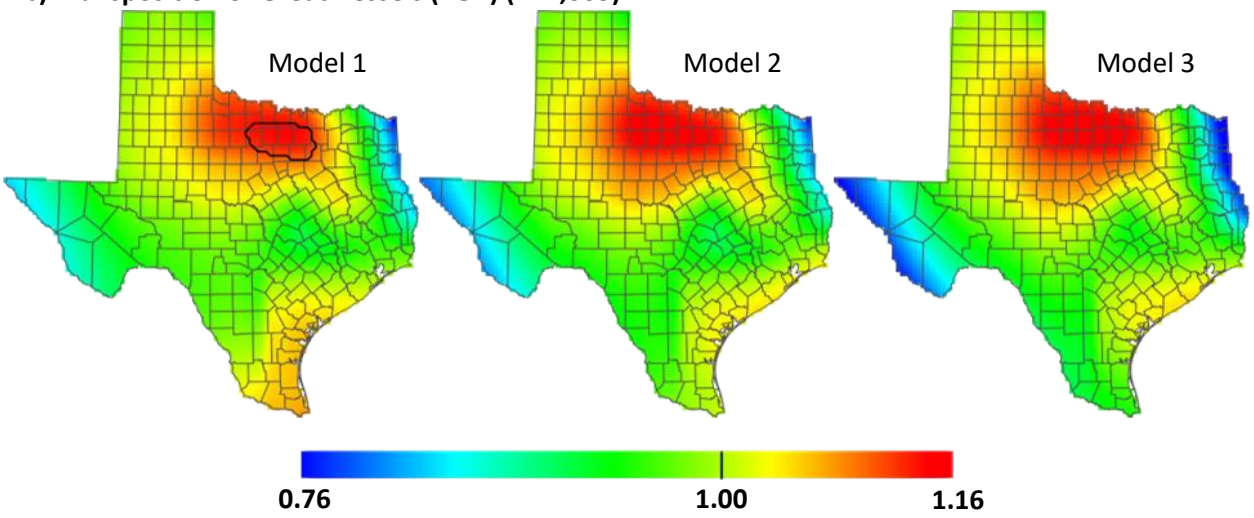


Figure 3.7: Geographic patterns of odds ratios for selected congenital heart defects among Texas deliveries, 1999-2011. Model 1: crude model with only location and birth defects; **Model 2**: adjusted model with maternal smoking status, plurality, age group, race/ethnicity, and education status; **Model 3**: fully adjusted model that includes Model 2 variables, as well as median income, urban indicator, average daily vehicle miles traveled for trucks by county, percent age-adjusted diabetes among women, percent uninsured, TRI facility density, and UNGD density. Black contour lines indicate statistically significant areas of increased or decreased risks. Odds ratio scale uses the prediction range for Model 1.

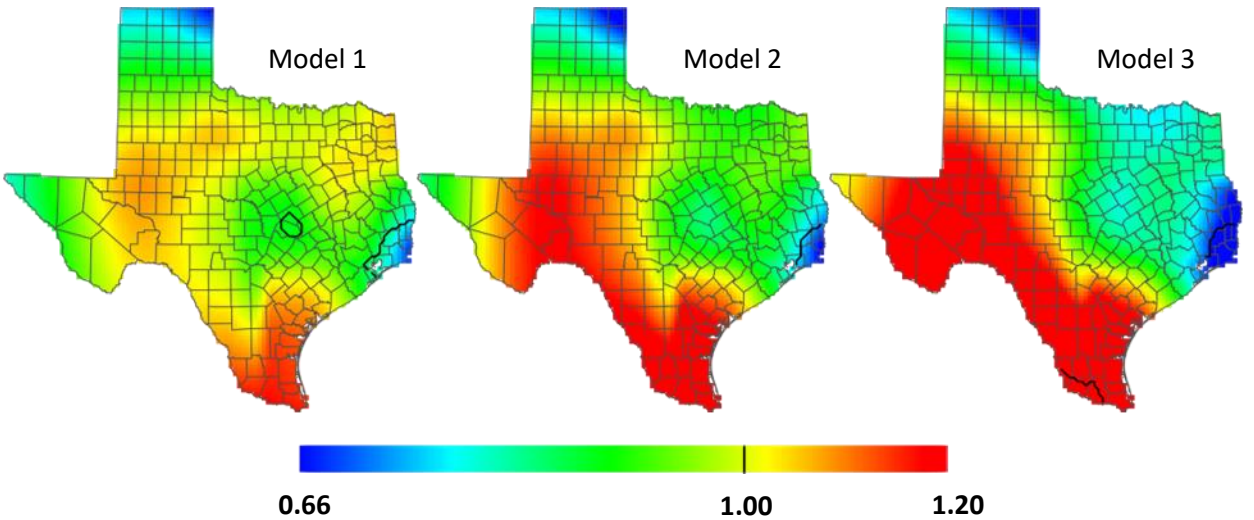
a) Hypoplastic Left Heart Syndrome (HLHS) (n=848)



b) Transposition of Great Vessels (TGV) (n=2,003)



c) Tetralogy of Fallot (TOF) (n=1,133)



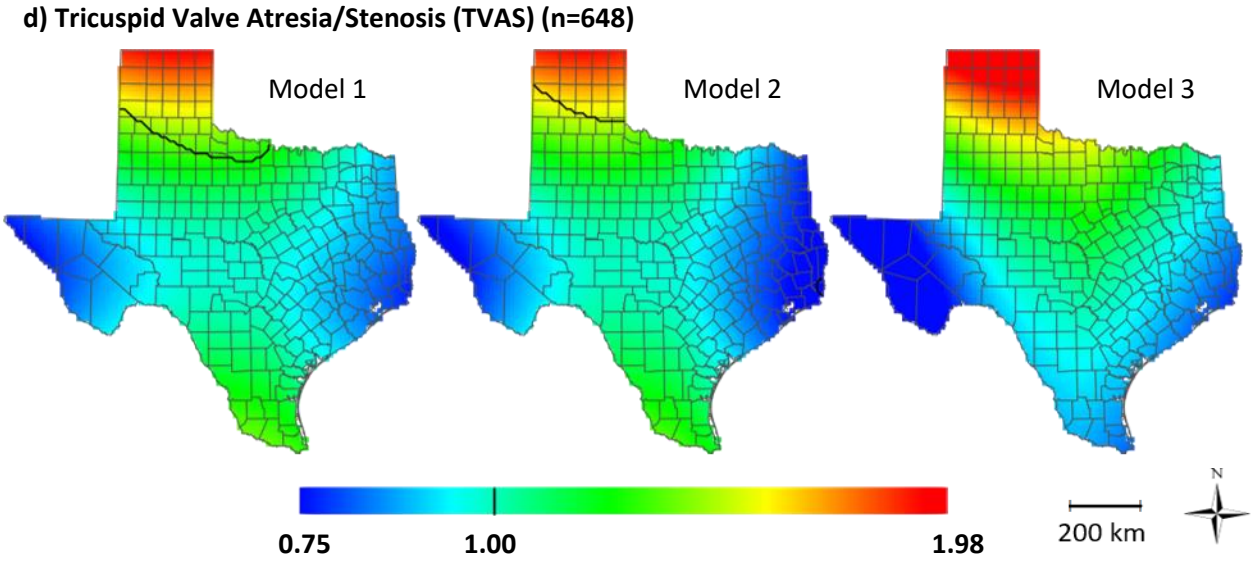


Figure 3.8: Geographic patterns of odds ratios for selected congenital heart birth defects among Texas deliveries, 1999-2011. Model 1: crude model with only location and birth defects; **Model 2**: adjusted model with maternal smoking status, plurality, age group, race/ethnicity, and education status; **Model 3**: fully adjusted model that includes Model 2 variables, as well as median income, urban indicator, average daily vehicle miles traveled for trucks by county, percent age-adjusted diabetes among women, percent uninsured, TRI facility density, and UNGD density. Black contour lines indicate statistically significant areas of increased or decreased risks. Odds ratio scale uses the prediction range for Model 1.

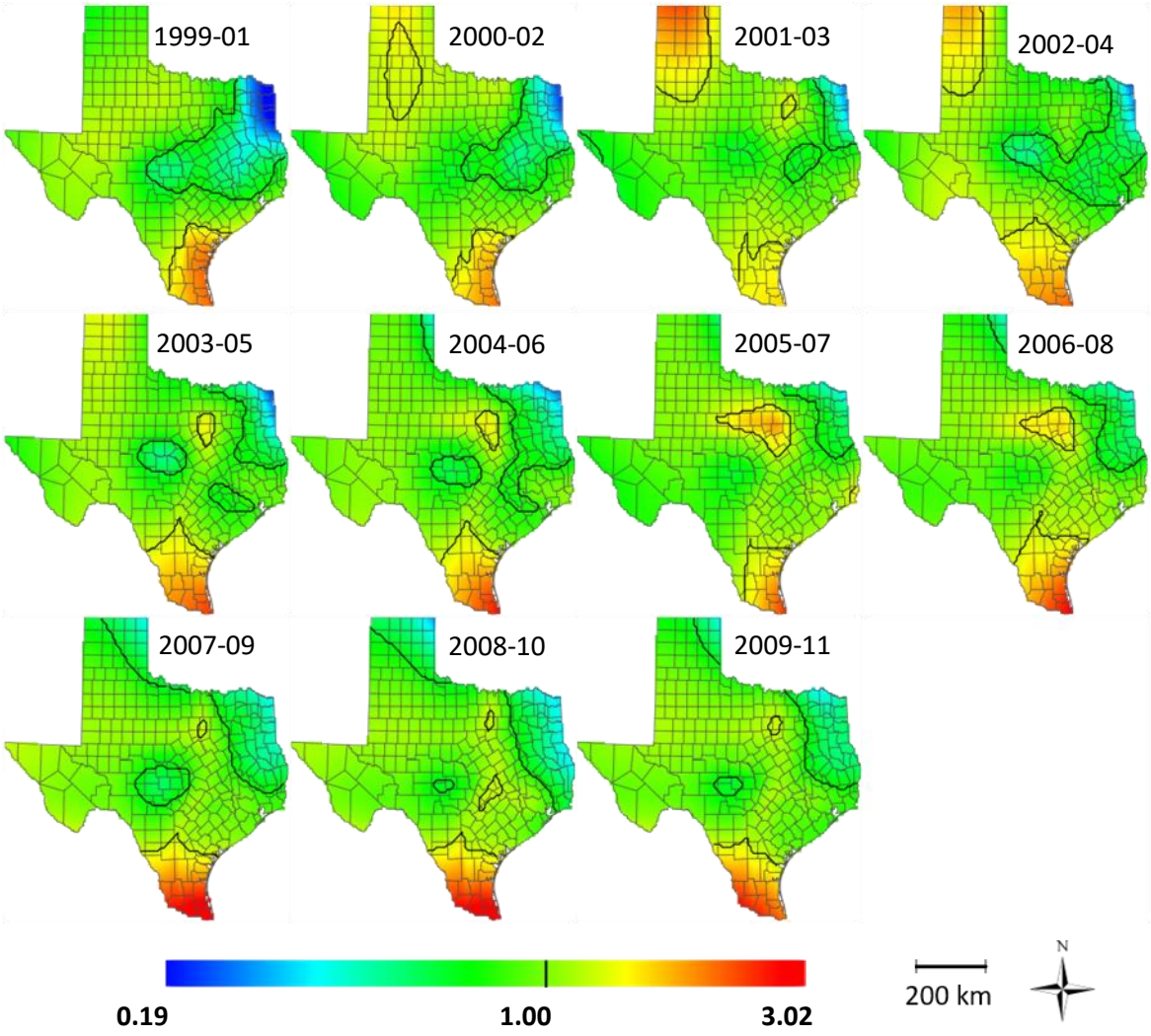


Figure 3.9: Geographic patterns of fully adjusted odds ratios (Model 3) for ventricular septal defects (VSD) among Texas births, 1999-2011 (Total N=22,205).Model 3: fully adjusted model that includes smoking status, plurality, age group, race/ethnicity, education status, median income, urban indicator, average daily vehicle miles traveled for trucks by county, percent age-adjusted diabetes among women, percent uninsured, TRI facility density, and UNGD density. Black contour lines indicate statistically significant areas of increased or decreased risks. Maps share scale for comparability.

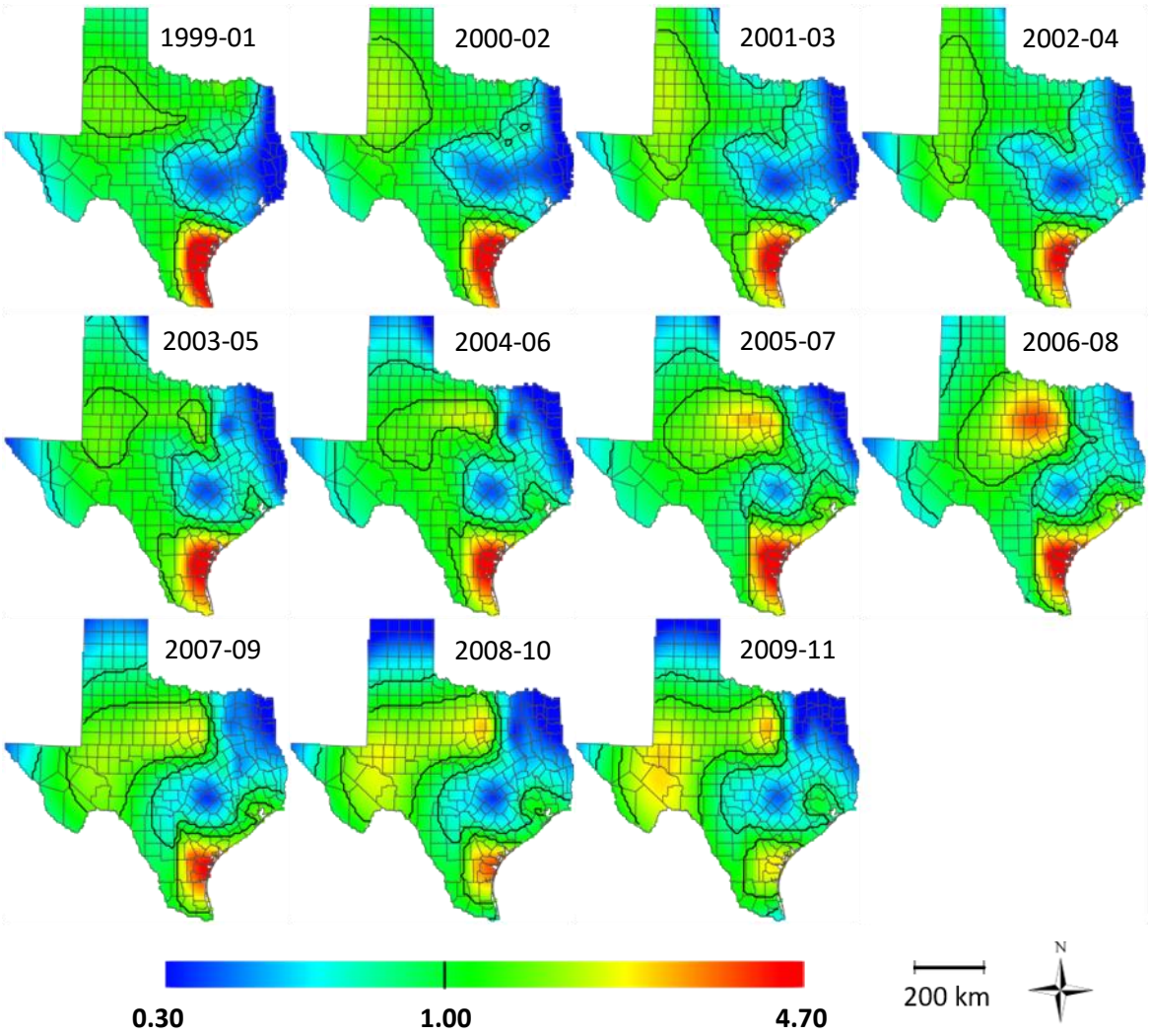


Figure 3.10: Geographic patterns of fully adjusted odds ratios (Model 3) for atrial septal defects (ASD) among Texas births, 1999-2011 (Total N=22,218). Model 3: fully adjusted model that includes the above maternal characteristics, as well as median income, urban indicator, average daily vehicle miles traveled for trucks by county, percent age-adjusted diabetes among women, percent uninsured, TRI facility density (1km), and UNGD density (1km). Black contour lines indicate statistically significant areas of increased or decreased risks. Maps share scale for comparability.

Table 3.1: Characteristics of Texas birth defect cases and controls, born in 1999-2011.

N(%)	Neural Tube (n=2,157)	Congenital Heart (n=42,445)	Orofacial Clefts (n=6,174)	Gastroschisis (n=2,179)	Controls† (n=642,399)
Infant Sex	**(4 missing)**				
Male	1,072 (49.7)	21,010 (49.5)	3,425 (55.5)	1,134 (52.0)	325,422 (50.7)
Female	1,081 (50.1)	21,435 (50.5)	2,749 (44.5)	1,045 (48.0)	316,977 (49.3)
Maternal Age					
11-19	314 (14.6)	5,397 (12.7)	863 (14.0)	934 (42.9)	85,578 (13.3)
20-24	601 (27.9)	11,176 (26.3)	1,739 (28.2)	895 (41.1)	175,452 (27.3)
25-29	587 (27.2)	11,230 (26.5)	1,609 (26.1)	251 (11.5)	174,373 (27.1)
30-34	445 (20.6)	8,912 (21.0)	1,239 (20.1)	72 (3.3)	133,203 (20.7)
35-39	173 (8.0)	4,625 (10.9)	568 (9.2)	23 (1.1)	60,830 (9.5)
40-58	37 (1.7)	1,105 (2.6)	156 (2.5)	4 (0.2)	12,963 (2.0)
Smoke During Pregnancy (Checked)					
Yes	98 (4.5)	2,467 (5.8)	463 (7.5)	179 (8.2)	35,110 (5.5)
No	2,059 (95.5)	39,978 (94.2)	5,711 (92.5)	2,000 (91.8)	607,289 (94.5)
Plurality of Pregnancy					
Singleton	2,061 (95.5)	39,412 (92.9)	5,972 (96.7)	2,143 (98.3)	623,568 (97.1)
Two or more fetuses	96 (4.5)	3,033 (7.1)	202 (3.3)	36 (1.7)	18,831 (2.9)
Race/ Ethnicity					
White non-Hispanic	670 (31.1)	14,695 (34.6)	2,411 (39.1)	774 (35.5)	228,171 (35.5)
Black non-Hispanic	183 (8.5)	4,647 (10.9)	465 (7.5)	153 (7.0)	74,332 (11.6)
Hispanic	1,260 (58.4)	21,649 (51.0)	3,012 (48.8)	1,206 (55.3)	312,065 (48.6)
Other non-Hispanic	44 (2.0)	1,454 (3.4)	286 (4.6)	46 (2.1)	27,831 (4.3)
Education Completed					
< High School	793 (36.8)	12,858 (30.3)	1,968 (31.9)	884 (40.6)	186,858 (29.1)

High School Graduate	630 (29.2)	12,382 (29.2)	1,862 (30.2)	772 (35.4)	180,747 (28.1)
>High School	734 (34.0)	17,205 (40.5)	2,344 (38.0)	523 (24.0)	274,794 (42.8)
Urbanization					
Rural	168 (7.8)	3,368 (7.9)	593 (9.6)	224 (10.3)	55,213 (8.6)
Urban	1,989 (92.2)	39,077 (92.1)	5,581 (90.4)	1,955 (89.7)	587,186 (91.4)
UNGD Density (1km), mean ± SD	0.1 ± 0.5	0.1 ± 0.5	0.09 ± 0.5	0.09 ± 0.5	0.09 ± 0.5
Average Truck Daily Vehicle Miles Traveled (1,000,000), mean ± SD	2.1 ± 1.8	2.0 ± 1.7	2.0 ± 1.8	2.0 ± 1.7	2.1 ±1.8
TRI Density, mean ± SD	0.1±0.7	0.1± 0.7	0.1 ± 0.7	0.1±0.8	0.1 ± 0.7
Household Median Income ($1000), mean ± SD	42.2 ± 20.6	45.3 ± 24.2	45.7 ± 24.3	40.3 ± 17.5	46.8 ± 24.6
Percent Diabetes, mean± SD	8.3 ± 0.8	8.4 ± 0.8	8.3 ± 0.8	8.3 ± 0.8	8.3 ± 0.8
Percent Uninsured, mean± SD	24.6 ± 3.8	24.8 ± 3.9	24.3 ± 3.6	24.5 ± 3.6	24.5 ± 3.6

Table 3.2: Texas regions that consist of areas of statistically significant increased (↑) and/or decreased (↓) ORs in the crude model (Model 1), after adjusting for maternal characteristics (Model 2), and after adjusting for maternal, community, and environmental factors (Model 3)

Region	Panhandle			North Texas			East Texas			Central Texas			Upper Gulf Coast			South-Central Texas			South Texas			West Texas		
Model	**M 1**	**M 2**	**M 3**	**M 1**	**M 2**	**M 3**	**M 1**	**M 2**	**M 3**	**M 1**	**M 2**	**M 3**	**M 1**	**M 2**	**M 3**	**M 1**	**M 2**	**M 3**	**M 1**	**M 2**	**M 3**	**M 1**	**M 2**	**M 3**
AN							↓						↓											
SB				↑	↑	↑				↓			↓						↑					
CL/P	↑						↓			↓			↓	↓		↓			↓					
CPO				↑			↑↓	↑↓	↓	↓			↓			↓			↓	↓				
Gas	↑			↑↓			↓	↓		↓	↓		↓	↓		↑↓	↑		↓	↓		↑		
Gas (Age<25)				↑↓			↓	↓	↓	↓			↓	↓	↓									
Gas (Age≥25)				↑↓	↓					↑↓	↓		↓			↑	↑			↑				
AVS				↑↓	↓		↓	↓	↓	↑			↓	↓		↑	↑		↑	↑			↑	
ECD	↑	↑		↑↓	↑↓		↓	↓		↓	↓		↑	↑		↑↓			↑			↓	↓	
HLHS									↓						↓									
PVAS	↓	↓	↓	↑↓	↑↓	↑	↓	↓	↓	↑↓	↑↓	↑	↓	↓	↓	↑	↑	↑	↑	↑	↑↓	↑↓	↑↓	↓
TGV				↑																				
TOF										↓			↓	↓	↓						↑			
TVAS	↑	↑		↑																				

↑↓= regions that consist of both statistically significant increased and decreased ORs

M1= Model 1
M2= Model 2
M3= Model 3
AN=Anencephaly, SB=Spina Bifida, CL/P=Cleft Lip with/without Palate, CP=Cleft Palate Only, Gas=Gastroschisis, AVS=Aortic Valve Stenosis, ECD=Endocardial Cushion Defect, HLHS=Hypoplastic Left Heart Syndrome, PVAS=Pulmonary Valve Atresia/Stenosis, TGV=Transposition of Great Vessels, TOF=Tetralogy of Fallot, TVAS=Tricuspid Valve Atresia/Stenosis

Table 3.3: Map odds ratio ranges (lower, upper) and global p-values for selected birth defects born between 1999-2011 in Texas

Model	Span Size†	Model 1	Global P-Value	Model 2	Global P-Value	Model 3	Global P-Value
Cleft Palate Only	0.20	(0.43, 1.36)	<0.001	(0.40, 1.34)	<0.001	(0.38, 1.22)	0.006
Cleft Lip with/without Palate	0.80	(0.70, 1.27)	<0.001	(0.78, 1.25)	<0.001	(0.78, 1.23)	<0.001
Anencephaly	0.85	(0.61, 1.20)	<0.001	(0.67, 1.29)	<0.001	(0.63, 1.35)	<0.001
Spina bifida	0.30	(0.65, 1.52)	<0.001	(0.68, 1.77)	<0.001	(0.67, 1.65)	<0.001
Gastroschisis	0.30	(0.63, 1.29)	<0.001	(0.65, 1.26)	<0.001	(0.64, 1.33)	<0.001
Gastroschisis (Age<25)	0.30	(0.45, 1.40)	<0.001	(0.54, 1.24)	<0.001	(0.49, 1.36)	<0.001
Gastroschisis (Age ≥ 25)	0.20	(0.16, 3.49)	<0.001	(0.27, 3.99)	0.022	(0.26, 4.09)	0.027
AVS	0.50	(0.53, 1.66)	<0.001	(0.46, 1.77)	<0.001	(0.45, 1.47)	0.009
ECD	0.30	(0.53, 2.14)	<0.001	(0.54, 1.99)	0.002	(0.56, 2.08)	0.009
HLHS	0.95	(0.80, 1.32)	0.042	(0.76, 1.13)	0.098	(0.62, 1.11)	0.042
PVAS	0.20	(0.45, 3.49)	<0.001	(0.44, 3.68)	<0.001	(0.43, 2.49)	<0.001
TGV	0.60	(0.76, 1.16)	0.007	(0.76, 1.17)	0.003	(0.72, 1.18)	0.025
TOF	0.55	(0.66, 1.20)	0.033	(0.61, 1.41)	<0.001	(0.55, 1.85)	0.005
TVAS	0.90	(0.75, 1.98)	<0.001	(0.69, 1.96)	<0.001	(0.55, 2.40)	<0.001

† span size was held constant across Models 1-3

AVS=Aortic Valve Stenosis, ECD=Endocardial Cushion Defect, HLHS=Hypoplastic Left Heart Syndrome, PVAS=Pulmonary Valve Atresia/Stenosis, TGV=Transposition of Great Vessels, TOF=Tetralogy of Fallot, TVAS=Tricuspid Valve Atresia/Stenosis

Table 3.4: Map odds ratio ranges (lower, upper) and global p-values for ventricular septal defects born between 1999-2011, three-year intervals, in Texas

Model	Span Size†	Model 1	Global P-Value	Model 2	Global P-Value	Model 3	Global P-Value
1999-2001	0.20	(0.14, 2.37)	<0.001	(0.16, 2.38)	<0.001	(0.14, 2.32)	<0.001
2000-2002	0.20	(0.18, 2.47)	<0.001	(0.20, 2.53)	<0.001	(0.22, 2.24)	<0.001
2001-2003	0.20	(0.19, 2.24)	<0.001	(0.20, 2.24)	<0.001	(0.26, 2.47)	<0.001
2002-2004	0.20	(0.23, 2.32)	<0.001	(0.25, 2.35)	<0.001	(0.25, 2.37)	<0.001
2003-2005	0.20	(0.23, 2.48)	<0.001	(0.24, 2.53)	<0.001	(0.22, 2.61)	<0.001
2004-2006	0.20	(0.28, 2.78)	<0.001	(0.28, 2.59)	<0.001	(0.26, 2.89)	<0.001
2005-2007	0.20	(0.32, 2.89)	<0.001	(0.36, 2.69)	<0.001	(0.38, 2.57)	<0.001
2006-2008	0.20	(0.36, 3.13)	<0.001	(0.41, 2.77)	<0.001	(0.39, 3.09)	<0.001
2007-2009	0.20	(0.43, 3.02)	<0.001	(0.47, 2.79)	<0.001	(0.37, 3.80)	<0.001
2008-2010	0.20	(0.33, 2.73)	<0.001	(0.36, 2.64)	<0.001	(0.30, 3.51)	<0.001
2009-2011	0.20	(0.41, 2.37)	<0.001	(0.42, 2.37)	<0.001	(0.36, 2.92)	<0.001

† span size was held constant across Models 1-3

Table 3.5: Map odds ratio ranges (lower, upper) and global p-values for atrial septal defects born between 1999-2011, three-year intervals, in Texas

Model	Span Size†	Model 1	Global P-Value	Model 2	Global P-Value	Model 3	Global P-Value
1999-2001	0.20	(0.26, 9.91)	<0.001	(0.21, 10.50)	<0.001	(0.16, 10.80)	<0.001
2000-2002	0.20	(0.24, 7.47)	<0.001	(0.24, 8.18)	<0.001	(0.19, 8.62)	<0.001
2001-2003	0.20	(0.17, 5.81)	<0.001	(0.16, 5.88)	<0.001	(0.14, 6.36)	<0.001
2002-2004	0.20	(0.20, 5.93)	<0.001	(0.18, 5.74)	<0.001	(0.13, 5.85)	<0.001
2003-2005	0.20	(0.19, 6.20)	<0.001	(0.16, 6.33)	<0.001	(0.11, 6.66)	<0.001
2004-2006	0.20	(0.19, 6.70)	<0.001	(0.17, 6.59)	<0.001	(0.12, 6.57)	<0.001
2005-2007	0.20	(0.21, 6.98)	<0.001	(0.20, 7.25)	<0.001	(0.14, 7.12)	<0.001
2006-2008	0.20	(0.33, 7.03)	<0.001	(0.33, 7.19)	<0.001	(0.30, 7.09)	<0.001
2007-2009	0.20	(0.32, 5.36)	<0.001	(0.31, 5.17)	<0.001	(0.25, 5.10)	<0.001
2008-2010	0.20	(0.22, 3.98)	<0.001	(0.21, 3.99)	<0.001	(0.18, 3.91)	<0.001
2009-2011	0.20	(0.20, 2.65)	<0.001	(0.18, 2.76)	<0.001	(0.16, 2.93)	<0.001

† span size was held constant across Models 1-3

CONCLUSIONS

This dissertation explored the use of novel spatial approaches for disease mapping and exposure assessment. Firstly, sampling designs to improve spatial analyses were evaluated for selection of controls using the Massachusetts state birth record in 2004. In addition, this work examined the effect of environmental factors and location on pregnancy outcomes in Texas from 1999-2011. The effect of living near unconventional natural gas developments (UNGD) was assessed in a variety of exposure measures using increasing distance measures and considered many potential variables that may confound the relationship with birth defects. Birth defect risk factors were further evaluated within a spatial context to potentially identify areas of high and low risk to further identify environmental teratogens.

Simple random sample (SRS) designs are common for case-control studies, but they may not be ideal for spatial studies where location is a significant factor. Unmatched spatially stratified random sampling (SSRS) selects controls across the study area using non-overlapping strata. In a simulation study using non-cases from a birth registry, the SSRS designs was more efficient with model estimators compared with SRS designs. Not only did SSRS yield an overall lower average MSE, lower theoretical standard error, and higher relative efficiency, SSRS designs performed better along the edges of the study area, a known issue with SRS designs. Map outputs were also more consistent when controls were spatially selected, specifically SSRS designs with one, two, or includes another stratified variable. Therefore, this novel design can be cost effective in selecting controls using only 14% of the total non-cases. Many practical uses for SSRS designs can be applied such as biorepository linkage and additional data collection. However, further exploration of sampling design performances is needed, particularly with geographic edge effects, sparse-data issues, and using realistic participant locations.

The SSRS was used to select controls from a large Texas birth cohort data set to investigate associations between UNGD exposure and birth defects. UNGDs may release air and water pollutants due to the number of chemicals used in the extraction process. Teratogens have been identified with hydraulic fracturing fluid and only a few studies have inconsistently examined the relationship between UNGDs and birth defects in different states. With a large, state-wide birth defect registry in Texas, this work analyzed exposure to UNGDs using proximity-density measures as continuous, tertiles, and 5^{th} to 95^{th} percentile difference within generalized linear model and generalized additive model frameworks. Birth defects subtypes with larger numbers of cases were also analyzed temporally to examine risk over time. Mothers living within the highest tertile of UNGD density were at risk for births with neural tube defects (NTD), gastroschisis among older mothers, and congenital heart defects (CHD) within 1km of maternal addresses. Risk generally decreased with distance for NTDs, and gastroschisis, but remained the same or increased with larger buffer radii for some CHDs. Additionally, adjusting for location in generalized models were not significantly different among birth defects, but appeared to attenuate risk for atrial septal defects and ventricular septal defects starting from 2005-2011. Accounting for maternal and community variables using an inter-percentile difference range also did not substantially explain risks associated with UNGDs. Orofacial defects were not associated with UNGDs in these analyses. The limited evidence on the effect of UNGD density as a function of distance should be further explored, as well as accounting for additional risk factors that may confound the relationship with birth defects. More studies with precise measures of chemical exposures with biomarkers to UNGD are needed to further our understanding of potential birth defect teratogens.

Spatial analyses may provide further insight on potential teratogen exposure that may vary spatially by identifying areas of high or low risk. As birth defect etiology is unknown, this work attempted to disentangle maternal and community risk factors in relation to the spatial distribution of birth defects in Texas within three nested models. The first model mapped crude risk, the second model included maternal characteristics, and the last model included maternal and environmental and community-level factors. Given that these risk factors are related to birth defects, spatial risk would be expected to decrease after adjustment in the model. CHDs, NTDs, gastroschisis, and orofacial defects risk was mapped across Texas, and more common CHDs were again examined temporally. Location of maternal address was significantly associated with all birth defects except hypoplastic left heart syndrome. Adjusting for maternal characteristics decreased risk for some birth defects. However, the addition of maternal and environmental characteristics depreciated many areas of statistical significance, suggesting that environmental and community factors explain some of the spatial variation that was observed. Pulmonary valve stenosis and atresia was the only defect that did not change after adding these variables. Geographic regions also illustrated distinctive areas of risk, with elevated risk for all defects in North and South Texas; temporal analyses observed an increase in risk over time in these areas which may suggest an introduction of a new environmental exposure. This work also observed low risk in East Texas for all birth defects, although this association may be due to inconsistent disease diagnosis among providers. Although risk was mapped across birth defects while accounting for many known risk factors, some areas remain elevated and future research is still needed to extrapolate important risk factors in areas of increased risk.

Birth defects can contribute to a lifetime of disability and can be costly to those administering and receiving care. This dissertation evaluated additional methods to increase

efficiency of spatial studies and observed an association with birth defects and UNGDs. Further, areas of increased risk were identified in specific areas of Texas, and additional work to extrapolate causes of birth defects is imperative in preventing them in the future. Chemicals used in UNGD extraction are still relatively unknown, and exposure to these chemicals may increase the risk for not only birth defects, but other diseases. Methodology to investigate birth defects must be carefully considered in order to fully understand this complex public health problem.

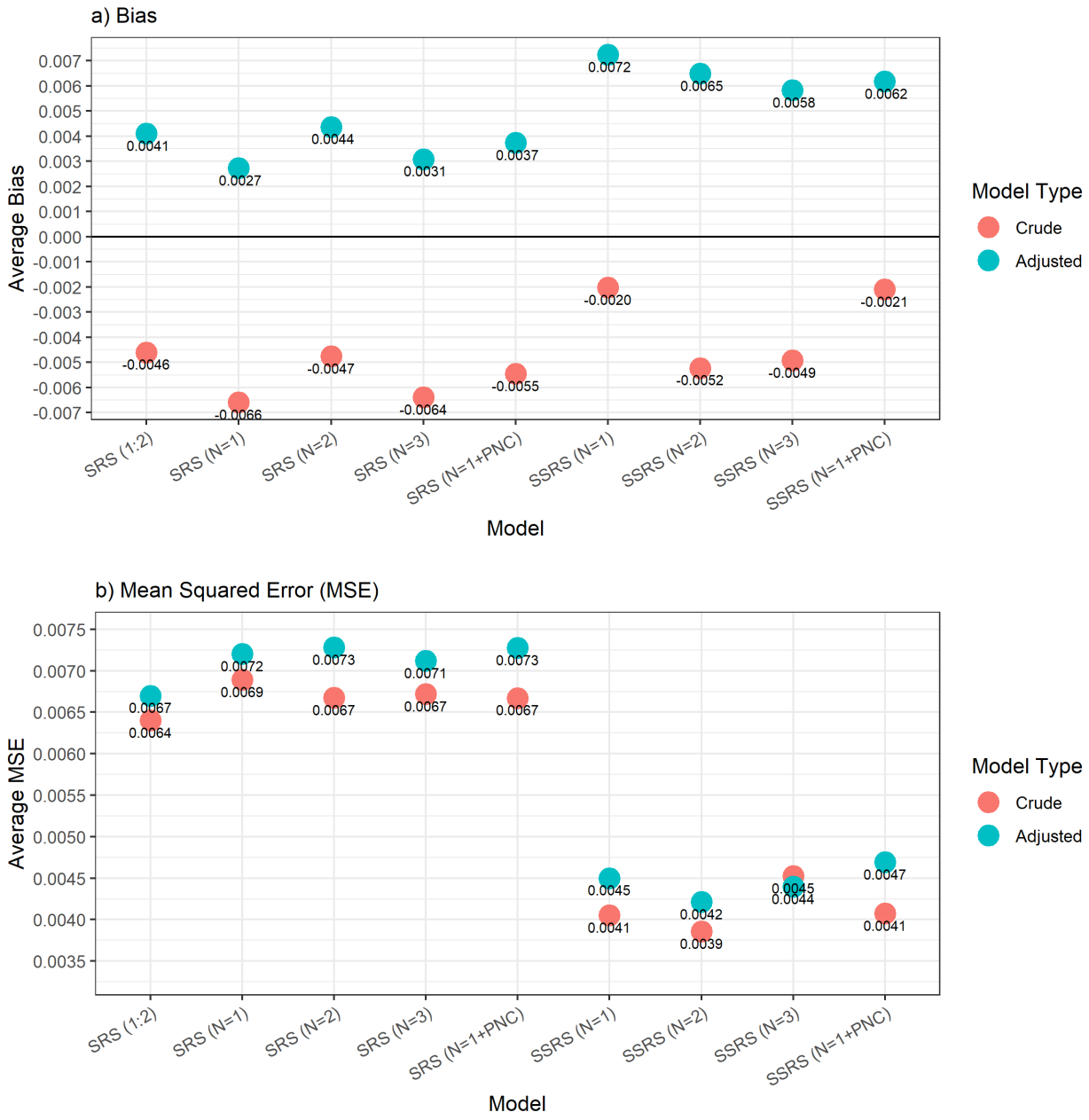
APPENDIX A – Unmatched Spatially Stratified Controls: A simulation study examining efficiency and precision using spatially-diverse controls and generalized additive models

The "sampcont()" function in the MapGAM package (Version 1.2-6) in R produces evenly sized, pre-defined stratums across the study area and randomly selects controls from within each stratum. Stratum size is defined by changing the nrow and ncol within the sampcont function and will create a new data frame with cases, controls with inverse-weights, and the grid of strata.

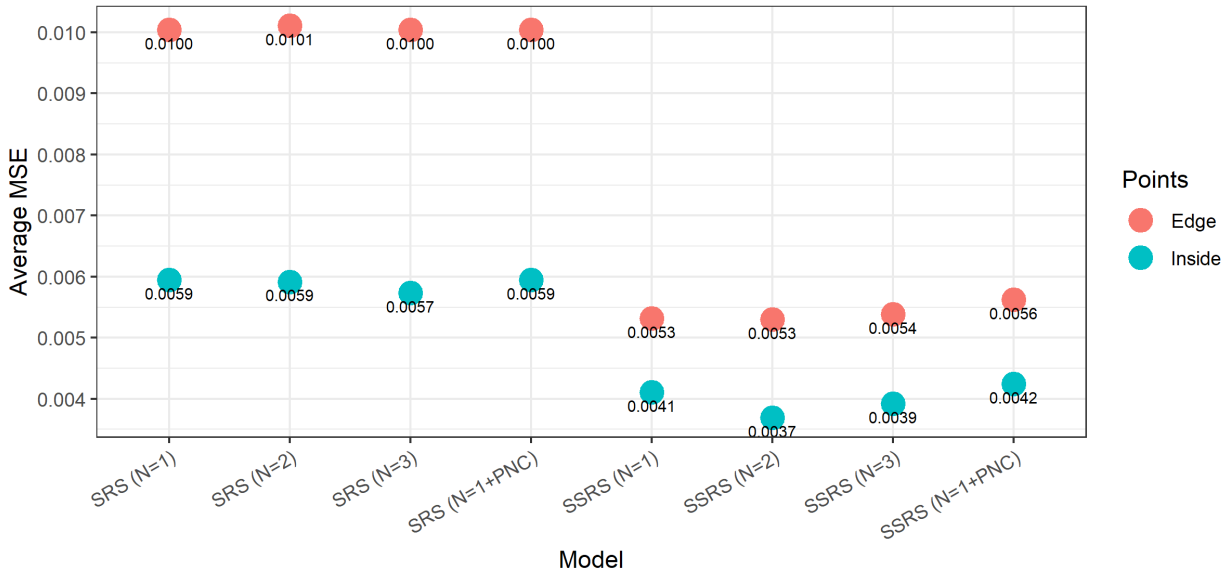
```
Sampcont=function (rdata, type = "stratified", casecol = 1, Xcol = 2,
   Ycol = 3, regions = NULL, addstrat = NULL, times = NULL,
   n = 1, nrow = 100, ncol = 100)
{
   polyGrid <- NULL
   if (type == "stratified") {
      if (!is.null(times)) {
         warning("times argument has been renamed; please use addstrat instead in the future")
         if (!is.null(addstrat))
            stop("use either addstrat or times, not both")
         addstrat = times
      }
      if (!is.null(addstrat) && length(addstrat) != dim(rdata)[1])
         stop("addstrat argument must be NULL or a vector/factor of length = rows in rdata")
      if (is.null(regions)) {
         XYnames = names(rdata)[c(Xcol, Ycol)]
         Xrange = range(rdata[, Xcol])
         Yrange = range(rdata[, Ycol])
         polyGrid = PBSmapping::makeGrid(x = seq(Xrange[1],
            Xrange[2], length.out = ncol), y = seq(Yrange[1],
            Yrange[2], length.out = nrow))
         names(rdata)[c(Xcol, Ycol)] = c("X", "Y")
         rdata$EID = 1:length(rdata$X)
```

```
    idpolys = PBSmapping::findCells(PBSmapping::as.EventData(rdata),
        polyGrid)
    rdata = merge(idpolys, rdata)
    regions = paste((1:ncol)[rdata$PID], (1:nrow)[rdata$SID],
        sep = ",")
    rdata = rdata[, !(names(rdata) %in% c("EID",
        "PID", "SID", "Bdry"))]
    names(rdata)[c(Xcol, Ycol)] = XYnames
    gridsize = c(nrow, ncol)
}
else {
    gridsize = NA
    if (length(regions) != dim(rdata)[1])
        stop("regions argument must be NULL or a vector/factor of length = rows in rdata")
}
strata = paste(regions, addstrat, sep = "")
eligible = rdata[, casecol] == 0
counts = table(strata[eligible])
if (median(counts) <= n)
    warning(paste("Most strata include", n, "or fewer controls;",
        "consider alternative sampling designs if this is unexpected"))
estrat = names(counts)
ns = pmin(n, counts)
dsamp = rdata[rdata[, casecol] == 1, ]
ncases = dim(dsamp)[1]
dsamp[ncases + 1:sum(ns), ] = NA
w = c(rep(1, ncases), rep(counts/ns, times = ns))
rownum = ncases
```

```
    for (i in 1:length(counts)) {
        ind = sample(1:counts[i], ns[i])
        controls = rdata[strata == estrat[i] & eligible,
            ][ind, ]
        dsamp[rownum + 1:ns[i], ] = controls
        rownum = rownum + ns[i]
    }
    n = length(w) - ncases
    cat(paste(n, "controls selected from", sum(eligible),
        "eligibles in", length(estrat), "strata."),
        fill = T)
  }
  if (type == "simple") {
    eligible = rdata[, casecol] == 0
    if (n > sum(eligible))
        stop(paste("rdata contains only ", n, " eligible controls"))
    dsamp = rdata[rdata[, casecol] == 1, ]
    ind = sample(1:dim(rdata)[1], n, prob = eligible)
    dsamp = rbind(dsamp, rdata[ind, ])
    w = c(rep(1, sum(!eligible)), rep(n/sum(eligible), n))
    gridsize = c(1, 1)
  }
  return(list(rdata = dsamp, w = w, ncont = n, type = type,
    gridsize = gridsize, grid = polyGrid))
}
```



Appendix Figure A.1: Averaged bias, and mean Squared Error (MSE) of crude and adjusted models for simple random sample (SRS) and spatially stratified random sampled (SRS)controls among 500 simulations using a rectangular grid



Appendix Figure A.2: mean squared error (MSE) between inner and edge map points among crude and adjusted models for spatially stratified controls (SSRS) compared to randomly selected (SRS) controls and across 500 simulations using a rectangular grid

Appendix Table A.1: Example of iterative adjusting rows and columns to select controls using spatially stratified random sampling (SSRS) N=1. Target number of controls is 8778

Iteration	Row	Column	Controls Selected
1	100	175	4724
2	150	263	8096
3	160	280	8730
4	161	281	8755
5	161	282	8801
6	162	280	8764
7	**162**	**281**	**8787**
8	162	282	8854

Iteration 1 was chosen based on the aspect ratio of Massachusetts, followed by incrementally added or subtracted by 50 to the row until it was near the target number of controls. Rows and columns were then adjusted while maintaining the state aspect ratio to reach target.

Appendix Table A.2: Theoretical standard errors of crude and adjusted models for randomly selected (SRS), and spatially stratified (SSRS) controls across 500 simulations among preterm births, Massachusetts, 2004, using a rectangular grid

		Theoretical Standard Error (SE)			
	N controls	Crude	Adjusted	Crude Relative Efficiency	Adjusted Relative Efficiency
True Model	64,785	1.89 e-02	2.14 e-02	-	-
SRS (1:2 Ratio)	8778	2.65 e-02	3.01 e-02	71%	71%
SRS (N=1)	8782	2.65 e-02	3.01 e-02	71%	71%
SRS (N=2)	8785	2.65 e-02	3.01 e-02	71%	71%
SRS (N=3)	8792	2.65 e-02	3.01 e-02	71%	71%
SRS (N=1+PNC)	8793	2.65 e-02	3.01 e-02	71%	71%
SSRS (N=1)	8782	2.18 e-02	2.76 e-02	87%	77%
SSRS (N=2)	8785	2.19 e-02	2.78 e-02	86%	77%
SSRS (N=3)	8792	2.25 e-02	2.82 e-02	84%	76%
SSRS (N=1+PNC)	8793	2.21 e-02	2.71 e-02	86%	79%

*Relative Efficiency = True model SE / selected model SE

APPENDIX B – Chapter 2: Birth Defects and Unconventional Natural Gas Developments in Texas, 1999-2011

Appendix Table B.1: Odds ratios (OR) and 95% confidence intervals (CI) for the associations between model covariates and neural tube defects (Spina Bifida and Anencephaly) born between 1999-2011 in Texas

Defect/Model	**1km OR (95% CI)**	**3km OR (95% CI)**	**7.5km OR (95% CI)**
Spina Bifida (n=1,463)			
Span size	0.30	0.30	0.30
Increased Well Count[a]	3	24	132
Model 2			
Well Density[a]	1.06 (0.96, 1.18)	0.94 (0.82, 1.08)	0.92 (0.81, 1.04)
Model 3			
Well Density[a]	1.06 (0.96, 1.18)	0.91 (0.78, 1.05)	0.93 (0.82, 1.05)
Non- Smoker	Ref	Ref	Ref
Smoker	0.69 (0.53, 0.89)	0.68 (0.52, 0.88)	0.68 (0.52, 0.88)
Singleton	Ref	Ref	Ref
Two + Fetus	0.94 (0.69, 1.28)	0.94 (0.69, 1.28)	0.93 (0.68, 1.27)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.74 (0.62, 0.89)	0.74 (0.62, 0.88)	0.74 (0.62, 0.88)
Age 25-29	0.92 (0.80, 1.06)	0.93 (0.81, 1.07)	0.93 (0.80, 1.07)
Age 30-34	1.77 (1.52, 2.06)	1.76 (1.51, 2.06)	1.76 (1.51, 2.06)
Age 35-39	1.06 (0.87, 1.30)	1.07 (0.87, 1.30)	1.06 (0.87, 1.30)
Age 40-60	0.83 (0.54, 1.27)	0.83 (0.54, 1.26)	0.83 (0.54, 1.27)
Non- Hispanic White	Ref	Ref	Ref
Black non-hispanic	0.89 (0.72, 1.09)	0.87 (0.70, 1.07)	0.88 (0.71, 1.08)
Hispanic	1.07 (0.94, 1.22)	1.06 (0.93, 1.21)	1.06 (0.93, 1.21)
Other non-hispanic	0.67 (0.45, 1.01)	0.66 (0.44, 0.99)	0.67 (0.45, 1.00)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.35 (1.18, 1.55)	1.36 (1.19, 1.57)	1.36 (1.18, 1.56)
Greater than HS	0.63 (0.55, 0.72)	0.63 (0.55, 0.72)	0.63 (0.55, 0.72)
Model 4			
Well Density[a]	1.09 (0.98, 1.21)	0.92 (0.80, 1.06)	0.95 (0.84, 1.07)
Non- Smoker	Ref	Ref	Ref
Smoker	0.71 (0.55, 0.93)	0.70 (0.54, 0.92)	0.71 (0.54, 0.92)
Singleton	Ref	Ref	Ref
Two + Fetus	0.93 (0.68, 1.27)	0.93 (0.68, 1.27)	0.93 (0.68, 1.26)
Age 20-24	Ref	Ref	Ref

Age 10-19	0.79 (0.66, 0.94)	0.78 (0.65, 0.93)	0.78 (0.65, 0.94)
Age 25-29	0.94 (0.81, 1.08)	0.94 (0.82, 1.09)	0.94 (0.81, 1.08)
Age 30-34	1.94 (1.66, 2.27)	1.93 (1.65, 2.26)	1.93 (1.65, 2.26)
Age 35-39	1.18 (0.97, 1.45)	1.18 (0.96, 1.45)	1.18 (0.96, 1.45)
Age 40-60	0.80 (0.52, 1.23)	0.80 (0.52, 1.23)	0.80 (0.52, 1.23)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.83 (0.67, 1.02)	0.81 (0.66, 1.00)	0.82 (0.66, 1.01)
Hispanic	0.98 (0.86, 1.13)	0.98 (0.85, 1.12)	0.98 (0.85, 1.12)
Other non-Hispanic	0.67 (0.45,1.00)	0.66 (0.44, 0.99)	0.66 (0.44, 1.00)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.32 (1.15, 1.52)	1.33 (1.16, 1.53)	1.33 (1.15, 1.53)
Greater than HS	0.69 (0.60, 0.79)	0.69 (0.59, 0.79)	0.69 (0.59, 0.79)
Median Income($10,000)[b]	0.92 (0.89, 0.95)	0.92 (0.89, 0.95)	0.92 (0.89, 0.95)
Urban	Ref	Ref	Ref
Rural	0.92 (0.75, 1.14)	0.95 (0.77, 1.17)	0.94 (0.77, 1.16)
Average Truck Miles Traveled (IQR=800,805)[c]	1.03 (1.00, 1.05)	1.02 (1.00, 1.05)	1.02 (1.00, 1.05)
Anencephaly (n= 700)			
Span size	0.85	0.85	0.85
Increased Well Count[a]	3	26	142
Model 2			
Well Density[a]	1.17 (1.05, 1.31)	1.10 (0.92, 1.30)	1.04 (0.89, 1.22)
Model 3			
Well Density[a]	1.23 (1.10, 1.37)	1.11 (0.92, 1.33)	1.08 (0.91, 1.27)
Non- Smoker	Ref	Ref	Ref
Smoker	0.73 (0.50, 1.04)	0.72 (0.50, 1.04)	0.72 (0.50, 1.04)
Singleton	Ref	Ref	Ref
Two + Fetus	3.20 (2.34, 4.37)	3.13 (2.29, 4.27)	3.14 (2.30, 4.29)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.74 (0.58, 0.94)	0.74 (0.58, 0.94)	0.74 (0.58, 0.94)
Age 25-29	0.84 (0.69, 1.03)	0.84 (0.69, 1.03)	0.85 (0.69, 1.04)
Age 30-34	1.53 (1.21, 1.92)	1.52 (1.21, 1.92)	1.52 (1.21, 1.92)
Age 35-39	0.60 (0.42, 0.84)	0.60 (0.43, 0.84)	0.60 (0.43, 0.85)
Age 40-60	1.01 (0.58, 1.75)	1.01 (0.58, 1.75)	1.01 (0.58, 1.75)
Non- Hispanic White	Ref	Ref	Ref

Black non-Hispanic	1.37 (1.03, 1.83)	1.34 (1.00, 1.78)	1.32 (0.99, 1.76)
Hispanic	1.51 (1.23, 1.85)	1.47 (1.20, 1.80)	1.47 (1.20, 1.80)
Other non-Hispanic	1.68 (1.04, 2.71)	1.65 (1.02, 2.66)	1.64 (1.02, 2.65)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.81 (1.48, 2.22)	1.81 (1.48, 2.22)	1.82 (1.49, 2.22)
Greater than HS	0.64 (0.52, 0.79)	0.64 (0.52, 0.79)	0.64 (0.52, 0.79)
Model 4			
Well Density[a]	1.25 (1.12, 1.40)	1.12 (0.93, 1.34)	1.10 (0.93, 1.29)
Non- Smoker	Ref	Ref	Ref
Smoker	0.78 (0.54, 1.12)	0.77 (0.54, 1.12)	0.77 (0.53, 1.12)
Singleton	Ref	Ref	Ref
Two + Fetus	3.24 (2.36, 4.44)	3.19 (2.32, 4.37)	3.20 (2.33, 4.39)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.81 (0.63, 1.03)	0.81 (0.63, 1.03)	0.81 (0.64, 1.03)
Age 25-29	0.86 (0.70, 1.05)	0.85 (0.70, 1.05)	0.86 (0.70, 1.05)
Age 30-34	1.76 (1.39, 2.22)	1.74 (1.38, 2.20)	1.74 (1.38, 2.20)
Age 35-39	0.66 (0.47, 0.94)	0.67 (0.47, 0.94)	0.67 (0.48, 0.95)
Age 40-60	0.96 (0.55, 1.67)	0.96 (0.55, 1.67)	0.97 (0.56, 1.68)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.24 (0.93, 1.67)	1.22 (0.91, 1.64)	1.20 (0.89, 1.61)
Hispanic	1.38 (1.12, 1.71)	1.35 (1.10, 1.67)	1.35 (1.09, 1.67)
Other non-Hispanic	1.76 (1.09, 2.85)	1.73 (1.07, 2.79)	1.72 (1.06, 2.78)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.76 (1.44, 2.15)	1.76 (1.44, 2.15)	1.77 (1.44, 2.16)
Greater than HS	0.73 (0.59, 0.91)	0.73 (0.59, 0.91)	0.73 (0.59, 0.91)
Median Income($10,000)[b]	0.88 (0.84, 0.93)	0.89 (0.84, 0.93)	0.89 (0.84, 0.93)
Urban	Ref	Ref	Ref
Rural	0.95 (0.70, 1.28)	0.98 (0.72, 1.32)	0.99 (0.73, 1.33)
Average Truck Miles Traveled (IQR=800,805)[c]	1.02 (0.99, 1.04)	1.01 (0.99, 1.04)	1.01 (0.99, 1.04)

[a] ORs correspond to an increase in wells from the 5th to the 95th percentile of the distribution within a buffer distance during year of pregnancy

[b] ORs correspond to a $10,000 increase in median income at block group of mother's maternal address at time of delivery

[c] ORs correspond to an interquartile range increase in average truck miles traveled by county.

Appendix Table B.2: Odds ratios (OR) and 95% confidence intervals (CI) for the associations between model covariates and orofacial defects (cleft palate only and cleft lip with and without palate) born between 1999-2011 in Texas

Defect/Model	**1km OR (95% CI)**	**3km OR (95% CI)**	**7.5km OR (95% CI)**
Cleft Palate Only (n=2,071)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	3	26	149
Model 2			
Well Density[a]	1.02 (0.93, 1.12)	1.01 (0.91, 1.11)	0.99 (0.89, 1.10)
Model 3			
Well Density[a]	0.96 (0.87, 1.07)	0.98 (0.88, 1.08)	0.93 (0.84, 1.04)
Non- Smoker	Ref	Ref	Ref
Smoker	1.15 (0.98,1.35)	1.15 (0.98, 1.35)	1.15 (0.98, 1.36)
Singleton	Ref	Ref	Ref
Two + Fetus	0.78 (0.61, 1.00)	0.78 (0.61, 1.01)	0.79 (0.61, 1.01)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.68 (0.59, 0.80)	0.69 (0.59, 0.80)	0.69 (0.59, 0.80)
Age 25-29	0.86 (0.76, 0.97)	0.86 (0.76, 0.97)	0.86 (0.76, 0.97)
Age 30-34	1.01 (0.88, 1.15)	1.01 (0.89, 1.15)	1.01 (0.89, 1.15)
Age 35-39	0.93 (0.79, 1.09)	0.93 (0.79, 1.09)	0.93 (0.79, 1.09)
Age 40-60	2.03 (1.55, 2.64)	2.02 (1.55, 2.64)	2.03 (1.56, 2.65)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.53 (0.45, 0.63)	0.54 (0.45, 0.63)	0.53 (0.45, 0.63)
Hispanic	0.70 (0.63, 0.78)	0.70 (0.63, 0.78)	0.70 (0.63, 0.78)
Other non-Hispanic	0.91 (0.73, 1.12)	0.91 (0.74, 1.12)	0.91 (0.73, 1.12)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.06 (0.95, 1.20)	1.06 (0.95, 1.20)	1.06 (0.94, 1.20)
Greater than HS	0.79 (0.70, 0.89)	0.79 (0.71, 0.89)	0.79 (0.71, 0.89)
Model 4			
Well Density[a]	0.96 (0.87, 1.07)	0.98 (0.88, 1.08)	0.94 (0.84, 1.04)
Non- Smoker	Ref	Ref	Ref
Smoker	1.15 (0.98, 1.35)	1.15 (0.98, 1.35)	1.16 (0.98, 1.36)
Singleton	Ref	Ref	Ref
Two + Fetus	0.77 (0.60, 0.99)	0.77 (0.60, 0.99)	0.77 (0.60, 0.99)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.69 (0.59,0.81)	0.69 (0.59, 0.81)	0.69 (0.59, 0.81)

Age 25-29	0.86 (0.77, 0.98)	0.87 (0.77, 0.98)	0.87 (0.77, 0.98)
Age 30-34	1.02 (0.89, 1.17)	1.02 (0.89, 1.17)	1.02 (0.89, 1.17)
Age 35-39	0.93 (0.79, 1.10)	0.94 (0.79, 1.10)	0.93 (0.79, 1.10)
Age 40-60	2.04 (1.56, 2.67)	2.04 (1.56, 2.66)	2.05 (1.56, 2.68)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.52 (0.43, 0.62)	0.52 (0.43, 0.62)	0.52 (0.43, 0.62)
Hispanic	0.69 (0.61, 0.77)	0.69 (0.62, 0.77)	0.69 (0.61, 0.77)
Other non-Hispanic	0.90 (0.72, 1.11)	0.90 (0.72, 1.11)	0.90 (0.72, 1.11)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.06 (0.94, 1.20)	1.06 (0.94, 1.20)	1.06 (0.94, 1.19)
Greater than HS	0.79 (0.70, 0.90)	0.80 (0.71, 0.90)	0.80 (0.71, 0.90)
Median Income($10,000)[b]	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)
Urban	Ref	Ref	Ref
Rural	0.83 (0.71, 0.98)	0.83 (0.71, 0.98)	0.83 (0.71, 0.98)
Average Truck Miles Traveled (IQR=675,984)[c]	0.98 (0.96, 1.00)	0.98 (0.96, 1.00)	0.98 (0.96, 1.00)
Cleft Lip with/ without palate (n=4,116)			
Span size	0.80	0.80	0.80
Increased Well Count[a]	3	27	149
Model 2			
Well Density[a]	1.05 (0.99, 1.13)	0.98 (0.90, 1.06)	0.96 (0.89, 1.04)
Model 3			
Well Density[a]	1.04 (0.98, 1.12)	0.96 (0.89, 1.04)	0.95 (0.88, 1.03)
Non- Smoker	Ref	Ref	Ref
Smoker	1.29 (1.14, 1.47)	1.29 (1.14, 1.47)	1.29 (1.14, 1.47)
Singleton	Ref	Ref	Ref
Two + Fetus	1.14 (0.96, 1.36)	1.14 (0.96, 1.35)	1.14 (0.96, 1.36)
Age 20-24	Ref	Ref	Ref
Age 10-19	1.02 (0.92, 1.13)	1.02 (0.93, 1.13)	1.02 (0.92, 1.13)
Age 25-29	0.88 (0.81, 0.96)	0.88 (0.81, 0.96)	0.88 (0.81, 0.96)
Age 30-34	1.01 (0.92, 1.11)	1.02 (0.93, 1.12)	1.02 (0.92, 1.13)
Age 35-39	0.95 (0.84, 1.11)	0.95 (0.84, 1.07)	0.95 (0.84, 1.07)
Age 40-60	1.02 (0.83, 1.27)	1.02 (0.82, 1.26)	1.02 (0.82, 1.26)
Non- Hispanic White	Ref	Ref	Ref

Black non-Hispanic	0.59 (0.52, 0.67)	0.59 (0.52, 0.67)	0.59 (0.52, 0.67)
Hispanic	1.01 (0.93, 1.09)	1.00 (0.92, 1.09)	1.00 (0.92, 1.09)
Other non-Hispanic	1.02 (0.87, 1.19)	1.02 (0.87, 1.18)	1.01 (0.87, 1.18)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.82 (0.76, 0.89)	0.82 (0.76, 0.89)	0.82 (0.76, 0.89)
Greater than HS	0.82 (0.75, 0.89)	0.82 (0.75, 0.89)	0.82 (0.75, 0.89)
Model 4			
Well Density[a]	1.04 (0.98, 1.12)	0.96 (0.88, 1.04)	0.95 (0.88, 1.03)
Non- Smoker	Ref	Ref	Ref
Smoker	1.27 (1.11, 1.44)	1.26 (1.11, 1.44)	1.26 (1.11, 1.44)
Singleton	Ref	Ref	Ref
Two + Fetus	1.15 (0.97, 1.37)	1.15 (0.96, 1.37)	1.15 (0.96, 1.37)
Age 20-24	Ref	Ref	Ref
Age 10-19	1.04 (0.94, 1.15)	1.04 (0.94, 1.15)	1.04 (0.95, 1.15)
Age 25-29	0.88 (0.81, 0.96)	0.89 (0.82, 0.96)	0.89 (0.81, 0.97)
Age 30-34	1.04 (0.94, 1.14)	1.05 (0.95, 1.14)	1.04 (0.95, 1.15)
Age 35-39	0.99 (0.88, 1.12)	0.99 (0.88, 1.12)	0.99 (0.88, 1.12)
Age 40-60	1.06 (0.86, 1.32)	1.06 (0.86, 1.32)	1.06 (0.86, 1.32)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.56 (0.49, 0.63)	0.55 (0.48, 0.63)	0.55 (0.48, 0.63)
Hispanic	0.97 (0.89, 1.05)	0.96 (0.88, 1.05)	0.96 (0.88, 1.05)
Other non-Hispanic	1.01 (0.86, 1.18)	1.00 (0.86, 1.18)	1.00 (0.86, 1.17)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.81 (0.74, 0.88)	0.81 (0.74, 0.88)	0.81 (0.74, 0.88)
Greater than HS	0.86 (0.79, 0.93)	0.85 (0.78, 0.93)	0.85 (0.78, 0.93)
Median Income($10,000)[b]	0.97 (0.95, 0.98)	0.96 (0.95, 0.98)	0.97 (0.95, 0.98)
Urban	Ref	Ref	Ref
Rural	1.04 (0.93, 1.17)	1.05 (0.94, 1.17)	1.05 (0.94, 1.17)
Average Truck Miles Traveled (IQR=769,913)[c]	1.00 (0.99, 1.02)	1.00 (0.99, 1.02)	1.00 (0.99, 1.02)

[a] ORs correspond to an increase in wells from the 5th to the 95th percentile of the distribution within a buffer distance during year of pregnancy

[b] ORs correspond to a $10,000 increase in median income at block group of mother's maternal address at time of delivery

[c] ORs correspond to an interquartile range increase in average truck miles traveled by county.

Appendix Table B.3. Odds ratios (OR) and 95% confidence intervals (CI) for the associations between model covariates and gastroschisis defects (gastroschisis age≤25, gastroschisis age>25, all gastroschisis) born between 1999-2011 in Texas.

Defect/Model	**1 km OR (95% CI)**	**3 km OR (95% CI)**	**7.5 km OR (95% CI)**
Gastroschisis (age ≤24) (n=1,829)			
Span size	0.30	0.30	0.30
Increased Well Count[a]	3	25	141
Model 2			
Well Density[a]	1.09 (0.99,1.20)	0.99 (0.88, 1.10)	1.09 (0.98, 1.22)
Model 3			
Well Density[a]	1.04 (0.95, 1.14)	0.98 (0.88, 1.10)	1.09 (0.98, 1.21)
Non- Smoker	Ref	Ref	Ref
Smoker	0.70 (0.58, 0.84)	0.70 (0.58, 0.84)	0.70 (0.58, 0.84)
Singleton	Ref	Ref	Ref
Two + Fetus	0.90 (0.60, 1.36)	0.90 (0.60, 1.36)	0.91 (0.61, 1.38)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.42 (0.35, 0.51)	0.42 (0.34, 0.51)	0.42 (0.35, 0.51)
Hispanic	0.85 (0.75, 0.96)	0.85 (0.75, 0.95)	0.85 (0.76, 0.96)
Other non-Hispanic	2.07 (1.45, 2.96)	2.10 (1.47, 2.99)	2.08 (1.46, 2.96)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.13 (1.01, 1.26)	1.13 (1.01, 1.26)	1.13 (1.01, 1.26)
Greater than HS	1.00 (0.88, 1.14)	1.01 (0.88, 1.15)	1.01 (0.88, 1.14)
Model 4			
Well Density[a]	1.04 (0.95, 1.14)	0.99 (0.88, 1.10)	1.10 (0.98, 1.22)
Non- Smoker	Ref	Ref	Ref
Smoker	0.70 (0.58, 0.84)	0.70 (0.58, 0.84)	0.70 (0.58, 0.84)
Singleton	Ref	Ref	Ref
Two + Fetus	0.91 (0.61, 1.38)	0.91 (0.60, 1.38)	0.93 (0.61, 1.40)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.42 (0.34, 0.51)	0.42 (0.34, 0.51)	0.42 (0.34, 0.51)
Hispanic	0.84 (0.74, 0.95)	0.84 (0.74, 0.95)	0.84 (0.75, 0.96)
Other non-Hispanic	2.02 (1.41, 2.90)	2.05 (1.43, 2.93)	2.03 (1.42, 2.91)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.13 (1.01, 1.26)	1.13 (1.02, 1.26)	1.13 (1.01, 1.26)
Greater than HS	1.00 (0.87, 1.14)	1.00 (0.87, 1.14)	1.00 (0.87, 1.14)
Median Income ($10,000)[b]	1.01 (0.98, 1.04)	1.01 (0.98, 1.04)	1.01 (0.98, 1.04)
Urban	Ref	Ref	Ref
Rural	0.94 (0.80, 1.11)	0.95 (0.80, 1.12)	0.94 (0.79, 1.10)

Average Truck Miles Traveled (IQR=775,153)[c]	1.01 (0.99, 1.03)	1.01 (0.99, 1.04)	1.01 (0.99, 1.03)
Gastroschisis (age>24) (n=350)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	3	24	140
Model 2			
Well Density[a]	1.13 (1.02, 1.25)	1.14 (0.94, 1.39)	0.98 (0.82, 1.16)
Model 3			
Well Density[a]	1.10 (0.99,1.23)	1.08 (0.88, 1.34)	0.97 (0.79, 1.18)
Non- Smoker	Ref	Ref	Ref
Smoker	4.04 (2.75, 5.95)	4.02 (2.73, 5.92)	3.96 (2.69, 5.83)
Singleton	Ref	Ref	Ref
Two + Fetus	1.27 (0.70, 2.29)	1.20 (0.64, 2.24)	1.35 (0.68, 2.66)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.49 (0.32, 0.77)	0.49 (0.32, 0.77)	0.49 (0.31, 0.77)
Hispanic	0.68 (0.50, 0.93)	0.68 (0.50, 0.93)	0.68 (0.50, 0.92)
Other non-Hispanic	0.27 (0.15, 0.49)	0.27 (0.15, 0.49)	0.27 (0.15, 0.48)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.02 (0.75, 1.40)	1.02 (0.74, 1.39)	1.02 (0.74, 1.40)
Greater than HS	0.39 (0.29, 0.52)	0.39 (0.29, 0.52)	0.38 (0.29, 0.51)
Model 4			
Well Density[a]	1.10 (0.98, 1.23)	1.09 (0.88, 1.34)	0.96 (0.78, 1.17)
Non- Smoker	Ref	Ref	Ref
Smoker	4.43 (2.94, 6.65)	4.42 (2.93, 6.65)	4.32 (2.88, 6.49)
Singleton	Ref	Ref	Ref
Two + Fetus	1.24 (0.69, 2.26)	1.18 (0.63, 2.21)	1.35 (0.68, 2.66)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.47 (0.29, 0.74)	0.46 (0.29, 0.74)	0.46 (0.29, 0.74)
Hispanic	0.65 (0.47, 0.91)	0.65 (0.47, 0.91)	0.65 (0.47, 0.91)
Other non-Hispanic	0.28 (0.15, 0.52)	0.28 (0.15, 0.51)	0.28 (0.15, 0.51)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.98 (0.70, 1.38)	0.97 (0.69, 1.36)	0.97 (0.69, 1.37)
Greater than HS	0.39 (0.29, 0.53)	0.39 (0.29, 0.53)	0.39 (0.29, 0.53)
Median Income ($10,000)[b]	0.97 (0.91, 1.04)	0.97 (0.91, 1.04)	0.97 (0.91, 1.04)
Urban	Ref	Ref	Ref
Rural	0.81 (0.55, 1.18)	0.81 (0.55, 1.18)	0.81 (0.56, 1.18)
Average Truck Miles Traveled (IQR= 786,967)	1.00 (0.94, 1.06)	1.00 (0.94, 1.06)	0.99 (0.94, 1.05)

Gastroschisis (all cases) (n=2,179)			
Span size	0.30	0.30	0.30
Increased Well Count[a]	3	24	139
Model 2			
Well Density[a]	1.00 (0.91, 1.10)	1.03 (0.95, 1.13)	1.02 (0.94, 1.11)
Model 3			
Well Density[a]	1.03 (0.95, 1.13)	1.04 (0.96, 1.13)	1.06 (0.97, 1.15)
Non- Smoker	Ref	Ref	Ref
Smoker	0.94 (0.79, 1.11)	0.93 (0.79, 1.10)	0.93 (0.79, 1.10)
Singleton	Ref	Ref	Ref
Two + Fetus	0.94 (0.79, 1.11)	1.78 (1.28, 2.50)	1.78 (1.27, 2.48)
Age 25-60	Ref	Ref	Ref
Age 10-24	7.69 (6.81, 8.67)	7.69 (6.81, 8.67)	7.69 (6.81, 8.67)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.41 (0.34, 0.48)	0.40 (0.34, 0.48)	0.41 (0.34, 0.48)
Hispanic	0.93 (0.83, 1.04)	0.93 (0.83, 1.04)	0.93 (0.83, 1.04)
Other non-Hispanic	0.72 (0.54, 0.98)	0.73 (0.54, 0.98)	0.73 (0.54, 0.99)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.86 (0.78, 0.95)	0.86 (0.78, 0.95)	0.86 (0.78, 0.95)
Greater than HS	0.77 (0.69, 0.87)	0.77 (0.69, 0.87)	0.77 (0.69, 0.87)
Model 4			
Well Density[a]	1.04 (0.96, 1.14)	1.05 (0.96, 1.14)	1.06 (0.97, 1.15)
Non- Smoker	Ref	Ref	Ref
Smoker	1.07 (0.91, 1.27)	0.93 (0.79, 1.10)	0.93 (0.79, 1.10)
Singleton	Ref	Ref	Ref
Two + Fetus	1.84 (1.32, 2.57)	1.83 (1.31, 2.56)	1.82 (1.30, 2.55)
Age 25-60	Ref	Ref	Ref
Age 10-24	7.59 (6.71, 8.57)	7.58 (6.71, 8.56)	7.58 (6.71, 8.57)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	7.59 (6.71, 8.57)	0.38 (0.32, 0.46)	0.39 (0.32, 0.46)
Hispanic	0.38 (0.32, 0.46)	0.90 (0.80, 1.01)	0.90 (0.80, 1.01)
Other non-Hispanic	0.90 (0.80, 1.01)	0.71 (0.52, 0.96)	0.71 (0.53, 0.97)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.17 (1.06, 1.29)	0.86 (0.77, 0.95)	0.86 (0.77, 0.95)
Greater than HS	0.92 (0.81, 1.04)	0.79 (0.70, 0.89)	0.79 (0.70, 0.89)
Median Income ($10,000)[b]	0.98 (0.95, 1.00)	0.98 (0.95, 1.00)	0.98 (0.95, 1.00)
Urban	Ref	Ref	Ref
Rural	1.08 (0.93, 1.26)	0.92 (0.80, 1.07)	0.93 (0.80, 1.07)

Average Truck Miles Traveled (IQR=756,433)[c]	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)

[a] ORs correspond to an increase in wells from the 5th to the 95th percentile of the distribution within a buffer distance during year of pregnancy.
[b] ORs correspond to a $10,000 increase in median income at block group of mother's maternal address at time of delivery.
[c] ORs correspond to an interquartile range increase in average truck miles traveled by county.

Appendix Table B.4: Odds ratios (OR) and 95% confidence intervals (CI) for the associations between model covariates and congenital heart defects (pulmonary valve atresia/stenosis, transposition of great vessels, tetralogy of Fallot, endocardial cushion defects, tricuspid valve atresia/stenosis, aortic valve stenosis, and hypoplastic left heart syndrome) born between 1999-2011 in Texas

Defect/Model	**1km OR (95% CI)**	**3km OR (95% CI)**	**7.5km OR (95% CI)**
Pulmonary Valve Atresia/ Stenosis (n=3,611)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	3	28	155
Model 2			
Well Density[a]	1.08 (1.02, 1.15)	1.15 (1.08, 1.23)	1.19 (1.12, 1.26)
Model 3			
Well Density[a]	1.06 (1.00, 1.12)	1.16 (1.09, 1.24)	1.20 (1.13, 1.27)
Non- Smoker	Ref	Ref	Ref
Smoker	0.95 (0.82, 1.10)	0.95 (0.83, 1.10)	0.96 (0.83, 1.11)
Singleton	Ref	Ref	Ref
Two + Fetus	2.65 (2.30, 3.04)	2.67 (2.33, 3.07)	2.69 (2.34, 3.08)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.92 (0.83, 1.03)	0.92 (0.82, 1.03)	0.93 (0.83, 1.04)
Age 25-29	0.87 (0.80, 0.96)	0.87 (0.79, 0.96)	0.87 (0.79, 0.95)
Age 30-34	1.14 (1.03, 1.26)	1.14 (1.03, 1.26)	1.14 (1.03, 1.26)
Age 35-39	1.37 (1.21, 1.54)	1.36 (1.21, 1.53)	1.36 (1.21, 1.53)
Age 40-60	0.77 (0.62, 0.95)	0.77 (0.62, 0.95)	0.78 (0.63, 0.96)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.26 (1.13, 1.41)	1.25 (1.12, 1.40)	1.25 (1.12, 1.40)
Hispanic	0.98 (0.90, 1.07)	0.98 (0.90, 1.07)	0.98 (0.90, 1.07)
Other non-Hispanic	0.97 (0.79, 1.18)	0.96 (0.79, 1.17)	0.96 (0.79, 1.17)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.93 (0.85, 1.02)	0.93 (0.85, 1.02)	0.93 (0.85, 1.02)
Greater than HS	0.77 (0.71, 0.84)	0.77 (0.70, 0.84)	0.77 (0.70, 0.84)
Model 4			
Well Density[a]	1.07 (1.01, 1.13)	1.17 (1.10, 1.25)	1.21 (1.13, 1.29)
Non- Smoker	Ref	Ref	Ref
Smoker	0.91 (0.79, 1.05)	0.91 (0.79, 1.05)	0.92 (0.79, 1.06)
Singleton	Ref	Ref	Ref
Two + Fetus	2.75 (2.39, 3.16)	2.79 (2.42, 3.20)	2.80 (2.44, 3.22)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.94 (0.84, 1.05)	0.94 (0.84, 1.05)	0.95 (0.84, 1.06)
Age 25-29	0.88 (0.81, 0.97)	0.88 (0.80, 0.97)	0.88 (0.80, 0.97)
Age 30-34	1.17 (1.05, 1.29)	1.17 (1.05, 1.30)	1.17 (1.05, 1.30)
Age 35-39	1.42 (1.26, 1.60)	1.41 (1.25, 1.59)	1.41 (1.25, 1.59)
Age 40-60	0.81 (0.66, 1.00)	0.81 (0.66, 1.00)	0.82 (0.66, 1.01)

Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.19 (1.06, 1.34)	1.18 (1.05, 1.33)	1.18 (1.05, 1.33)
Hispanic	0.94 (0.86, 1.03)	0.94 (0.86, 1.03)	0.94 (0.85, 1.03)
Other non-Hispanic	0.99 (0.81, 1.20)	0.98 (0.80, 1.19)	0.98 (0.80, 1.20)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.91 (0.83, 0.99)	0.91 (0.83, 0.99)	0.91 (0.83, 0.99)
Greater than HS	0.80 (0.73, 0.87)	0.79 (0.73, 0.87)	0.79 (0.72, 0.86)
Median Income($10,000)[b]	0.96 (0.94, 0.98)	0.96 (0.94, 0.98)	0.96 (0.94, 0.98)
Urban	Ref	Ref	Ref
Rural	1.04 (0.92, 1.17)	1.02 (0.90, 1.16)	1.02 (0.90, 1.15)
Average Truck Miles Traveled (IQR=770,415)[c]	1.01 (0.99, 1.02)	1.00 (0.98, 1.02)	1.00 (0.98, 1.02
Transposition of Great Vessels (n=2,003)			
Span size	0.60	0.60	0.60
Increased Well Count[a]	3	27	148
Model 2			
Well Density[a]	0.99 (0.90, 1.09)	0.97 (0.87, 1.08)	1.02 (0.92, 1.12)
Model 3			
Well Density[a]	1.00 (0.91, 1.10)	0.99 (0.89, 1.10)	1.02 (0.92, 1.13)
Non- Smoker	Ref	Ref	Ref
Smoker	0.91 (0.75, 1.10)	0.91 (0.75, 1.10)	0.91 (0.75, 1.10)
Singleton	Ref	Ref	Ref
Two + Fetus	1.37 (1.08, 1.73)	1.37 (1.08, 1.73)	1.37 (1.08, 1.73)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.87 (0.74, 1.02)	0.87 (0.74, 1.02)	0.87 (0.74, 1.02)
Age 25-29	1.07 (0.94, 1.21)	1.07 (0.94, 1.21)	1.07 (0.94, 1.21)
Age 30-34	1.38 (1.20, 1.58)	1.38 (1.20, 1.58)	1.38 (1.20, 1.58)
Age 35-39	1.49 (1.27, 1.75)	1.49 (1.27, 1.75)	1.49 (1.27, 1.75)
Age 40-60	1.01 (0.76, 1.35)	1.01 (0.76, 1.35)	1.01 (0.76, 1.35)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.90 (0.76, 1.06)	0.90 (0.76, 1.06)	0.90 (0.76, 1.06)
Hispanic	1.04 (0.93, 1.17)	1.04 (0.93, 1.17)	1.04 (0.93, 1.17)
Other non-Hispanic	1.03 (0.82, 1.31)	1.04 (0.82, 1.31)	1.03 (0.82, 1.31)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.03 (0.91, 1.16)	1.03 (0.91, 1.16)	1.03 (0.91, 1.16)
Greater than HS	0.82 (0.73, 0.92)	0.82 (0.73, 0.92)	0.82 (0.73, 0.92)
Model 4			
Well Density[a]	1.00 (0.91, 1.10)	0.99 (0.88, 1.10)	1.02 (0.92, 1.13)
Non- Smoker	Ref	Ref	Ref

Smoker	0.89 (0.73, 1.08)	0.89 (0.73, 1.08)	0.89 (0.73, 1.08)
Singleton	Ref	Ref	Ref
Two + Fetus	1.38 (1.09, 1.75)	1.38 (1.09, 1.75)	1.38 (1.09, 1.75)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.87 (0.74, 1.02)	0.87 (0.74, 1.02)	0.87 (0.74, 1.02)
Age 25-29	1.08 (0.95, 1.22)	1.08 (0.95, 1.22)	1.08 (0.95, 1.22)
Age 30-34	1.40 (1.21, 1.60)	1.40 (1.21, 1.60)	1.40 (1.22, 1.60)
Age 35-39	1.51 (1.29, 1.78)	1.51 (1.29, 1.78)	1.51 (1.28, 1.78)
Age 40-60	1.05 (0.78, 1.40)	1.05 (0.78, 1.40)	1.05 (0.78, 1.41)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.88 (0.74, 1.05)	0.88 (0.74, 1.05)	0.88 (0.74, 1.05)
Hispanic	1.03 (0.91, 1.16)	1.03 (0.91, 1.16)	1.03 (0.91, 1.16)
Other non-Hispanic	1.04 (0.82, 1.32)	1.04 (0.82, 1.32)	1.04 (0.82, 1.32)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.02 (0.91, 1.15)	1.02 (0.90, 1.15)	1.02 (0.90, 1.15)
Greater than HS	0.83 (0.74, 0.94)	0.83 (0.74, 0.94)	0.83 (0.74, 0.94)
Median Income($10,000)[b]	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)	0.99 (0.96, 1.01)
Urban	Ref	Ref	Ref
Rural	1.15 (0.98, 1.35)	1.15 (0.98, 1.36)	1.15 (0.98, 1.35)
Average Truck Miles Traveled (IQR=675,034)[c]	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)
Tetralogy of Fallot (n=1,133)			
Span size	0.55	0.55	0.55
Increased Well Count[a]	3	28	153
Model 2			
Well Density[a]	1.05 (0.94, 1.17)	1.04 (0.91, 1.19)	1.06 (0.93, 1.20)
Model 3			
Well Density[a]	1.00 (0.90, 1.12)	1.02 (0.89, 1.17)	1.05 (0.92, 1.20)
Non- Smoker	Ref	Ref	Ref
Smoker	0.75 (0.57, 0.98)	0.75 (0.57, 0.98)	0.75 (0.57, 0.98)
Singleton	Ref	Ref	Ref
Two + Fetus	1.75 (1.34, 2.30)	1.76 (1.34, 2.30)	1.76 (1.34, 2.31)
Age 20-24	Ref	Ref	Ref
Age 10-19	1.06 (0.87, 1.31)	1.06 (0.87, 1.30)	1.07 (0.87, 1.31)
Age 25-29	0.98 (0.82, 1.16)	0.98 (0.82, 1.16)	0.98 (0.82, 1.16)
Age 30-34	1.23 (1.02, 1.48)	1.23 (1.02, 1.48)	1.23 (1.02, 1.48)
Age 35-39	1.72 (1.40, 2.12)	1.72 (1.40, 2.12)	1.72 (1.40, 2.12)
Age 40-60	1.00 (0.68, 1.46)	1.00 (0.68, 1.46)	1.00 (0.68, 1.46)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.34 (1.11, 1.61)	1.33 (1.11, 1.61)	1.34 (1.11, 1.61)

Hispanic	0.77 (0.66, 0.90)	0.77 (0.66, 0.90)	0.77 (0.66, 0.90)
Other non-Hispanic	1.33 (1.01, 1.75)	1.33 (1.01, 1.75)	1.33 (1.01, 1.75)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.97 (0.82, 1.14)	0.97 (0.82, 1.14)	0.97 (0.82, 1.14)
Greater than HS	0.88 (0.76, 1.03)	0.88 (0.76, 1.03)	0.88 (0.76, 1.03)
Model 4			
Well Density[a]	1.01 (0.90, 1.13)	1.02 (0.89, 1.17)	1.05 (0.92, 1.20)
Non- Smoker	Ref	Ref	Ref
Smoker	0.75 (0.57, 0.98)	0.75 (0.57, 0.98)	0.75 (0.57, 0.98)
Singleton	Ref	Ref	Ref
Two + Fetus	1.76 (1.34, 2.31)	1.76 (1.34, 2.32)	1.77 (1.35, 2.32)
Age 20-24	Ref	Ref	Ref
Age 10-19	1.06 (0.86, 1.30)	1.06 (0.86, 1.30)	1.06 (0.86, 1.30)
Age 25-29	0.98 (0.83, 1.16)	0.98 (0.83, 1.16)	0.98 (0.83, 1.16)
Age 30-34	1.23 (1.02, 1.49)	1.23 (1.02, 1.49)	1.24 (1.02, 1.49)
Age 35-39	1.73 (1.40, 2.14)	1.73 (1.40, 2.14)	1.73 (1.40, 2.14)
Age 40-60	1.02 (0.69, 1.50)	1.02 (0.69, 1.50)	1.02 (0.69, 1.50)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.32 (1.08, 1.61)	1.32 (1.08, 1.61)	1.32 (1.08, 1.61)
Hispanic	0.76 (0.65, 0.90)	0.76 (0.65, 0.90)	0.76 (0.65, 0.90)
Other non-Hispanic	1.32 (1.00, 1.75)	1.32 (1.00, 1.75)	1.32 (1.00, 1.74)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.97 (0.82, 1.14)	0.97 (0.82, 1.14)	0.97 (0.82, 1.14)
Greater than HS	0.89 (0.76, 1.04)	0.89 (0.76, 1.04)	0.89 (0.76, 1.04)
Median Income($10,000)[b]	1.00 (0.97, 1.03)	1.00 (0.97, 1.03)	1.00 (0.97, 1.03)
Urban	Ref	Ref	Ref
Rural	1.10 (0.89, 1.37)	1.10 (0.89, 1.37)	1.10 (0.88, 1.36)
Average Truck Miles Traveled (IQR=675,034)[c]	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)
Endocardial Cushion Defects (n=849)			
Span size	0.30	0.30	0.30
Increased Well Count[a]	3	28	155
Model 2			
Well Density[a]	1.00 (0.87, 1.15)	1.02 (0.87, 1.19)	1.05 (0.91, 1.22)
Model 3			
Well Density[a]	0.99 (0.87,1.14)	1.04 (0.88, 1.22)	1.07 (0.92, 1.25)
Non- Smoker	Ref	Ref	Ref
Smoker	0.96 (0.73, 1.27)	0.96 (0.72, 1.27)	0.96 (0.73, 1.27)
Singleton	Ref	Ref	Ref

Two + Fetus	2.01 (1.47, 2.73)	2.00 (1.47, 2.72)	2.01 (1.48, 2.73)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.93 (0.74, 1.18)	0.93 (0.74, 1.18)	0.93 (0.74, 1.18)
Age 25-29	1.01 (0.84, 1.22)	1.01 (0.84, 1.22)	1.01 (0.84, 1.22)
Age 30-34	1.22 (0.98, 1.51)	1.22 (0.98, 1.51)	1.22 (0.99, 1.51)
Age 35-39	1.32 (1.02, 1.71)	1.32 (1.02, 1.71)	1.32 (1.02, 1.70)
Age 40-60	1.20 (0.81, 1.79)	1.21 (0.81, 1.79)	1.21 (0.81, 1.80)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.13 (0.90, 1.41)	1.12 (0.90, 1.41)	1.12 (0.90, 1.41)
Hispanic	0.89 (0.75, 1.06)	0.89 (0.75, 1.06)	0.89 (0.75, 1.06)
Other non-Hispanic	0.71 (0.46, 1.11)	0.71 (0.46, 1.10)	0.71 (0.46, 1.10)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.93 (0.78, 1.12)	0.94 (0.78, 1.12)	0.94 (0.78, 1.12)
Greater than HS	0.76 (0.64, 0.91)	0.76 (0.64, 0.91)	0.76 (0.63, 0.90)
Model 4			
Well Density[a]	1.01 (0.88, 1.16)	1.06 (0.90, 1.24)	1.09 (0.94, 1.27)
Non- Smoker	Ref	Ref	Ref
Smoker	0.94 (0.71, 1.25)	0.94 (0.71, 1.24)	0.94 (0.71, 1.25)
Singleton	Ref	Ref	Ref
Two + Fetus	2.09 (1.53, 2.85)	2.09 (1.54, 2.85)	2.10 (1.54, 2.86)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.95 (0.75, 1.20)	0.95 (0.75, 1.20)	0.95 (0.75, 1.20)
Age 25-29	1.03 (0.85, 1.24)	1.02 (0.85, 1.24)	1.02 (0.85, 1.24)
Age 30-34	1.25 (1.00, 1.55)	1.25 (1.01, 1.55)	1.25 (1.01, 1.55)
Age 35-39	1.37 (1.06, 1.77)	1.37 (1.05, 1.77)	1.36 (1.05, 1.77)
Age 40-60	1.25 (0.84, 1.87)	1.25 (0.84, 1.87)	1.25 (0.84, 1.87)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.05 (0.83, 1.32)	1.04 (0.82, 1.32)	1.04 (0.82, 1.32)
Hispanic	0.84 (0.70, 1.01)	0.84 (0.70, 1.01)	0.84 (0.70, 1.01)
Other non-Hispanic	0.70 (0.45, 1.09)	0.70 (0.45, 1.08)	0.70 (0.45, 1.08)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.92 (0.76, 1.10)	0.92 (0.76, 1.10)	0.92 (0.76, 1.10)
Greater than HS	0.77 (0.65, 0.93)	0.77 (0.64, 0.92)	0.77 (0.64, 0.92)
Median Income($10,000)[b]	0.97 (0.94, 1.01)	0.97 (0.94, 1.01)	0.97 (0.94, 1.01)
Urban	Ref	Ref	Ref
Rural	0.75 (0.57, 1.00)	0.75 (0.57, 1.00)	0.75 (0.56, 1.00)
Average Truck Miles Traveled (IQR=467,354)[c]	1.01 (0.99, 1.03)	1.01 (0.98, 1.03)	1.01 (0.98, 1.03)
Tricuspid Valve Atresia/ Stenosis (n=648)			

Span size	0.9	0.9	0.9
Increased Well Count[a]	4	29	155
Model 2			
Well Density[a]	1.28 (1.10, 1.48)	1.16 (0.99, 1.36)	1.14 (0.98, 1.32)
Model 3			
Well Density[a]	1.28 (1.10, 1.49)	1.18 (1.00, 1.38)	1.15 (0.99, 1.34)
Non- Smoker	Ref	Ref	Ref
Smoker	0.79 (0.55, 1.12)	0.78 (0.55, 1.12)	0.79 (0.55, 1.12)
Singleton	Ref	Ref	Ref
Two + Fetus	1.33 (0.89, 1.98)	1.37 (0.92, 2.05)	1.38 (0.92, 2.06)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.73 (0.56, 0.96)	0.74 (0.56, 0.97)	0.74 (0.56, 0.97)
Age 25-29	0.91 (0.73, 1.12)	0.91 (0.74, 1.12)	0.91 (0.74, 1.13)
Age 30-34	1.09 (0.86, 1.38)	1.08 (0.85, 1.38)	1.08 (0.85, 1.37)
Age 35-39	1.11 (0.83, 1.49)	1.12 (0.84, 1.50)	1.12 (0.83, 1.50)
Age 40-60	0.81 (0.48, 1.36)	0.81 (0.49, 1.36)	0.82 (0.49, 1.37)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.55 (1.20, 2.00)	1.55 (1.20, 2.00)	1.56 (1.21, 2.01)
Hispanic	1.04 (0.85, 1.28)	1.04 (0.84, 1.27)	1.04 (0.84, 1.27)
Other non-Hispanic	1.33 (0.90, 1.97)	1.34 (0.90, 1.99)	1.35 (0.91, 2.01)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.18 (0.96, 1.46)	1.18 (0.95, 1.45)	1.17 (0.95, 1.45)
Greater than HS	0.89 (0.72, 1.10)	0.89 (0.72, 1.09)	0.89 (0.72, 1.10)
Model 4			
Well Density[a]	1.30 (1.12, 1.51)	1.18 (1.00, 1.38)	1.15 (0.99, 1.35)
Non- Smoker	Ref	Ref	Ref
Smoker	0.75 (0.52, 1.07)	0.74 (0.52, 1.07)	0.75 (0.52, 1.07)
Singleton	Ref	Ref	Ref
Two + Fetus	1.37 (0.92, 2.05)	1.41 (0.94, 2.11)	1.41 (0.94, 2.11)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.74 (0.56, 0.98)	0.74 (0.56, 0.98)	0.75 (0.57, 0.99)
Age 25-29	0.93 (0.75, 1.14)	0.93 (0.75, 1.15)	0.93 (0.75, 1.15)
Age 30-34	1.13 (0.89, 1.44)	1.12 (0.88, 1.43)	1.12 (0.88, 1.43)
Age 35-39	1.16 (0.86, 1.56)	1.17 (0.87, 1.57)	1.17 (0.87, 1.57)
Age 40-60	0.89 (0.53, 1.49)	0.89 (0.53, 1.49)	0.89 (0.53, 1.49)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.44 (1.11, 1.89)	1.46 (1.12, 1.91)	1.47 (1.12, 1.92)
Hispanic	0.97 (0.79, 1.21)	0.98 (0.79, 1.21)	0.98 (0.79, 1.21)
Other non-Hispanic	1.34 (0.90, 2.00)	1.36 (0.91, 2.03)	1.37 (0.92, 2.04)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.16 (0.94, 1.43)	1.15 (0.93, 1.43)	1.15 (0.93, 1.42)
Greater than HS	0.93 (0.75, 1.14)	0.92 (0.75, 1.14)	0.92 (0.75, 1.14)

Median Income($10,000)[b]	0.96 (0.92, 1.00)	0.96 (0.92, 1.00)	0.96 (0.92, 1.00)
Urban	Ref	Ref	Ref
Rural	1.22 (0.92, 1.61)	1.22 (0.92, 1.62)	1.22 (0.92, 1.62)
Average Truck Miles Traveled (IQR=436,433)[c]	1.02 (0.99, 1.04)	1.02 (0.99, 1.04)	1.02 (0.99, 1.04)
Aortic Valve Stenosis (n=933)			
Span size	0.50	0.50	0.50
Increased Well Count[a]	4	30	158
Model 2			
Well Density[a]	1.21 (1.05, 1.38)	1.21 (1.06, 1.38)	1.22 (1.08, 1.37)
Model 3			
Well Density[a]	1.21 (1.05, 1.38)	1.23 (1.08, 1.40)	1.22 (1.09, 1.38)
Non- Smoker	Ref	Ref	Ref
Smoker	0.99 (0.75, 1.29)	0.99 (0.76, 1.29)	0.99 (0.76, 1.29)
Singleton	Ref	Ref	Ref
Two + Fetus	1.36 (0.96, 1.92)	1.43 (1.01, 2.01)	1.44 (1.02, 2.02)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.84 (0.66, 1.07)	0.84 (0.66, 1.07)	0.85 (0.67, 1.08)
Age 25-29	1.07 (0.89, 1.29)	1.08 (0.90, 1.29)	1.08 (0.90, 1.30)
Age 30-34	1.45 (1.19, 1.77)	1.45 (1.18, 1.77)	1.45 (1.18, 1.77)
Age 35-39	1.62 (1.28, 2.05)	1.63 (1.29, 2.06)	1.63 (1.29, 2.06)
Age 40-60	0.95 (0.62, 1.45)	0.96 (0.63, 1.46)	0.96 (0.63, 1.47)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.59 (0.45, 0.77)	0.59 (0.45, 0.77)	0.59 (0.45, 0.77)
Hispanic	0.72 (0.61, 0.85)	0.72 (0.61, 0.85)	0.71 (0.60, 0.84)
Other non-Hispanic	0.69 (0.46, 1.02)	0.68 (0.46, 1.01)	0.69 (0.46, 1.02)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.12 (0.94, 1.34)	1.12 (0.94, 1.34)	1.12 (0.94, 1.34)
Greater than HS	0.75 (0.64, 0.90)	0.75 (0.63, 0.89)	0.75 (0.63, 0.89)
Model 4			
Well Density[a]	1.19 (1.04, 1.37)	1.22 (1.07, 1.40)	1.22 (1.08, 1.37)
Non- Smoker	Ref	Ref	Ref
Smoker	1.01 (0.78, 1.33)	1.02 (0.78, 1.33)	1.02 (0.78, 1.34)
Singleton	Ref	Ref	Ref
Two + Fetus	1.31 (0.93, 1.86)	1.37 (0.97, 1.94)	1.38 (0.98, 1.95)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.83 (0.65, 1.06)	0.84 (0.66, 1.07)	0.84 (0.66, 1.08)
Age 25-29	1.06 (0.88, 1.28)	1.06 (0.88, 1.28)	1.07 (0.89, 1.28)
Age 30-34	1.42 (1.16, 1.74)	1.41 (1.15, 1.73)	1.41 (1.16, 1.73)
Age 35-39	1.58 (1.24, 2.00)	1.58 (1.25, 2.01)	1.58 (1.25, 2.01)

Age 40-60	0.90 (0.59, 1.38)	0.90 (0.59, 1.38)	0.90 (0.59, 1.39)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.63 (0.47, 0.82)	0.63 (0.48, 0.82)	0.63 (0.48, 0.83)
Hispanic	0.75 (0.63, 0.90)	0.75 (0.63, 0.90)	0.75 (0.63, 0.90)
Other non-Hispanic	0.69 (0.46, 1.03)	0.69 (0.46, 1.02)	0.69 (0.47, 1.03)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.14 (0.95, 1.36)	1.13 (0.95, 1.36)	1.13 (0.95, 1.35)
Greater than HS	0.74 (0.62, 0.88)	0.73 (0.61, 0.87)	0.73 (0.61, 0.87)
Median Income($10,000)[b]	1.03 (0.99,1.06)	1.03 (0.99, 1.06)	1.03 (0.99, 1.06)
Urban	Ref	Ref	Ref
Rural	0.93 (0.73, 1.19)	0.92 (0.72, 1.17)	0.92 (0.72, 1.17)
Average Truck Miles Traveled (IQR=491,962)[c]	0.98 (0.96, 1.01)	0.98 (0.96, 1.00)	0.98 (0.96, 1.00)
Hypoplastic Left Heart Syndome (n=848)			
Span size	0.95	0.95	0.95
Increased Well Count[a]	4	29	158
Model 2			
Well Density[a]	1.31 (1.15, 1.48)	1.25 (1.10, 1.42)	1.25 (1.12, 1.40)
Model 3			
Well Density[a]	1.33 (1.17, 1.51)	1.28 (1.14, 1.45)	1.28 (1.15, 1.44)
Non- Smoker	Ref	Ref	Ref
Smoker	0.90 (0.68, 1.19)	0.90 (0.68, 1.19)	0.91 (0.69, 1.20)
Singleton	Ref	Ref	Ref
Two + Fetus	1.19 (0.81, 1.75)	1.26 (0.86, 1.85)	1.27 (0.87, 1.86)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.94 (0.75, 1.19)	0.95 (0.76, 1.19)	0.96 (0.77, 1.21)
Age 25-29	0.90 (0.74, 1.08)	0.90 (0.75, 1.09)	0.90 (0.75, 1.09)
Age 30-34	1.25 (1.02, 1.54)	1.25 (1.02, 1.54)	1.25 (1.01, 1.53)
Age 35-39	1.01 (0.77, 1.32)	1.02 (0.78, 1.34)	1.02 (0.78, 1.34)
Age 40-60	0.80 (0.50, 1.26)	0.80 (0.51, 1.27)	0.81 (0.51, 1.28)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.05 (0.84, 1.31)	1.05 (0.84, 1.32)	1.06 (0.85, 1.33)
Hispanic	0.77 (0.65, 0.91)	0.77 (0.65, 0.92)	0.77 (0.64, 0.91)
Other non-Hispanic	0.59 (0.38, 0.91)	0.59 (0.38, 0.91)	0.60 (0.38, 0.93)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.91 (0.76, 1.09)	0.90 (0.75, 1.08)	0.90 (0.75, 1.08)
Greater than HS	0.67 (0.56, 0.80)	0.67 (0.56, 0.80)	0.67 (0.56, 0.80)
Model 4			
Well Density[a]	1.35 (1.19, 1.54)	1.29 (1.15, 1.46)	1.30 (1.16, 1.45)

Non- Smoker	Ref	Ref	Ref
Smoker	0.91 (0.68, 1.20)	0.91 (0.69, 1.20)	0.92 (0.69, 1.21)
Singleton	Ref	Ref	Ref
Two + Fetus	1.21 (0.82, 1.78)	1.28 (0.87, 1.88)	1.29 (0.88, 1.90)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.94 (0.75, 1.18)	0.95 (0.75, 1.19)	0.96 (0.76, 1.20)
Age 25-29	0.90 (0.74, 1.08)	0.90 (0.75, 1.09)	0.90 (0.75, 1.09)
Age 30-34	1.27 (1.03, 1.56)	1.26 (1.02, 1.55)	1.26 (1.02, 1.55)
Age 35-39	1.02 (0.77, 1.34)	1.03 (0.78, 1.36)	1.03 (0.78, 1.35)
Age 40-60	0.81 (0.51, 1.30)	0.82 (0.51, 1.30)	0.82 (0.52, 1.31)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.00 (0.79, 1.26)	1.01 (0.80, 1.28)	1.02 (0.81, 1.29)
Hispanic	0.74 (0.61, 0.88)	0.74 (0.62, 0.89)	0.74 (0.62, 0.89)
Other non-Hispanic	0.56 (0.36, 0.88)	0.57 (0.36, 0.89)	0.58 (0.37, 0.90)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.91 (0.76, 1.09)	0.90 (0.75, 1.08)	0.90 (0.75, 1.08)
Greater than HS	0.67 (0.56, 0.81)	0.67 (0.56, 0.80)	0.67 (0.56, 0.80)
Median Income($10,000)[b]	0.99 (0.96, 1.03)	1.00 (0.96, 1.03)	1.00 (0.96, 1.03)
Urban	Ref	Ref	Ref
Rural	0.94 (0.73, 1.22)	0.94 (0.72, 1.21)	0.94 (0.73, 1.21)
Average Truck Miles Traveled (IQR=467,354)[c]	1.02 (0.99, 1.04)	1.01 (0.99, 1.03)	1.01 (0.99, 1.04)

[a] ORs correspond to an increase in wells from the 5th to the 95th percentile of the distribution within a buffer distance during year of pregnancy

[b] ORs correspond to a $10,000 increase in median income at block group of mother's maternal address at time of delivery

[c] ORs correspond to an interquartile range increase in average truck miles traveled by county.

Appendix Table B.5: Odds ratios (OR) and 95% confidence intervals (CI) for the associations between model covariates and ventricular septal defects stratified by overlapping 3-year time intervals, born between 1999-2011 in Texas

Defect/Model	**1km OR (95% CI)**	**3km OR (95% CI)**	**7.5km OR (95% CI)**
Ventricular Septal Defects 1999-2001 (n=3,421)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	2	18	95
Model 2			
Well Density[a]	1.11 (1.04, 1.18)	1.03 (0.95, 1.12)	0.99 (0.89, 1.10)
Model 3			
Well Density[a]	1.12 (1.05, 1.20)	1.05 (0.97, 1.14)	1.02 (0.92, 1.13)
Non- Smoker	Ref	Ref	Ref
Smoker	0.93 (0.80, 1.08)	0.94 (0.81, 1.10)	0.95 (0.81, 1.10)
Singleton	Ref	Ref	Ref
Two + Fetus	2.13 (1.83, 2.48)	2.12 (1.82, 2.47)	2.11 (1.81, 2.46)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.93 (0.83, 1.05)	0.93 (0.83, 1.04)	0.93 (0.83, 1.04)
Age 25-29	1.06 (0.96, 1.17)	1.06 (0.96, 1.17)	1.06 (0.96, 1.17)
Age 30-34	1.18 (1.07, 1.31)	1.18 (1.07, 1.31)	1.18 (1.07, 1.31)
Age 35-39	1.70 (1.50, 1.94)	1.70 (1.49, 1.93)	1.70 (1.49, 1.93)
Age 40-60	2.02 (1.61, 2.55)	2.04 (1.61, 2.57)	2.05 (1.62, 2.58)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.84 (0.74, 0.97)	0.84 (0.74, 0.96)	0.84 (0.74, 0.96)
Hispanic	1.02 (0.93, 1.11)	1.01 (0.93, 1.11)	1.01 (0.92, 1.11)
Other non-Hispanic	0.60 (0.48, 0.76)	0.60 (0.47, 0.75)	0.60 (0.47, 0.75)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.15 (1.05, 1.25)	1.15 (1.05, 1.26)	1.15 (1.05, 1.26)
Greater than HS	1.02 (0.93, 1.11)	1.02 (0.93, 1.11)	1.01 (0.93, 1.11)
Model 4			
Well Density[a]	1.13 (1.06, 1.21)	1.06 (0.98, 1.16)	1.04 (0.94, 1.15)
Non- Smoker	Ref	Ref	Ref
Smoker	0.93 (0.80, 1.09)	0.95 (0.81, 1.11)	0.95 (0.82, 1.11)
Singleton	Ref	Ref	Ref
Two + Fetus	2.13 (1.82, 2.48)	2.11 (1.81, 2.46)	2.11 (1.81, 2.46)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.93 (0.83, 1.05)	0.93 (0.83, 1.04)	0.93 (0.83, 1.04)
Age 25-29	1.06 (0.96, 1.16)	1.06 (0.96, 1.16)	1.06 (0.96, 1.16)
Age 30-34	1.18 (1.06, 1.31)	1.17 (1.06, 1.30)	1.17 (1.06, 1.30)
Age 35-39	1.68 (1.47, 1.92)	1.68 (1.47, 1.91)	1.68 (1.47, 1.91)
Age 40-60	2.00 (1.58, 2.52)	2.01 (1.59, 2.53)	2.02 (1.60, 2.55)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.85 (0.73, 0.97)	0.84 (0.73, 0.97)	0.84 (0.73, 0.97)

Hispanic	1.02 (0.93, 1.12)	1.01 (0.92, 1.11)	1.01 (0.92, 1.11)
Other non-Hispanic	0.59 (0.47, 0.75)	0.59 (0.47, 0.74)	0.59 (0.47, 0.74)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.15 (1.05, 1.26)	1.15 (1.05, 1.26)	1.15 (1.05, 1.26)
Greater than HS	1.00 (0.91, 1.10)	1.00 (0.91, 1.10)	1.00 (0.91, 1.10)
Median Income($10,000)[b]	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)
Urban	Ref	Ref	Ref
Rural	0.82 (0.70, 0.96)	0.83 (0.71, 0.97)	0.83 (0.71, 0.97)
Average Truck Miles Traveled (IQR=890,306)[c]	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)
Ventricular Septal Defects 2000-2002 (n=3,771)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	2	18	97
Model 2			
Well Density[a]	0.99 (0.93, 1.04)	0.95 (0.87, 1.03)	0.91 (0.81, 1.02)
Model 3			
Well Density[a]	0.97 (0.92, 1.03)	0.94 (0.86, 1.02)	0.88 (0.78, 0.99)
Non- Smoker	Ref	Ref	Ref
Smoker	1.16 (1.00, 1.36)	1.17 (1.00, 1.36)	1.17 (1.01, 1.36)
Singleton	Ref	Ref	Ref
Two + Fetus	2.34 (2.03, 2.70)	2.34 (2.03, 2.70)	2.35 (2.03, 2.70)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.80 (0.72, 0.90)	0.80 (0.72, 0.90)	0.80 (0.71, 0.90)
Age 25-29	0.99 (0.90, 1.09)	0.99 (0.91, 1.09)	0.99 (0.91, 1.09)
Age 30-34	1.01 (0.92, 1.12)	1.02 (0.92, 1.12)	1.01 (0.92, 1.12)
Age 35-39	1.42 (1.25, 1.60)	1.42 (1.26, 1.60)	1.42 (1.26, 1.60)
Age 40-60	2.00 (1.61, 2.50)	2.00 (1.60, 2.50)	2.00 (1.60, 2.50)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.76 (0.67, 0.87)	0.76 (0.67, 0.87)	0.76 (0.67, 0.87)
Hispanic	1.07 (0.98, 1.17)	1.07 (0.98, 1.17)	1.07 (0.98, 1.17)
Other non-Hispanic	0.72 (0.59, 0.88)	0.72 (0.59, 0.88)	0.72 (0.59, 0.88)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.18 (1.08, 1.29)	1.18 (1.08, 1.29)	1.18 (1.08, 1.29)
Greater than HS	1.05 (0.96, 1.15)	1.05 (0.96, 1.15)	1.05 (0.96, 1.15)
Model 4			
Well Density[a]	0.97 (0.92, 1.03)	0.94 (0.86, 1.02)	0.89 (0.78, 1.00)
Non- Smoker	Ref	Ref	Ref
Smoker	1.17 (1.01, 1.37)	1.18 (1.01, 1.37)	1.18 (1.01, 1.37)
Singleton	Ref	Ref	Ref

Two + Fetus	2.34 (2.03, 2.70)	2.34 (2.03, 2.70)	2.35 (2.03, 2.70)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.80 (0.72, 0.90)	0.80 (0.72, 0.90)	0.80 (0.71, 0.90)
Age 25-29	0.99 (0.90, 1.09)	0.99 (0.90, 1.09)	0.99 (0.91, 1.09)
Age 30-34	1.01 (0.91, 1.12)	1.01 (0.92, 1.12)	1.01 (0.91, 1.12)
Age 35-39	1.42 (1.25, 1.61)	1.42 (1.25, 1.61)	1.42 (1.25, 1.61)
Age 40-60	2.00 (1.60, 2.50)	1.99 (1.60, 2.50)	2.00 (1.60, 2.50)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.75 (0.65, 0.86)	0.75 (0.65, 0.86)	0.75 (0.65, 0.86)
Hispanic	1.06 (0.97, 1.16)	1.06 (0.97, 1.16)	1.06 (0.97, 1.16)
Other non-Hispanic	0.71 (0.58, 0.87)	0.71 (0.58, 0.87)	0.71 (0.58, 0.87)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.18 (1.08, 1.29)	1.18 (1.08, 1.29)	1.18 (1.08, 1.29)
Greater than HS	1.05 (0.96, 1.15)	1.05 (0.96, 1.15)	1.04 (0.95, 1.15)
Median Income($10,000)[b]	1.00 (0.99, 1.02)	1.00 (0.99, 1.02)	1.00 (0.98, 1.02)
Urban	Ref	Ref	Ref
Rural	0.92 (0.80, 1.06)	0.92 (0.80, 1.06)	0.92 (0.80, 1.06)
Average Truck Miles Traveled (IQR=892,162)[c]	1.02 (1.00, 1.04)	1.02 (1.00, 1.05)	1.03 (1.01, 1.05)
Ventricular Septal Defects 2001-2003 (n=4,012)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	2	19	100
Model 2			
Well Density[a]	0.95 (0.89, 1.02)	0.92 (0.94, 1.01)	0.93 (0.85, 1.03)
Model 3			
Well Density[a]	0.95 (0.89, 1.01)	0.92 (0.94, 1.00)	0.92 (0.79, 1.07)
Non- Smoker	Ref	Ref	Ref
Smoker	0.92 (0.79, 1.07)	0.92 (0.79, 1.07)	2.91 (2.54, 3.33)
Singleton	Ref	Ref	Ref
Two + Fetus	2.89 (2.53, 3.31)	2.89 (2.53, 3.31)	0.84 (0.75, 0.94)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.84 (0.75, 0.94)	0.84 (0.75, 0.94)	0.84 (0.75, 0.94)
Age 25-29	1.20 (1.10, 1.31)	1.20 (1.10, 1.31)	1.20 (1.10, 1.32)
Age 30-34	1.11 (1.01, 1.23)	1.11 (1.01, 1.23)	1.11 (1.01, 1.23)
Age 35-39	1.37 (1.22, 1.54)	1.37 (1.22, 1.54)	1.38 (1.22, 1.55)
Age 40-60	1.52 (1.22, 1.88)	1.52 (1.23, 1.88)	1.52 (1.23, 1.89)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.86 (0.77, 0.98)	0.87 (0.77, 0.98)	0.87 (0.77, 0.98)
Hispanic	1.11 (1.01, 1.21)	1.11 (1.02, 1.21)	1.11 (1.01, 1.21)
Other non-Hispanic	1.05 (0.87, 1.27)	1.05 (0.87, 1.27)	1.04 (0.86, 1.27)

High School (HS) Education	Ref	Ref	Ref
Less than HS	0.89 (0.82, 0.97)	0.89 (0.82, 0.97)	0.89 (0.82, 0.97)
Greater than HS	0.86 (0.79, 0.94)	0.86 (0.79, 0.94)	0.86 (0.79, 0.94)
Model 4			
Well Density[a]	0.95 (0.89, 1.01)	0.92 (0.84, 1.01)	0.90 (0.81, 0.99)
Non- Smoker	Ref	Ref	Ref
Smoker	0.92 (0.79, 1.07)	0.92 (0.79, 1.07)	0.92 (0.79, 1.07)
Singleton	Ref	Ref	Ref
Two + Fetus	2.89 (2.52, 3.31)	2.89 (2.52, 3.31)	2.90 (2.53, 3.32)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.84 (0.75, 0.94)	0.84 (0.75, 0.94)	0.84 (0.75, 0.94)
Age 25-29	1.20 (1.10, 1.32)	1.20 (1.10, 1.31)	1.20 (1.10, 1.32)
Age 30-34	1.11 (1.01, 1.23)	1.11 (1.01, 1.23)	1.11 (1.01, 1.23)
Age 35-39	1.37 (1.22, 1.54)	1.37 (1.22, 1.54)	1.37 (1.22, 1.54)
Age 40-60	1.51 (1.22, 1.88)	1.51 (1.22, 1.88)	1.52 (1.22, 1.89)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.86 (0.76, 0.98)	0.86 (0.76, 0.98)	0.86 (0.76, 0.98)
Hispanic	1.10 (1.01, 1.21)	1.10 (1.01, 1.21)	1.10 (1.01, 1.21)
Other non-Hispanic	1.05 (0.86, 1.27)	1.04 (0.86, 1.27)	1.04 (0.86, 1.26)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.89 (0.82, 0.97)	0.89 (0.82, 0.97)	0.89 (0.82, 0.97)
Greater than HS	0.86 (0.79, 0.94)	0.86 (0.79, 0.94)	0.86 (0.79, 0.94)
Median Income($10,000)[b]	1.00 (0.99, 1.02)	1.00 (0.99, 1.02)	1.00 (0.99, 1.02)
Urban	Ref	Ref	Ref
Rural	0.95 (0.83, 1.09)	0.95 (0.83, 1.09)	0.96 (0.83, 1.10)
Average Truck Miles Traveled (IQR=892,162)[c]	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)
Ventricular Septal Defects 2002-2004 (n=4,301)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	2	19	103
Model 2			
Well Density[a]	1.00 (0.94, 1.06)	0.96 (0.89, 1.03)	0.99 (0.90, 1.08)
Model 3			
Well Density[a]	1.01 (0.95, 1.07)	0.97 (0.90, 1.05)	0.99 (0.90, 1.08)
Non- Smoker	Ref	Ref	Ref
Smoker	0.96 (0.83, 1.11)	0.96 (0.83, 1.11)	0.96 (0.83, 1.11)
Singleton	Ref	Ref	Ref
Two + Fetus	2.75 (2.42, 3.12)	2.75 (2.42, 3.12)	2.75 (2.42, 3.12)
Age 20-24	Ref	Ref	Ref

Age 10-19	0.87 (0.78, 0.97)	0.87 (0.78, 0.97)	0.87 (0.78, 0.97)
Age 25-29	1.03 (0.95, 1.12)	1.03 (0.95, 1.12)	1.03 (0.95, 1.12)
Age 30-34	1.18 (1.07, 1.29)	1.17 (1.07, 1.29)	1.18 (1.07, 1.29)
Age 35-39	1.55 (1.38, 1.73)	1.54 (1.38, 1.73)	1.55 (1.38, 1.73)
Age 40-60	1.32 (1.07, 1.63)	1.32 (1.07, 1.63)	1.32 (1.07, 1.63)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.88 (0.78, 0.99)	0.88 (0.78, 0.99)	0.88 (0.78, 0.99)
Hispanic	0.97 (0.89, 1.05)	0.96 (0.89, 1.05)	0.97 (0.89, 1.05)
Other non-Hispanic	0.90 (0.75, 1.07)	0.90 (0.75, 1.07)	0.90 (0.75, 1.07)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.04 (0.96, 1.13)	1.04 (0.96, 1.13)	1.04 (0.96, 1.13)
Greater than HS	0.94 (0.87, 1.02)	0.94 (0.87, 1.02)	0.94 (0.87, 1.02)
Model 4			
Well Density[a]	1.01 (0.95, 1.07)	0.97 (0.90, 1.05)	0.99 (0.90, 1.09)
Non- Smoker	Ref	Ref	Ref
Smoker	0.96 (0.83, 1.12)	0.96 (0.83, 1.12)	0.96 (0.83, 1.12)
Singleton	Ref	Ref	Ref
Two + Fetus	2.75 (2.42, 3.13)	2.75 (2.42, 3.13)	2.75 (2.42, 3.13)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.88 (0.79, 0.98)	0.88 (0.79, 0.98)	0.88 (0.79, 0.98)
Age 25-29	1.03 (0.95, 1.13)	1.03 (0.95, 1.13)	1.03 (0.95, 1.13)
Age 30-34	1.19 (1.08, 1.30)	1.19 (1.08, 1.30)	1.19 (1.08, 1.30)
Age 35-39	1.59 (1.42, 1.79)	1.59 (1.42, 1.79)	1.59 (1.42, 1.79)
Age 40-60	1.36 (1.10, 1.68)	1.36 (1.10, 1.68)	1.36 (1.10, 1.68)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.84 (0.74, 0.94)	0.84 (0.74, 0.94)	0.84 (0.74, 0.94)
Hispanic	0.93 (0.85, 1.01)	0.93 (0.85, 1.01)	0.93 (0.85, 1.01)
Other non-Hispanic	0.88 (0.74, 1.06)	0.89 (0.74, 1.06)	0.88 (0.74, 1.06)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.03 (0.95, 1.11)	1.03 (0.95, 1.11)	1.03 (0.95, 1.11)
Greater than HS	0.96 (0.88, 1.04)	0.96 (0.88, 1.04)	0.96 (0.88, 1.04)
Median Income($10,000)[b]	0.98 (0.97, 1.00)	0.98 (0.97, 1.00)	0.98 (0.97, 1.00)
Urban	Ref	Ref	Ref
Rural	0.87 (0.76, 0.99)	0.87 (0.77, 0.99)	0.87 (0.77, 0.99)
Average Truck Miles Traveled (IQR=892,162)[c]	1.02 (1.00, 1.04)	1.02 (1.00, 1.04)	1.02 (1.00, 1.040
Ventricular Septal Defects 2003-2005 (n=4,725)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	2	20	105

Model 2			
Well Density[a]	1.07 (1.01, 1.12)	1.00 (0.93, 1.07)	1.01 (0.94, 1.09)
Model 3			
Well Density[a]	1.07 (1.01, 1.12)	1.00 (0.93, 1.08)	1.01 (0.94, 1.09)
Non- Smoker	Ref	Ref	Ref
Smoker	1.04 (0.91, 1.20)	1.05 (0.91, 1.20)	1.05 (0.91, 1.20)
Singleton	Ref	Ref	Ref
Two + Fetus	2.11 (1.87, 2.38)	2.11 (1.87, 2.38)	2.11 (1.87, 2.38)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.94 (0.85, 1.05)	0.94 (0.85, 1.04)	0.94 (0.85, 1.04)
Age 25-29	1.22 (1.12, 1.32)	1.22 (1.12, 1.32)	1.22 (1.12, 1.32)
Age 30-34	1.21 (1.11, 1.32)	1.20 (1.10, 1.31)	1.20 (1.10, 1.31)
Age 35-39	1.31 (1.18, 1.46)	1.31 (1.18, 1.46)	1.31 (1.18, 1.46)
Age 40-60	1.74 (1.43, 2.12)	1.74 (1.43, 2.12)	1.74 (1.43, 2.12)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.80 (0.72, 0.89)	0.80 (0.72, 0.89)	0.80 (0.72, 0.89)
Hispanic	0.97 (0.90, 1.05)	0.97 (0.90, 1.05)	0.97 (0.90, 1.05)
Other non-Hispanic	0.87 (0.73, 1.04)	0.87 (0.73, 1.03)	0.87 (0.73, 1.03)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.93 (0.86, 1.01)	0.93 (0.86, 1.01)	0.93 (0.86, 1.01)
Greater than HS	0.92 (0.85, 0.99)	0.92 (0.85, 0.99)	0.92 (0.85, 0.99)
Model 4			
Well Density[a]	1.07 (1.02, 1.13)	1.01 (0.94, 1.08)	1.02 (0.95, 1.10)
Non- Smoker	Ref	Ref	Ref
Smoker	1.04 (0.90, 1.19)	1.04 (0.91, 1.20)	1.04 (0.91, 1.20)
Singleton	Ref	Ref	Ref
Two + Fetus	2.12 (1.88, 2.39)	2.11 (1.87, 2.39)	2.11 (1.87, 2.39)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.95 (0.86, 1.05)	0.95 (0.85, 1.05)	0.95 (0.85, 1.05)
Age 25-29	1.22 (1.13, 1.33)	1.22 (1.13, 1.33)	1.22 (1.13, 1.33)
Age 30-34	1.22 (1.12, 1.33)	1.22 (1.12, 1.33)	1.22 (1.12, 1.33)
Age 35-39	1.34 (1.20, 1.49)	1.33 (1.20, 1.49)	1.33 (1.20, 1.49)
Age 40-60	1.78 (1.46, 2.17)	1.78 (1.46, 2.17)	1.78 (1.46, 2.17)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.76 (0.68, 0.85)	0.76 (0.68, 0.85)	0.76 (0.68, 0.85)
Hispanic	0.93 (0.86, 1.01)	0.93 (0.86, 1.01)	0.93 (0.86, 1.01)
Other non-Hispanic	0.86 (0.72, 1.02)	0.85 (0.72, 1.02)	0.85 (0.72, 1.02)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.93 (0.86, 1.00)	0.92 (0.85, 1.00)	0.92 (0.85, 1.00)
Greater than HS	0.94 (0.87, 1.01)	0.93 (0.86, 1.01)	0.93 (0.86, 1.01)
Median Income($10,000)[b]	0.98 (0.97, 0.99)	0.98 (0.97, 1.00)	0.98 (0.97, 1.00)
Urban	Ref	Ref	Ref

Rural	0.83 (0.74, 0.94)	0.84 (0.74, 0.95)	0.84 (0.74, 0.95)
Average Truck Miles Traveled (IQR=930,584)[c]	1.00 (0.99, 1.02)	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)
Ventricular Septal Defects 2004-2006 (n=5,173)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	2	22	114
Model 2			
Well Density[a]	0.98 (0.93, 1.03)	0.96 (0.91, 1.02)	0.99 (0.92, 1.06)
Model 3			
Well Density[a]	0.98 (0.93, 1.03)	0.95 (0.89, 1.01)	0.98 (0.91, 1.05)
Non- Smoker	Ref	Ref	Ref
Smoker	1.00 (0.87, 1.14)	1.00 (0.87, 1.14)	1.00 (0.87, 1.14)
Singleton	Ref	Ref	Ref
Two + Fetus	2.07 (1.84, 2.32)	2.08 (1.85, 2.32)	2.07 (1.84, 2.32)
Age 20-24	Ref	Ref	Ref
Age 10-19	1.03 (0.94, 1.14)	1.04 (0.94, 1.14)	1.03 (0.94, 1.14)
Age 25-29	1.07 (0.99, 1.16)	1.08 (1.00, 1.16)	1.07 (0.99, 1.16)
Age 30-34	1.11 (1.02, 1.21)	1.11 (1.02, 1.21)	1.11 (1.02, 1.21)
Age 35-39	1.30 (1.17, 1.44)	1.30 (1.17, 1.44)	1.30 (1.17, 1.44)
Age 40-60	1.12 (0.93, 1.34)	1.12 (0.93, 1.34)	1.11 (0.93, 1.34)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.91 (0.81, 1.01)	0.91 (0.81, 1.01)	0.91 (0.81, 1.01)
Hispanic	1.00 (0.93, 1.07)	1.00 (0.93, 1.07)	1.00 (0.93, 1.07)
Other non-Hispanic	0.89 (0.76, 1.04)	0.89 (0.76, 1.04)	0.89 (0.76, 1.04)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.05 (0.98, 1.13)	1.05 (0.98, 1.13)	1.05 (0.98, 1.13)
Greater than HS	0.97 (0.90, 1.05)	0.97 (0.90, 1.05)	0.97 (0.90, 1.05)
Model 4			
Well Density[a]	0.98 (0.93, 1.03)	0.95 (0.90, 1.01)	0.99 (0.92, 1.06)
Non- Smoker	Ref	Ref	Ref
Smoker	0.99 (0.87, 1.13)	0.99 (0.87, 1.13)	0.99 (0.87, 1.13)
Singleton	Ref	Ref	Ref
Two + Fetus	2.07 (1.84, 2.32)	2.08 (1.85, 2.32)	2.07 (1.84, 2.32)
Age 20-24	Ref	Ref	Ref
Age 10-19	1.04 (0.94, 1.15)	1.04 (0.94, 1.15)	1.04 (0.94, 1.15)
Age 25-29	1.08 (1.00, 1.16)	1.08 (1.00, 1.16)	1.08 (1.00, 1.16)
Age 30-34	1.12 (1.03, 1.22)	1.12 (1.03, 1.22)	1.12 (1.03, 1.22)
Age 35-39	1.31 (1.18, 1.46)	1.31 (1.18, 1.46)	1.31 (1.18, 1.46)
Age 40-60	1.13 (0.94, 1.36)	1.13 (0.94, 1.36)	1.13 (0.94, 1.36)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.89 (0.79, 0.99)	0.89 (0.79, 0.99)	0.89 (0.79, 0.99)

Hispanic	0.98 (0.91, 1.06)	0.98 (0.91, 1.06)	0.98 (0.91, 1.06)
Other non-Hispanic	0.89 (0.76, 1.04)	0.89 (0.76, 1.04)	0.89 (0.76, 1.04)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.05 (0.97, 1.13)	1.05 (0.97, 1.13)	1.05 (0.97, 1.13)
Greater than HS	0.98 (0.91, 1.06)	0.98 (0.91, 1.06)	0.98 (0.91, 1.06)
Median Income($10,000)[b]	0.99 (0.98, 1.00)	0.99 (0.98, 1.00)	0.99 (0.98, 1.00)
Urban	Ref	Ref	Ref
Rural	0.89 (0.79, 0.99)	0.89 (0.79, 0.99)	0.89 (0.79, 0.99)
Average Truck Miles Traveled (IQR=935,348)	0.98 (0.97, 1.00)	0.99 (0.97, 1.00)	0.98 (0.97, 1.00)
Ventricular Septal Defects 2005-2007 (n=5,726)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	3	24	129
Model 2			
Well Density[a]	0.93 (0.87, 1.00)	0.96 (0.90, 1.03)	1.00 (0.94, 1.07)
Model 3			
Well Density[a]	0.93 (0.87, 1.00)	0.96 (0.90, 1.03)	1.01 (0.94, 1.08)
Non- Smoker	Ref	Ref	Ref
Smoker	1.09 (0.96, 1.24)	1.09 (0.96, 1.24)	1.09 (0.95, 1.23)
Singleton	Ref	Ref	Ref
Two + Fetus	2.52 (2.25, 2.82)	2.53 (2.26, 2.83)	2.53 (2.26, 2.83)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.80 (0.73, 0.88)	0.81 (0.73, 0.89)	0.81 (0.73, 0.88)
Age 25-29	1.05 (0.97, 1.13)	1.04 (0.97, 1.12)	1.04 (0.97, 1.12)
Age 30-34	1.12 (1.03, 1.21)	1.12 (1.03, 1.21)	1.12 (1.03, 1.21)
Age 35-39	1.35 (1.22, 1.48)	1.34 (1.22, 1.48)	1.34 (1.21, 1.47)
Age 40-60	1.21 (1.01, 1.44)	1.20 (1.01, 1.44)	1.21 (1.01, 1.44)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.86 (0.77, 0.95)	0.86 (0.77, 0.95)	0.86 (0.77, 0.95)
Hispanic	1.10 (1.02, 1.18)	1.10 (1.02, 1.18)	1.10 (1.02, 1.18)
Other non-Hispanic	0.80 (0.69, 0.93)	0.80 (0.69, 0.92)	0.80 (0.68, 0.92)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.09 (1.02, 1.17)	1.09 (1.01, 1.17)	1.09 (1.02, 1.17)
Greater than HS	1.01 (0.94, 1.08)	1.00 (0.93, 1.08)	1.00 (0.93, 1.08)
Model 4			
Well Density[a]	0.93 (0.87, 1.00)	0.97 (0.90, 1.04)	1.01 (0.94, 1.08)
Non- Smoker	Ref	Ref	Ref
Smoker	1.08 (0.95, 1.23)	1.08 (0.95, 1.23)	1.08 (0.95, 1.23)
Singleton	Ref	Ref	Ref

Two + Fetus	2.53 (2.26, 2.84)	2.54 (2.27, 2.84)	2.54 (2.27, 2.85)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.81 (0.74, 0.89)	0.81 (0.74, 0.89)	0.81 (0.74, 0.89)
Age 25-29	1.05 (0.97, 1.13)	1.05 (0.97, 1.13)	1.05 (0.97, 1.13)
Age 30-34	1.12 (1.04, 1.22)	1.12 (1.04, 1.22)	1.13 (1.04, 1.22)
Age 35-39	1.36 (1.23, 1.50)	1.36 (1.23, 1.50)	1.36 (1.23, 1.50)
Age 40-60	1.22 (1.02, 1.46)	1.22 (1.02, 1.45)	1.22 (1.02, 1.46)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.84 (0.76, 0.94)	0.84 (0.76, 0.94)	0.84 (0.76, 0.94)
Hispanic	1.09 (1.01, 1.17)	1.09 (1.01, 1.17)	1.09 (1.01, 1.17)
Other non-Hispanic	0.80 (0.69, 0.93)	0.80 (0.69, 0.93)	0.80 (0.69, 0.93)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.09 (1.01, 1.17)	1.09 (1.01, 1.17)	1.09 (1.01, 1.17)
Greater than HS	1.01 (0.94, 1.09)	1.01 (0.94, 1.09)	1.01 (0.94, 1.09)
Median Income($10,000)[b]	0.99 (0.98, 1.00)	0.99 (0.98, 1.00)	0.99 (0.98, 1.00)
Urban	Ref	Ref	Ref
Rural	0.97 (0.87, 1.08)	0.97 (0.87, 1.07)	0.96 (0.87, 1.07)
Average Truck Miles Traveled (IQR=935,348)[c]	0.99 (0.97, 1.00)	0.99 (0.97, 1.00)	0.98 (0.97, 1.00)
Ventricular Septal Defects 2006-2008 (n=6,063)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	3	27	154
Model 2			
Well Density[a]	0.94 (0.89, 1.00)	0.94 (0.88, 1.01)	0.97 (0.89, 1.04)
Model 3			
Well Density[a]	0.95 (0.89, 1.01)	0.95 (0.89, 1.02)	0.98 (0.91, 1.06)
Non- Smoker	Ref	Ref	Ref
Smoker	0.79 (0.69, 0.90)	0.79 (0.69, 0.90)	0.79 (0.70, 0.90)
Singleton	Ref	Ref	Ref
Two + Fetus	2.29 (2.05, 2.56)	2.29 (2.05, 2.56)	2.29 (2.05, 2.56)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.85 (0.78, 0.94)	0.85 (0.78, 0.94)	0.85 (0.78, 0.94)
Age 25-29	0.97 (0.90, 1.04)	0.97 (0.90, 1.04)	0.97 (0.90, 1.04)
Age 30-34	1.13 (1.05, 1.22)	1.13 (1.05, 1.22)	1.13 (1.05, 1.22)
Age 35-39	1.17 (1.07, 1.29)	1.17 (1.07, 1.29)	1.17 (1.07, 1.29)
Age 40-60	1.01 (0.85, 1.21)	1.01 (0.85, 1.21)	1.01 (0.85, 1.21)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.88 (0.80, 0.97)	0.88 (0.80, 0.97)	0.88 (0.80, 0.97)
Hispanic	1.09 (1.02, 1.17)	1.09 (1.02, 1.17)	1.09 (1.02, 1.17)
Other non-Hispanic	0.73 (0.63, 0.84)	0.73 (0.63, 0.84)	0.72 (0.63, 0.84)

High School (HS) Education	Ref	Ref	Ref
Less than HS	1.20 (1.11, 1.28)	1.19 (1.11, 1.28)	1.20 (1.11, 1.28)
Greater than HS	1.01 (0.95, 1.09)	1.01 (0.95, 1.09)	1.01 (0.95, 1.09)
Model 4			
Well Density[a]	0.95 (0.89, 1.01)	0.95 (0.89, 1.02)	0.98 (0.91, 1.06)
Non- Smoker	Ref	Ref	Ref
Smoker	0.79 (0.69, 0.90)	0.79 (0.69, 0.90)	0.79 (0.69, 0.90)
Singleton	Ref	Ref	Ref
Two + Fetus	2.28 (2.04, 2.55)	2.28 (2.04, 2.55)	2.29 (2.04, 2.55)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.85 (0.78, 0.93)	0.85 (0.78, 0.93)	0.85 (0.78, 0.93)
Age 25-29	0.97 (0.90, 1.04)	0.97 (0.90, 1.04)	0.97 (0.90, 1.04)
Age 30-34	1.13 (1.05, 1.22)	1.13 (1.05, 1.22)	1.13 (1.04, 1.22)
Age 35-39	1.17 (1.06, 1.28)	1.17 (1.06, 1.28)	1.17 (1.06, 1.28)
Age 40-60	1.01 (0.84, 1.21)	1.01 (0.84, 1.21)	1.01 (0.84, 1.21)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.89 (0.80, 0.98)	0.89 (0.80, 0.98)	0.89 (0.80, 0.98)
Hispanic	1.10 (1.03, 1.19)	1.10 (1.03, 1.19)	1.10 (1.03, 1.19)
Other non-Hispanic	0.73 (0.63, 0.85)	0.73 (0.63, 0.85)	0.73 (0.63, 0.85)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.20 (1.12, 1.28)	1.20 (1.11, 1.28)	1.20 (1.12, 1.28)
Greater than HS	1.01 (0.94, 1.08)	1.01 (0.94, 1.08)	1.01 (0.94, 1.08)
Median Income($10,000)[b]	1.00 (0.99, 1.02)	1.00 (0.99, 1.02)	1.00 (0.99, 1.02)
Urban	Ref	Ref	Ref
Rural	1.02 (0.93, 1.13)	1.02 (0.93, 1.13)	1.02 (0.92, 1.13)
Average Truck Miles Traveled (IQR=944,940)[c]	0.99 (0.97, 1.00)	0.99 (0.97, 1.00)	0.99 (0.97, 1.00)
Ventricular Septal Defect 2007-2009 (n=6,480)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	4	31	182
Model 2			
Well Density[a]	0.98 (0.92, 1.05)	0.99 (0.92, 1.06)	1.03 (0.96, 1.10)
Model 3			
Well Density[a]	0.99 (0.92, 1.06)	0.99 (0.92, 1.06)	1.03 (0.97, 1.10)
Non- Smoker	Ref	Ref	Ref
Smoker	0.74 (0.65, 0.85)	0.74 (0.65, 0.85)	0.74 (0.65, 0.85)
Singleton	Ref	Ref	Ref
Two + Fetus	1.98 (1.79, 2.21)	1.99 (1.79, 2.21)	1.99 (1.79, 2.21)
Age 20-24	Ref	Ref	Ref

Age 10-19	0.87 (0.80, 0.95)	0.87 (0.80, 0.95)	0.87 (0.80, 0.95)
Age 25-29	1.03 (0.96, 1.10)	1.03 (0.96, 1.10)	1.03 (0.96, 1.10)
Age 30-34	1.11 (1.03, 1.19)	1.11 (1.03, 1.19)	1.11 (1.03, 1.19)
Age 35-39	1.34 (1.22, 1.46)	1.34 (1.22, 1.46)	1.34 (1.22, 1.46)
Age 40-60	1.03 (0.87, 1.23)	1.03 (0.87, 1.23)	1.03 (0.87, 1.23)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.88 (0.80, 0.96)	0.88 (0.80, 0.96)	0.88 (0.80, 0.96)
Hispanic	1.07 (1.00, 1.15)	1.07 (1.00, 1.15)	1.07 (1.00, 1.15)
Other non-Hispanic	0.73 (0.63, 0.84)	0.73 (0.63, 0.84)	0.73 (0.63, 0.84)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.17 (1.09, 1.26)	1.17 (1.09, 1.26)	1.17 (1.09, 1.26)
Greater than HS	0.95 (0.89, 1.02)	0.95 (0.89, 1.02)	0.95 (0.89, 1.02)
Model 4			
Well Density[a]	0.99 (0.92, 1.05)	0.98 (0.92, 1.05)	1.03 (0.96, 1.10)
Non- Smoker	Ref	Ref	Ref
Smoker	0.74 (0.65, 0.85)	0.74 (0.65, 0.85)	0.74 (0.65, 0.85)
Singleton	Ref	Ref	Ref
Two + Fetus	1.99 (1.79, 2.21)	1.99 (1.79, 2.21)	1.99 (1.79, 2.21)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.87 (0.80, 0.95)	0.87 (0.80, 0.95)	0.87 (0.80, 0.95)
Age 25-29	1.03 (0.96, 1.10)	1.03 (0.96, 1.10)	1.03 (0.96, 1.10)
Age 30-34	1.11 (1.03, 1.20)	1.11 (1.03, 1.20)	1.11 (1.03, 1.20)
Age 35-39	1.34 (1.22, 1.46)	1.34 (1.22, 1.46)	1.34 (1.22, 1.46)
Age 40-60	1.03 (0.87, 1.23)	1.03 (0.87, 1.23)	1.03 (0.87, 1.23)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.88 (0.80, 0.97)	0.88 (0.80, 0.97)	0.88 (0.80, 0.97)
Hispanic	1.08 (1.01, 1.16)	1.08 (1.01, 1.16)	1.08 (1.01, 1.16)
Other non-Hispanic	0.73 (0.63, 0.84)	0.73 (0.63, 0.84)	0.73 (0.63, 0.84)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.17 (1.09, 1.25)	1.17 (1.09, 1.25)	1.17 (1.09, 1.26)
Greater than HS	0.95 (0.89, 1.02)	0.95 (0.89, 1.02)	0.95 (0.89, 1.02)
Median Income($10,000)[b]	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
Urban	Ref	Ref	Ref
Rural	1.03 (0.93, 1.14)	1.03 (0.93, 1.14)	1.03 (0.93, 1.13)
Average Truck Miles Traveled (IQR=944,940)[c]	0.99 (0.98, 1.01)	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)
Ventricular Septal Defect 2008-2010 (n=6,576)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	4	34	206

Model 2			
Well Density[a]	1.03 (0.98, 1.09)	0.99 (0.93, 1.06)	1.05 (0.98, 1.12)
Model 3			
Well Density[a]	1.03 (0.98, 1.09)	1.00 (0.93, 1.07)	1.06 (0.99,1.14)
Non- Smoker	Ref	Ref	Ref
Smoker	0.93 (0.81, 1.06)	0.93 (0.81, 1.06)	1.08 (0.95, 1.06)
Singleton	Ref	Ref	Ref
Two + Fetus	2.04 (1.84, 2.27)	2.04 (1.84, 2.27)	2.04 (1.84, 2.27)
Age 20-24	Ref	Ref	Ref
Age 10-19	1.08 (0.99, 1.18)	1.08 (0.99, 1.18)	1.08 (0.99, 1.18)
Age 25-29	1.02 (0.95, 1.09)	1.02 (0.95, 1.09)	1.02 (0.95, 1.09)
Age 30-34	1.12 (1.04, 1.21)	1.12 (1.04, 1.21)	1.12 (1.04, 1.21)
Age 35-39	1.24 (1.14, 1.36)	1.24 (1.14, 1.36)	1.24 (1.14, 1.36)
Age 40-60	1.37 (1.17, 1.62)	1.37 (1.16, 1.62)	1.37 (1.17, 1.62)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.77 (0.70, 0.85)	0.77 (0.70, 0.85)	1.29 (1.18, 0.85)
Hispanic	1.05 (0.98, 1.12)	1.05 (0.98, 1.12)	1.05 (0.98, 1.12)
Other non-Hispanic	0.81 (0.71, 0.93)	0.81 (0.71, 0.93)	1.23 (1.07, 0.93)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.11 (1.04, 1.19)	1.11 (1.04, 1.19)	1.11 (1.04, 1.19)
Greater than HS	0.91 (0.86, 0.98)	0.91 (0.86, 0.98)	1.09 (1.02, 0.98)
Model 4			
Well Density[a]	1.04 (0.98, 1.09)	1.00 (0.94, 1.07)	1.07 (1.00, 1.14)
Non- Smoker	Ref	Ref	Ref
Smoker	0.91 (0.80, 1.04)	0.91 (0.80, 1.04)	0.91 (0.80, 1.04)
Singleton	Ref	Ref	Ref
Two + Fetus	2.08 (1.87, 2.32)	2.08 (1.87, 2.32)	2.08 (1.87, 2.32)
Age 20-24	Ref	Ref	Ref
Age 10-19	1.10 (1.00, 1.20)	1.10 (1.00, 1.20)	1.10 (1.00, 1.20)
Age 25-29	1.03 (0.96, 1.10)	1.03 (0.96, 1.10)	1.03 (0.96, 1.10)
Age 30-34	1.14 (1.06, 1.23)	1.14 (1.06, 1.23)	1.14 (1.05, 1.23)
Age 35-39	1.28 (1.17, 1.40)	1.28 (1.17, 1.40)	1.28 (1.17, 1.40)
Age 40-60	1.44 (1.22, 1.70)	1.44 (1.22, 1.70)	1.44 (1.22, 1.70)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.73 (0.67, 0.81)	0.73 (0.66, 0.81)	0.73 (0.67, 0.81)
Hispanic	1.01 (0.94, 1.08)	1.01 (0.94, 1.08)	1.01 (0.94, 1.08)
Other non-Hispanic	0.80 (0.70, 0.92)	0.81 (0.70, 0.92)	0.81 (0.70, 0.92)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.10 (1.03, 1.17)	1.10 (1.03, 1.17)	1.10 (1.03, 1.17)
Greater than HS	0.94 (0.88, 1.00)	0.94 (0.88, 1.00)	0.94 (0.88, 1.00)
Median Income($10,000)[b]	0.97 (0.96, 0.99)	0.97 (0.96,0.99)	0.97 (0.96, 0.99)
Urban	Ref	Ref	Ref

Rural	0.96 (0.87, 1.06)	0.96 (0.87, 1.06)	0.96 (0.87, 1.06)
Average Truck Miles Traveled (IQR=945,507)[c]	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)
Ventricular Septal Defects 2009-2011 (n=6,600)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	4	37	229
Model 2			
Well Density[a]	1.02 (0.97, 1.07)	1.08 (1.02, 1.14)	1.06 (1.00, 1.13)
Model 3			
Well Density[a]	1.02 (0.97, 1.07)	1.09 (1.02, 1.15)	1.07 (1.01, 1.14)
Non- Smoker	Ref	Ref	Ref
Smoker	1.03 (0.91, 1.17)	1.03 (0.91, 1.17)	1.03 (0.91, 1.17)
Singleton	Ref	Ref	Ref
Two + Fetus	2.35 (2.11, 2.61)	2.35 (2.11, 2.61)	2.35 (2.12, 2.61)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.91 (0.83, 0.99)	0.91 (0.83, 0.99)	0.91 (0.83, 0.99)
Age 25-29	1.06 (0.99, 1.14)	1.07 (0.99, 1.14)	1.07 (0.99, 1.14)
Age 30-34	1.14 (1.06, 1.23)	1.14 (1.06, 1.23)	1.14 (1.06, 1.23)
Age 35-39	1.22 (1.11, 1.33)	1.22 (1.11, 1.33)	1.22 (1.11, 1.33)
Age 40-60	1.65 (1.42, 1.92)	1.66 (1.42, 1.93)	1.65 (1.42, 1.92)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.91 (0.83, 1.00)	0.91 (0.83, 1.00)	0.91 (0.83, 1.00)
Hispanic	1.00 (0.93, 1.06)	1.00 (0.93, 1.07)	1.00 (0.93, 1.06)
Other non-Hispanic	0.85 (0.74, 0.96)	0.85 (0.75, 0.96)	0.85 (0.75, 0.96)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.07 (1.00, 1.14)	1.07 (1.00, 1.14)	1.07 (1.00, 1.14)
Greater than HS	0.85 (0.79, 0.91)	0.85 (0.79, 0.91)	0.85 (0.79, 0.91)
Model 4			
Well Density[a]	1.02 (0.98, 1.07)	1.09 (1.03, 1.16)	1.09 (1.02, 1.16)
Non- Smoker	Ref	Ref	Ref
Smoker	1.02 (0.90, 1.16)	1.02 (0.90, 1.16)	1.02 (0.90, 1.16)
Singleton	Ref	Ref	Ref
Two + Fetus	2.39 (2.15, 2.65)	2.39 (2.15, 2.65)	2.39 (2.15, 2.66)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.92 (0.84, 1.00)	0.92 (0.84, 1.00)	0.92 (0.84, 1.00)
Age 25-29	1.07 (1.00, 1.15)	1.07 (1.00, 1.15)	1.07 (1.00, 1.15)
Age 30-34	1.16 (1.08, 1.25)	1.16 (1.08, 1.26)	1.17 (1.08, 1.26)
Age 35-39	1.24 (1.14, 1.36)	1.25 (1.14, 1.36)	1.24 (1.14, 1.36)
Age 40-60	1.70 (1.46, 1.98)	1.71 (1.47, 1.99)	1.70 (1.46, 1.98)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.86 (0.78, 0.95)	0.86 (0.78, 0.95)	0.86 (0.78, 0.95)

Hispanic	0.96 (0.89, 1.02)	0.96 (0.89, 1.03)	0.96 (0.89, 1.02)
Other non-Hispanic	0.83 (0.73, 0.95)	0.83 (0.73, 0.95)	0.83 (0.73, 0.95)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.06 (0.99, 1.13)	1.06 (0.99, 1.13)	1.06 (0.99, 1.13)
Greater than HS	0.87 (0.81, 0.93)	0.87 (0.81, 0.93)	0.87 (0.81, 0.93)
Median Income($10,000)[b]	0.97 (0.96, 0.99)	0.97 (0.96, 0.99)	0.97 (0.96, 0.99)
Urban	Ref	Ref	Ref
Rural	0.95 (0.86, 1.05)	0.95 (0.86, 1.05)	0.95 (0.86, 1.05)
Average Truck Miles Traveled (IQR=949,711)[c]	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)

[a] ORs correspond to an increase in wells from the 5th to the 95th percentile of the distribution within a buffer distance during year of pregnancy

[b] ORs correspond to a $10,000 increase in median income at block group of mother's maternal address at time of delivery

[c] ORs correspond to an interquartile range increase in average truck miles traveled by county.

Appendix Table B.6. Odds ratios (OR) and 95% confidence intervals (CI) for the associations between model covariates and atrial septal defects stratified by overlapping 3-year time intervals, born between 1999-2011 in Texas.

Defect/Model	**1km OR (95% CI)**	**3km OR (95% CI)**	**7.5km OR (95% CI)**
Atrial Septal Defects 1999-2001 (n=3,021)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	2	20	101
Model 2			
Well Density[a]	0.96 (0.89, 1.02)	1.05 (0.96, 1.15)	1.15 (1.04, 1.26)
Model 3			
Well Density[a]	0.95 (0.89, 1.01)	1.04 (0.95, 1.14)	1.14 (1.03, 1.25)
Non- Smoker	Ref	Ref	Ref
Smoker	1.62 (1.41, 1.87)	1.61 (1.40, 1.86)	1.61 (1.40, 1.85)
Singleton	Ref	Ref	Ref
Two + Fetus	3.26 (2.81, 3.78)	3.28 (2.82, 3.80)	3.28 (2.82, 3.80)
Age 20-24	Ref	Ref	Ref
Age 10-19	1.01 (0.89, 1.14)	1.01 (0.90, 1.15)	1.01 (0.90, 1.15)
Age 25-29	1.19 (1.07, 1.32)	1.19 (1.07, 1.32)	1.19 (1.07, 1.33)
Age 30-34	1.30 (1.16, 1.46)	1.31 (1.16, 1.47)	1.31 (1.17, 1.47)
Age 35-39	1.34 (1.16, 1.54)	1.35 (1.17, 1.55)	1.35 (1.18, 1.56)
Age 40-60	1.32 (1.00, 1.74)	1.28 (0.97, 1.69)	1.28 (0.97, 1.69)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.28 (1.12, 1.45)	1.28 (1.13, 1.46)	1.29 (1.14, 1.46)
Hispanic	1.06 (0.96, 1.17)	1.07 (0.97, 1.18)	1.07 (0.97, 1.18)
Other non-Hispanic	0.89 (0.70, 1.13)	0.89 (0.70, 1.13)	0.89 (0.70, 1.13)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.90 (0.82, 0.99)	0.90 (0.82, 1.00)	0.91 (0.82, 1.00)
Greater than HS	0.78 (0.71, 0.86)	0.78 (0.71, 0.86)	0.79 (0.72, 0.87)
Model 4			
Well Density[a]	0.95 (0.89, 1.02)	1.05 (0.95, 1.15)	1.14 (1.04, 1.26)
Non- Smoker	Ref	Ref	Ref
Smoker	1.61 (1.39, 1.85)	1.60 (1.39, 1.85)	1.60 (1.39, 1.84)
Singleton	Ref	Ref	Ref
Two + Fetus	3.25 (2.80, 3.77)	3.27 (2.82, 3.79)	3.27 (2.82, 3.79)
Age 20-24	Ref	Ref	Ref
Age 10-19	1.01 (0.90, 1.15)	1.02 (0.90, 1.15)	1.02 (0.90, 1.15)
Age 25-29	1.19 (1.07, 1.33)	1.19 (1.07, 1.33)	1.20 (1.08, 1.33)
Age 30-34	1.31 (1.17, 1.48)	1.31 (1.17, 1.48)	1.32 (1.17, 1.48)
Age 35-39	1.35 (1.17, 1.56)	1.36 (1.18, 1.57)	1.37 (1.19, 1.58)
Age 40-60	1.32 (1.00, 1.75)	1.28 (0.96, 1.69)	1.28 (0.97, 1.70)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.27 (1.11, 1.45)	1.28 (1.12, 1.46)	1.28 (1.12, 1.47)

Hispanic	1.06 (0.96, 1.17)	1.07 (0.97, 1.18)	1.07 (0.97, 1.18)
Other non-Hispanic	0.88 (0.70, 1.12)	0.89 (0.70, 1.13)	0.89 (0.70, 1.13)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.90 (0.81, 0.99)	0.90 (0.82, 0.99)	0.90 (0.82, 1.00)
Greater than HS	0.78 (0.71, 0.87)	0.79 (0.71, 0.87)	0.79 (0.72, 0.87)
Median Income($10,000)[b]	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)
Urban	Ref	Ref	Ref
Rural	0.94 (0.81, 1.08)	0.93 (0.80, 1.07)	0.91 (0.79, 1.05)
Average Truck Miles Traveled (IQR=749,629)[c]	0.97 (0.95, 0.99)	0.97 (0.95, 0.99)	0.97 (0.95, 0.99)
Atrial Septal Defects 2000-2002 (n=3,223)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	2	19	102
Model 2			
Well Density[a]	0.99 (0.93, 1.06)	1.04 (0.95, 1.13)	1.11 (1.01, 1.22)
Model 3			
Well Density[a]	0.98 (0.93, 1.06)	1.04 (0.96, 1.14)	1.11 (1.01, 1.22)
Non- Smoker	Ref	Ref	Ref
Smoker	1.05 (0.91, 1.21)	1.04 (0.91, 1.20)	1.05 (0.91, 1.21)
Singleton	Ref	Ref	Ref
Two + Fetus	2.95 (2.55, 3.41)	2.95 (2.55, 3.41)	2.95 (2.55, 3.41)
Age 20-24	Ref	Ref	Ref
Age 10-19	1.21 (1.07, 1.37)	1.21 (1.07, 1.37)	1.21 (1.07, 1.37)
Age 25-29	1.11 (1.01, 1.23)	1.12 (1.01, 1.23)	1.12 (1.01, 1.23)
Age 30-34	1.15 (1.04, 1.28)	1.15 (1.04, 1.28)	1.15 (1.04, 1.28)
Age 35-39	1.58 (1.38, 1.81)	1.58 (1.38, 1.81)	1.58 (1.38, 1.81)
Age 40-60	1.21 (0.93, 1.57)	1.21 (0.94, 1.58)	1.21 (0.93, 1.57)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.27 (1.12, 1.44)	1.27 (1.12, 1.44)	1.27 (1.12, 1.44)
Hispanic	1.01 (0.91, 1.11)	1.01 (0.92, 1.11)	1.01 (0.92, 1.11)
Other non-Hispanic	0.79 (0.63, 0.99)	0.79 (0.63, 0.99)	0.80 (0.63, 1.00)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.84 (0.77, 0.93)	0.84 (0.77, 0.93)	0.84 (0.77, 0.93)
Greater than HS	0.78 (0.71, 0.86)	0.78 (0.71, 0.86)	0.78 (0.71, 0.85)
Model 4			
Well Density[a]	0.99 (0.93, 1.06)	1.05 (0.96, 1.14)	1.11 (1.01, 1.22)
Non- Smoker	Ref	Ref	Ref
Smoker	1.05 (0.91, 1.20)	1.04 (0.90, 1.20)	1.05 (0.91, 1.20)
Singleton	Ref	Ref	Ref

Two + Fetus	2.96 (2.56, 3.43)	2.97 (2.57, 3.43)	2.97 (2.57, 3.43)
Age 20-24	Ref	Ref	Ref
Age 10-19	1.21 (1.07, 1.37)	1.21 (1.07, 1.37)	1.21 (1.07, 1.37)
Age 25-29	1.12 (1.01, 1.24)	1.12 (1.01, 1.24)	1.12 (1.01, 1.24)
Age 30-34	1.17 (1.05, 1.30)	1.17 (1.05, 1.30)	1.17 (1.05, 1.30)
Age 35-39	1.61 (1.40, 1.85)	1.61 (1.40, 1.85)	1.61 (1.40, 1.84)
Age 40-60	1.22 (0.94, 1.58)	1.22 (0.94, 1.59)	1.22 (0.94, 1.58)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.26 (1.11, 1.44)	1.27 (1.11, 1.45)	1.27 (1.11, 1.45)
Hispanic	1.00 (0.91, 1.11)	1.00 (0.91, 1.11)	1.01 (0.91, 1.11)
Other non-Hispanic	0.80 (0.64, 1.01)	0.80 (0.64, 1.01)	0.81 (0.64, 1.01)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.84 (0.77, 0.92)	0.84 (0.77, 0.92)	0.84 (0.77, 0.92)
Greater than HS	0.79 (0.72, 0.87)	0.79 (0.72, 0.87)	0.79 (0.71, 0.86)
Median Income($10,000)[b]	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)
Urban	Ref	Ref	Ref
Rural	0.96 (0.84, 1.10)	0.96 (0.83, 1.10)	0.95 (0.82, 1.09)
Average Truck Miles Traveled (IQR=761,333)[c]	0.97 (0.95, 0.99)	0.97 (0.95, 0.99)	0.97 (0.95, 0.99)
Atrial Septal Defects 2001-2003 (n=3,494)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	2	20	107
Model 2			
Well Density[a]	0.99 (0.92, 1.05)	1.05 (0.96, 1.14)	1.10 (1.01, 1.20)
Model 3			
Well Density[a]	0.98 (0.92, 1.04)	1.04 (0.96, 1.13)	1.10 (1.01, 1.20)
Non- Smoker	Ref	Ref	Ref
Smoker	1.17 (1.02, 1.34)	1.16 (1.02, 1.33)	1.16 (1.01, 1.33)
Singleton	Ref	Ref	Ref
Two + Fetus	2.61 (2.28, 2.99)	2.61 (2.28, 2.99)	2.61 (2.28, 2.99)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.82 (0.73, 0.92)	0.82 (0.73, 0.92)	0.82 (0.73, 0.92)
Age 25-29	0.91 (0.82, 1.00)	0.91 (0.82, 1.00)	0.91 (0.82, 1.00)
Age 30-34	1.02 (0.92, 1.13)	1.02 (0.92, 1.13)	1.02 (0.92, 1.13)
Age 35-39	1.33 (1.17, 1.52)	1.33 (1.17, 1.52)	1.34 (1.17, 1.53)
Age 40-60	1.48 (1.16, 1.89)	1.49 (1.17, 1.89)	1.48 (1.16, 1.89)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.05 (0.93, 1.18)	1.05 (0.94, 1.18)	1.06 (0.94, 1.19)
Hispanic	0.84 (0.76, 0.92)	0.84 (0.77, 0.92)	0.84 (0.77, 0.92)
Other non-Hispanic	0.86 (0.70, 1.05)	0.86 (0.71, 1.05)	0.86 (0.71, 1.05)

High School (HS) Education	Ref	Ref	Ref
Less than HS	1.05 (0.96, 1.15)	1.05 (0.96, 1.15)	1.05 (0.97, 1.15)
Greater than HS	0.91 (0.83, 0.99)	0.91 (0.83, 1.00)	0.91 (0.83, 1.00)
Model 4			
Well Density[a]	0.98 (0.92, 1.05)	1.05 (0.96, 1.14)	1.11 (1.01, 1.21)
Non- Smoker	Ref	Ref	Ref
Smoker	1.16 (1.01, 1.33)	1.16 (1.01, 1.33)	1.16 (1.01, 1.33)
Singleton	Ref	Ref	Ref
Two + Fetus	2.63 (2.30, 3.02)	2.63 (2.30, 3.02)	2.64 (2.30, 3.02)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.82 (0.73, 0.92)	0.82 (0.73, 0.92)	0.82 (0.73, 0.92)
Age 25-29	0.91 (0.82, 1.00)	0.91 (0.82, 1.00)	0.91 (0.82, 1.00)
Age 30-34	1.02 (0.92, 1.14)	1.02 (0.92, 1.14)	1.03 (0.93, 1.14)
Age 35-39	1.36 (1.19, 1.55)	1.36 (1.19, 1.56)	1.37 (1.20, 1.56)
Age 40-60	1.53 (1.20, 1.96)	1.54 (1.20, 1.97)	1.53 (1.20, 1.96)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.03 (0.91, 1.16)	1.03 (0.91, 1.17)	1.03 (0.91, 1.17)
Hispanic	0.82 (0.75, 0.91)	0.83 (0.76, 0.91)	0.83 (0.75, 0.91)
Other non-Hispanic	0.85 (0.70, 1.04)	0.86 (0.70, 1.05)	0.86 (0.70, 1.05)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.05 (0.96, 1.15)	1.05 (0.96, 1.15)	1.05 (0.96, 1.15)
Greater than HS	0.92 (0.84, 1.01)	0.92 (0.84, 1.01)	0.92 (0.84, 1.01)
Median Income($10,000)[b]	0.99 (0.97, 1.00)	0.99 (0.97, 1.00)	0.99 (0.97, 1.00)
Urban	Ref	Ref	Ref
Rural	0.93 (0.82, 1.07)	0.93 (0.81, 1.06)	0.92 (0.80, 1.05)
Average Truck Miles Traveled (IQR=912,620)[c]	0.98 (0.96, 1.01)	0.98 (0.96, 1.00)	0.98 (0.96, 1.00)
Atrial Septal Defects 2002-2004 (n=4,015)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	2	21	110
Model 2			
Well Density[a]	1.09 (1.03, 1.14)	1.10 (1.02, 1.18)	1.19 (1.09, 1.30)
Model 3			
Well Density[a]	1.09 (1.04, 1.14)	1.10 (1.02, 1.19)	1.20 (1.10, 1.31)
Non- Smoker	Ref	Ref	Ref
Smoker	1.19 (1.05, 1.35)	1.19 (1.05, 1.35)	1.19 (1.05, 1.36)
Singleton	Ref	Ref	Ref
Two + Fetus	2.71 (2.39, 3.07)	2.71 (2.39, 3.07)	2.72 (2.39, 3.08)
Age 20-24	Ref	Ref	Ref

Age 10-19	1.00 (0.90, 1.12)	1.00 (0.90, 1.12)	1.01 (0.90, 1.12)
Age 25-29	1.10 (1.01, 1.20)	1.10 (1.01, 1.20)	1.10 (1.01, 1.20)
Age 30-34	1.23 (1.12, 1.36)	1.24 (1.12, 1.36)	1.24 (1.12, 1.36)
Age 35-39	1.20 (1.05, 1.36)	1.20 (1.06, 1.37)	1.20 (1.06, 1.37)
Age 40-60	1.84 (1.50, 2.25)	1.83 (1.50, 2.24)	1.84 (1.50, 2.25)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.21 (1.08, 1.35)	1.21 (1.08, 1.35)	1.22 (1.09, 1.36)
Hispanic	0.95 (0.87, 1.03)	0.95 (0.87, 1.03)	0.95 (0.87, 1.04)
Other non-Hispanic	0.85 (0.71, 1.03)	0.85 (0.71, 1.03)	0.85 (0.71, 1.03)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.05 (0.97, 1.14)	1.05 (0.97, 1.14)	1.05 (0.97, 1.14)
Greater than HS	0.86 (0.79, 0.94)	0.86 (0.79, 0.94)	0.86 (0.79, 0.94)
Model 4			
Well Density[a]	1.09 (1.04, 1.15)	1.11 (1.03, 1.19)	1.21 (1.11, 1.32)
Non- Smoker	Ref	Ref	Ref
Smoker	1.17 (1.02, 1.33)	1.17 (1.02, 1.33)	1.17 (1.02, 1.33)
Singleton	Ref	Ref	Ref
Two + Fetus	2.76 (2.43, 3.13)	2.76 (2.43, 3.13)	2.77 (2.44, 3.14)
Age 20-24	Ref	Ref	Ref
Age 10-19	1.00 (0.90, 1.12)	1.01 (0.90, 1.12)	1.01 (0.90, 1.12)
Age 25-29	1.11 (1.01, 1.21)	1.11 (1.01, 1.21)	1.11 (1.01, 1.21)
Age 30-34	1.27 (1.15, 1.40)	1.27 (1.15, 1.40)	1.27 (1.15, 1.40)
Age 35-39	1.25 (1.10, 1.42)	1.26 (1.10, 1.43)	1.26 (1.10, 1.43)
Age 40-60	1.94 (1.58, 2.38)	1.93 (1.58, 2.37)	1.94 (1.58, 2.38)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.14 (1.01, 1.28)	1.14 (1.01, 1.28)	1.14 (1.02, 1.29)
Hispanic	0.90 (0.82, 0.98)	0.90 (0.82, 0.98)	0.90 (0.82, 0.98)
Other non-Hispanic	0.85 (0.71, 1.03)	0.85 (0.71, 1.03)	0.86 (0.71, 1.04)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.03 (0.95, 1.12)	1.03 (0.95, 1.12)	1.04 (0.95, 1.13)
Greater than HS	0.88 (0.81, 0.96)	0.88 (0.80, 0.96)	0.88 (0.81, 0.96)
Median Income($10,000)[b]	0.96 (0.95, 0.98)	0.96 (0.95, 0.98)	0.96 (0.95, 0.98)
Urban	Ref	Ref	Ref
Rural	0.89 (0.78, 1.01)	0.89 (0.78, 1.01)	0.88 (0.77, 1.00)
Average Truck Miles Traveled (IQR=919,545)[c]	0.98 (0.96, 1.00)	0.98 (0.96, 1.00)	0.98 (0.95, 1.00)
Atrial Septal Defects 2003-2005 (n=4,806)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	2	21	111

Model 2			
Well Density[a]	1.04 (1.00, 1.09)	1.10 (1.04, 1.18)	1.16 (1.09, 1.23)
Model 3			
Well Density[a]	1.04 (0.99, 1.08)	1.10 (1.03, 1.17)	1.18 (1.11, 1.25)
Non- Smoker	Ref	Ref	Ref
Smoker	1.13 (1.01, 1.27)	1.14 (1.01, 1.27)	1.14 (1.02, 1.28)
Singleton	Ref	Ref	Ref
Two + Fetus	3.68 (3.28, 4.12)	3.68 (3.28, 4.12)	3.71 (3.31, 4.16)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.98 (0.89, 1.08)	0.98 (0.89, 1.08)	0.98 (0.89, 1.08)
Age 25-29	1.06 (0.98, 1.15)	1.06 (0.98, 1.15)	1.06 (0.98, 1.15)
Age 30-34	0.97 (0.89, 1.06)	0.97 (0.89, 1.06)	0.97 (0.89, 1.06)
Age 35-39	1.07 (0.96, 1.20)	1.07 (0.96, 1.20)	1.07 (0.96, 1.20)
Age 40-60	1.26 (1.04, 1.53)	1.26 (1.04, 1.53)	1.25 (1.03, 1.52)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.08 (0.98, 1.20)	1.08 (0.98, 1.19)	1.08 (0.98, 1.19)
Hispanic	1.03 (0.95, 1.11)	1.03 (0.95, 1.11)	1.03 (0.95, 1.11)
Other non-Hispanic	0.88 (0.74, 1.05)	0.88 (0.74, 1.05)	0.88 (0.73, 1.05)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.96 (0.89, 1.04)	0.96 (0.89, 1.04)	0.96 (0.89, 1.04)
Greater than HS	0.93 (0.86, 1.00)	0.93 (0.86, 1.00)	0.93 (0.86, 1.00)
Model 4			
Well Density[a]	1.04 (1.00, 1.09)	1.11 (1.04, 1.18)	1.19 (1.12, 1.27)
Non- Smoker	Ref	Ref	Ref
Smoker	1.11 (0.99, 1.24)	1.11 (0.99, 1.25)	1.11 (0.99, 1.25)
Singleton	Ref	Ref	Ref
Two + Fetus	3.69 (3.30, 4.14)	3.69 (3.29, 4.13)	3.72 (3.32, 4.17)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.98 (0.89, 1.08)	0.98 (0.89, 1.08)	0.98 (0.89, 1.08)
Age 25-29	1.06 (0.98, 1.15)	1.06 (0.98, 1.15)	1.06 (0.98, 1.15)
Age 30-34	0.99 (0.91, 1.08)	0.99 (0.91, 1.08)	0.99 (0.91, 1.08)
Age 35-39	1.09 (0.97, 1.22)	1.09 (0.97, 1.22)	1.09 (0.97, 1.22)
Age 40-60	1.32 (1.08, 1.61)	1.32 (1.08, 1.61)	1.31 (1.08, 1.60)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.03 (0.92, 1.14)	1.02 (0.92, 1.14)	1.02 (0.92, 1.13)
Hispanic	0.99 (0.91, 1.07)	0.99 (0.91, 1.07)	0.99 (0.91, 1.07)
Other non-Hispanic	0.89 (0.74, 1.06)	0.89 (0.74, 1.06)	0.88 (0.74, 1.05)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.95 (0.88, 1.02)	0.94 (0.87, 1.02)	0.95 (0.87, 1.02)
Greater than HS	0.95 (0.88, 1.03)	0.95 (0.88, 1.03)	0.95 (0.88, 1.03)
Median Income($10,000)[b]	0.97 (0.95, 0.98)	0.97 (0.95, 0.98)	0.97 (0.95, 0.98)
Urban	Ref	Ref	Ref

Rural	0.86 (0.77, 0.96)	0.85 (0.76, 0.95)	0.84 (0.75, 0.94)
Average Truck Miles Traveled (IQR=928,049)[c]	0.96 (0.95, 0.98)	0.96 (0.94, 0.98)	0.96 (0.94, 0.98)
Atrial Septal Defects 2004-2006 (n=5,401)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	3	23	118
Model 2			
Well Density[a]	1.04 (0.98, 1.11)	1.11 (1.04, 1.18)	1.14 (1.07, 1.22)
Model 3			
Well Density[a]	1.05 (0.98, 1.11)	1.11 (1.05, 1.18)	1.16 (1.08, 1.24)
Non- Smoker	Ref	Ref	Ref
Smoker	1.18 (1.05, 1.32)	1.18 (1.05, 1.32)	1.18 (1.05, 1.32)
Singleton	Ref	Ref	Ref
Two + Fetus	2.94 (2.63, 3.28)	2.95 (2.64, 3.29)	2.96 (2.65, 3.31)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.91 (0.83, 1.00)	0.91 (0.83, 1.00)	0.91 (0.83, 1.00)
Age 25-29	0.94 (0.87, 1.02)	0.94 (0.87, 1.02)	0.94 (0.87, 1.02)
Age 30-34	0.93 (0.86, 1.01)	0.93 (0.86, 1.01)	0.93 (0.86, 1.01)
Age 35-39	0.84 (0.76, 0.93)	0.84 (0.76, 0.93)	0.84 (0.76, 0.93)
Age 40-60	0.98 (0.81, 1.18)	0.99 (0.82, 1.19)	0.99 (0.82, 1.19)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.18 (1.07, 1.29)	1.18 (1.07, 1.29)	1.18 (1.07, 1.29)
Hispanic	0.95 (0.88, 1.02)	0.95 (0.88, 1.02)	0.95 (0.88, 1.02)
Other non-Hispanic	1.02 (0.87, 1.20)	1.02 (0.87, 1.20)	1.02 (0.87, 1.20)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.96 (0.89, 1.04)	0.96 (0.89, 1.04)	0.96 (0.89, 1.04)
Greater than HS	0.82 (0.77, 0.88)	0.82 (0.77, 0.88)	0.82 (0.76, 0.88)
Model 4			
Well Density[a]	1.05 (0.99, 1.12)	1.12 (1.05, 1.19)	1.16 (1.09, 1.25)
Non- Smoker	Ref	Ref	Ref
Smoker	1.17 (1.05, 1.31)	1.17 (1.05, 1.31)	1.17 (1.05, 1.31)
Singleton	Ref	Ref	Ref
Two + Fetus	2.92 (2.62, 3.26)	2.93 (2.62, 3.27)	2.94 (2.63, 3.28)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.91 (0.83, 1.00)	0.92 (0.83, 1.01)	0.92 (0.84, 1.01)
Age 25-29	0.95 (0.88, 1.03)	0.95 (0.88, 1.03)	0.95 (0.88, 1.03)
Age 30-34	0.94 (0.87, 1.03)	0.94 (0.87, 1.03)	0.94 (0.87, 1.03)
Age 35-39	0.85 (0.77, 0.95)	0.86 (0.77, 0.95)	0.86 (0.77, 0.95)
Age 40-60	0.98 (0.81, 1.18)	0.98 (0.82, 1.19)	0.99 (0.82, 1.19)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.16 (1.05, 1.28)	1.16 (1.05, 1.28)	1.16 (1.05, 1.28)

Hispanic	0.94 (0.87, 1.02)	0.94 (0.87, 1.02)	0.94 (0.87, 1.02)
Other non-Hispanic	1.03 (0.87, 1.20)	1.02 (0.87, 1.20)	1.03 (0.87, 1.20)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.96 (0.89, 1.03)	0.96 (0.89, 1.03)	0.96 (0.89, 1.03)
Greater than HS	0.83 (0.77, 0.90)	0.83 (0.77, 0.90)	0.83 (0.77, 0.89)
Median Income($10,000)[b]	0.98 (0.97, 1.00)	0.98 (0.97, 1.00)	0.98 (0.97, 1.00)
Urban	Ref	Ref	Ref
Rural	0.92 (0.83, 1.02)	0.91 (0.82, 1.01)	0.91 (0.82, 1.01)
Average Truck Miles Traveled (IQR=944,940)[c]	0.95 (0.93, 0.96)	0.94 (0.93, 0.96)	0.94 (0.92, 0.96)
Atrial Septal Defects 2005-2007 (n=5,760)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	3	25	136
Model 2			
Well Density[a]	1.11 (1.05, 1.17)	1.07 (1.00, 1.13)	1.11 (1.05, 1.18)
Model 3			
Well Density[a]	1.13 (1.06, 1.19)	1.08 (1.01, 1.14)	1.12 (1.05, 1.18)
Non- Smoker	Ref	Ref	Ref
Smoker	1.23 (1.11, 1.38)	1.23 (1.10, 1.37)	1.24 (1.11, 1.38)
Singleton	Ref	Ref	Ref
Two + Fetus	2.56 (2.31, 2.83)	2.55 (2.30, 2.83)	2.55 (2.30, 2.83)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.97 (0.88, 1.06)	0.97 (0.88, 1.06)	0.97 (0.88, 1.06)
Age 25-29	1.04 (0.97, 1.12)	1.04 (0.97, 1.12)	1.04 (0.97, 1.12)
Age 30-34	0.99 (0.91, 1.08)	0.99 (0.92, 1.08)	0.99 (0.92, 1.08)
Age 35-39	1.32 (1.19, 1.45)	1.32 (1.20, 1.45)	1.32 (1.20, 1.45)
Age 40-60	1.39 (1.16, 1.67)	1.39 (1.15, 1.66)	1.39 (1.16, 1.67)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.06 (0.97, 1.16)	1.06 (0.97, 1.16)	1.06 (0.97, 1.16)
Hispanic	0.91 (0.85, 0.98)	0.91 (0.85, 0.98)	0.91 (0.85, 0.98)
Other non-Hispanic	0.75 (0.65, 0.88)	0.76 (0.65, 0.88)	0.76 (0.65, 0.88)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.97 (0.90, 1.04)	0.97 (0.91, 1.04)	0.98 (0.91, 1.05)
Greater than HS	0.91 (0.85, 0.98)	0.91 (0.85, 0.98)	0.92 (0.85, 0.98)
Model 4			
Well Density[a]	1.12 (1.06, 1.19)	1.07 (1.01, 1.14)	1.11 (1.05, 1.18)
Non- Smoker	Ref	Ref	Ref
Smoker	0.97 (0.90, 1.04)	1.21 (1.08, 1.35)	1.21 (1.09, 1.36)
Singleton	Ref	Ref	Ref

Two + Fetus	2.55 (2.30, 2.83)	2.55 (2.30, 2.82)	2.55 (2.30, 2.82)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.97 (0.88, 1.06)	0.97 (0.88, 1.06)	0.97 (0.88, 1.06)
Age 25-29	1.05 (0.98, 1.13)	1.06 (0.98, 1.14)	1.06 (0.98, 1.14)
Age 30-34	1.01 (0.93, 1.09)	1.01 (0.93, 1.09)	1.01 (0.93, 1.10)
Age 35-39	1.34 (1.22, 1.48)	1.34 (1.22, 1.48)	1.35 (1.22, 1.48)
Age 40-60	1.42 (1.18, 1.71)	1.42 (1.18, 1.70)	1.43 (1.19, 1.71)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.04 (0.95, 1.14)	1.04 (0.95, 1.14)	1.04 (0.95, 1.14)
Hispanic	0.90 (0.84, 0.97)	0.90 (0.84, 0.96)	0.90 (0.84, 0.96)
Other non-Hispanic	0.78 (0.67, 0.90)	0.78 (0.67, 0.91)	0.78 (0.67, 0.91)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.96 (0.90, 1.04)	0.97 (0.90, 1.04)	0.97 (0.90, 1.04)
Greater than HS	0.93 (0.87, 1.00)	0.94 (0.87, 1.01)	0.94 (0.87, 1.01)
Median Income($10,000)[b]	0.97 (0.96, 0.99)	0.97 (0.96, 0.99)	0.97 (0.96, 0.99)
Urban	Ref	Ref	Ref
Rural			
Average Truck Miles Traveled (IQR=944,940)[c]	0.95 (0.94, 0.97)	0.96 (0.94, 0.97)	0.95 (0.94, 0.97)
Atrial Septal Defects 2006-2008 (n=6,047)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	3	29	162
Model 2			
Well Density[a]	1.03 (0.98, 1.07)	1.05 (1.00, 1.110	1.07 (1.01, 1.14)
Model 3			
Well Density[a]	1.04 (0.99, 1.08)	1.06 (1.01, 1.12)	1.11 (1.04, 1.17)
Non- Smoker	Ref	Ref	Ref
Smoker	0.98 (0.87, 1.09)	0.98 (0.88, 1.09)	0.98 (0.87, 1.09)
Singleton	Ref	Ref	Ref
Two + Fetus	2.61 (2.36, 2.88)	2.61 (2.37, 2.88)	2.63 (2.38, 2.88)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.90 (0.82, 0.98)	0.90 (0.82, 0.98)	0.90 (0.82, 0.98)
Age 25-29	1.05 (0.98, 1.13)	1.05 (0.98, 1.13)	1.05 (0.98, 1.13)
Age 30-34	1.02 (0.94, 1.10)	1.02 (0.94, 1.10)	1.02 (0.94, 1.10)
Age 35-39	1.34 (1.22, 1.47)	1.34 (1.22, 1.47)	1.34 (1.22, 1.47)
Age 40-60	1.57 (1.32, 1.86)	1.56 (1.32, 1.86)	1.56 (1.32, 1.86)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.24 (1.14, 1.35)	1.24 (1.13, 1.35)	1.24 (1.14, 1.35)
Hispanic	1.00 (0.94, 1.07)	1.00 (0.94, 1.07)	1.01 (0.94, 1.07)

Other non-Hispanic	0.81 (0.71, 0.94)	0.81 (0.71, 0.94)	0.82 (0.71, 0.94)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.03 (0.96, 1.11)	1.03 (0.96, 1.11)	1.03 (0.96, 1.11)
Greater than HS	0.89 (0.83, 0.95)	0.89 (0.83, 0.95)	0.89 (0.83, 0.95)
Model 4			
Well Density[a]	1.04 (0.99, 1.08)	1.06 (1.00, 1.12)	1.10 (1.03, 1.17)
Non- Smoker	Ref	Ref	Ref
Smoker	0.96 (0.86, 1.08)	0.96 (0.86, 1.08)	0.96 (0.86, 1.08)
Singleton	Ref	Ref	Ref
Two + Fetus	2.62 (2.37, 2.89)	2.62 (2.37, 2.89)	2.63 (2.38, 2.89)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.90 (0.82, 0.98)	0.90 (0.82, 0.98)	0.90 (0.82, 0.98)
Age 25-29	1.05 (0.98, 1.13)	1.05 (0.98, 1.13)	1.05 (0.98, 1.13)
Age 30-34	1.03 (0.95, 1.12)	1.03 (0.95, 1.12)	1.03 (0.95, 1.12)
Age 35-39	1.38 (1.25, 1.52)	1.38 (1.26, 1.52)	1.39 (1.26, 1.52)
Age 40-60	1.64 (1.38, 1.94)	1.63 (1.37, 1.94)	1.63 (1.37, 1.94)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.21 (1.11, 1.33)	1.21 (1.11, 1.33)	1.21 (1.11, 1.33)
Hispanic	0.99 (0.92, 1.06)	0.99 (0.92, 1.06)	0.99 (0.92, 1.06)
Other non-Hispanic	0.82 (0.71, 0.94)	0.82 (0.71, 0.94)	0.82 (0.71, 0.94)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.02 (0.95, 1.10)	1.02 (0.95, 1.10)	1.02 (0.95, 1.10)
Greater than HS	0.90 (0.84, 0.97)	0.90 (0.84, 0.97)	0.90 (0.84, 0.97)
Median Income($10,000)[b]	0.97 (0.96, 0.99)	0.97 (0.96, 0.99)	0.97 (0.96, 0.99)
Urban	Ref	Ref	Ref
Rural	1.04 (0.95, 1.15)	1.04 (0.95, 1.15)	1.04 (0.95, 1.15)
Average Truck Miles Traveled (IQR=945,507)[c]	0.96 (0.94, 0.98)	0.96 (0.94, 0.98)	0.96 (0.94, 0.98)
Atrial Septal Defects 2007-2009 (n=6,,303)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	4	34	189
Model 2			
Well Density[a]	1.06 (1.00, 1.12)	1.11 (1.05, 1.18)	1.14 (1.07, 1.20)
Model 3			
Well Density[a]	1.06 (1.00, 1.12)	1.11 (1.05, 1.18)	1.13 (1.07, 1.20)
Non- Smoker	Ref	Ref	Ref
Smoker	1.06 (0.95, 1.18)	1.05 (0.95, 1.18)	1.06 (0.95, 1.18)
Singleton	Ref	Ref	Ref
Two + Fetus	3.78 (3.43, 4.17)	3.78 (3.43, 4.17)	3.78 (3.43, 4.16)

Age 20-24	Ref	Ref	Ref
Age 10-19	0.88 (0.81, 0.96)	0.88 (0.81, 0.96)	0.88 (0.81, 0.96)
Age 25-29	1.09 (1.02, 1.17)	1.09 (1.01, 1.17)	1.09 (1.02, 1.17)
Age 30-34	1.01 (0.94, 1.09)	1.01 (0.94, 1.09)	1.01 (0.94, 1.10)
Age 35-39	1.21 (1.10, 1.33)	1.21 (1.10, 1.33)	1.21 (1.10, 1.33)
Age 40-60	1.67 (1.41, 1.97)	1.67 (1.41, 1.97)	1.67 (1.42, 1.97)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.27 (1.17, 1.39)	1.28 (1.17, 1.39)	1.28 (1.17, 1.39)
Hispanic	1.00 (0.94, 1.07)	1.01 (0.94, 1.08)	1.01 (0.94, 1.08)
Other non-Hispanic	1.02 (0.89, 1.18)	1.03 (0.89, 1.18)	1.03 (0.89, 1.18)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.93 (0.87, 1.00)	0.93 (0.87, 1.00)	0.93 (0.87, 1.00)
Greater than HS	0.77 (0.72, 0.82)	0.77 (0.72, 0.82)	0.77 (0.72, 0.82)
Model 4			
Well Density[a]	1.06 (1.00, 1.12)	1.11 (1.05, 1.180	1.13 (1.07, 1.20)
Non- Smoker	Ref	Ref	Ref
Smoker	1.03 (0.92, 1.15)	1.03 (0.92, 1.15)	1.03 (0.92, 1.15)
Singleton	Ref	Ref	Ref
Two + Fetus	3.84 (3.48, 4.23)	3.84 (3.49, 4.24)	3.84 (3.49, 4.23)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.89 (0.82, 0.97)	0.89 (0.82, 0.97)	0.89 (0.82, 0.97)
Age 25-29	1.10 (1.02, 1.18)	1.09 (1.02, 1.17)	1.10 (1.02, 1.18)
Age 30-34	1.04 (0.97, 1.13)	1.04 (0.97, 1.13)	1.04 (0.97, 1.13)
Age 35-39	1.27 (1.15, 1.39)	1.27 (1.15, 1.39)	1.27 (1.15, 1.40)
Age 40-60	1.74 (1.47, 2.05)	1.74 (1.47, 2.05)	1.74 (1.48, 2.06)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.21 (1.11, 1.32)	1.21 (1.11, 1.32)	1.21 (1.11, 1.33)
Hispanic	0.97 (0.90, 1.04)	0.97 (0.90, 1.04)	0.97 (0.90, 1.04)
Other non-Hispanic	1.05 (0.91, 1.20)	1.05 (0.91, 1.21)	1.05 (0.91, 1.21)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.91 (0.85, 0.98)	0.91 (0.85, 0.98)	0.91 (0.85, 0.97)
Greater than HS	0.79 (0.74, 0.85)	0.79 (0.74, 0.85)	0.79 (0.74, 0.85)
Median Income($10,000)[b]	0.95 (0.94, 0.97)	0.95 (0.94, 0.97)	0.95 (0.94, 0.97)
Urban	Ref	Ref	Ref
Rural	1.01 (0.92, 1.10)	1.00 (0.91, 1.10)	1.00 (0.91, 1.10)
Average Truck Miles Traveled (IQR=949,711)[c]	0.94 (0.93, 0.96)	0.94 (0.93,0.96)	0.94 (0.93, 0.96)
Atrial Septal Defects 2008-2010 (n=6734)			

Span size	0.20	0.20	0.20
Increased Well Count[a]	4	39	226
Model 2			
Well Density[a]	1.04 (0.99, 1.09)	1.12 (1.07, 1.18)	1.21 (1.15, 1.28)
Model 3			
Well Density[a]	1.04 (0.99, 1.09)	1.13 (1.07, 1.19)	1.22 (1.16, 1.29)
Non- Smoker	Ref	Ref	Ref
Smoker	0.98 (0.88, 1.09)	0.98 (0.88, 1.09)	0.98 (0.88, 1.09)
Singleton	Ref	Ref	Ref
Two + Fetus	3.15 (2.87, 3.45)	3.15 (2.87, 3.45)	3.15 (2.87, 3.45)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.86 (0.79, 0.94)	0.86 (0.79, 0.94)	0.86 (0.79, 0.94)
Age 25-29	0.93 (0.87, 1.00)	0.93 (0.87, 1.00)	0.93 (0.87, 1.00)
Age 30-34	0.97 (0.90, 1.05)	0.97 (0.90, 1.05)	0.97 (0.90, 1.05)
Age 35-39	1.05 (0.96, 1.15)	1.05 (0.96, 1.15)	1.05 (0.95, 1.15)
Age 40-60	1.62 (1.37, 1.90)	1.62 (1.38, 1.90)	1.63 (1.38, 1.90)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.15 (1.06, 1.25)	1.15 (1.06, 1.25)	1.15 (1.06, 1.25)
Hispanic	0.93 (0.87, 0.99)	0.93 (0.87, 0.99)	0.93 (0.87, 0.99)
Other non-Hispanic	0.96 (0.84, 1.10)	0.97 (0.85, 1.10)	0.97 (0.85, 1.10)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.10 (1.03, 1.17)	1.10 (1.03, 1.17)	1.10 (1.03, 1.17)
Greater than HS	0.87 (0.81, 0.93)	0.87 (0.81, 0.93)	0.87 (0.81, 0.93)
Model 4			
Well Density[a]	1.04 (0.99, 1.09)	1.13 (1.08, 1.20)	1.22 (1.16, 1.29)
Non- Smoker	Ref	Ref	Ref
Smoker	0.93 (0.84, 1.03)	0.93 (0.83, 1.03)	0.93 (0.83, 1.03)
Singleton	Ref	Ref	Ref
Two + Fetus	3.27 (2.98, 3.59)	3.27 (2.98, 3.59)	3.27 (2.98, 3.59)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.88 (0.81, 0.96)	0.88 (0.81, 0.96)	0.88 (0.81, 0.96)
Age 25-29	0.95 (0.89, 1.02)	0.95 (0.89, 1.02)	0.95 (0.88, 1.02)
Age 30-34	1.03 (0.95, 1.11)	1.03 (0.95, 1.11)	1.02 (0.95, 1.11)
Age 35-39	1.14 (1.04, 1.26)	1.14 (1.04, 1.26)	1.14 (1.04, 1.26)
Age 40-60	1.93 (1.64, 2.28)	1.94 (1.65, 2.28)	1.95 (1.66, 2.28)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.04 (0.95, 1.13)	1.04 (0.95, 1.13)	1.04 (0.96, 1.13)
Hispanic	0.86 (0.80, 0.92)	0.86 (0.80, 0.92)	0.86 (0.81, 0.92)
Other non-Hispanic	0.95 (0.83, 1.08)	0.95 (0.84, 1.08)	0.96 (0.84, 1.08)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.06 (0.99, 1.13)	1.06 (0.99, 1.13)	1.06 (0.99, 1.13)
Greater than HS	0.93 (0.87, 0.99)	0.93 (0.87, 0.99)	0.93 (0.87, 0.99)

Median Income($10,000)[b]	0.92 (0.91, 0.93)	0.92 (0.91, 0.93)	0.92 (0.91, 0.93)
Urban	Ref	Ref	Ref
Rural	0.95 (0.87, 1.04)	0.95 (0.87, 1.04)	0.95 (0.87, 1.04)
Average Truck Miles Traveled (IQR=949,711)[c]	0.93 (0.92, 0.95)	0.93 (0.92, 0.95)	0.93 (0.92, 0.95)
Atrial Septal Defects 2009-2011 (n=7,187)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	5	43	253
Model 2			
Well Density[a]	1.07 (1.02, 1.12)	1.17 (1.11, 1.23)	1.24 (1.18, 1.31)
Model 3			
Well Density[a]	1.07 (1.02, 1.13)	1.19 (1.13, 1.26)	1.24 (1.17, 1.30)
Non- Smoker	Ref	Ref	Ref
Smoker	1.18 (1.06, 1.31)	1.19 (1.07, 1.32)	1.18 (1.06, 1.31)
Singleton	Ref	Ref	Ref
Two + Fetus	2.56 (2.34, 2.81)	2.58 (2.35, 2.82)	2.55 (2.32, 2.79)
Age 20-24	Ref	Ref	Ref
Age 10-19	1.00 (0.92, 1.08)	1.00 (0.92, 1.09)	1.00 (0.92, 1.09)
Age 25-29	0.96 (0.89, 1.02)	0.96 (0.89, 1.02)	0.96 (0.90, 1.02)
Age 30-34	1.09 (1.01, 1.17)	1.09 (1.02, 1.17)	1.09 (1.02, 1.18)
Age 35-39	0.99 (0.90, 1.08)	0.99 (0.90, 1.08)	0.99 (0.90, 1.08)
Age 40-60	1.14 (0.98, 1.33)	1.14 (0.98, 1.33)	1.14 (0.98, 1.33)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.32 (1.22, 1.44)	1.33 (1.22, 1.44)	1.33 (1.22, 1.44)
Hispanic	0.96 (0.90, 1.02)	0.96 (0.91, 1.03)	0.96 (0.91, 1.03)
Other non-Hispanic	1.11 (0.98, 1.26)	1.11 (0.98, 1.27)	1.12 (0.98, 1.27)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.98 (0.92, 1.05)	0.99 (0.92, 1.05)	0.99 (0.93, 1.05)
Greater than HS	0.82 (0.77, 0.87)	0.82 (0.77, 0.87)	0.82 (0.77, 0.87)
Model 4			
Well Density[a]	1.07 (1.02, 1.12)	1.19 (1.12, 1.25)	1.22 (1.16, 1.29)
Non- Smoker	Ref	Ref	Ref
Smoker	1.11 (1.00, 1.24)	1.12 (1.01, 1.24)	1.11 (1.00, 1.24)
Singleton	Ref	Ref	Ref
Two + Fetus	2.61 (2.38, 2.85)	2.62 (2.39, 2.87)	2.59 (2.36, 2.83)
Age 20-24	Ref	Ref	Ref
Age 10-19	1.02 (0.94, 1.11)	1.02 (0.94, 1.11)	1.02 (0.94, 1.11)
Age 25-29	0.96 (0.90, 1.03)	0.96 (0.90, 1.03)	0.97 (0.90, 1.03)
Age 30-34	1.12 (1.04, 1.21)	1.12 (1.04, 1.21)	1.13 (1.05, 1.21)
Age 35-39	1.05 (0.96, 1.15)	1.05 (0.96, 1.15)	1.06 (0.97, 1.16)

Age 40-60	1.22 (1.04, 1.42)	1.22 (1.04, 1.42)	1.22 (1.05, 1.43)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.26 (1.16, 1.37)	1.26 (1.16, 1.37)	1.26 (1.16, 1.37)
Hispanic	0.92 (0.87, 0.98)	0.92 (0.87, 0.99)	0.93 (0.87, 0.99)
Other non-Hispanic	1.11 (0.97, 1.26)	1.11 (0.98, 1.26)	1.11 (0.98, 1.27)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.96 (0.90, 1.02)	0.96 (0.90, 1.03)	0.96 (0.90, 1.03)
Greater than HS	0.86 (0.80, 0.91)	0.86 (0.81, 0.91)	0.86 (0.81, 0.91)
Median Income($10,000)[b]	0.94 (0.93, 0.95)	0.94 (0.93, 0.95)	0.94 (0.93, 0.95)
Urban	Ref	Ref	Ref
Rural	0.91 (0.83, 0.99)	0.91 (0.83, 0.99)	0.91 (0.84, 1.00)
Average Truck Miles Traveled (IQR=933,908.)[c]	0.92 (0.91, 0.94)	0.92 (0.91, 0.94)	0.92 (0.91, 0.94)

[a] ORs correspond to an increase in wells from the 5th to the 95th percentile of the distribution within a buffer distance during year of pregnancy

[b] ORs correspond to a $10,000 increase in median income at block group of mother's maternal address at time of delivery

[c] ORs correspond to an interquartile range increase in average truck miles traveled by county.

Appendix Table B.7: Sensitivity analysis accounting for diabetes prevalence among age-adjusted women. Odds ratios (OR) and 95% confidence intervals (CI) for the associations between model covariates and select defects (anencephaly, hypoplastic left heart syndrome, aortic valve stenosis, pulmonary valve atresia/stenosis, and atrial septal defects 2007-2009) delivered between 1999-2011 in Texas

Defect/Model	**1km OR (95% CI)**	**3km OR (95% CI)**	**7.5km OR (95% CI)**
Anencephaly (n=700)			
Span size	0.85	0.85	0.85
Increased Well Count[a]	3	26	142
Model 2a			
Diabetes[b]	1.13 (1.03, 1.23)	-	-
Model 2b			
Well Density[a]	1.16 (1.04, 1.31)	1.08 (0.91, 1.29)	1.02 (0.87, 1.20)
Diabetes	1.12 (1.02, 1.23)	1.12 (1.02, 1.23)	1.12 (1.02, 1.23)
Model 4			
Well Density[a]	1.26 (1.12, 1.40)	1.12 (0.93, 1.35)	1.10 (0.93, 1.29)
Diabetes	0.99 (0.89, 1.09)	1.00 (0.90, 1.10)	0.99 (0.90, 1.10)
Non- Smoker	Ref	Ref	Ref
Smoker	0.78 (0.54, 1.13)	0.78 (0.53, 1.13)	0.77 (0.53, 1.12)
Singleton	Ref	Ref	Ref
Two + Fetus	3.26 (2.36, 4.51)	3.19 (2.31, 4.42)	3.21 (2.32, 4.45)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.81 (0.64, 1.03)	0.81 (0.63, 1.03)	0.81 (0.64, 1.03)
Age 25-29	0.86 (0.70, 1.05)	0.85 (0.70, 1.05)	0.86 (0.70, 1.05)
Age 30-34	1.76 (1.39, 2.23)	1.74 (1.38, 2.21)	1.74 (1.38, 2.21)
Age 35-39	0.67 (0.47, 0.94)	0.67 (0.47, 0.94)	0.67 (0.48, 0.95)
Age 40-60	0.96 (0.55, 1.67)	0.96 (0.55, 1.67)	0.97 (0.56, 1.68)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.25 (0.93, 1.67)	1.22 (0.91, 1.64)	1.20 (0.89, 1.61)
Hispanic	1.38 (1.12, 1.71)	1.35 (1.09, 1.68)	1.35 (1.09, 1.67)
Other non-Hispanic	1.77 (1.09, 2.86)	1.73 (1.07, 2.79)	1.72 (1.07, 2.79)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.75 (1.43, 2.15)	1.75 (1.43, 2.15)	1.76 (1.44, 2.16)
Greater than HS	0.73 (0.59, 0.91)	0.73 (0.59, 0.91)	0.73 (0.59, 0.91)
Median Income($10,000)[c]	0.88 (0.84, 0.93)	0.88 (0.84, 0.93)	0.88 (0.84, 0.93)
Urban	Ref	Ref	Ref
Rural	0.95 (0.70, 1.28)	0.98 (0.72, 1.32)	0.99 (0.73, 1.33)
Average Truck Miles Traveled (IQR=513424)[d]	1.02 (0.99, 1.04)	1.01 (0.99, 1.04)	1.01 (0.99, 1.04)

Hypoplastic Left Heart Syndrome (n=848)			
Span size	0.95	0.95	0.95
Increased Well Count[a]	4	29	158
Model 2a			
Diabetes[b]	1.05 (0.97, 1.14)	-	-
Model 2b			
Well Density[a]	1.30 (1.15, 1.47)	1.31 (1.13, 1.52)	1.25 (1.11, 1.40)
Diabetes	1.04 (0.96, 1.13)	1.04 (0.96, 1.13)	1.04 (0.95, 1.13)
Model 4			
Well Density[a]	1.35 (1.19, 1.53)	1.37 (1.18, 1.60)	1.30 (1.16, 1.45)
Diabetes	1.02 (0.94, 1.12)	1.02 (0.94, 1.12)	1.04 (0.95, 1.13)
Non- Smoker	Ref	Ref	Ref
Smoker	0.90 (0.68, 1.20)	0.91 (0.69, 1.20)	0.91 (0.69, 1.21)
Singleton	Ref	Ref	Ref
Two + Fetus	1.20 (0.82, 1.77)	1.28 (0.87, 1.88)	1.29 (0.88, 1.89)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.94 (0.75, 1.18)	0.94 (0.75, 1.18)	0.96 (0.76, 1.20)
Age 25-29	0.90 (0.74, 1.08)	0.90 (0.75, 1.09)	0.90 (0.75, 1.09)
Age 30-34	1.27 (1.03, 1.56)	1.26 (1.02, 1.55)	1.26 (1.02, 1.55)
Age 35-39	1.02 (0.77, 1.34)	1.03 (0.79, 1.36)	1.03 (0.78, 1.35)
Age 40-60	0.82 (0.51, 1.30)	0.82 (0.52, 1.30)	0.82 (0.52, 1.31)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.00 (0.79, 1.26)	1.01 (0.80, 1.27)	0.96 (0.76, 1.20)
Hispanic	0.74 (0.61, 0.88)	0.74 (0.62, 0.89)	0.90 (0.75, 1.09)
Other non-Hispanic	0.56 (0.36, 0.88)	0.57 (0.36, 0.89)	1.26 (1.02, 1.55)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.91 (0.76, 1.10)	0.90 (0.75, 1.09)	0.90 (0.75, 1.08)
Greater than HS	0.67 (0.56, 0.81)	0.67 (0.56, 0.80)	0.67 (0.56, 0.80)
Median Income($10,000)[c]	1.00 (0.96, 1.03)	1.00 (0.96, 1.03)	1.00 (0.96, 1.03)
Urban	Ref	Ref	Ref
Rural	0.94 (0.73, 1.22)	0.94 (0.72, 1.21)	0.94 (0.73, 1.21)
Average Truck Miles Traveled (IQR=467,354)	1.02 (1.00, 1.04)	1.01 (0.99, 1.04)	1.01 (0.99, 1.04)
Aortic Valve Stenosis (n=933)			
Span size	0.50	0.50	0.50
Increased Well Count[a]	4	30	158
Model 2a			
Diabetes[b]	1.05 (0.97, 1.13)	-	-

Model 2b			
Well Density[a]	1.20 (1.05, 1.38)	1.21 (1.06, 1.38)	1.21 (1.07, 1.37)
Diabetes	1.04 (0.96, 1.13)	1.04 (0.96, 1.13)	1.04 (0.96, 1.12)
Model 4			
Well Density[a]	1.18 (1.03, 1.36)	1.22 (1.07, 1.39)	1.21 (1.07, 1.36)
Diabetes	1.09 (1.00, 1.18)	1.09 (1.00, 1.18)	1.09 (1.00, 1.18)
Non- Smoker	Ref	Ref	Ref
Smoker	0.99 (0.76, 1.30)	0.99 (0.76, 1.30)	1.02 (0.78, 1.33)
Singleton	Ref	Ref	Ref
Two + Fetus	1.32 (0.93, 1.87)	1.38 (0.98, 1.95)	1.39 (0.98, 1.96)
Age 20-24	Ref	Ref	Ref
Age 10-19	1.21 (0.95, 1.55)	1.21 (0.95, 1.54)	0.84 (0.66, 1.07)
Age 25-29	1.29 (1.01, 1.64)	1.29 (1.01, 1.64)	1.07 (0.89, 1.28)
Age 30-34	1.72 (1.33, 2.24)	1.72 (1.32, 2.23)	1.42 (1.16, 1.74)
Age 35-39	1.92 (1.44, 2.55)	1.92 (1.45, 2.55)	1.59 (1.26, 2.01)
Age 40-60	1.11 (0.70, 1.75)	1.11 (0.70, 1.74)	0.92 (0.60, 1.41)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.62 (0.47, 0.81)	0.62 (0.47, 0.81)	0.62 (0.47, 0.82)
Hispanic	0.75 (0.63, 0.90)	0.76 (0.63, 0.90)	0.75 (0.63, 0.90)
Other non-Hispanic	0.69 (0.47, 1.03)	0.69 (0.46, 1.02)	0.69 (0.47, 1.03)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.87 (0.73, 1.04)	0.87 (0.73, 1.04)	1.14 (0.96, 1.37)
Greater than HS	0.64 (0.53, 0.78)	0.64 (0.53, 0.78)	0.73 (0.61, 0.87)
Median Income($10,000)[c]	1.03 (1.00, 1.07)	1.03 (1.00, 1.07)	1.03 (1.00, 1.07)
Urban	Ref	Ref	Ref
Rural	1.08 (0.84, 1.37)	1.09 (0.86, 1.39)	0.92 (0.72, 1.17)
Average Truck Miles Traveled (IQR=491,962)[d]	0.98 (0.96, 1.01)	0.98 (0.96, 1.00)	0.98 (0.96, 1.01)
Pulmonary Valve Atresia/Stenosis (n=3,611)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	3	28	155
Model 2a			
Diabetes[b]	1.02 (0.97, 1.06)	-	-
Model 2b			
Well Density[a]	1.08 (1.02, 1.15)	1.15 (1.08, 1.23)	1.18 (1.11, 1.26)
Diabetes	1.01 (0.97, 1.05)	1.01 (0.97, 1.06)	1.01 (0.97, 1.05)
Model 4			
Well Density[a]	1.07 (1.01, 1.13)	1.17 (1.10, 1.25)	1.21 (1.13, 1.29)
Diabetes	1.00 (0.96, 1.05)	1.00 (0.96, 1.05)	1.01 (0.97, 1.05)

Non- Smoker	Ref	Ref	Ref
Smoker	0.91 (0.79, 1.05)	0.91 (0.79, 1.05)	0.92 (0.79, 1.06)
Singleton	Ref	Ref	Ref
Two + Fetus	2.75 (2.39, 3.16)	2.79 (2.42, 3.20)	2.80 (2.44, 3.22)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.94 (0.84, 1.05)	0.94 (0.84, 1.05)	0.95 (0.84, 1.06)
Age 25-29	0.88 (0.81, 0.97)	0.88 (0.80, 0.97)	0.88 (0.80, 0.97)
Age 30-34	1.17 (1.05, 1.29)	1.17 (1.05, 1.30)	1.17 (1.05, 1.30)
Age 35-39	1.42 (1.26, 1.60)	1.41 (1.25, 1.59)	1.41 (1.25, 1.59)
Age 40-60	0.81 (0.66, 1.00)	0.81 (0.66, 1.00)	0.82 (0.66, 1.01)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.19 (1.06, 1.34)	1.18 (1.05, 1.33)	1.18 (1.05, 1.33)
Hispanic	0.94 (0.86, 1.03)	0.94 (0.86, 1.03)	0.94 (0.85, 1.03)
Other non-Hispanic	0.99 (0.81, 1.20)	0.98 (0.80, 1.19)	0.98 (0.80, 1.20)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.91 (0.83, 0.99)	0.91 (0.83, 0.99)	0.91 (0.83, 0.99)
Greater than HS	0.80 (0.73, 0.87)	0.79 (0.73, 0.87)	0.79 (0.72, 0.86)
Median Income($10,000)[c]	0.96 (0.94, 0.98)	0.96 (0.94, 0.98)	0.96 (0.94, 0.98)
Urban	Ref	Ref	Ref
Rural	1.04 (0.92, 1.17)	1.02 (0.90, 1.16)	1.02 (0.90, 1.15)
Average Truck Miles Traveled (IQR=770,415)[d]	1.01 (0.99, 1.02)	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)
Atrial Septal Defects 2007-2009 (n=6,303)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	4	34	189
Model 2a			
Diabetes[b]	1.07 (1.04, 1.11)	-	-
Model 2b			
Well Density[a]	1.05 (1.00, 1.11)	1.10 (1.04, 1.17)	1.13 (1.06, 1.19)
Diabetes	1.07 (1.04, 1.11)	1.07 (1.04, 1.11)	1.07 (1.04, 1.10)
Model 4			
Well Density[a]	1.06 (1.00, 1.12)	1.10 (1.04, 1.17)	1.12 (1.06, 1.19)
Diabetes	1.07 (1.03, 1.10)	1.06 (1.03, 1.10)	
Non- Smoker	Ref	Ref	Ref
Smoker	1.03 (0.92, 1.15)	1.03 (0.92, 1.15)	1.03 (0.92, 1.15)
Singleton	Ref	Ref	Ref
Two + Fetus	3.83 (3.48, 4.23)	3.84 (3.48, 4.23)	3.84 (3.48, 4.23)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.89 (0.82, 0.98)	0.89 (0.82, 0.97)	0.90 (0.82, 0.98)
Age 25-29	1.10 (1.02, 1.18)	1.10 (1.02, 1.18)	1.10 (1.02, 1.18)

Age 30-34	1.05 (0.97, 1.13)	1.05 (0.97, 1.13)	1.05 (0.97, 1.13)
Age 35-39	1.27 (1.15, 1.40)	1.27 (1.15, 1.40)	1.27 (1.16, 1.40)
Age 40-60	1.74 (1.48, 2.06)	1.74 (1.48, 2.06)	1.75 (1.48, 2.07)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.22 (1.11, 1.33)	1.22 (1.11, 1.33)	1.22 (1.11, 1.33)
Hispanic	0.97 (0.90, 1.04)	0.97 (0.90, 1.04)	0.97 (0.90, 1.04)
Other non-Hispanic	1.05 (0.91, 1.21)	1.05 (0.91, 1.21)	1.05 (0.91, 1.21)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.91 (0.85, 0.98)	0.91 (0.85, 0.98)	0.91 (0.85, 0.98)
Greater than HS	0.79 (0.74, 0.85)	0.79 (0.74, 0.85)	0.79 (0.74, 0.85)
Median Income($10,000)[c]	0.96 (0.94, 0.97)	0.96 (0.94, 0.97)	0.96 (0.94, 0.97)
Urban	Ref	Ref	Ref
Rural	1.01 (0.92, 1.11)	1.01 (0.92, 1.11)	1.01 (0.92, 1.11)
Average Truck Miles Traveled (IQR=949,711)	0.94 (0.93, 0.96)	0.94 (0.93, 0.96)	0.94 (0.93, 0.96)

[a] ORs correspond to an increase in wells from the 5th to the 95th percentile of the distribution within a buffer distance during year of pregnancy

[b] ORs correspond to a 1-unit increase in diabetes prevalence percentage among age-adjusted women with diabetes

[c] ORs correspond to a $10,000 increase in median income at block group of mother's maternal address at time of delivery

[d] ORs correspond to an interquartile range increase in average truck miles traveled by county.

Appendix Table B.8: Sensitivity analysis accounting for opioid prescription rates. Odds ratios (OR) and 95% confidence intervals (CI) for the associations between model covariates and select defects (anencephaly, hypoplastic left heart syndrome, aortic valve stenosis, pulmonary valve atresia/stenosis, and atrial septal defects 2007-2009) delivered between 1999-2011 in Texas

Defect/Model	**1km OR (95% CI)**	**3km OR (95% CI)**	**7.5km OR (95% CI)**
Anencephaly (n=700)			
Span size	0.85	0.85	0.85
Increased Well Count[a]	3	26	142
Model 2a			
Opioid prescription[b]	1.00 (1.00, 1.01)	-	-
Model 2b			
Well Density[a]	1.17 (1.05, 1.31)	1.10 (0.93, 1.31)	1.04 (0.88, 1.22)
Opioid prescription[b]	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)
Model 4			
Well Density[a]	1.25 (1.12, 1.40)	1.12 (0.93, 1.35)	1.10 (0.93, 1.29)
Opioid prescription[b]	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)
Non- Smoker	Ref	Ref	Ref
Smoker	0.77 (0.53, 1.12)	1.12	0.77 (0.53, 1.11)
Singleton	Ref	Ref	Ref
Two + Fetus	3.19 (2.32, 4.40)	3.14 (2.27, 4.32)	3.15 (2.28, 4.34)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.80 (0.63, 1.02)	0.80 (0.63, 1.02)	0.80 (0.63, 1.02)
Age 25-29	0.85 (0.69, 1.04)	0.85 (0.69, 1.04)	0.85 (0.70, 1.05)
Age 30-34	1.75 (1.38, 2.21)	1.73 (1.37, 2.19)	1.73 (1.37, 2.19)
Age 35-39	0.67 (0.47, 0.94)	0.67 (0.47, 0.94)	0.67 (0.48, 0.95)
Age 40-60	0.96 (0.55, 1.68)	0.96 (0.55, 1.67)	0.96 (0.55, 1.68)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.25 (0.93, 1.69)	1.23 (0.92, 1.65)	1.21 (0.90, 1.63)
Hispanic	1.40 (1.13, 1.73)	1.37 (1.11, 1.69)	1.37 (1.11, 1.69)
Other non-Hispanic	1.79 (1.10, 2.89)	1.75 (1.08, 2.83)	1.74 (1.08, 2.82)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.77 (1.45, 2.17)	1.77 (1.45, 2.17)	1.78 (1.46, 2.18)
Greater than HS	0.74 (0.59, 0.92)	0.74 (0.59, 0.91)	0.74 (0.59, 0.92)
Median Income($10,000)[c]	0.89 (0.84, 0.93)	0.89 (0.85, 0.93)	0.89 (0.85, 0.93)
Urban	Ref	Ref	Ref
Rural	1.07 (0.79, 1.46)	1.11 (0.82, 1.50)	1.12 (0.82, 1.51)

Average Truck Miles Traveled (IQR=513,424.)[d]	1.02 (0.99, 1.05)	1.02 (0.99, 1.04)	1.02 (0.99, 1.05)
Hypoplastic Left Heart Syndrome (n=848)			
Span size	0.85	0.85	0.85
Increased Well Count[a]	4	29	158
Model 2a			
Opioid prescription[b]	1.00 (1.00, 1.01)	-	-
Model 2b			
Well Density[a]	1.28 (1.13, 1.46)	1.23 (1.08, 1.39)	1.23 (1.09, 1.38)
Opioid prescription[b]	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)
Model 4			
Well Density[a]	1.34 (1.18, 1.52)	1.28 (1.13, 1.45)	1.28 (1.13, 1.43)
Opioid prescription[b]	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)
Non- Smoker	Ref	Ref	Ref
Smoker	0.90 (0.68, 1.19)	0.90 (0.68, 1.20)	0.91 (0.69, 1.21)
Singleton	Ref	Ref	Ref
Two + Fetus	1.25 (0.85, 1.84)	1.31 (0.89, 1.93)	1.32 (0.90, 1.95)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.94 (0.75, 1.18)	0.94 (0.75, 1.18)	0.95 (0.76, 1.20)
Age 25-29	0.89 (0.74, 1.08)	0.89 (0.74, 1.08)	0.90 (0.74, 1.08)
Age 30-34	1.26 (1.02, 1.56)	1.25 (1.02, 1.55)	1.25 (1.01, 1.54)
Age 35-39	1.04 (0.79, 1.36)	1.05 (0.80, 1.38)	1.04 (0.79, 1.37)
Age 40-60	0.78 (0.48, 1.25)	0.78 (0.49, 1.26)	0.79 (0.49, 1.26)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.01 (0.80, 1.28)	1.02 (0.81, 1.30)	1.03 (0.82, 1.30)
Hispanic	0.74 (0.62, 0.89)	0.75 (0.62, 0.90)	0.75 (0.62, 0.90)
Other non-Hispanic	0.56 (0.36, 0.88)	0.57 (0.36, 0.89)	0.58 (0.37, 0.90)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.90 (0.75, 1.08)	0.89 (0.74, 1.07)	0.89 (0.74, 1.07)
Greater than HS	0.66 (0.55, 0.79)	0.66 (0.55, 0.79)	0.66 (0.55, 0.79)
Median Income($10,000)[c]	1.00 (0.96, 1.03)	1.00 (0.96, 1.04)	1.00 (0.96, 1.04)
Urban	Ref	Ref	Ref
Rural	0.98 (0.75, 1.27)	0.97 (0.75, 1.26)	0.97 (0.75, 1.27)
Average Truck Miles Traveled (IQR=467,354)[d]	1.02 (1.00, 1.04)	1.02 (1.00, 1.04)	1.02 (1.00, 1.04)

Aortic Valve Stenosis (n=933)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	4	30	158
Model 2a			
Opioid prescription[b]	1.00 (1.00, 1.00)	-	-
Model 2b			
Well Density[a]	1.18 (1.02, 1.36)	1.19 (1.04, 1.36)	1.20 (1.06, 1.36)
Opioid prescription[b]	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Model 4			
Well Density[a]	1.17 (1.02, 1.34)	1.23 (1.07, 1.40)	1.22 (1.08, 1.38)
Opioid prescription[b]	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Non- Smoker	Ref	Ref	Ref
Smoker	1.03 (0.79, 1.35)	1.03 (0.78, 1.35)	1.03 (0.79, 1.36)
Singleton	Ref	Ref	Ref
Two + Fetus	1.35 (0.95, 1.91)	1.40 (0.99, 1.98)	1.41 (1.00, 2.00)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.82 (0.64, 1.05)	0.82 (0.64, 1.05)	0.83 (0.65, 1.06)
Age 25-29	1.08 (0.90, 1.30)	1.08 (0.90, 1.30)	1.08 (0.90, 1.30)
Age 30-34	1.42 (1.15, 1.74)	1.42 (1.15, 1.73)	1.41 (1.15, 1.73)
Age 35-39	1.59 (1.26, 2.02)	1.60 (1.26, 2.03)	1.60 (1.26, 2.03)
Age 40-60	0.86 (0.56, 1.33)	0.86 (0.56, 1.33)	0.87 (0.56, 1.34)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.62 (0.47, 0.82)	0.62 (0.47, 0.81)	0.62 (0.47, 0.82)
Hispanic	0.77 (0.64, 0.92)	0.77 (0.64, 0.92)	0.77 (0.64, 0.91)
Other non-Hispanic	0.72 (0.48, 1.06)	0.71 (0.48, 1.06)	0.72 (0.48, 1.07)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.14 (0.95, 1.36)	1.14 (0.95, 1.36)	1.13 (0.95, 1.36)
Greater than HS	0.74 (0.62, 0.89)	0.74 (0.62, 0.88)	0.73 (0.62, 0.88)
Median Income($10,000)[c]	1.04 (1.00, 1.07)	1.04 (1.00, 1.07)	1.04 (1.00, 1.07)
Urban	Ref	Ref	Ref
Rural	0.87 (0.68, 1.12)	0.86 (0.67, 1.11)	0.86 (0.67, 1.11)
Average Truck Miles Traveled (IQR=491962.80)[d]	0.99 (0.97, 1.01)	0.98 (0.96, 1.01)	0.98 (0.96, 1.01)
Pulmonary Valve Atresia/Stenosis (n=3,611)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	3	28	155

Model 2a			
Opioid prescription[b]	1.00 (1.00, 1.00)	-	-
Model 2b			
Well Density[a]	1.09 (1.03, 1.16)	1.16 (1.09, 1.24)	1.20 (1.13, 1.27)
Opioid prescription[b]	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Model 4			
Well Density[a]	1.07 (1.01, 1.14)	1.18 (1.10, 1.26)	1.22 (1.14, 1.30)
Opioid prescription[b]	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Non- Smoker	Ref	Ref	Ref
Smoker	0.92 (0.79, 1.06)	0.92 (0.79, 1.06)	0.92 (0.80, 1.07)
Singleton	Ref	Ref	Ref
Two + Fetus	2.82 (2.45, 3.24)	2.86 (2.48, 3.28)	2.87 (2.50, 3.30)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.95 (0.85, 1.07)	0.95 (0.85, 1.07)	0.96 (0.86, 1.07)
Age 25-29	0.88 (0.80, 0.96)	0.88 (0.80, 0.96)	0.88 (0.80, 0.96)
Age 30-34	1.15 (1.03, 1.27)	1.15 (1.03, 1.27)	1.15 (1.03, 1.27)
Age 35-39	1.40 (1.24, 1.58)	1.39 (1.24, 1.58)	1.39 (1.23, 1.57)
Age 40-60	0.77 (0.62, 0.95)	0.77 (0.62, 0.95)	0.77 (0.62, 0.96)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.16 (1.03, 1.31)	1.15 (1.02, 1.29)	1.15 (1.02, 1.30)
Hispanic	0.92 (0.84, 1.01)	0.92 (0.84, 1.01)	0.92 (0.84, 1.01)
Other non-Hispanic	0.97 (0.79, 1.18)	0.96 (0.78, 1.17)	0.97 (0.79, 1.18)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.89 (0.82, 0.98)	0.89 (0.82, 0.98)	0.89 (0.82, 0.98)
Greater than HS	0.80 (0.73, 0.87)	0.79 (0.72, 0.86)	0.79 (0.72, 0.86)
Median Income($10,000)[c]	0.96 (0.94, 0.98)	0.96 (0.94, 0.98)	0.96 (0.94, 0.98)
Urban	Ref	Ref	Ref
Rural	1.06 (0.93, 1.20)	1.04 (0.91, 1.19)	1.04 (0.91, 1.18)
Average Truck Miles Traveled (IQR=770,415)[d]	1.00 (0.99, 1.02)	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)
Atrial Septal Defects 2007-2009 (n=6,303)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	3	28	155
Model 2a			
Opioid prescription[b]	1.00 (1.00, 1.00)	-	-
Model 2b			
Well Density[a]	1.06 (1.00, 1.12)	1.11 (1.05, 1.18)	1.14 (1.08, 1.21)

Opioid prescription[b]	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Model 4			
Well Density[a]	1.07 (1.01, 1.13)	1.12 (1.05, 1.19)	1.14 (1.08, 1.21)
Opioid prescription[b]	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Non- Smoker	Ref	Ref	Ref
Smoker	1.04 (0.93, 1.16)	1.04 (0.93, 1.16)	1.04 (0.93, 1.16)
Singleton	Ref	Ref	Ref
Two + Fetus	3.85 (3.49, 4.24)	3.85 (3.49, 4.25)	3.85 (3.49, 4.24)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.87 (0.80, 0.95)	0.87 (0.80, 0.95)	0.88 (0.80, 0.96)
Age 25-29	1.09 (1.01, 1.17)	1.09 (1.01, 1.17)	1.09 (1.01, 1.17)
Age 30-34	1.04 (0.96, 1.13)	1.04 (0.96, 1.12)	1.04 (0.96, 1.12)
Age 35-39	1.26 (1.15, 1.39)	1.26 (1.15, 1.39)	1.27 (1.15, 1.39)
Age 40-60	1.73 (1.46, 2.04)	1.73 (1.46, 2.04)	1.74 (1.47, 2.05)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.23 (1.13, 1.35)	1.23 (1.13, 1.35)	1.24 (1.13, 1.35)
Hispanic	0.98 (0.91, 1.06)	0.98 (0.91, 1.06)	0.99 (0.92, 1.06)
Other non-Hispanic	1.05 (0.91, 1.21)	1.05 (0.91, 1.21)	1.05 (0.91, 1.21)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.91 (0.85, 0.97)	0.91 (0.85, 0.98)	0.91 (0.85, 0.97)
Greater than HS	0.80 (0.74, 0.85)	0.80 (0.74, 0.85)	0.80 (0.74, 0.85)
Median Income($10,000)[c]	0.96 (0.94, 0.97)	0.96 (0.94, 0.97)	0.96 (0.94, 0.97)
Urban	Ref	Ref	Ref
Rural	1.03 (0.93, 1.13)	1.03 (0.93, 1.13)	1.03 (0.94, 1.14)
Average Truck Miles Traveled (IQR=949,711)[d]	0.95 (0.94, 0.97)	0.95 (0.94, 0.97)	0.95 (0.93, 0.97)

[a] ORs correspond to an increase in wells from the 5th to the 95th percentile of the distribution within a buffer distance during year of pregnancy

[b] ORs correspond to a 1-unit increase in rate of doctor prescription of opioids by county

[c] ORs correspond to a $10,000 increase in median income at block group of mother's maternal address at time of delivery

[d] ORs correspond to an interquartile range increase in average truck miles traveled by county.

Appendix Table B.9: Sensitivity analysis accounting for percent uninsured. Odds ratios (OR) and 95% confidence intervals (CI) for the associations between model covariates and select defects (anencephaly, hypoplastic left heart syndrome, aortic valve stenosis, pulmonary valve atresia/stenosis, and atrial septal defects 2007-2009) delivered between 1999-2011 in Texas

Defect/Model	**1km OR (95% CI)**	**3km OR (95% CI)**	**7.5km OR (95% CI)**
Anencephaly (n=700)			
Span size	0.85	0.85	0.85
Increased Well Count[a]	3	26	142
Model 2a			
Percent Uninsured[b]	1.06 (1.02, 1.11)	-	-
Model 2b			
Well Density[a]	1.18 (1.06, 1.32)	1.10 (0.93, 1.31)	1.05 (0.90, 1.23)
Percent Uninsured[b]	1.07 (1.03, 1.11)	1.07 (1.03, 1.11)	1.07 (1.03, 1.11)
Model 4			
Well Density[a]	1.25 (1.12, 1.40)	1.12 (0.93, 1.35)	1.10 (0.93, 1.29)
Percent Uninsured[b]	1.00 (0.95, 1.05)	1.00 (0.96, 1.05)	1.00 (0.96, 1.05)
Non- Smoker	Ref	Ref	Ref
Smoker	0.78 (0.54, 1.12)	0.77 (0.54, 1.12)	0.77 (0.53, 1.12)
Singleton	Ref	Ref	Ref
Two + Fetus	3.24 (2.35, 4.46)	3.19 (2.31, 4.39)	3.20 (2.32, 4.41)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.81 (0.63, 1.03)	0.81 (0.63, 1.03)	0.81 (0.64, 1.03)
Age 25-29	0.85 (0.70, 1.05)	0.85 (0.69, 1.05)	0.86 (0.70, 1.06)
Age 30-34	1.75 (1.39, 2.22)	1.74 (1.38, 2.20)	1.74 (1.38, 2.20)
Age 35-39	0.66 (0.47, 0.94)	0.67 (0.47, 0.94)	0.67 (0.48, 0.95)
Age 40-60	0.96 (0.55, 1.67)	0.96 (0.55, 1.67)	0.97 (0.56, 1.68)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.24 (0.93, 1.67)	1.22 (0.91, 1.64)	1.20 (0.89, 1.61)
Hispanic	1.38 (1.11, 1.71)	1.35 (1.09, 1.68)	1.35 (1.09, 1.67)
Other non-Hispanic	1.77 (1.09, 2.86)	1.72 (1.06, 2.79)	1.72 (1.06, 2.78)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.76 (1.44, 2.15)	1.76 (1.44, 2.15)	1.77 (1.44, 2.16)
Greater than HS	0.73 (0.59, 0.91)	0.73 (0.59, 0.91)	0.73 (0.59, 0.91)
Median Income($10,000)[c]	0.88 (0.84, 0.93)	0.89 (0.84, 0.93)	0.89 (0.84, 0.93)
Urban	Ref	Ref	Ref
Rural	0.95 (0.70, 1.28)	0.98 (0.72, 1.32)	0.99 (0.73, 1.34)
Average Truck Miles Traveled (IQR=513424)[d]	1.02 (0.99, 1.05)	1.01 (0.98, 1.04)	1.01 (0.98, 1.04)
	1km	3km	7.5km

Hypoplastic Left Heart Syndrome (n=848)			
Span size	0.85	0.85	0.85
Increased Well Count[a]	4	29	158
Model 2a			
Percent Uninsured[b]	1.00 (0.97, 1.03)	-	-
Model 2b			
Well Density[a]	1.31 (1.15, 1.48)	1.25 (1.10, 1.41)	1.25 (1.12, 1.40)
Percent Uninsured[b]	1.01 (0.97, 1.04)	1.00 (0.97, 1.04)	1.00 (0.97, 1.04)
Model 4			
Well Density[a]	1.36 (1.19, 1.54)	1.29 (1.15, 1.46)	1.30 (1.16, 1.45)
Percent Uninsured[b]	0.99 (0.95, 1.03)	0.99 (0.95, 1.03)	0.99 (0.95, 1.03)
Non- Smoker	Ref	Ref	Ref
Smoker	0.90 (0.68, 1.19)	0.91 (0.68, 1.20)	0.91 (0.69, 1.21)
Singleton	Ref	Ref	Ref
Two + Fetus	1.21 (0.82, 1.78)	1.28 (0.87, 1.88)	1.29 (0.88, 1.90)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.94 (0.75, 1.18)	0.95 (0.75, 1.19)	0.96 (0.76, 1.20)
Age 25-29	0.90 (0.74, 1.08)	0.90 (0.75, 1.09)	0.90 (0.75, 1.09)
Age 30-34	1.27 (1.03, 1.56)	1.26 (1.02, 1.56)	1.26 (1.02, 1.55)
Age 35-39	1.02 (0.77, 1.34)	1.03 (0.78, 1.35)	1.03 (0.78, 1.35)
Age 40-60	0.81 (0.51, 1.29)	0.81 (0.51, 1.30)	0.82 (0.52, 1.31)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.00 (0.79, 1.27)	1.02 (0.80, 1.28)	1.02 (0.81, 1.29)
Hispanic	0.74 (0.62, 0.89)	0.74 (0.62, 0.89)	0.74 (0.62, 0.89)
Other non-Hispanic	0.57 (0.36, 0.89)	0.57 (0.36, 0.89)	0.58 (0.37, 0.90)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.91 (0.76, 1.09)	0.90 (0.75, 1.08)	0.90 (0.75, 1.08)
Greater than HS	0.67 (0.56, 0.81)	0.67 (0.56, 0.80)	0.67 (0.56, 0.80)
Median Income($10,000)[c]	0.99 (0.06, 1.03)	0.99 (0.96, 1.03)	0.99 (0.96, 1.03)
Urban	Ref	Ref	Ref
Rural	0.94 (0.73, 1.21)	0.93 (0.72, 1.21)	0.93 (0.72, 1.21)
Average Truck Miles Traveled (IQR=467,354)[d]	1.02 (1.00, 1.05)	1.02 (0.99, 1.04)	1.02 (0.99, 1.04)
Aortic Valve Stenosis (n=933)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	4	30	158
Model 2a			

Percent Uninsured[b]	0.98 (0.95, 1.01)	-	-
Model 2b			
Well Density[a]	1.17 (1.01, 1.34)	1.18 (1.03, 1.35)	1.19 (1.05, 1.34)
Percent Uninsured[b]	0.99 (0.96, 1.02)	0.98 (0.95, 1.01)	0.98 (0.95, 1.02)
Model 4			
Well Density[a]	1.16 (1.01, 1.33)	1.21 (1.06, 1.39)	1.21 (1.07, 1.36)
Percent Uninsured[b]	1.05 (1.01, 1.09)	1.05 (1.01, 1.09)	1.05 (1.01, 1.09)
Non- Smoker	Ref	Ref	Ref
Smoker	1.02 (0.78, 1.33)	1.02 (0.78, 1.33)	1.02 (0.78, 1.34)
Singleton	Ref	Ref	Ref
Two + Fetus	1.32 (0.93, 1.87)	1.37 (0.97, 1.93)	1.38 (0.97, 1.95)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.82 (0.64, 1.04)	0.82 (0.64, 1.04)	0.83 (0.65, 1.05)
Age 25-29	1.09 (0.91, 1.31)	1.09 (0.91, 1.31)	1.09 (0.91, 1.31)
Age 30-34	1.43 (1.17, 1.75)	1.43 (1.16, 1.75)	1.42 (1.16, 1.74)
Age 35-39	1.62 (1.28, 2.06)	1.63 (1.29, 2.06)	1.63 (1.28, 2.06)
Age 40-60	0.93 (0.60, 1.42)	0.93 (0.60, 1.42)	0.93 (0.61, 1.43)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	0.62 (0.47, 0.82)	0.62 (0.47, 0.81)	0.62 (0.47, 0.82)
Hispanic	0.76 (0.64, 0.91)	0.76 (0.64, 0.91)	0.76 (0.64, 0.90)
Other non-Hispanic	0.71 (0.48, 1.06)	0.71 (0.48, 1.05)	0.71 (0.48, 1.06)
High School (HS) Education	Ref	Ref	Ref
Less than HS	1.14 (0.95, 1.36)	1.14 (0.95, 1.36)	1.13 (0.95, 1.36)
Greater than HS	0.74 (0.62, 0.88)	0.73 (0.61, 0.87)	0.73 (0.61, 0.87)
Median Income($10,000)[c]	1.04 (1.00, 1.07)	1.04 (1.00, 1.07)	1.04 (1.00, 1.07)
Urban	Ref	Ref	Ref
Rural	0.90 (0.70, 1.15)	0.89 (0.69, 1.13)	0.89 (0.70, 1.14)
Average Truck Miles Traveled (IQR=491,962)[d]	0.97 (0.94, 0.99)	0.96 (0.94, 0.99)	0.96 (0.94, 0.99)
Pulmonary Valve Atresia/Stenosis (n=3,611)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	3	28	155
Model 2a			
Percent Uninsured[b]	1.03 (1.02, 1.05)	-	-
Model 2b			
Well Density[a]	1.09 (1.03, 1.16)	1.16 (1.09, 1.24)	1.19 (1.12, 1.27)
Percent Uninsured[b]	1.03 (1.02, 1.05)	1.03 (1.02, 1.05)	1.04 (1.02, 1.05)
Model 4			

Well Density[a]	1.17 (1.09, 1.25)	1.17 (1.10, 1.26)	1.21 (1.13, 1.29)
Percent Uninsured[b]	1.05 (1.03, 1.07)	1.05 (1.03, 1.07)	1.05 (1.03, 1.07)
Non- Smoker	Ref	Ref	Ref
Smoker	0.91 (0.79, 1.05)	0.91 (0.79, 1.05)	0.91 (0.79, 1.06)
Singleton	Ref	Ref	Ref
Two + Fetus	2.77 (2.41, 3.18)	2.77 (2.41, 3.18)	2.78 (2.42, 3.20)
Age 20-24	Ref	Ref	Ref
Age 10-19	0.94 (0.84, 1.05)	0.94 (0.84, 1.05)	0.95 (0.85, 1.06)
Age 25-29	0.88 (0.81, 0.97)	0.88 (0.81, 0.97)	0.88 (0.81, 0.97)
Age 30-34	1.17 (1.06, 1.30)	1.17 (1.06, 1.30)	1.17 (1.06, 1.30)
Age 35-39	1.42 (1.26, 1.61)	1.42 (1.26, 1.61)	1.42 (1.26, 1.60)
Age 40-60	0.81 (0.66, 1.00)	0.81 (0.66, 1.00)	0.82 (0.66, 1.01)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.17 (1.04, 1.32)	1.17 (1.04, 1.32)	1.17 (1.04, 1.32)
Hispanic	0.93 (0.85, 1.02)	0.93 (0.85, 1.02)	0.93 (0.85, 1.02)
Other non-Hispanic	0.97 (0.79, 1.18)	0.97 (0.79, 1.18)	0.97 (0.80, 1.19)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.91 (0.83, 0.99)	0.91 (0.83, 0.99)	0.91 (0.83, 0.99)
Greater than HS	0.79 (0.72, 0.86)	0.79 (0.72, 0.86)	0.79 (0.72, 0.86)
Median Income($10,000)[c]	0.96 (0.94, 0.98)	0.96 (0.94, 0.98)	0.96 (0.94, 0.98)
Urban	Ref	Ref	Ref
Rural	1.04 (0.92, 1.18)	1.04 (0.92, 1.18)	1.04 (0.92, 1.18)
Average Truck Miles Traveled (IQR=770,415)[d]	0.97 (0.95, 0.99)	0.97 (0.95, 0.99)	0.97 (0.95, 0.99)
Atrial Septal Defects 2007-2009 (n=6,303)			
Span size	0.20	0.20	0.20
Increased Well Count[a]	4	34	189
Model 2a			
Percent Uninsured[b]	0.98 (0.97, 1.00)	-	-
Model 2b			
Well Density[a]	1.06 (1.00, 1.11)	1.11 (1.04, 1.18)	1.13 (1.07, 1.20)
Percent Uninsured[b]	0.98 (0.97, 1.00)	0.98 (0.97, 1.00)	0.98 (0.97, 1.00)
Model 4			
Well Density[a]	1.12 (1.05, 1.19)	1.11 (1.05, 1.18)	1.13 (1.07, 1.20)
Percent Uninsured[b]	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)
Non- Smoker	Ref	Ref	Ref
Smoker	1.03 (0.92, 1.15)	1.03 (0.92, 1.15)	1.03 (0.92, 1.15)
Singleton	Ref	Ref	Ref
Two + Fetus	3.84 (3.49, 4.24)	3.84 (3.49, 4.24)	3.84 (3.49, 4.23)
Age 20-24	Ref	Ref	Ref

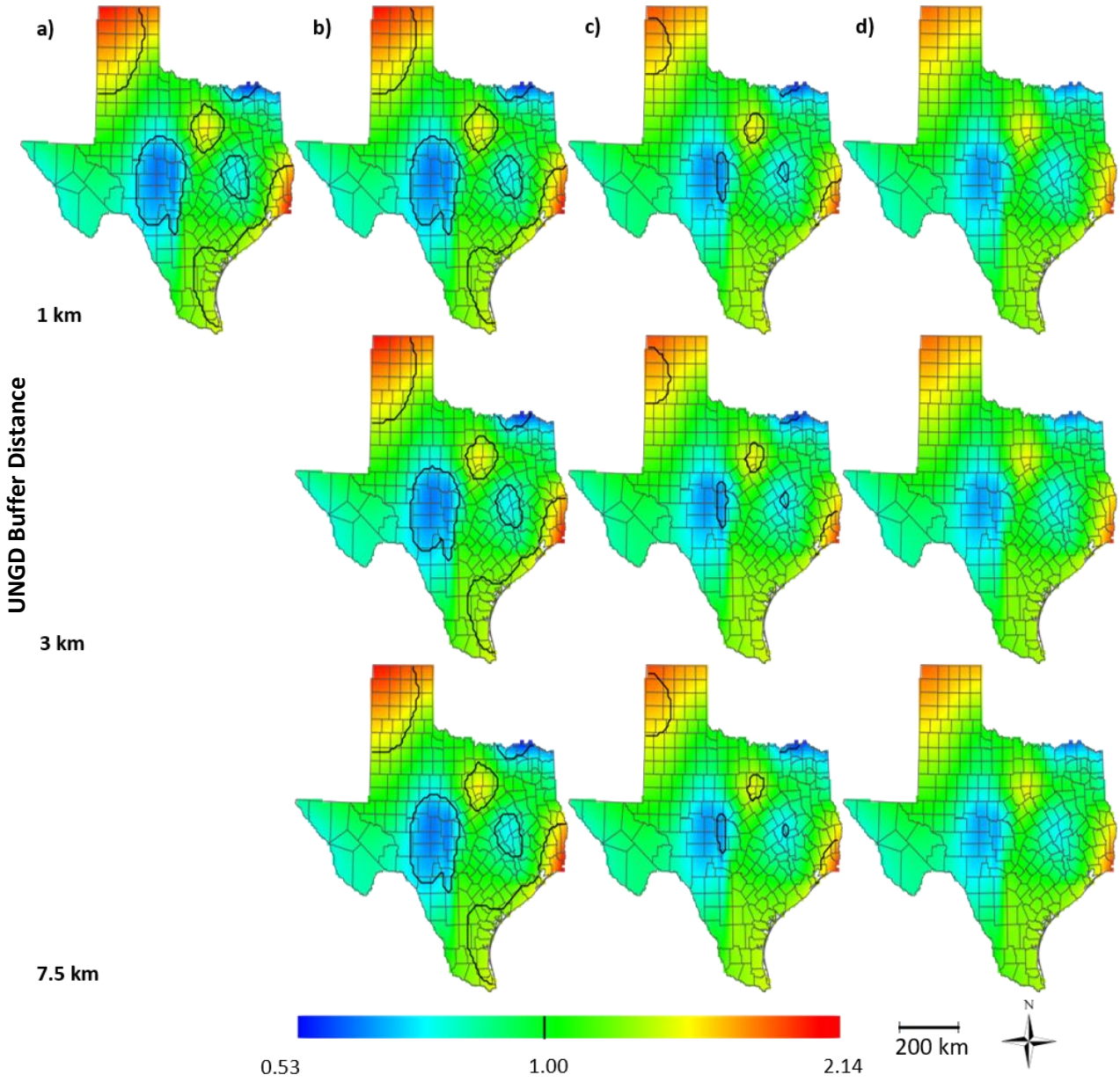
Age 10-19	0.89 (0.82, 0.97)	0.89 (0.82, 0.97)	0.89 (0.82, 0.97)
Age 25-29	1.09 (1.02, 1.17)	1.09 (1.02, 1.17)	1.10 (1.02, 1.18)
Age 30-34	1.04 (0.97, 1.13)	1.04 (0.97, 1.13)	1.04 (0.97, 1.13)
Age 35-39	1.27 (1.15, 1.39)	1.27 (1.15, 1.39)	1.27 (1.15, 1.40)
Age 40-60	1.74 (1.47, 2.05)	1.74 (1.47, 2.05)	1.74 (1.48, 2.06)
Non- Hispanic White	Ref	Ref	Ref
Black non-Hispanic	1.21 (1.11, 1.32)	1.21 (1.11, 1.32)	1.21 (1.11, 1.33)
Hispanic	0.97 (0.90, 1.04)	0.97 (0.90, 1.04)	0.97 (0.90, 1.04)
Other non-Hispanic	1.05 (0.91, 1.21)	1.05 (0.91, 1.21)	1.05 (0.91, 1.21)
High School (HS) Education	Ref	Ref	Ref
Less than HS	0.91 (0.85, 0.98)	0.91 (0.85, 0.98)	0.91 (0.85, 0.97)
Greater than HS	0.79 (0.74, 0.85)	0.79 (0.74, 0.85)	0.79 (0.74, 0.85)
Median Income($10,000)[c]	0.95 (0.94, 0.97)	0.95 (0.94, 0.97)	0.95 (0.94, 0.97)
Urban	Ref	Ref	Ref
Rural	1.00 (0.91, 1.10)	1.00 (0.91, 1.10)	1.00 (0.91, 1.10)
Average Truck Miles Traveled (IQR=949,711)[d]	0.95 (0.93, 0.96)	0.95 (0.93, 0.96)	0.94 (0.93, 0.96)

[a] ORs correspond to an increase in wells from the 5th to the 95th percentile of the distribution within a buffer distance during year of pregnancy

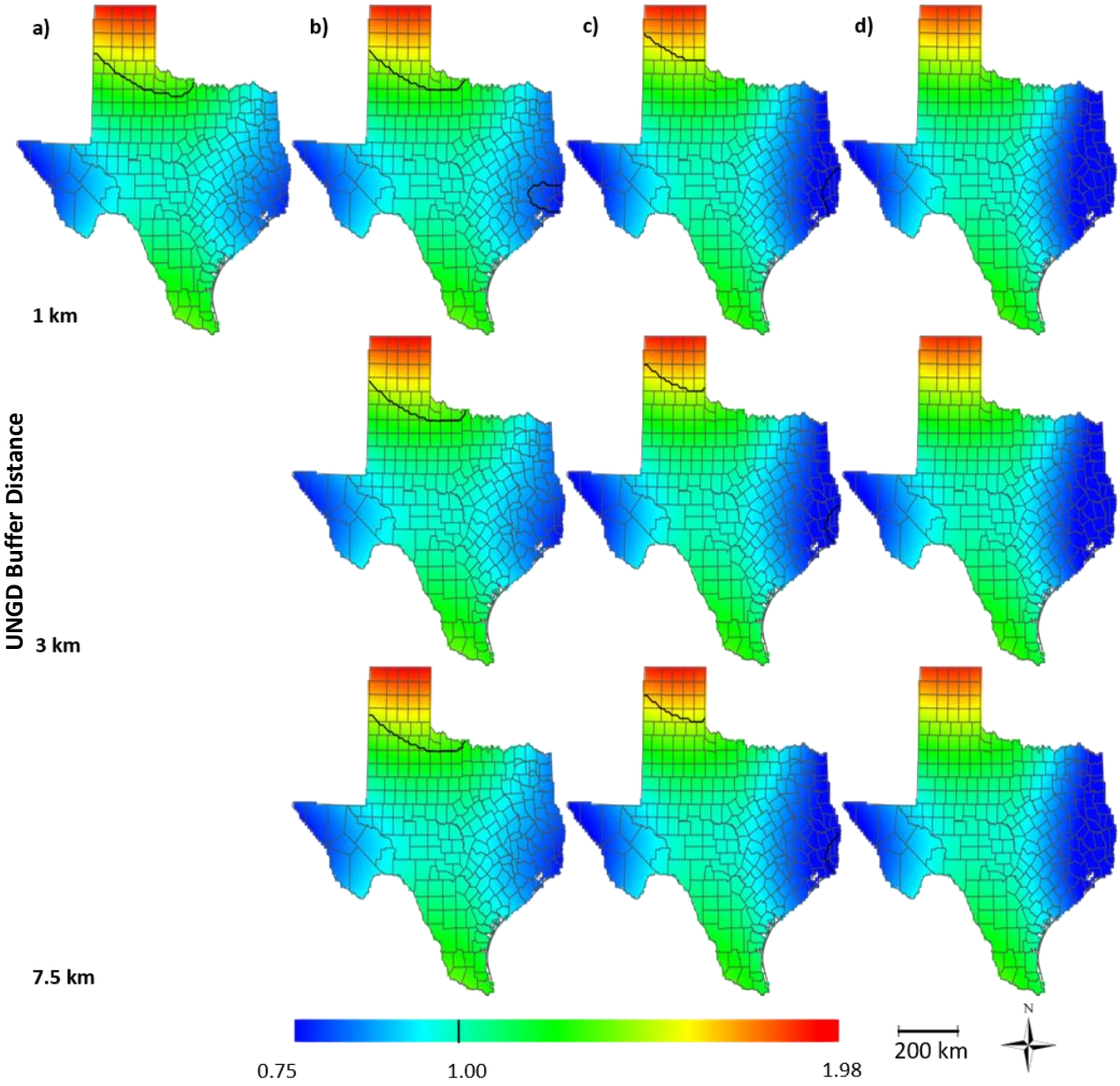
[b] ORs correspond to a 1-unit increase in percent uninsured by county

[c] ORs correspond to a $10,000 increase in median income at block group of mother's maternal address at time of delivery

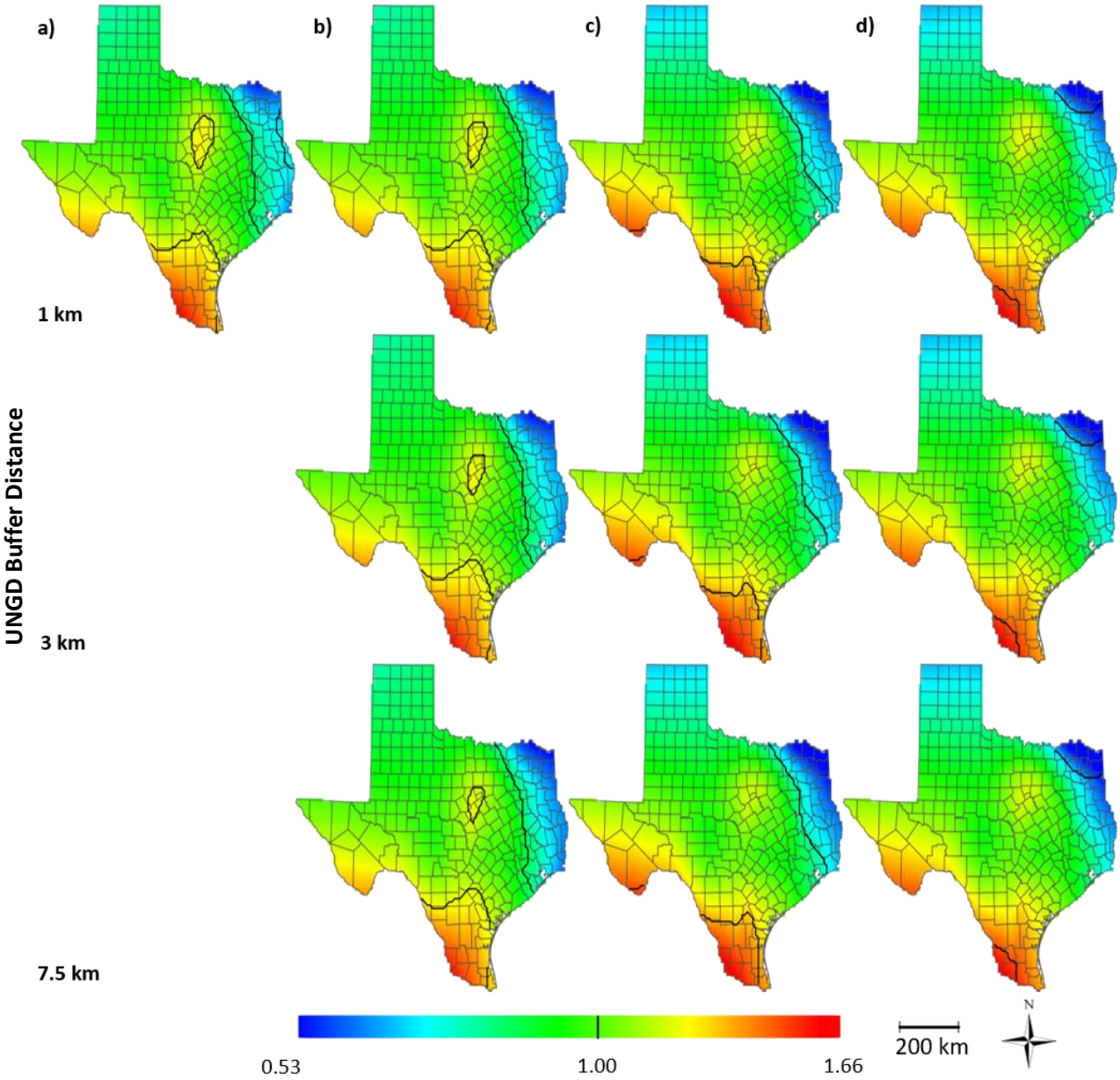
[d] ORs correspond to an interquartile range increase in average truck miles traveled by county.



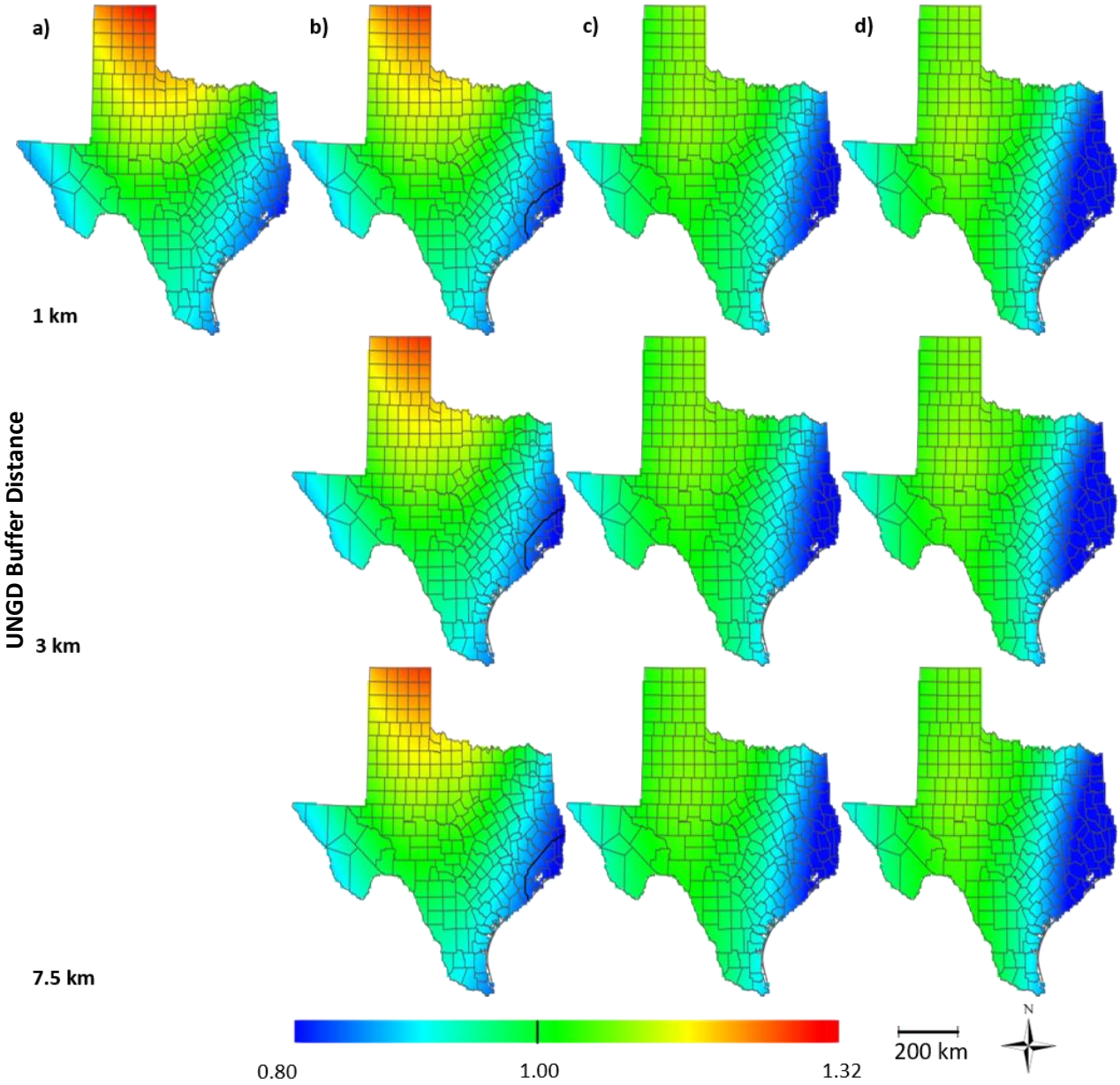
Appendix Figure C.1: Geographic patterns of endocardial cushion defects (ECD) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 1999-2011. (a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



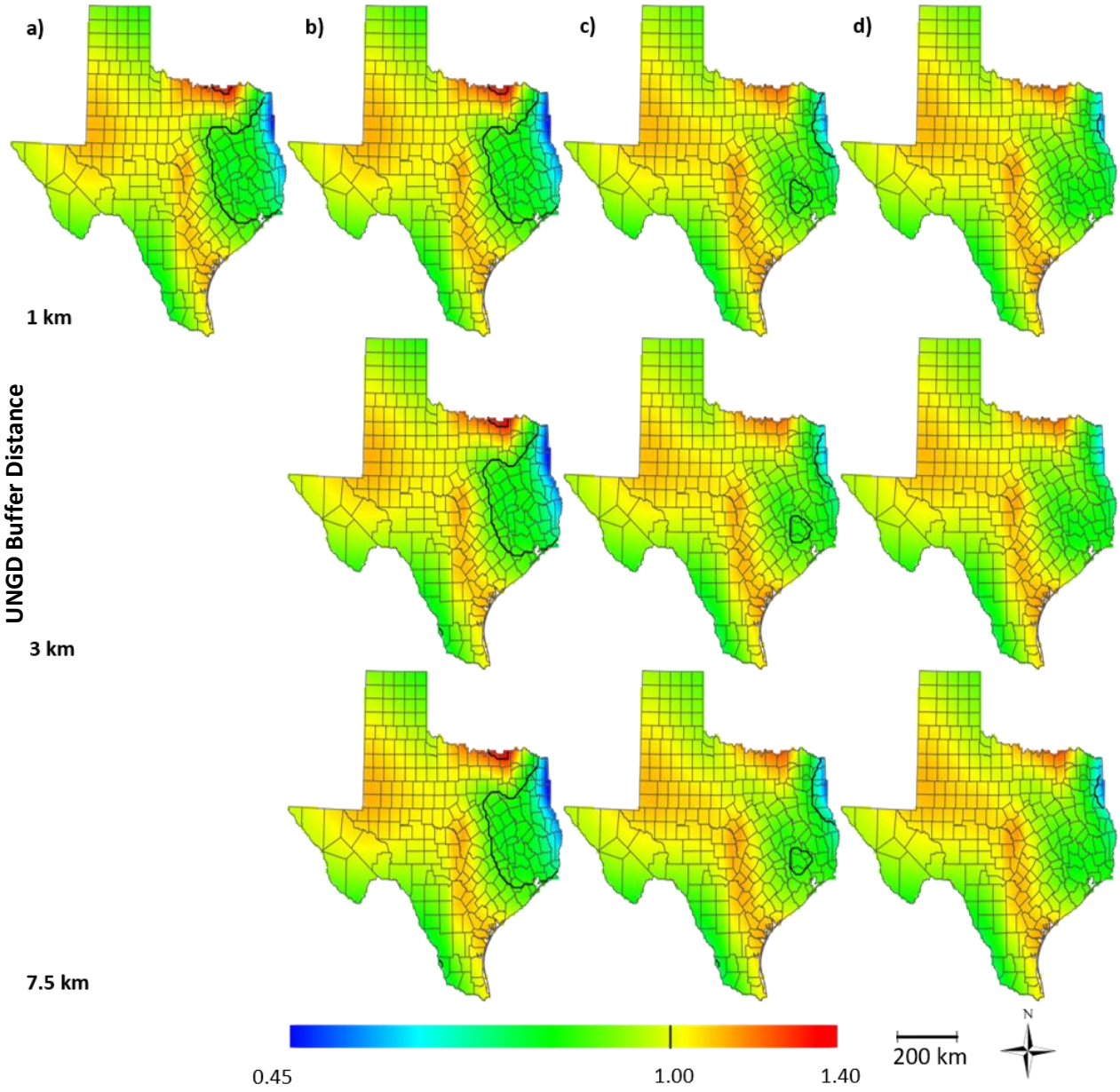
Appendix Figure C.2: Geographic patterns of tricuspid valve atresia/stenosis (TVAS) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 1999-2011.(a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



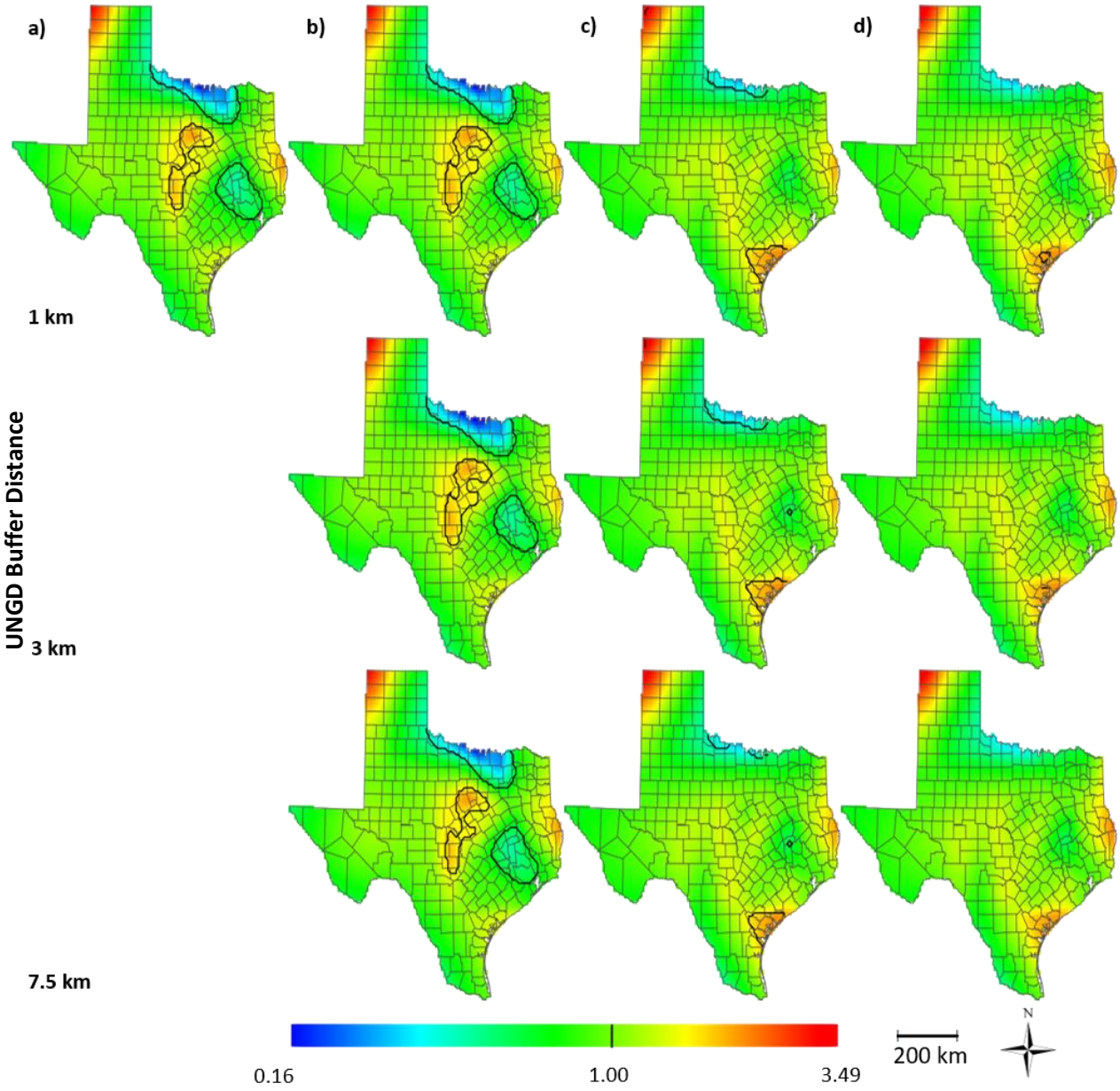
Appendix Figure C.3: Geographic patterns of aortic valve stenosis (AVS) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 1999-2011. (a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



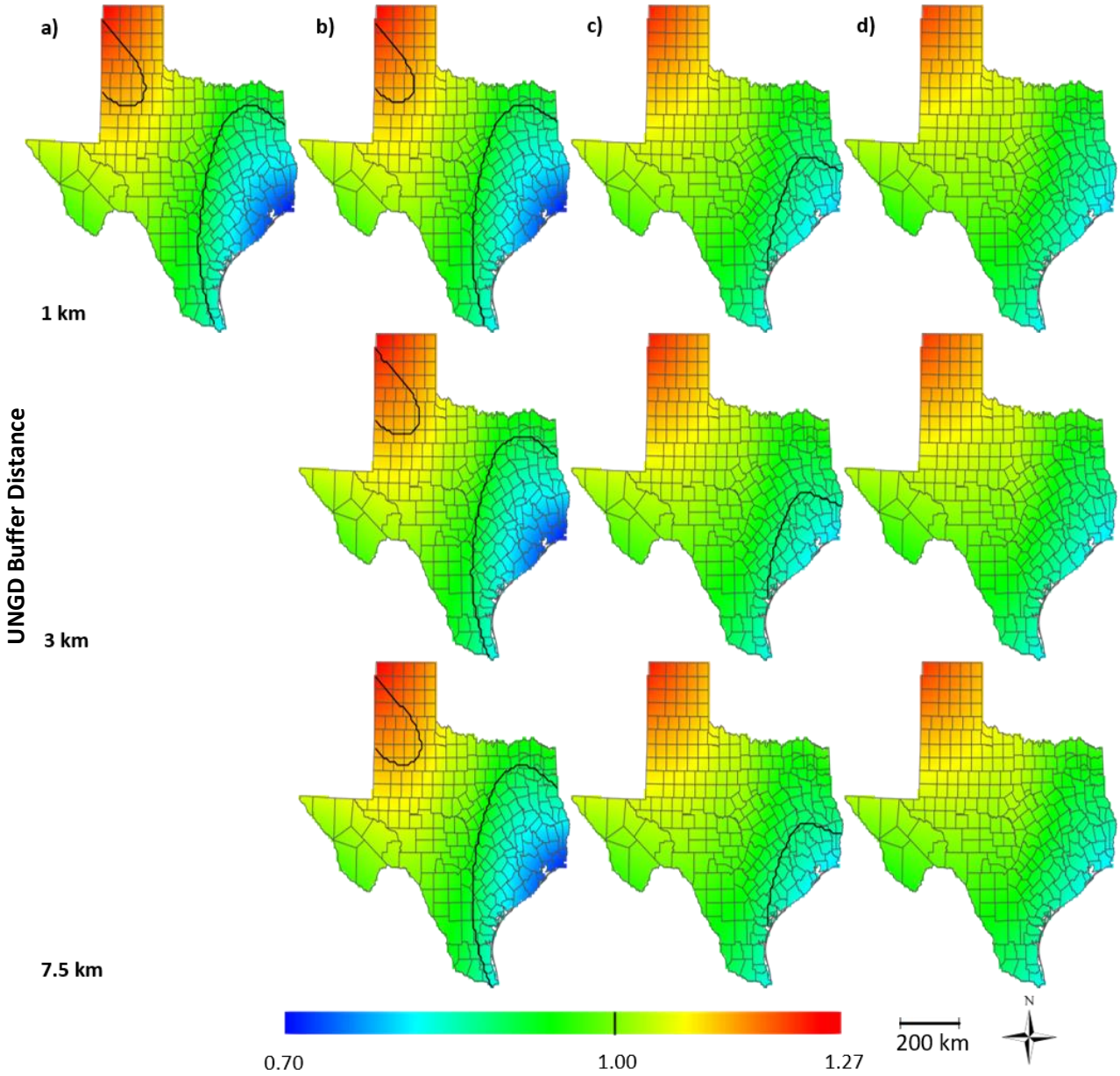
Appendix Figure C.4: Geographic patterns of hypoplastic left heart syndrome (HLHS) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 1999-2011.(a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



Appendix Figure C.5: Geographic patterns of gastroschisis (age< 25) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 1999-2011.
(a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.

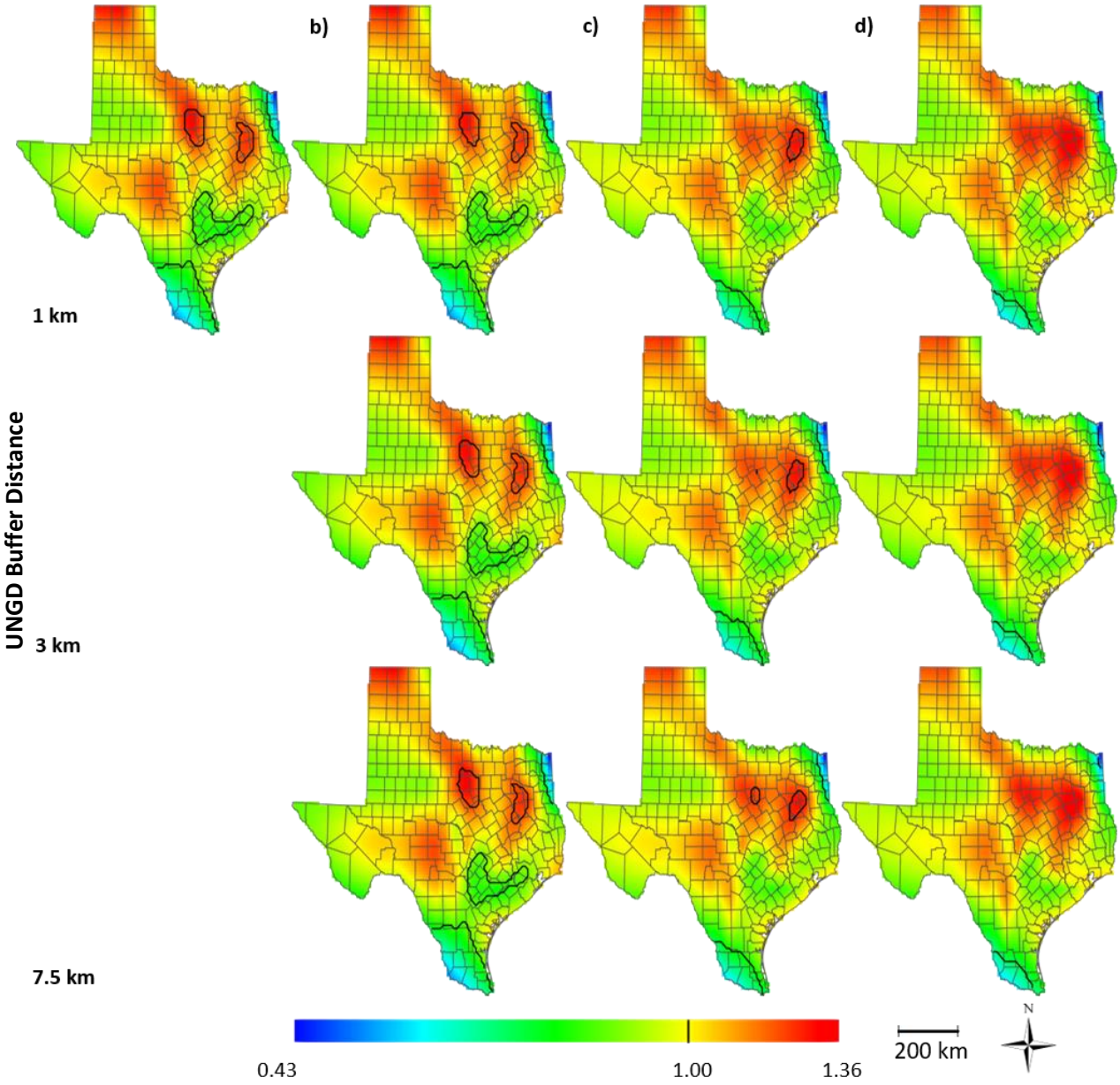


Appendix Figure C.6: Geographic patterns of gastroschisis (age≥ 25) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 1999-2011.
(a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.

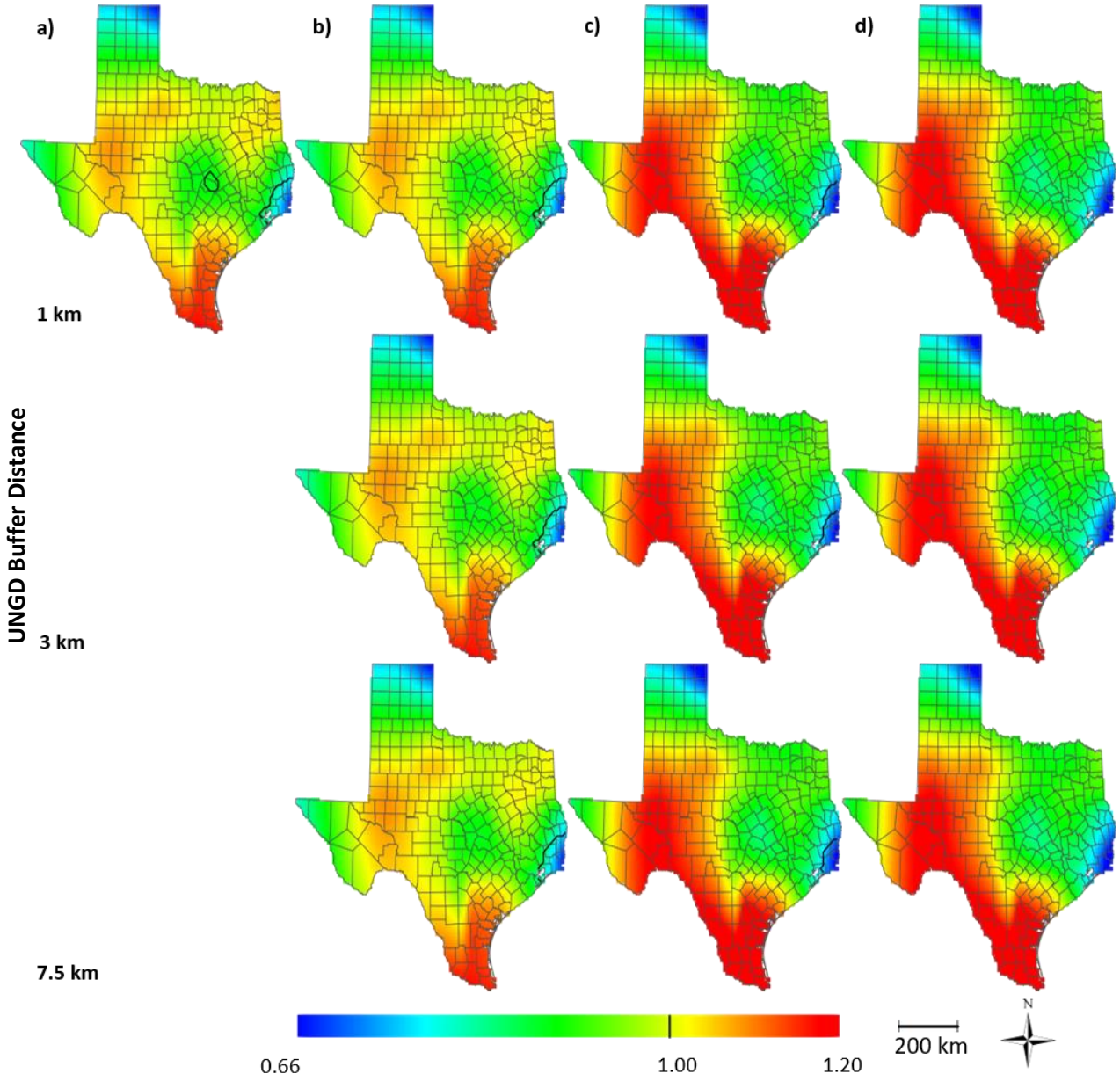


Appendix Figure C.7: Geographic patterns of cleft lip with/without palate and unconventional natural gas developments (UNGD) buffer radii among Texas births, 1999-2011.

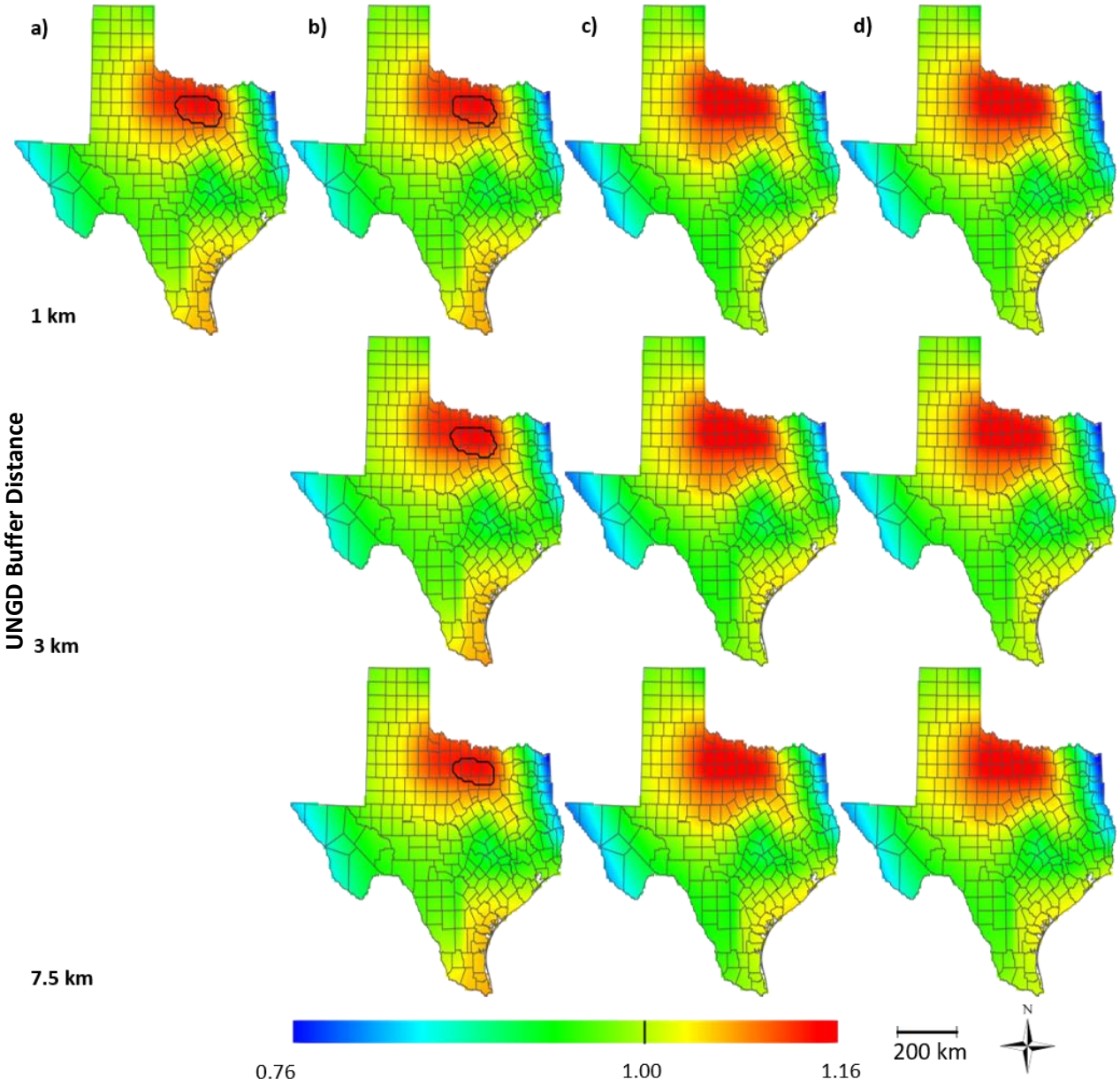
(a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



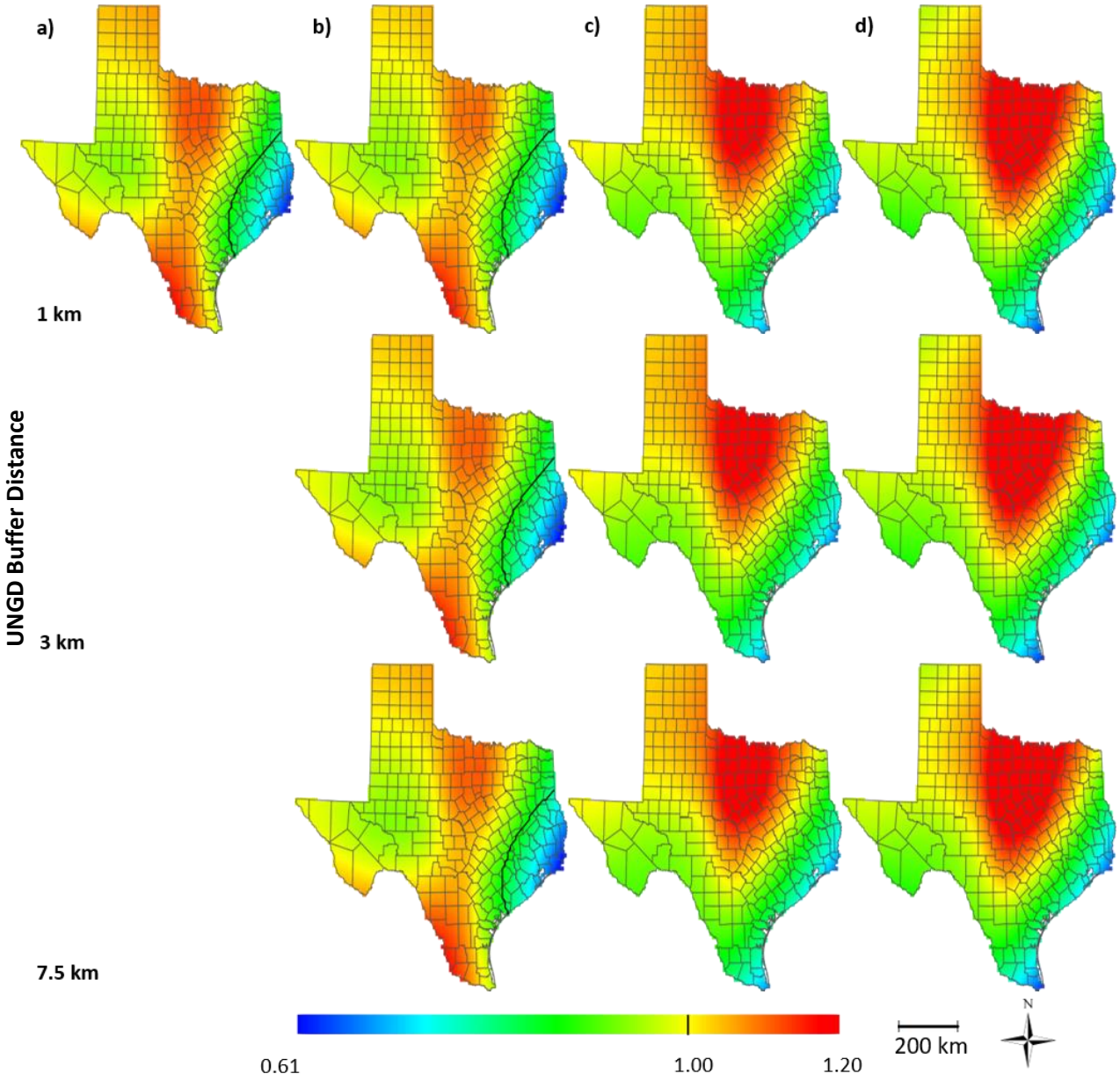
Appendix Figure C.8: Geographic patterns of cleft palate only and unconventional natural gas developments (UNGD) buffer radii among Texas births, 1999-2011.
(a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



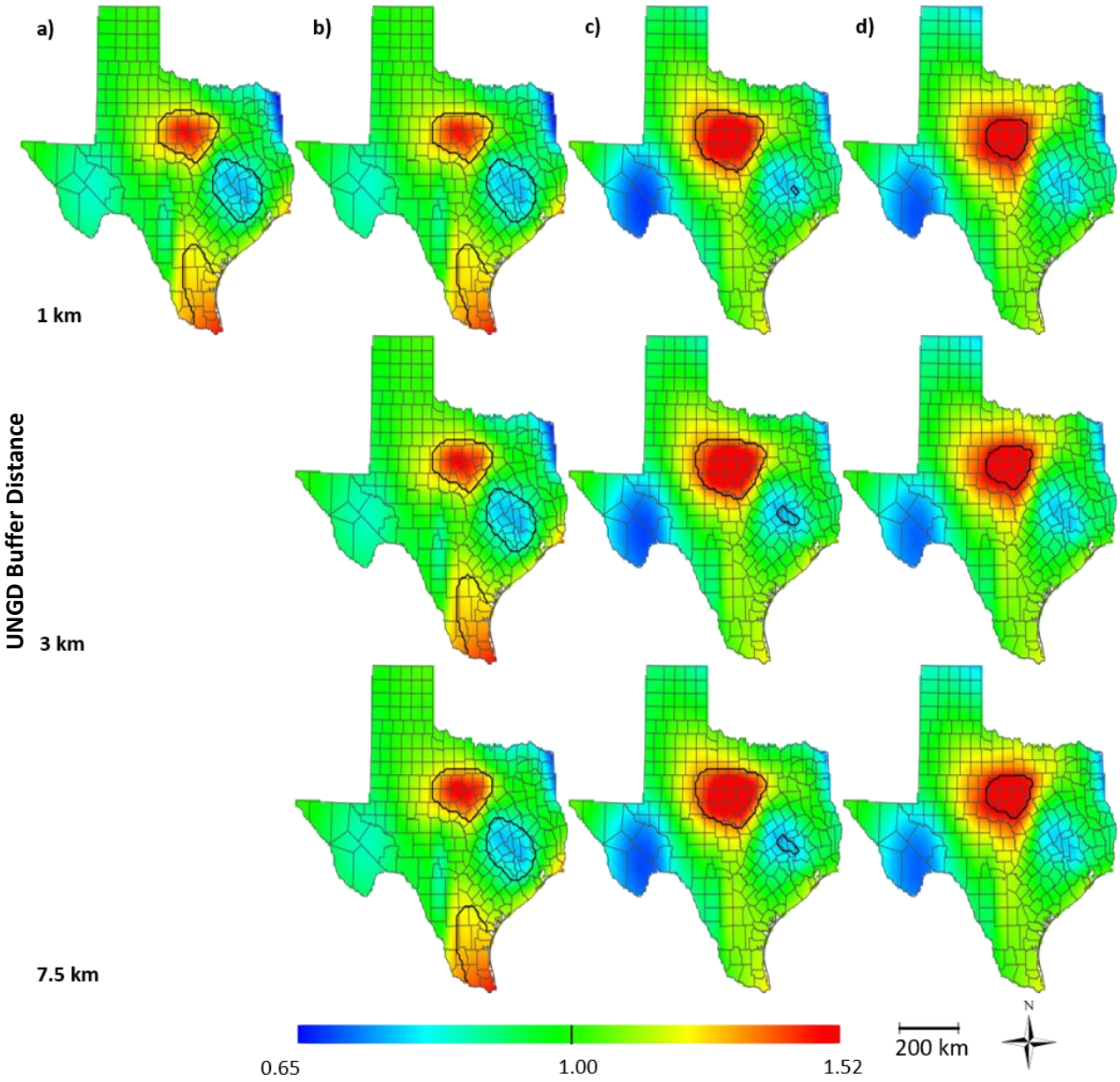
Appendix Figure C.9: Geographic patterns of tetralogy of Fallot (TOF) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 1999-2011.
(a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



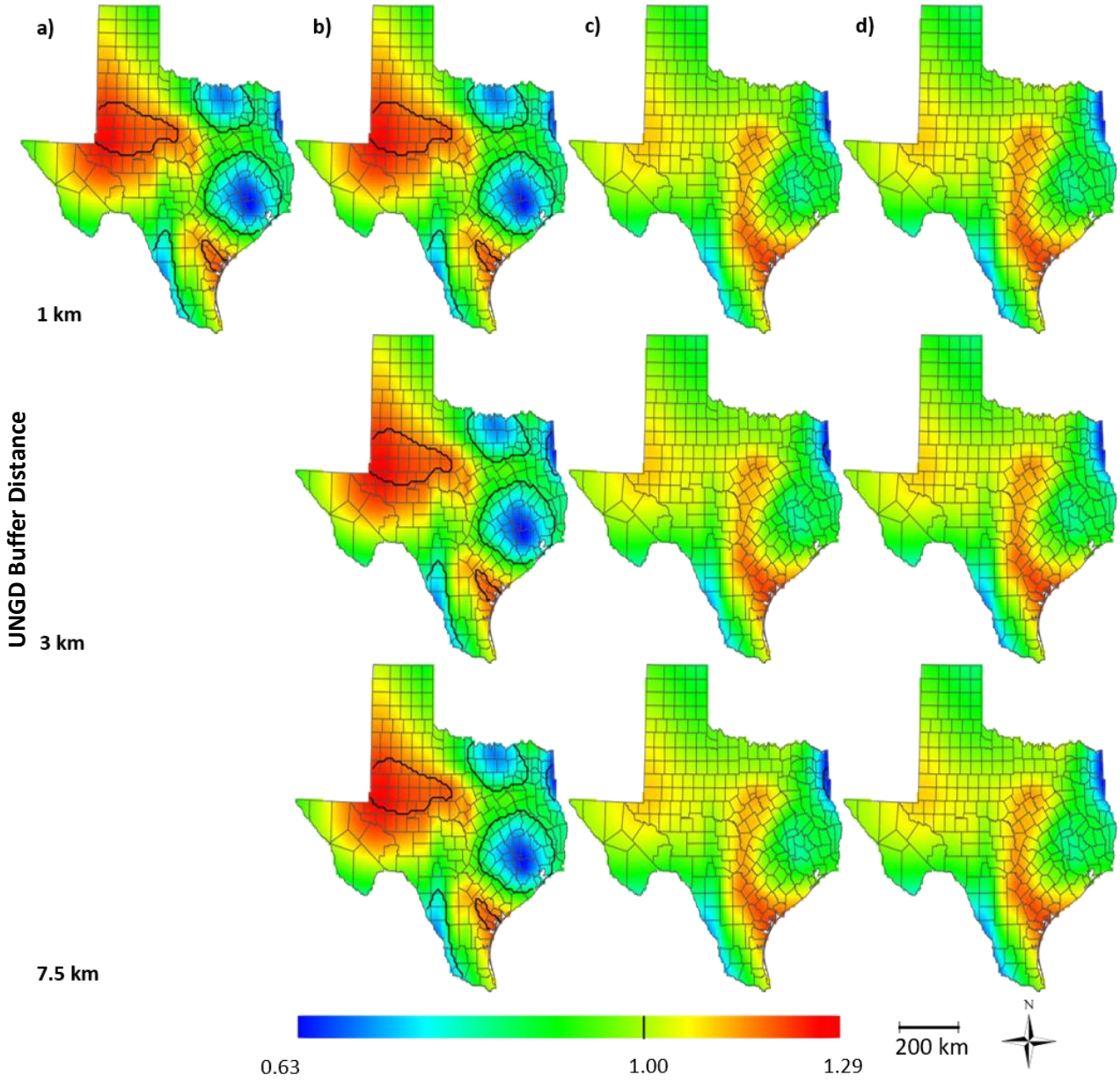
Appendix Figure C.10: Geographic patterns of transposition of great vessels (TGV) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 1999-2011. (a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



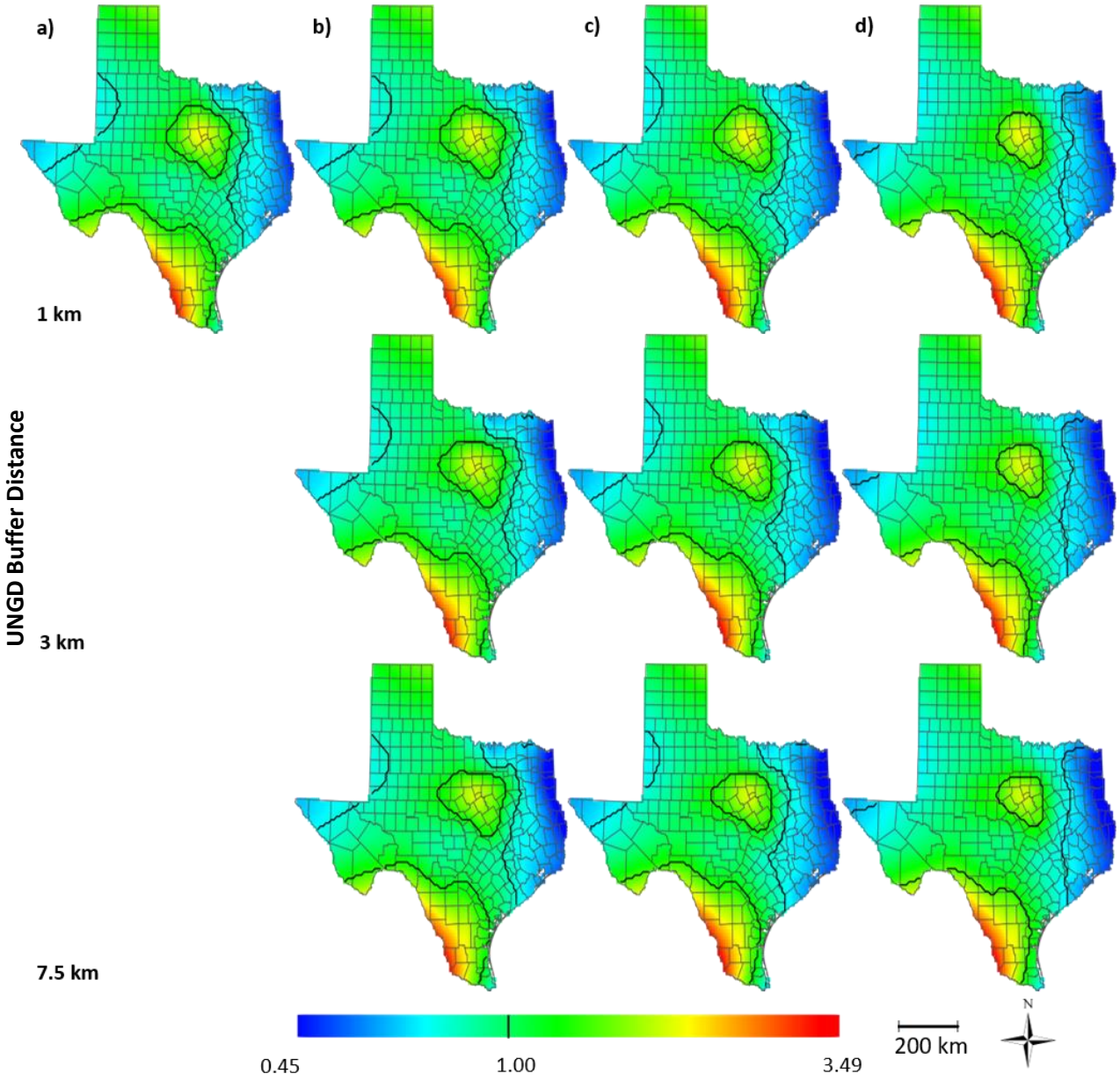
Appendix Figure C.11: Geographic patterns of anencephaly and unconventional natural gas developments (UNGD) buffer radii among Texas births, 1999-2011.(a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



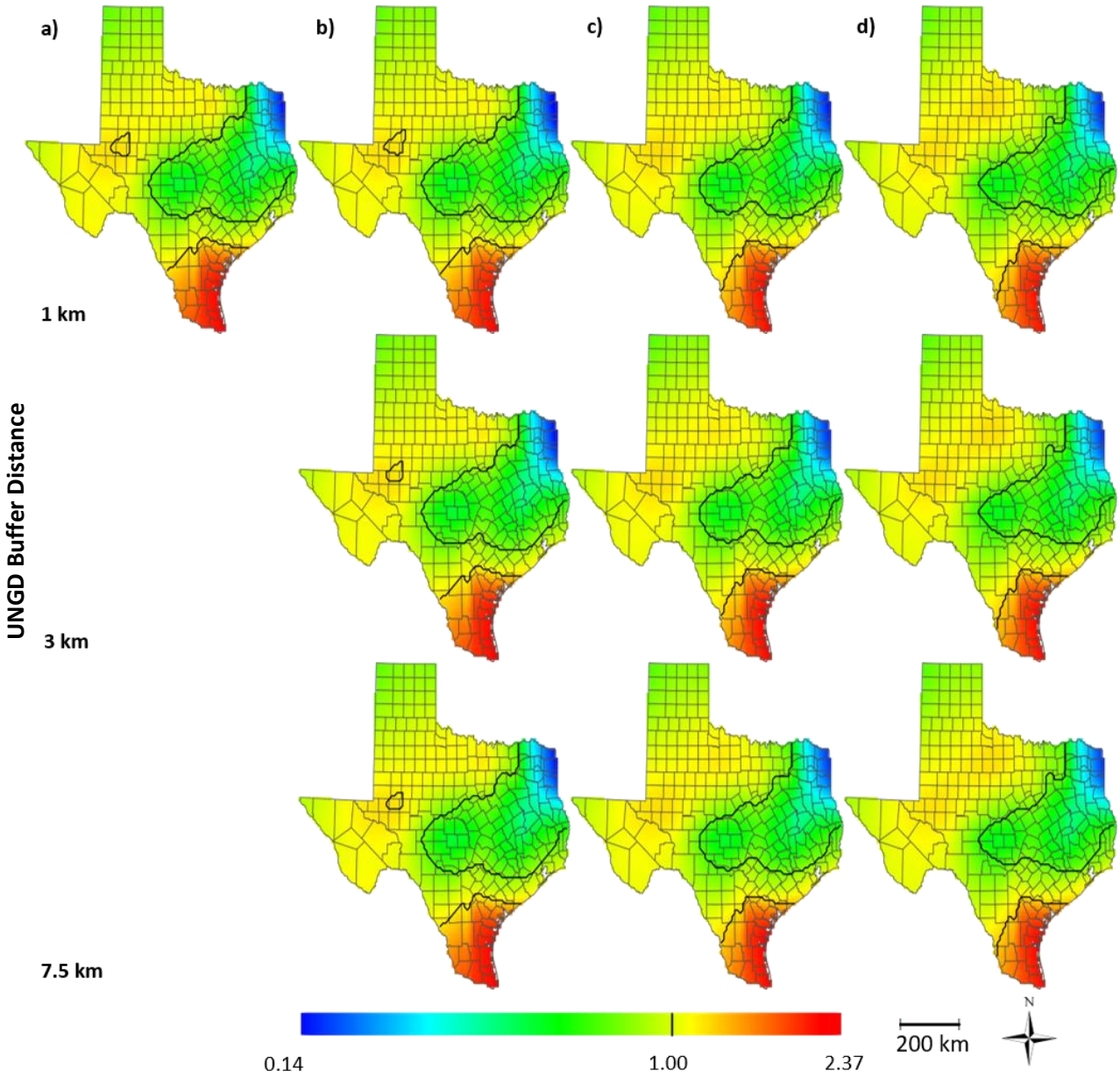
Appendix Figure C.12: Geographic patterns of spina bifida and unconventional natural gas developments (UNGD) buffer radii among Texas births, 1999-2011.(a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



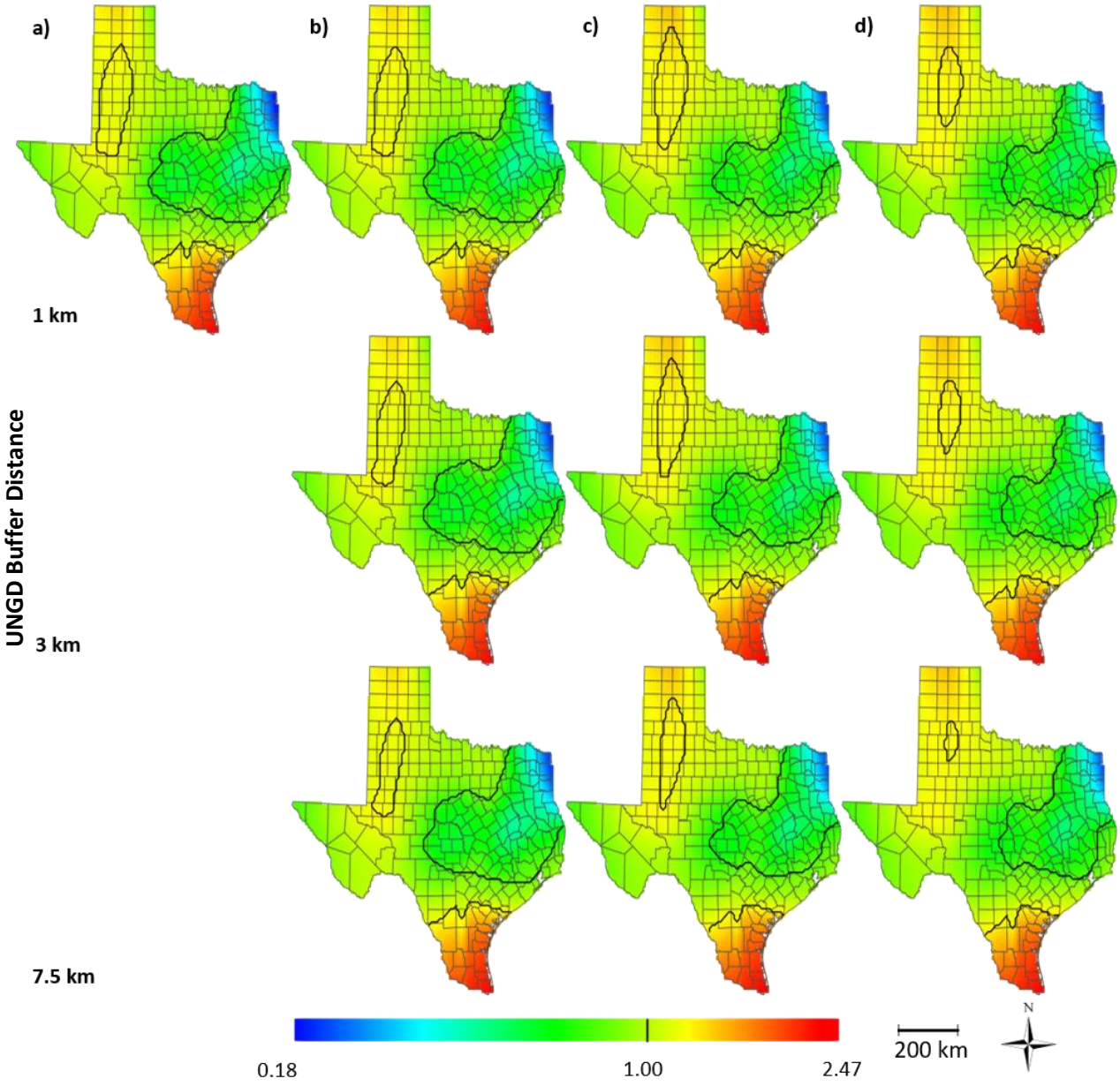
Appendix Figure C.13: Geographic patterns of gastroschisis (all) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 1999-2011.
(a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



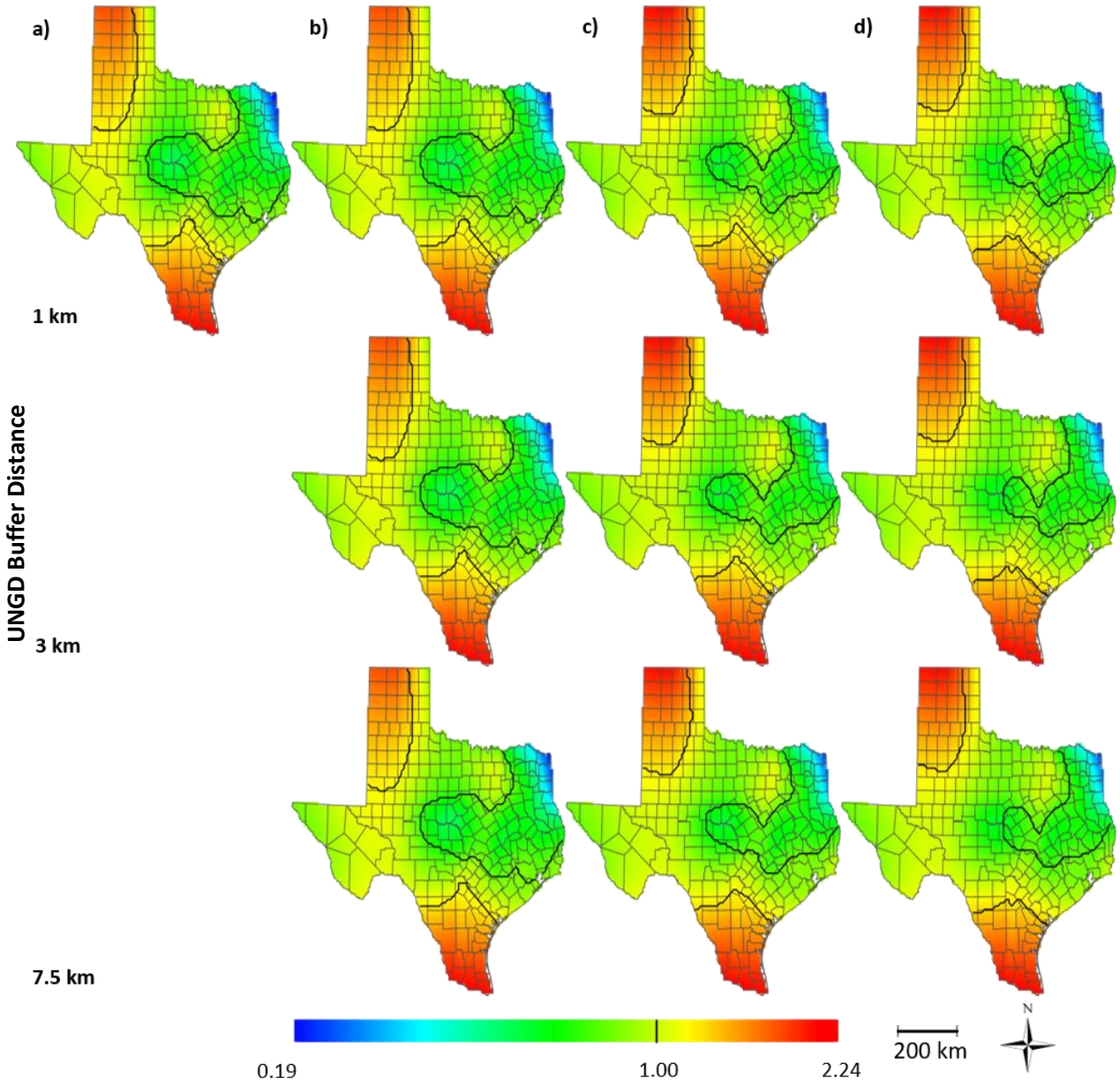
Appendix Figure C.14: Geographic patterns of pulmonary valve atresia/stenosis (PVAS) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 1999-2011.(a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



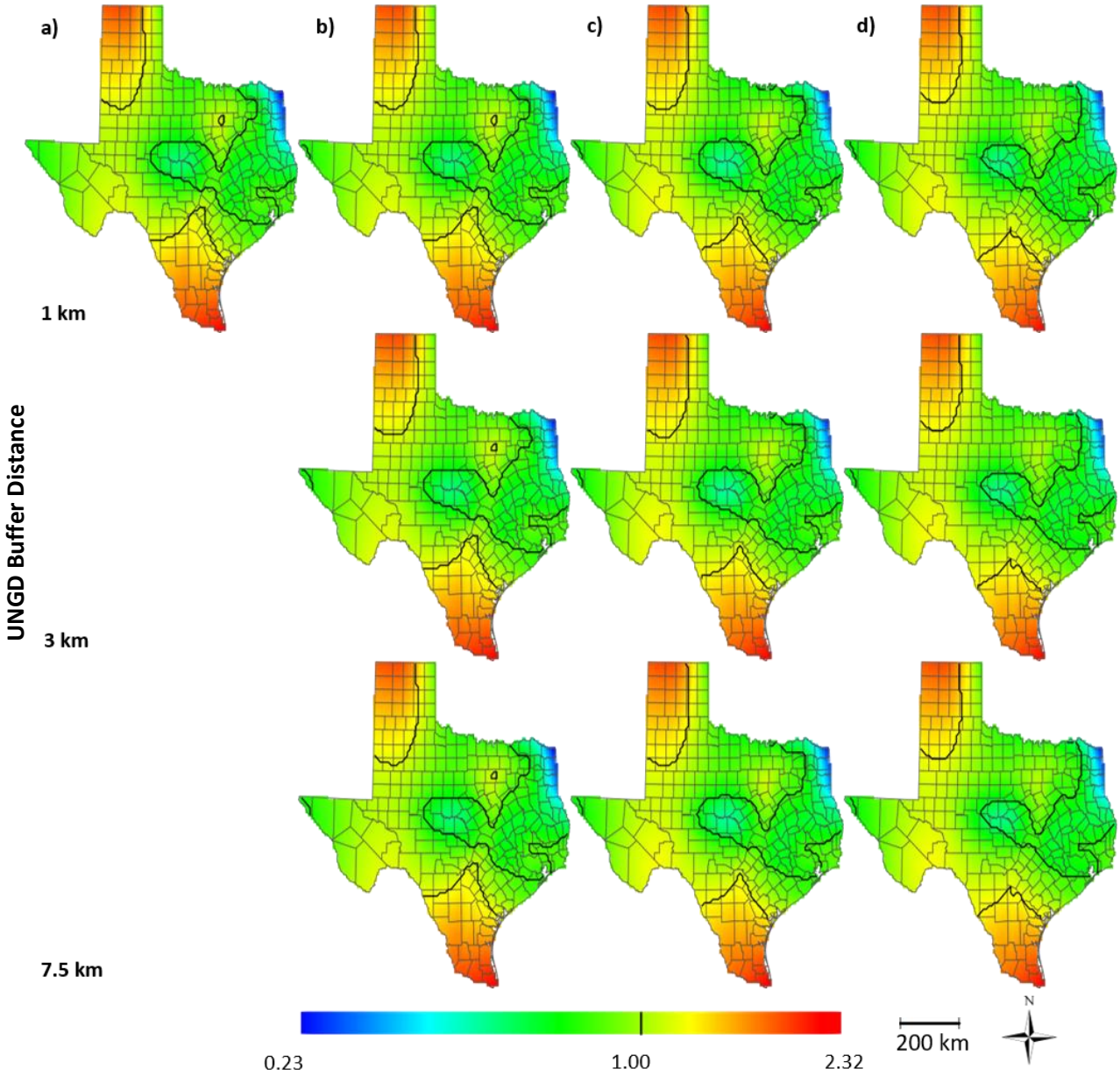
Appendix Figure C.15: Geographic patterns of ventricular septal defects (VSD) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 1999-2001.(a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



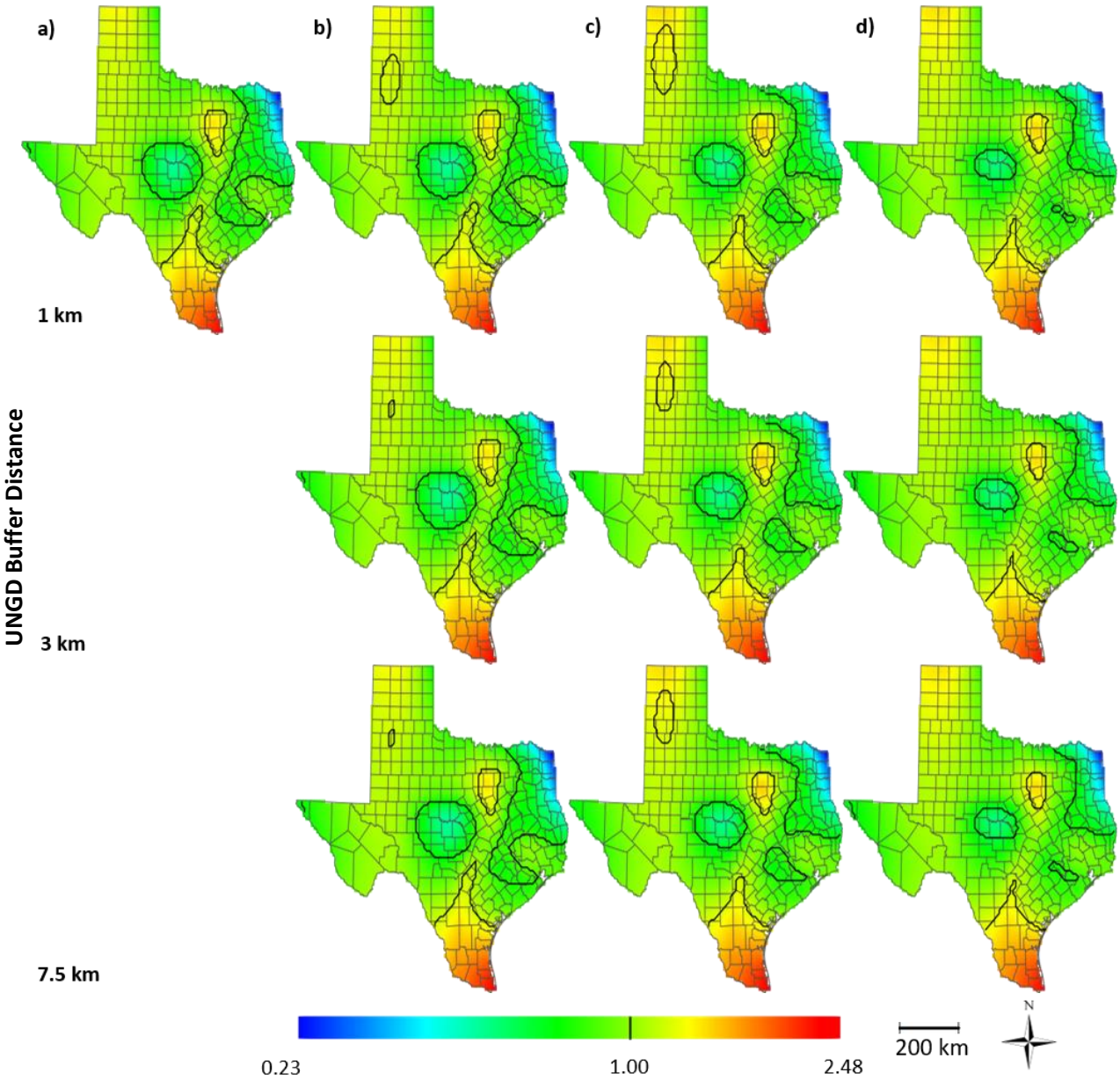
Appendix Figure C.16: Geographic patterns of ventricular septal defects (VSD) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 2000-2002. (a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



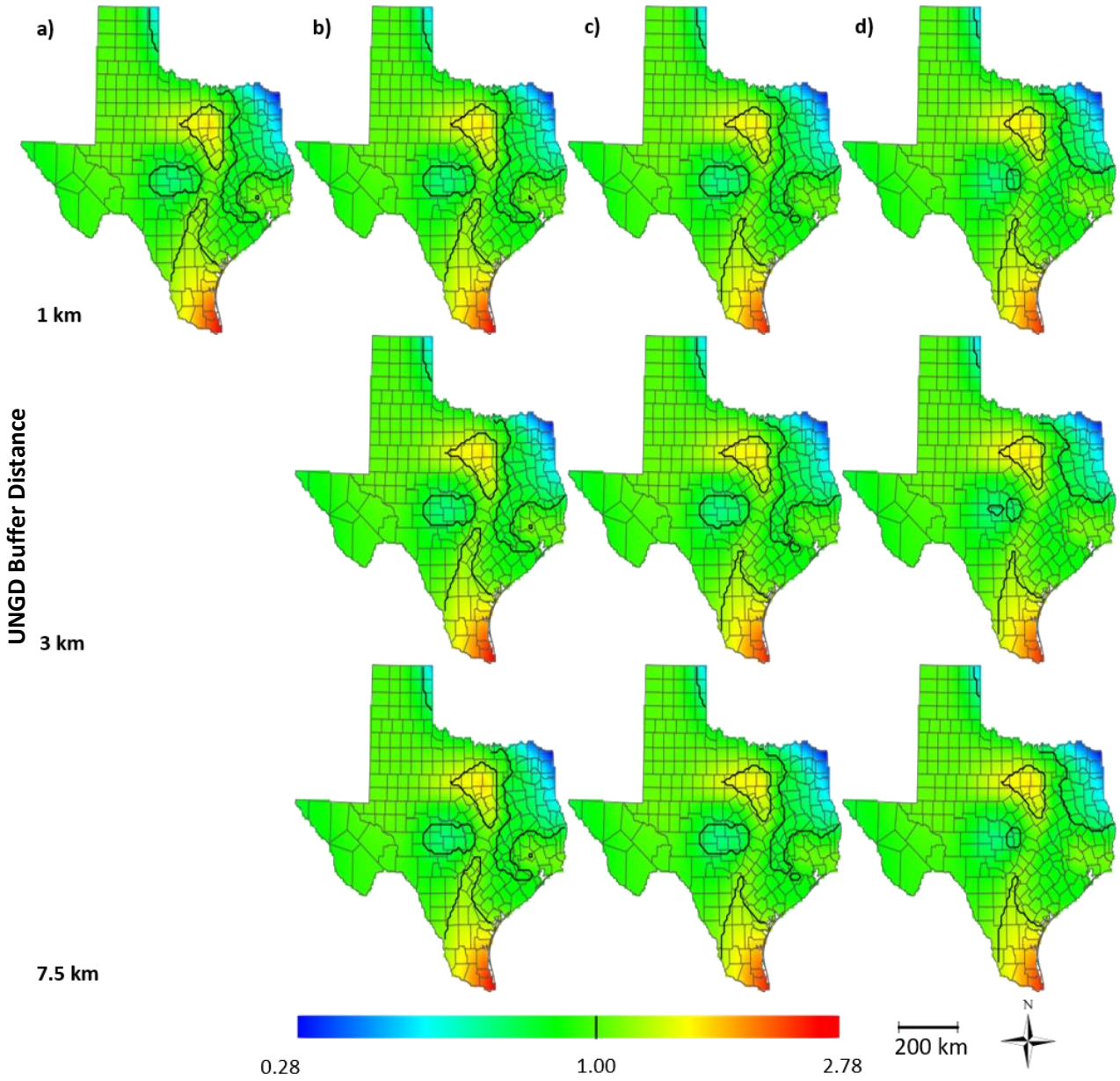
Appendix Figure C.17: Geographic patterns of ventricular septal defects (VSD) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 2001-2003. (a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



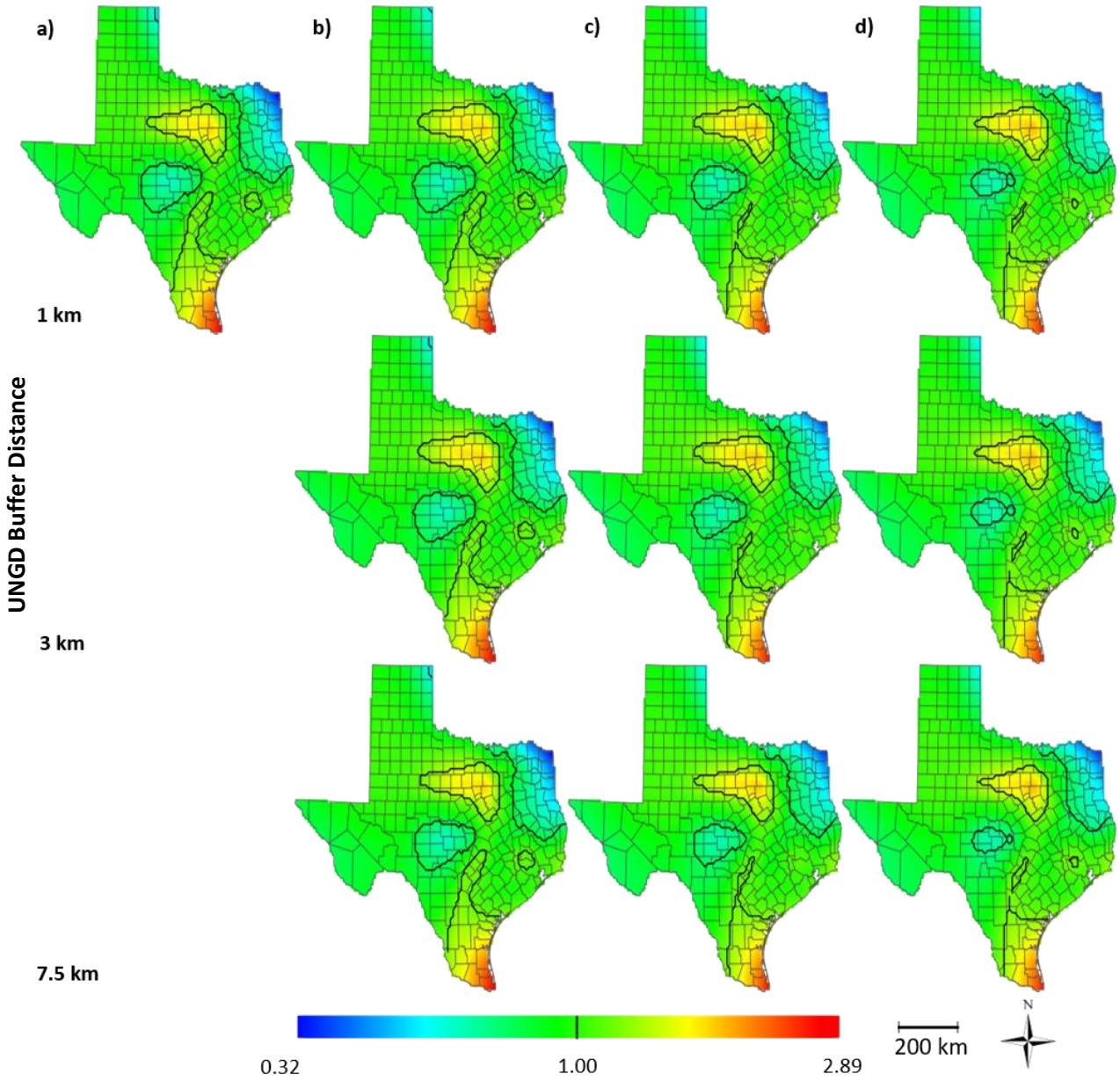
Appendix Figure C.18: Geographic patterns of ventricular septal defects (VSD) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 2002-2004.(a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



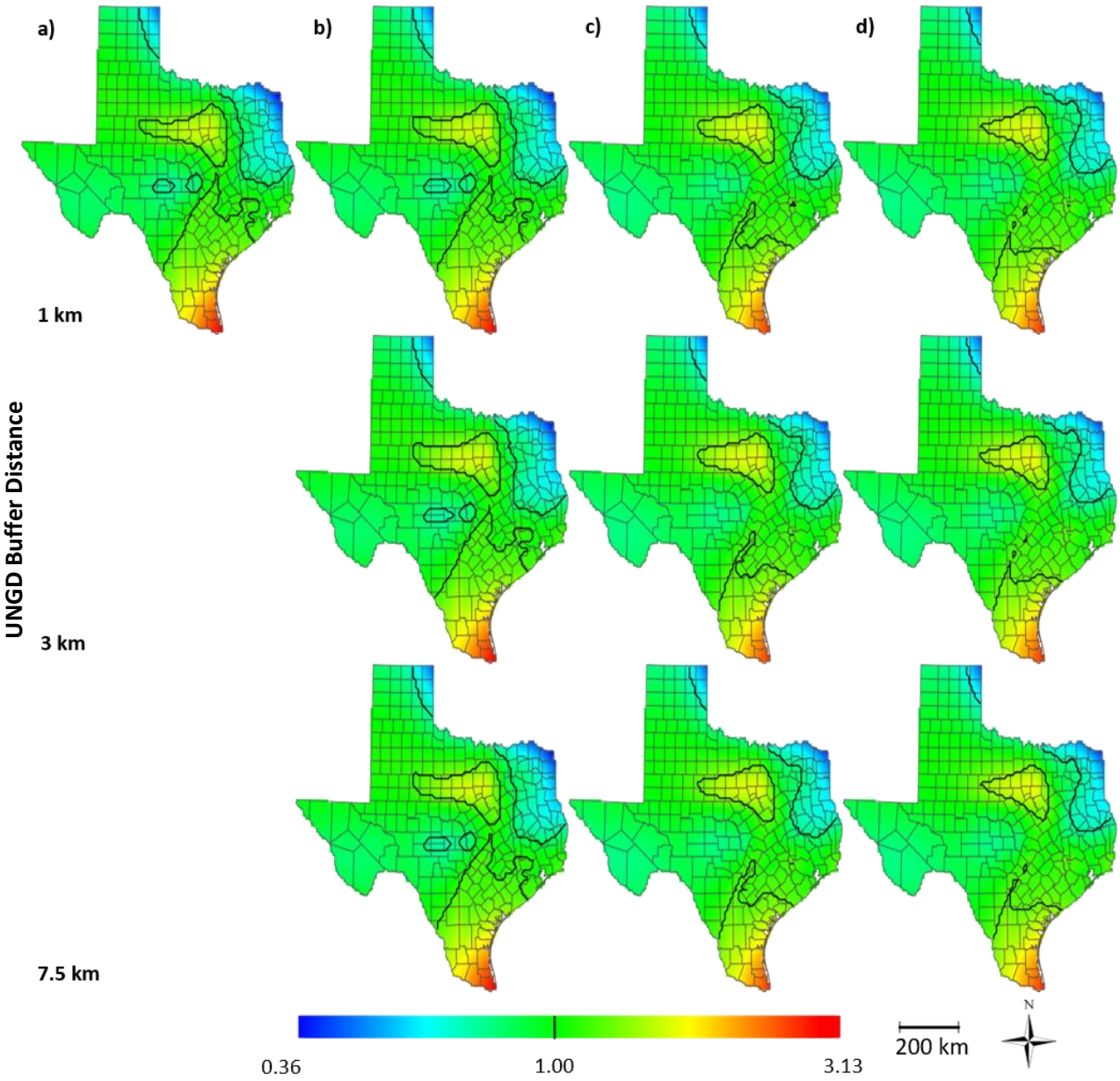
Appendix Figure C.19: Geographic patterns of ventricular septal defects (VSD) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 2003-2005.(a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



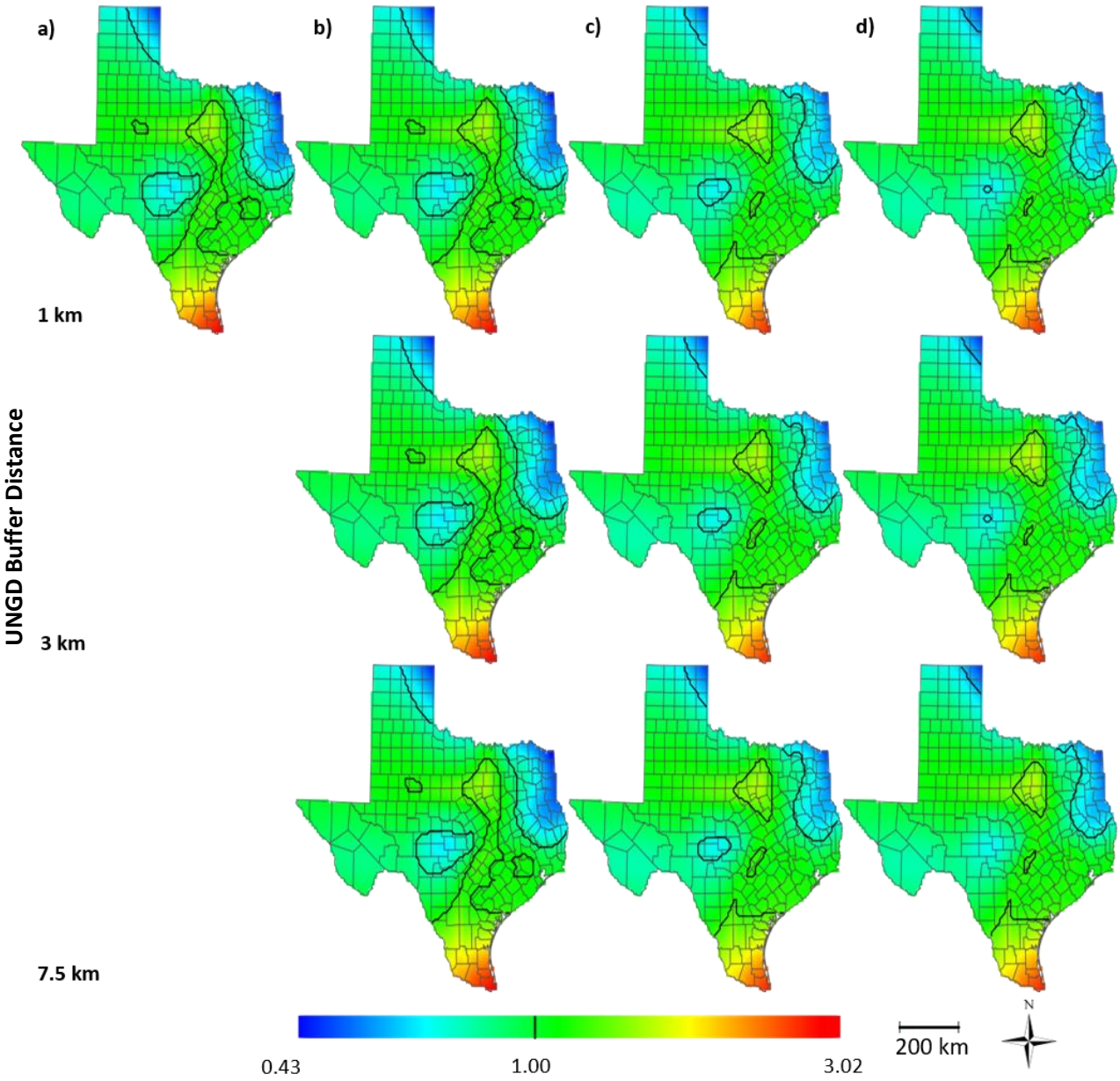
Appendix Figure C.20: Geographic patterns of ventricular septal defects (VSD) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 2004-2006.(a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



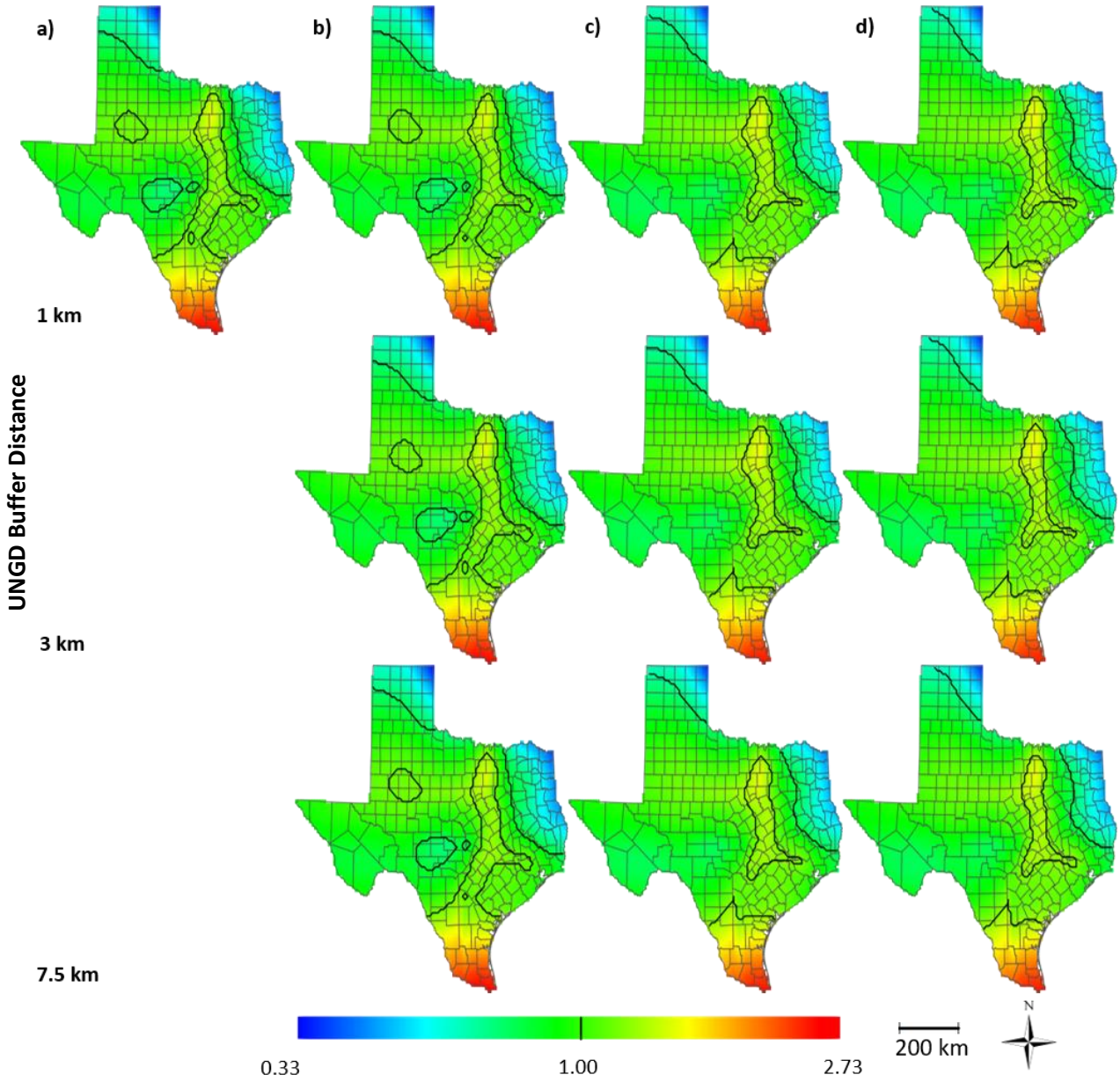
Appendix Figure C.21: Geographic patterns of ventricular septal defects (VSD) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 2005-2007. (a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



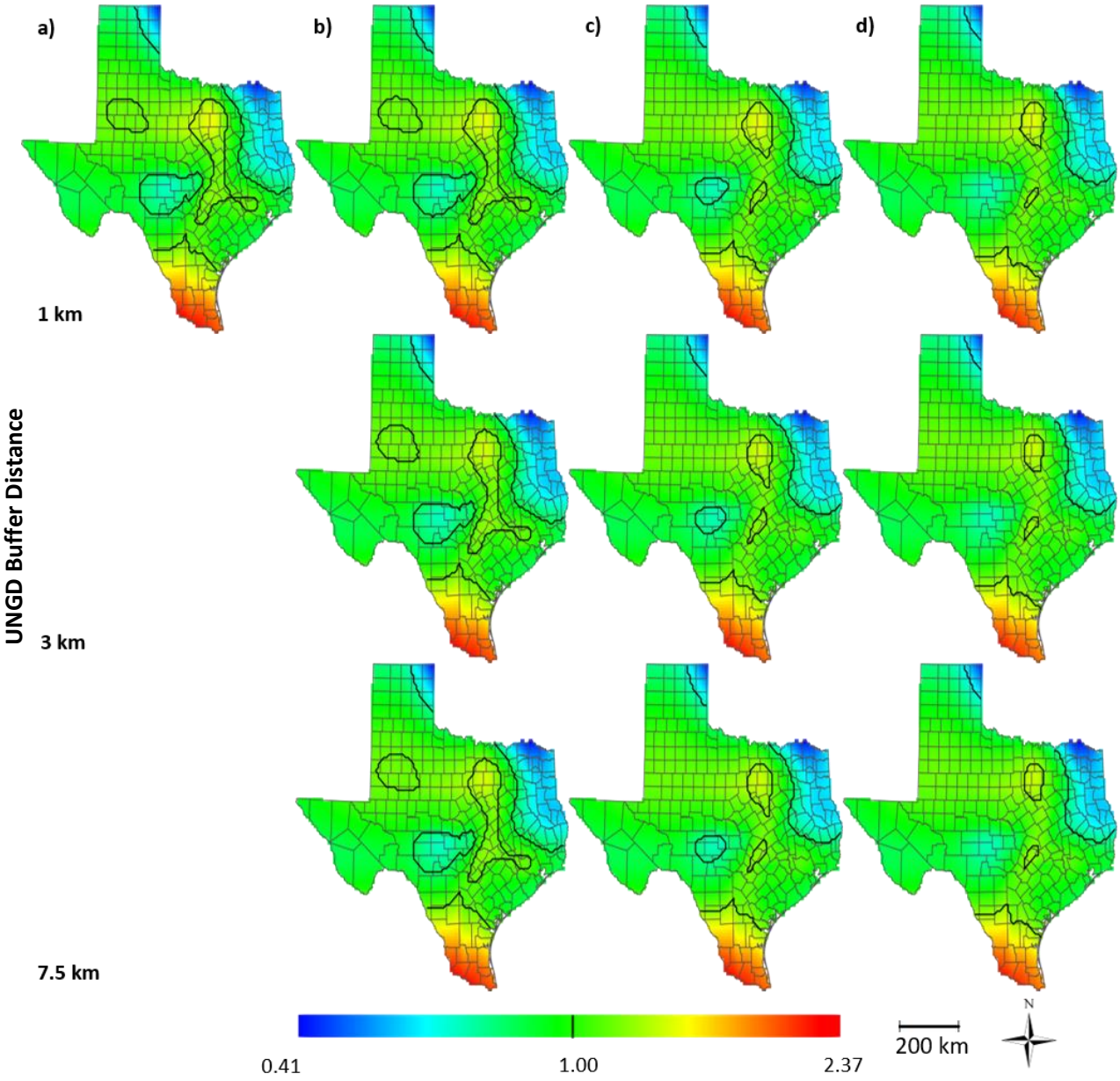
Appendix Figure C.22: Geographic patterns of ventricular septal defects (VSD) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 2006-2008. (a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



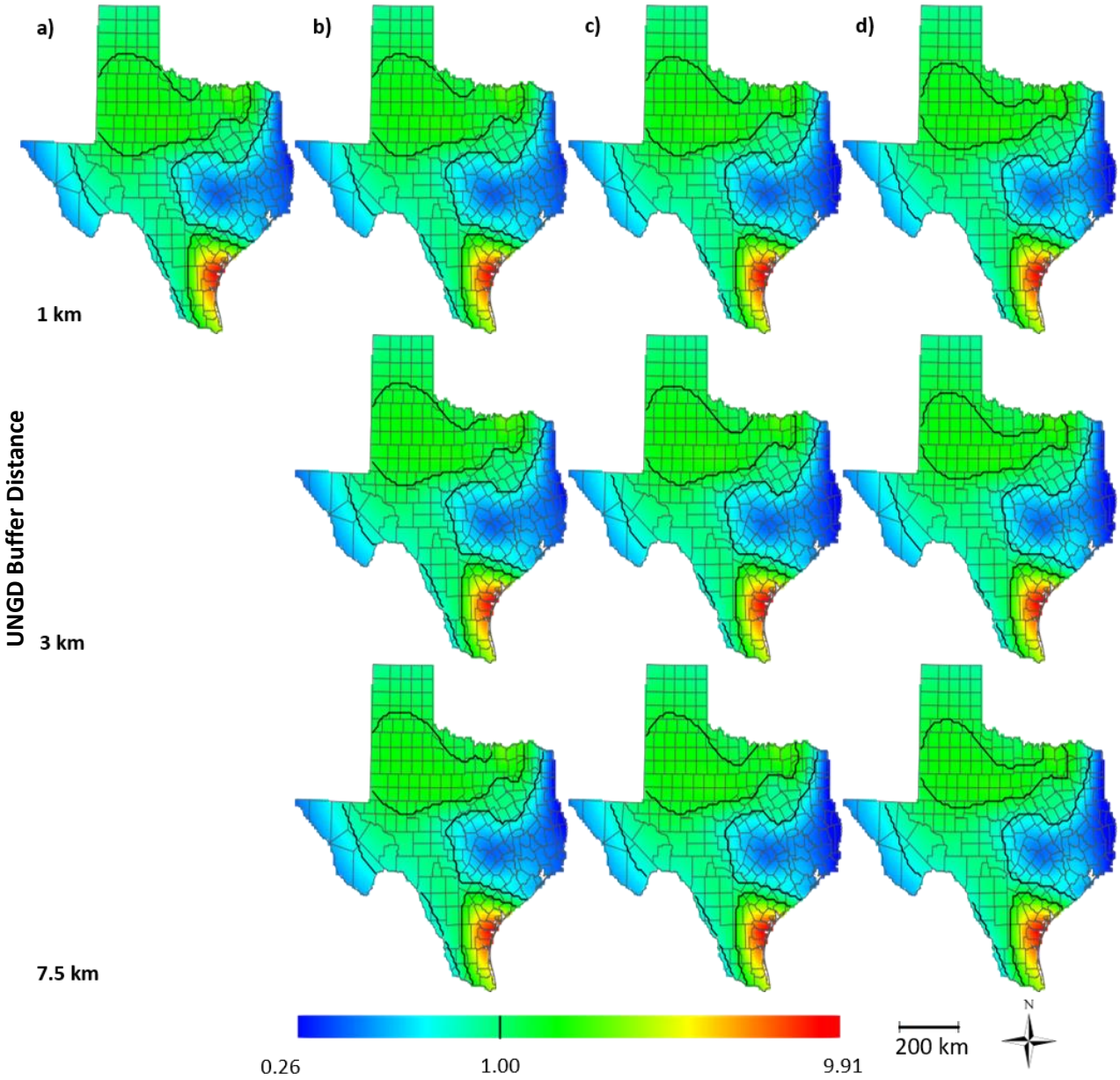
Appendix Figure C.23: Geographic patterns of ventricular septal defects (VSD) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 2007-2009. (a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



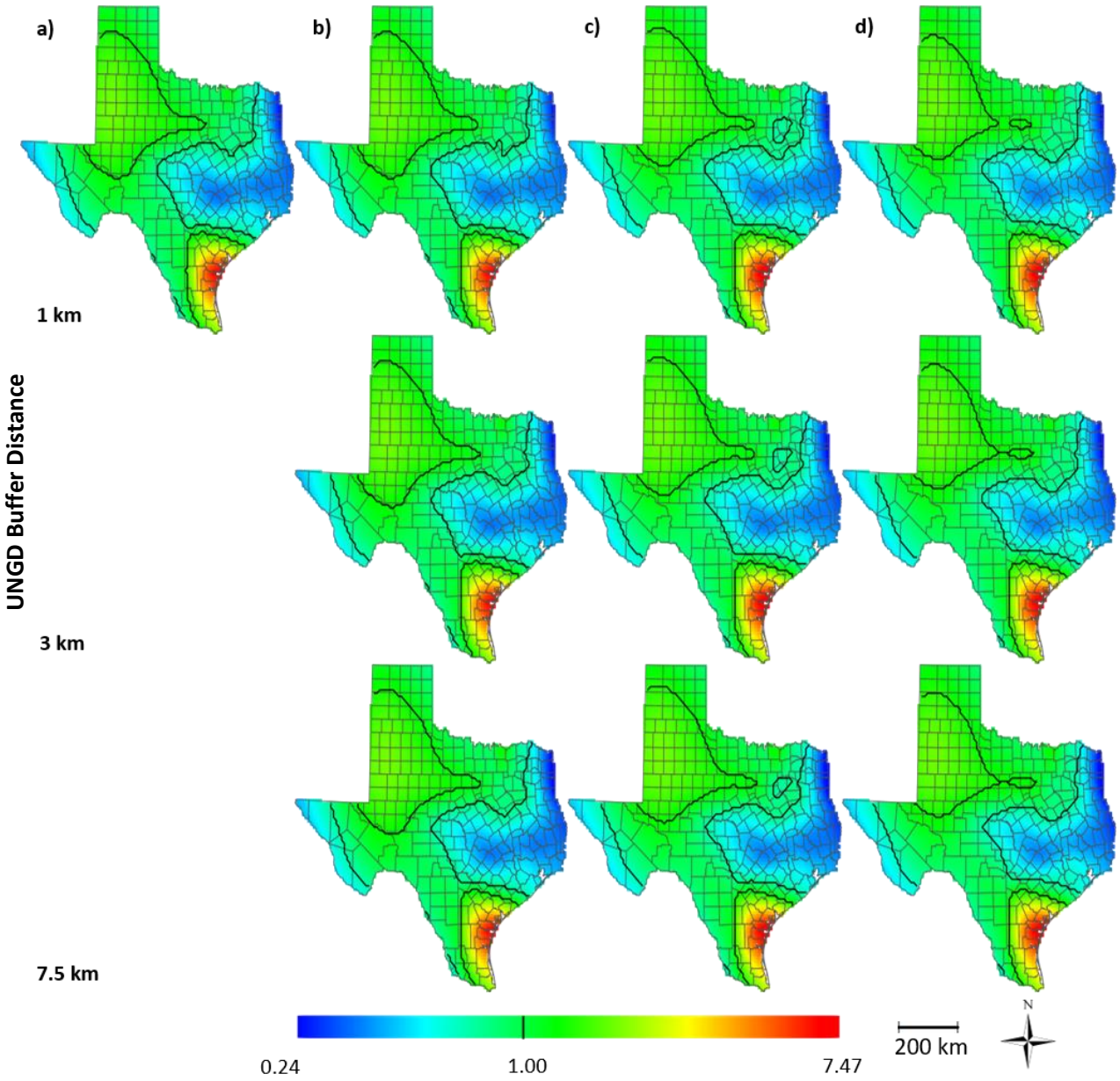
Appendix Figure C.24: Geographic patterns of ventricular septal defects (VSD) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 2008-2010. (a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



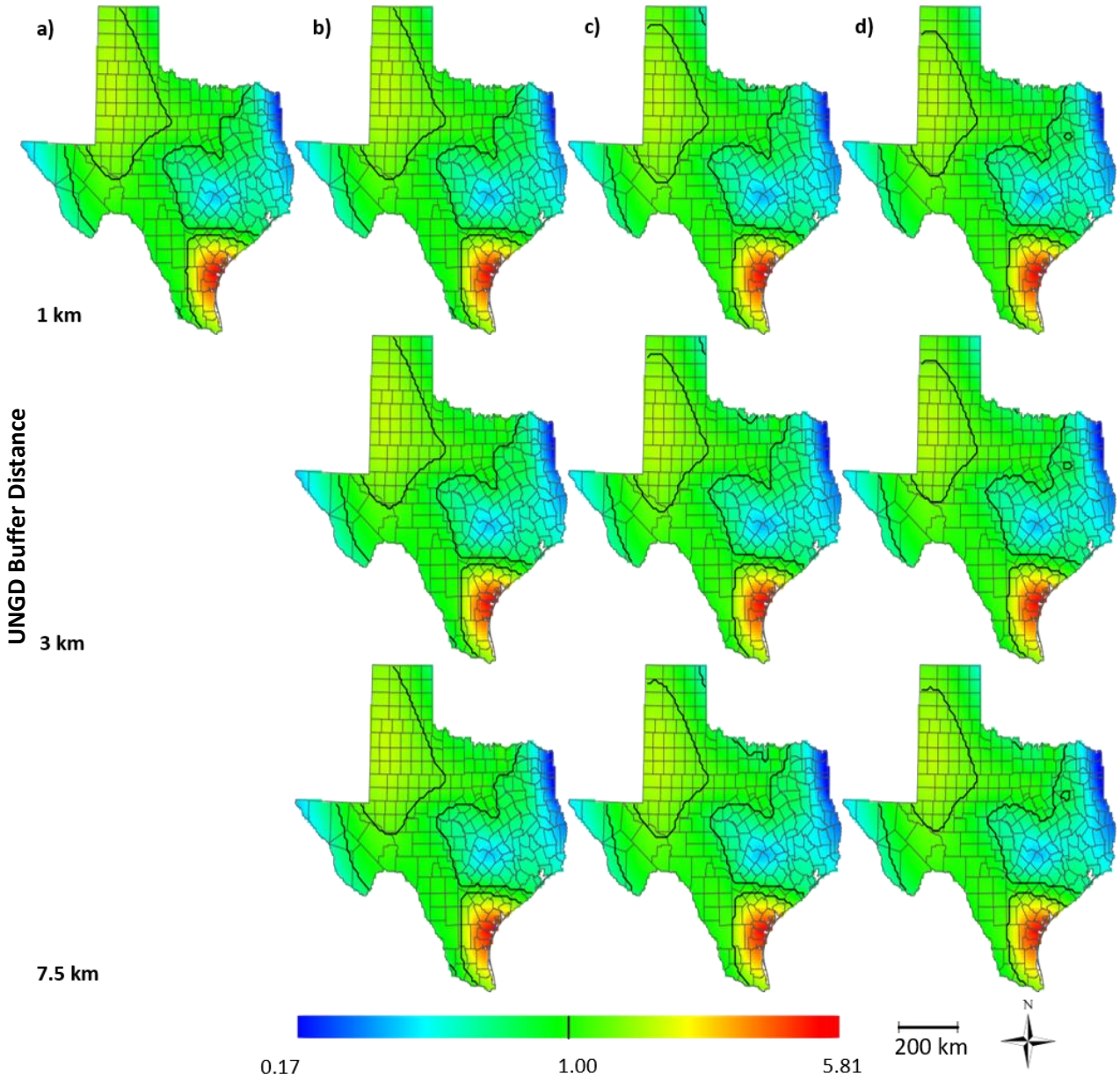
Appendix Figure C.25: Geographic patterns of ventricular septal defects (VSD) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 2009-2011. (a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



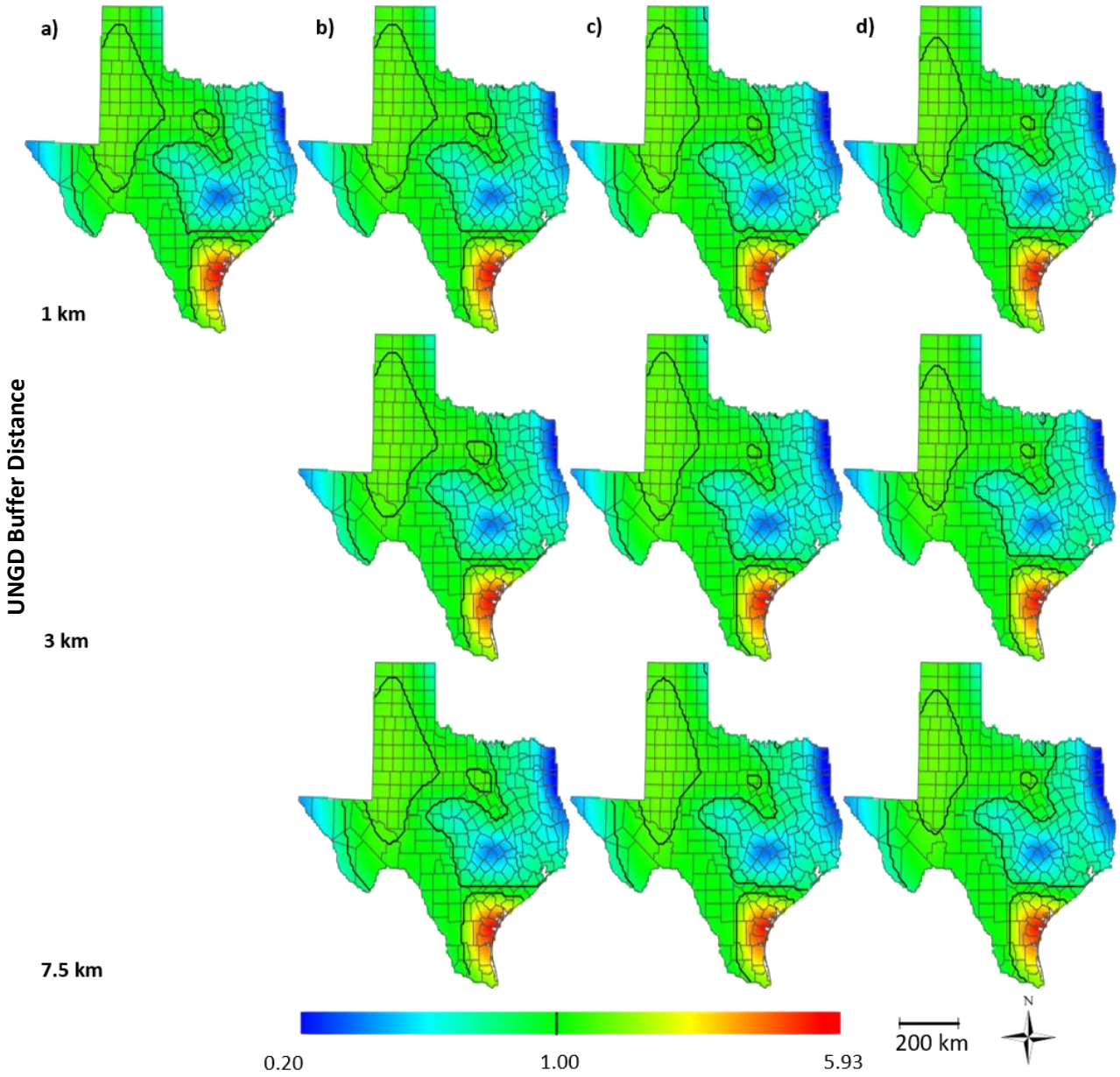
Appendix Figure C.26: Geographic patterns of atrial septal defects (ASD) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 1999-2001. (a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



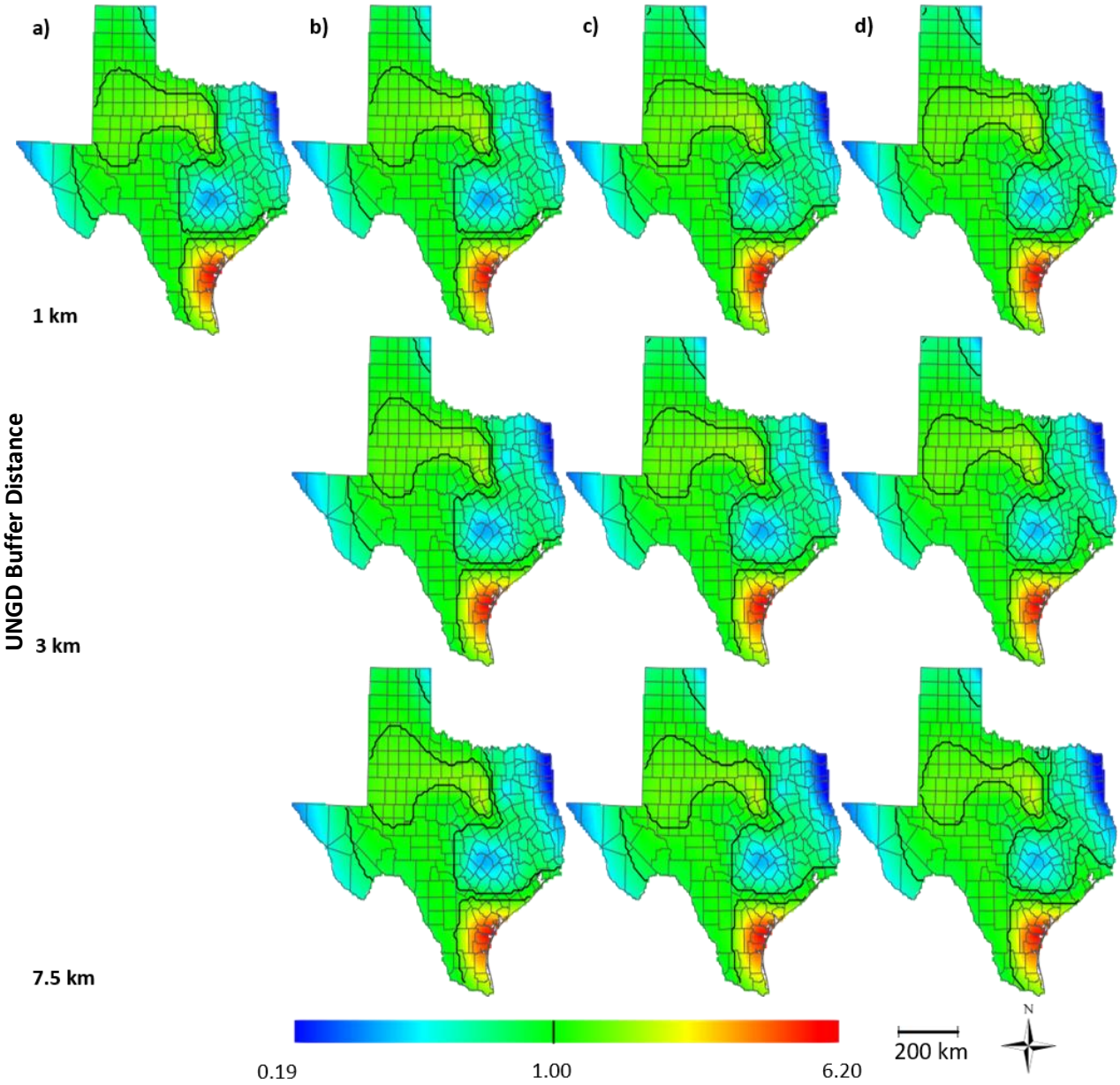
Appendix Figure C.27: Geographic patterns of atrial septal defects (ASD) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 2000-2002. (a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



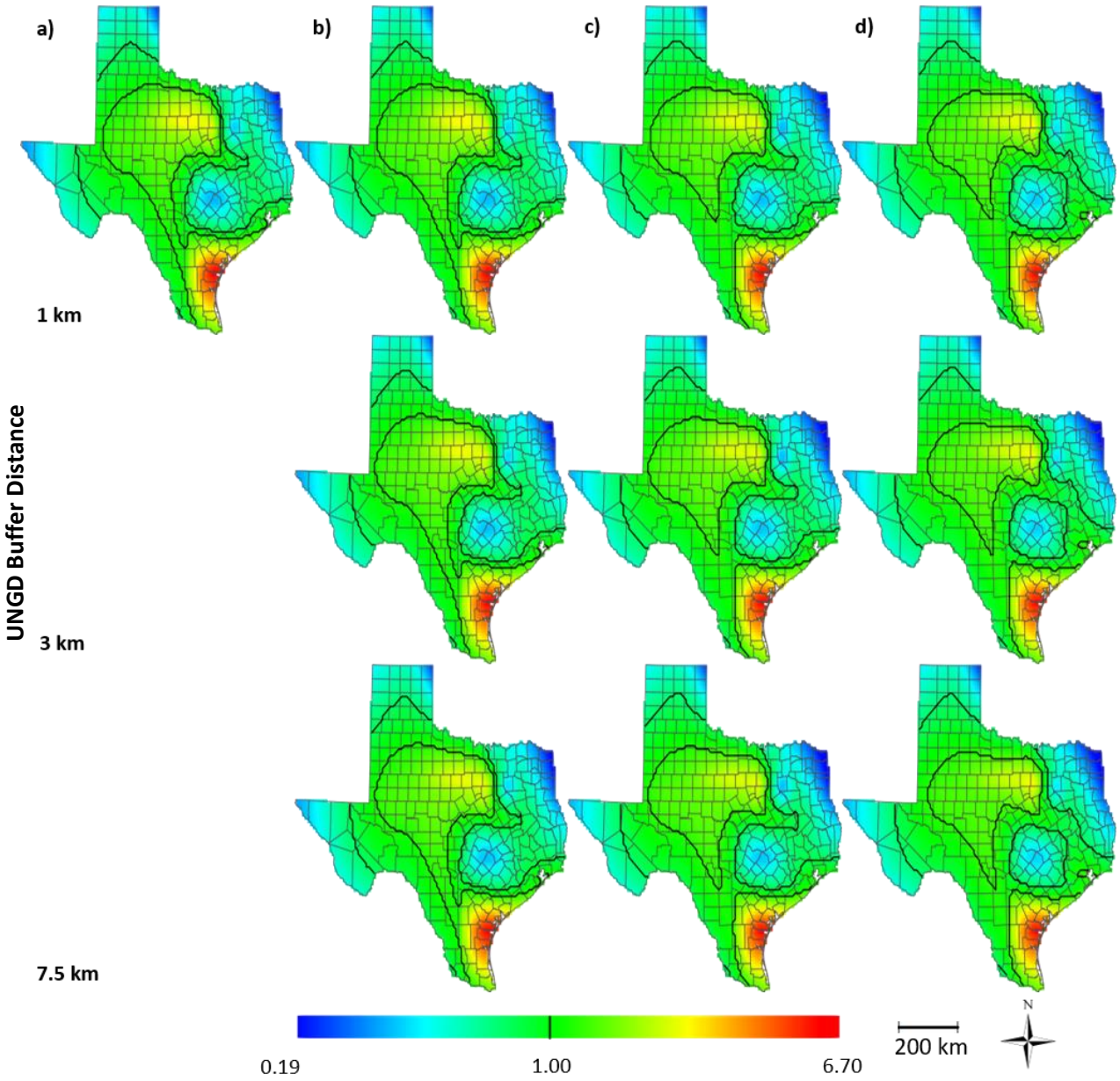
Appendix Figure C.28: Geographic patterns of atrial septal defects (ASD) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 2001-2003. (a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



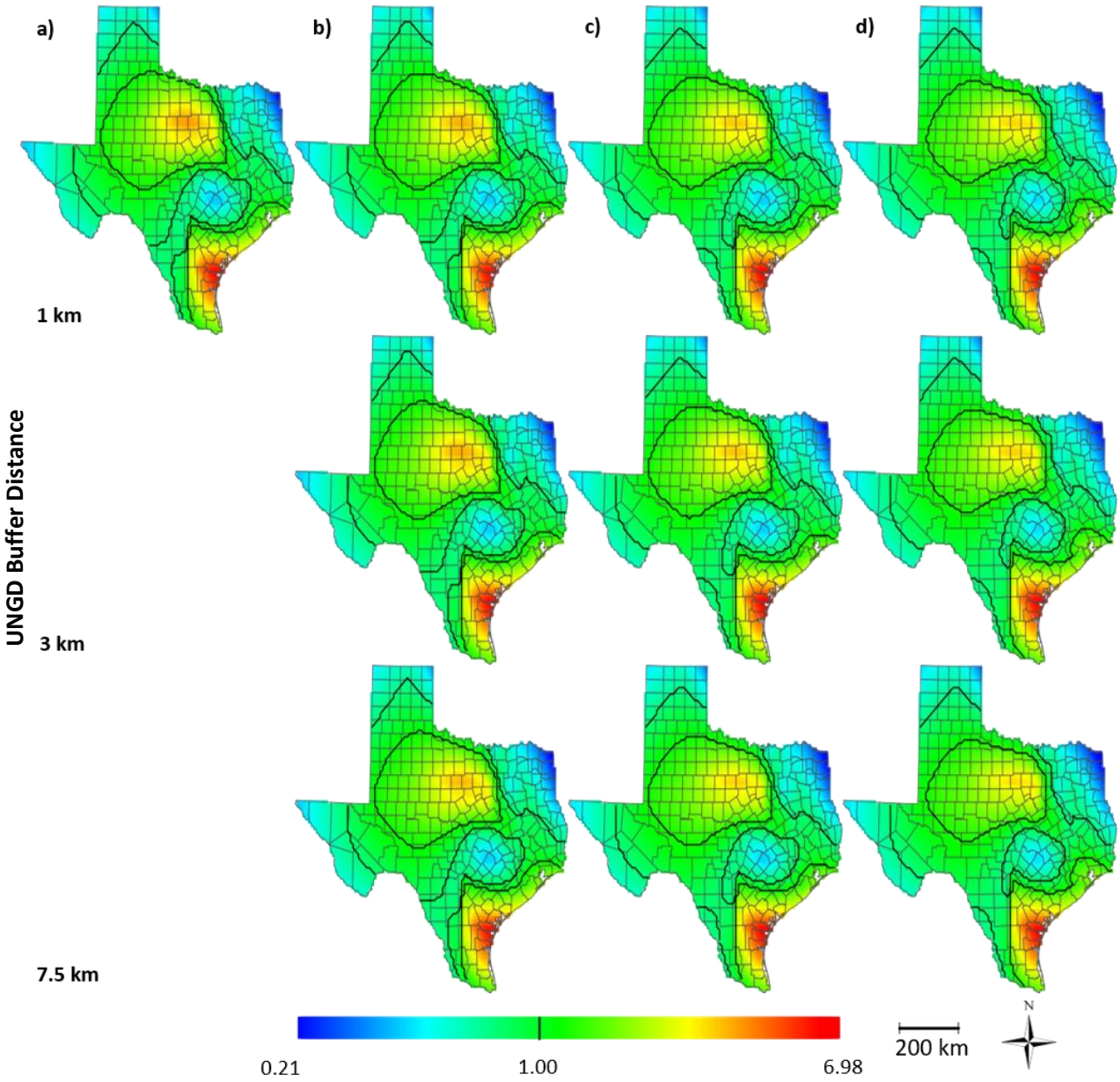
Appendix Figure C.29: Geographic patterns of atrial septal defects (ASD) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 2002-2004. (a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



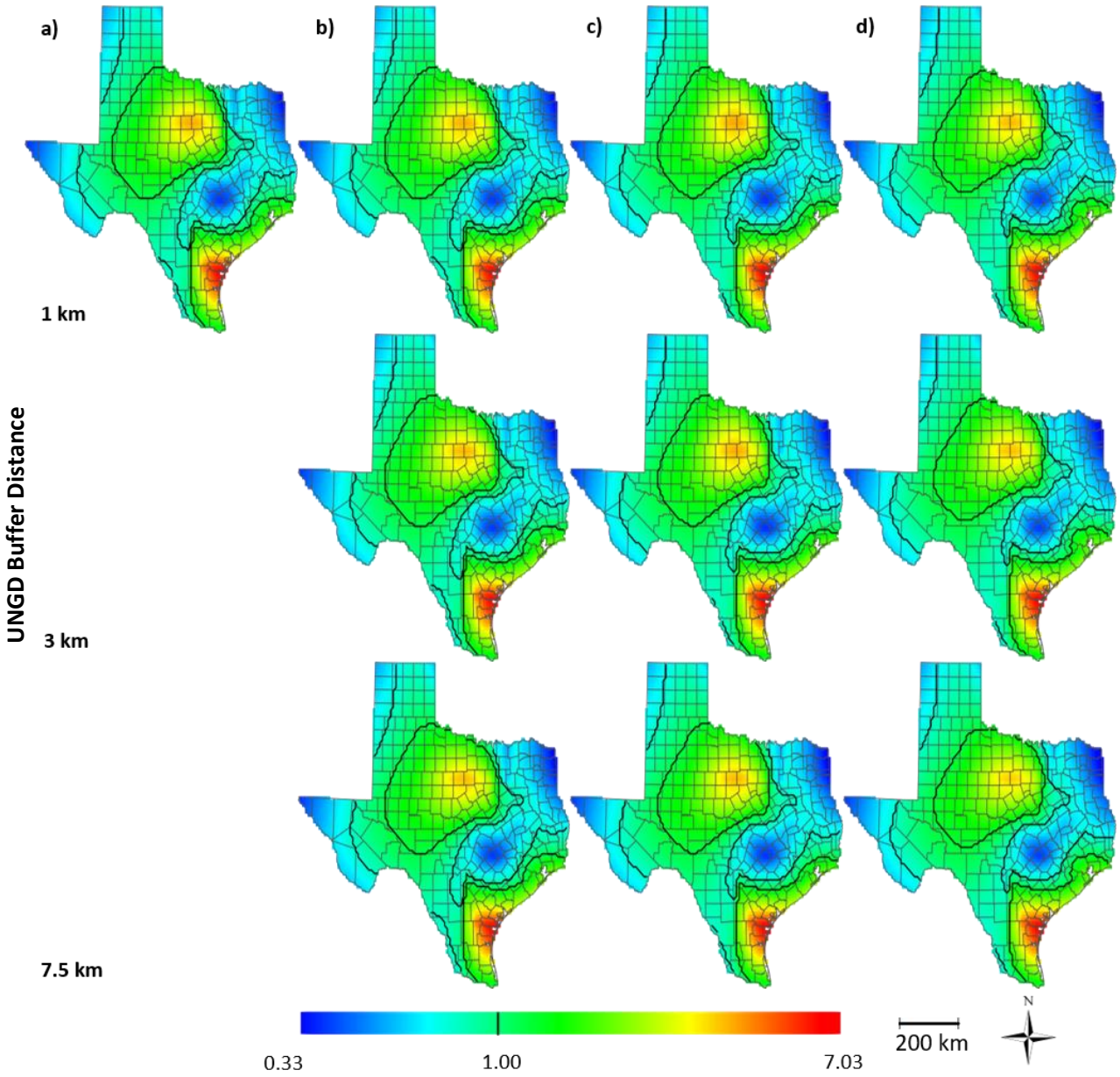
Appendix Figure C.30: Geographic patterns of atrial septal defects (ASD) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 2003-2005. (a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



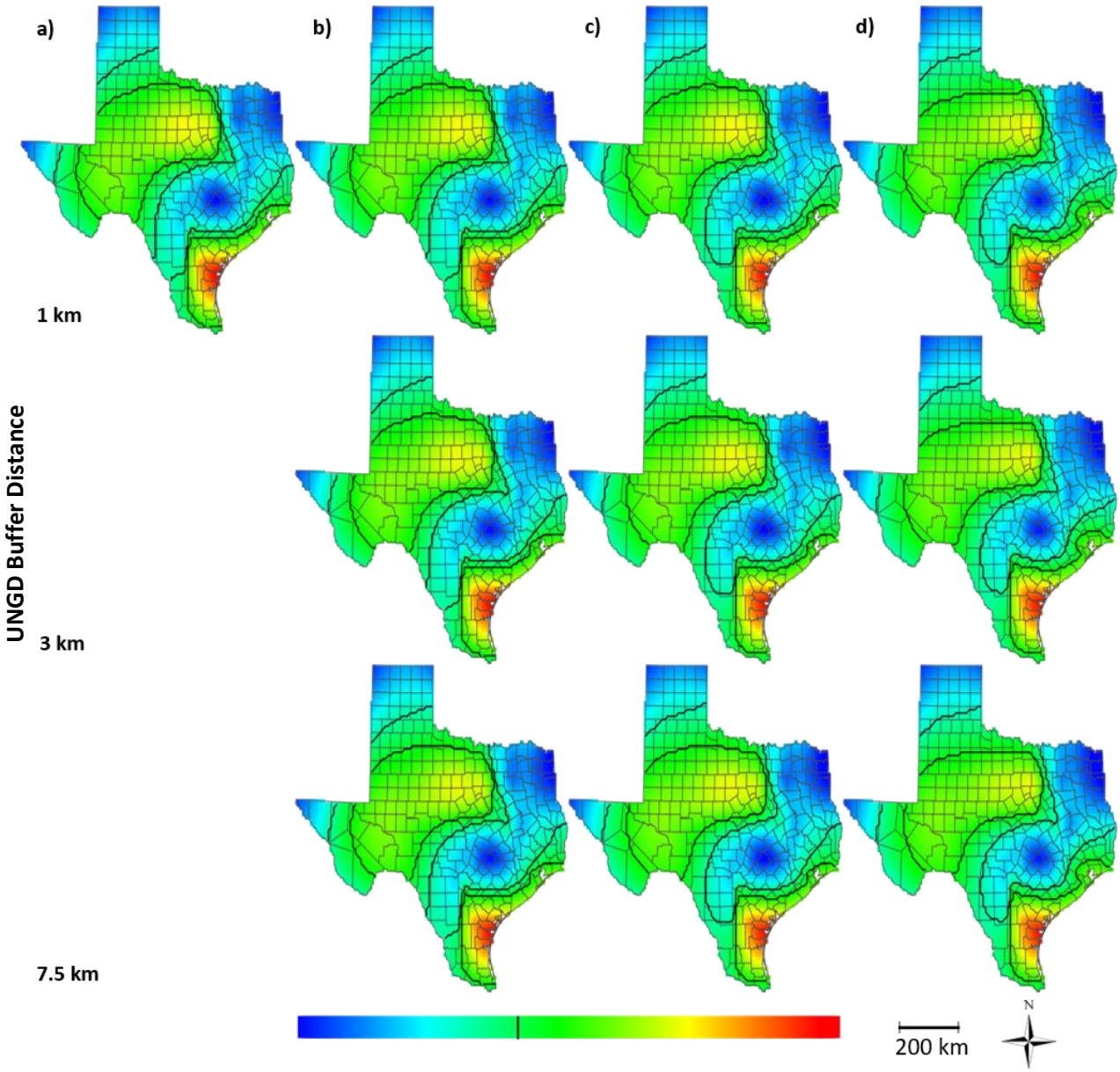
Appendix Figure C.31: Geographic patterns of atrial septal defects (ASD) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 2004-2006. (a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



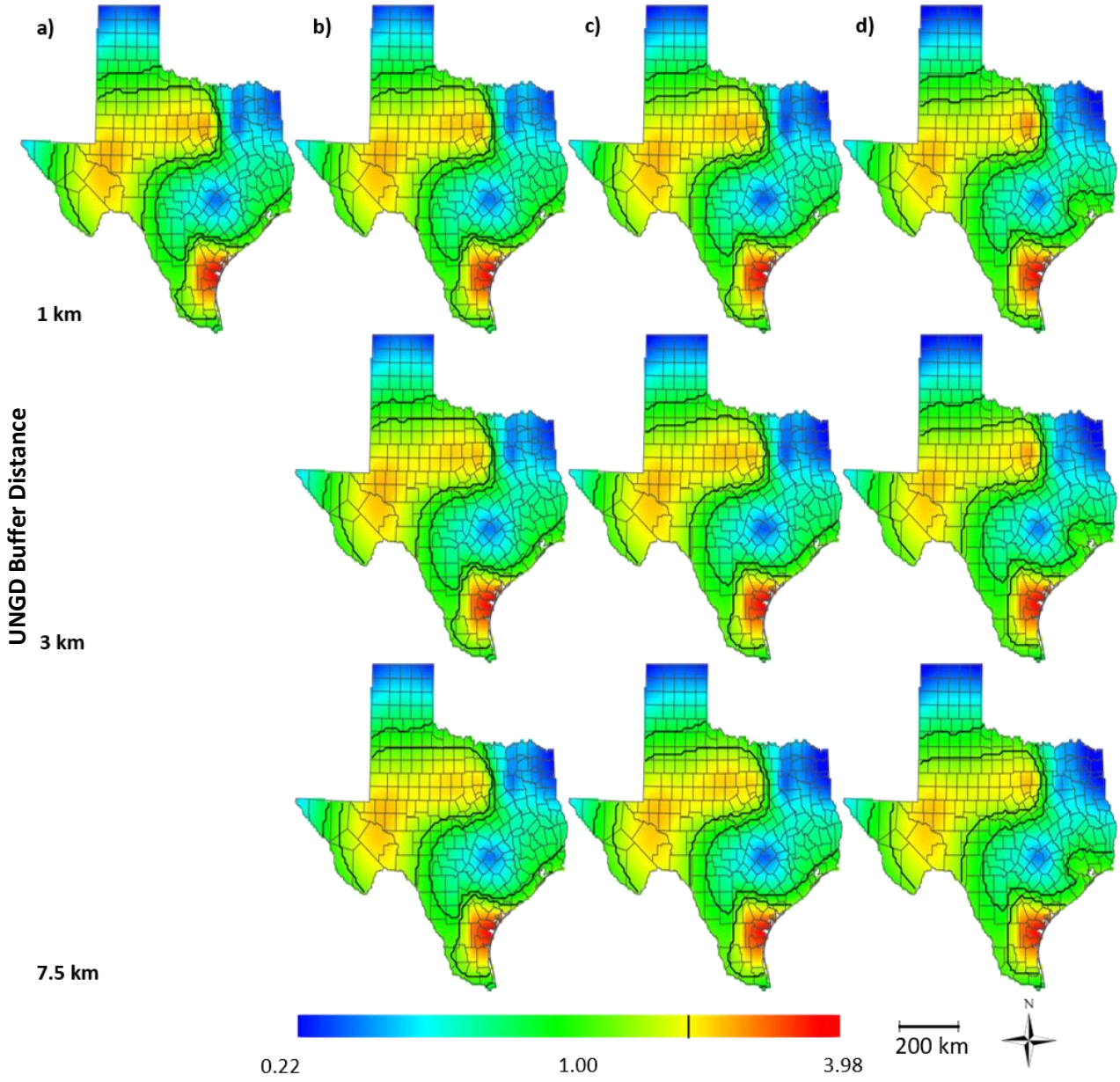
Appendix Figure C.32: Geographic patterns of atrial septal defects (ASD) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 2005-2007. (a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



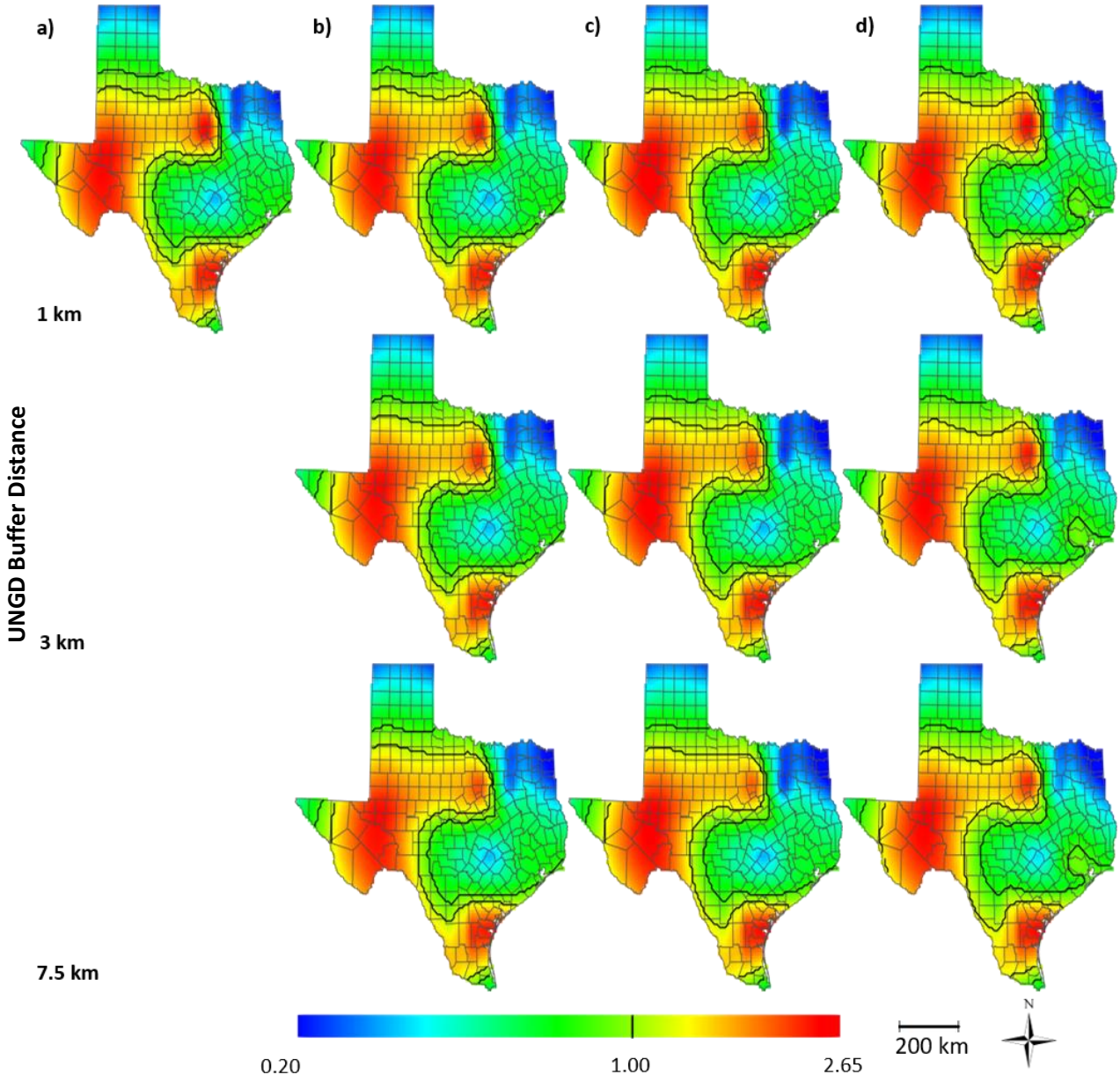
Appendix Figure C.33: Geographic patterns of atrial septal defects (ASD) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 2006-2008. (a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



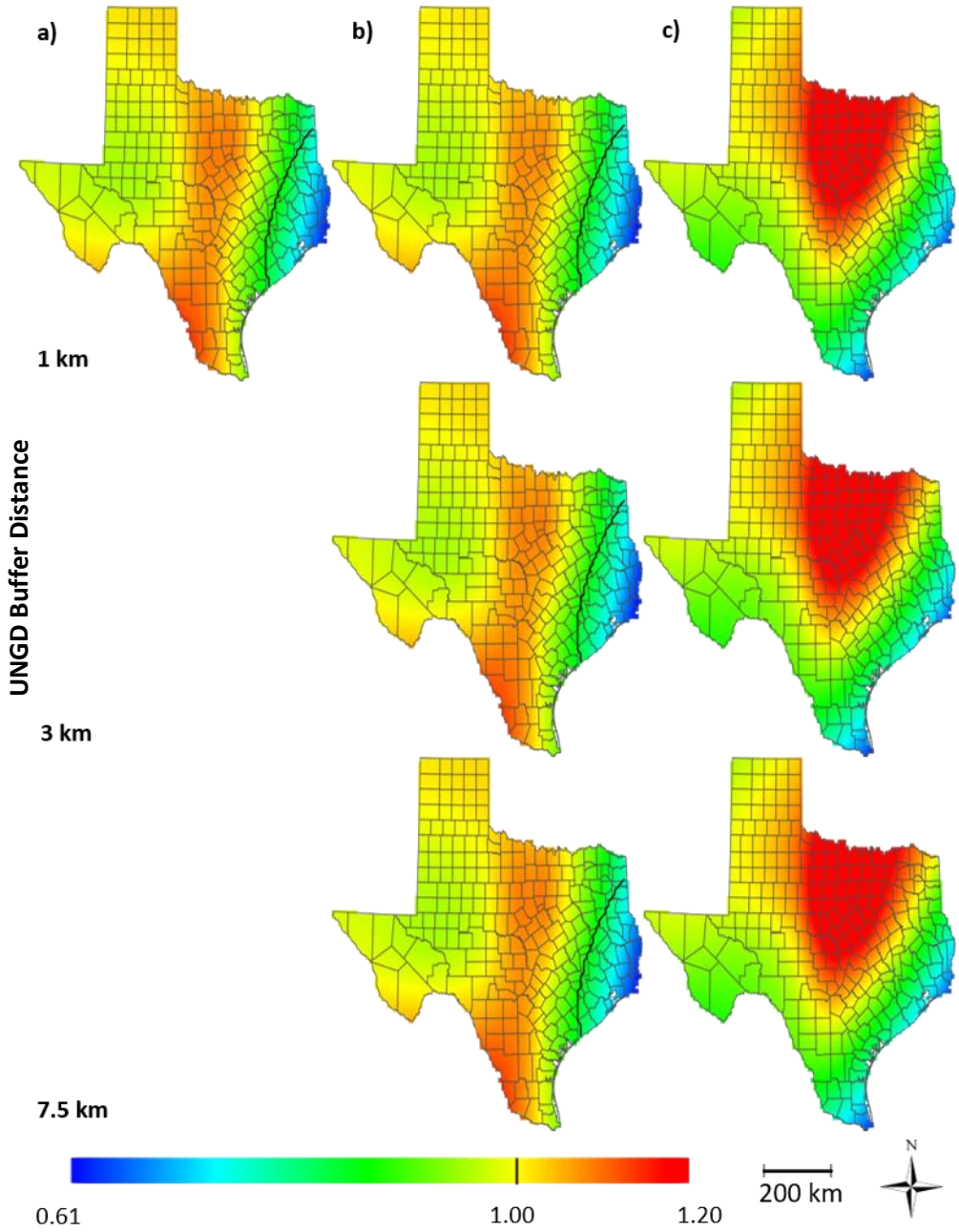
Appendix Figure C.34: Geographic patterns of atrial septal defects (ASD) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 2007-2009. (a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



Appendix Figure C.35: Geographic patterns of atrial septal defects (ASD) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 2008-2010. (a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.

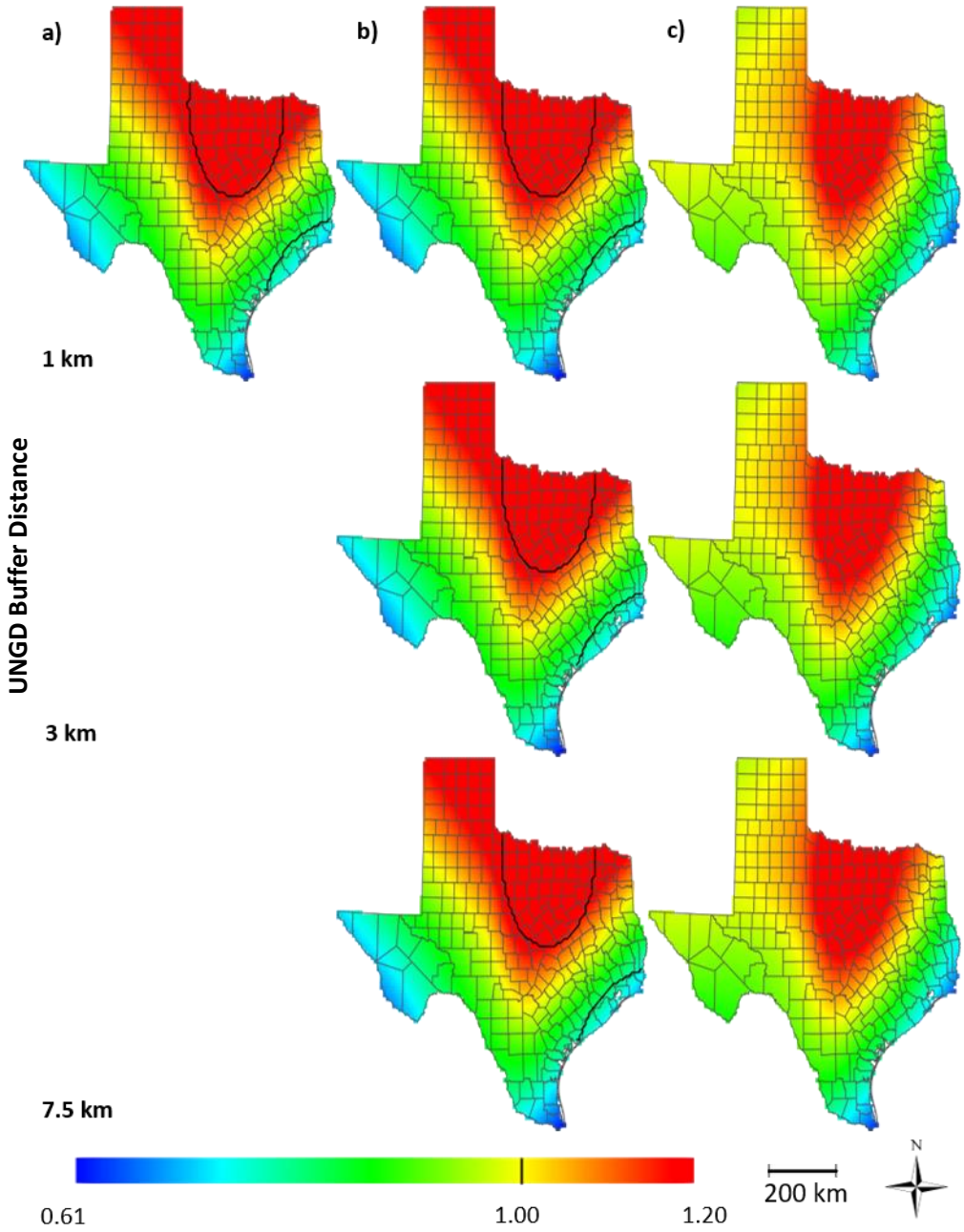


Appendix Figure C.36: Geographic patterns of atrial septal defects (ASD) and unconventional natural gas developments (UNGD) buffer radii among Texas births, 2009-2011. (a) model 1: crude model with only location and no UNGD adjustment, (b) model 2: adjusted model with UNGD density, (c) model 3: with additional adjustment for maternal smoking, plurality, maternal age, race/ethnicity, and education status, (d) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.

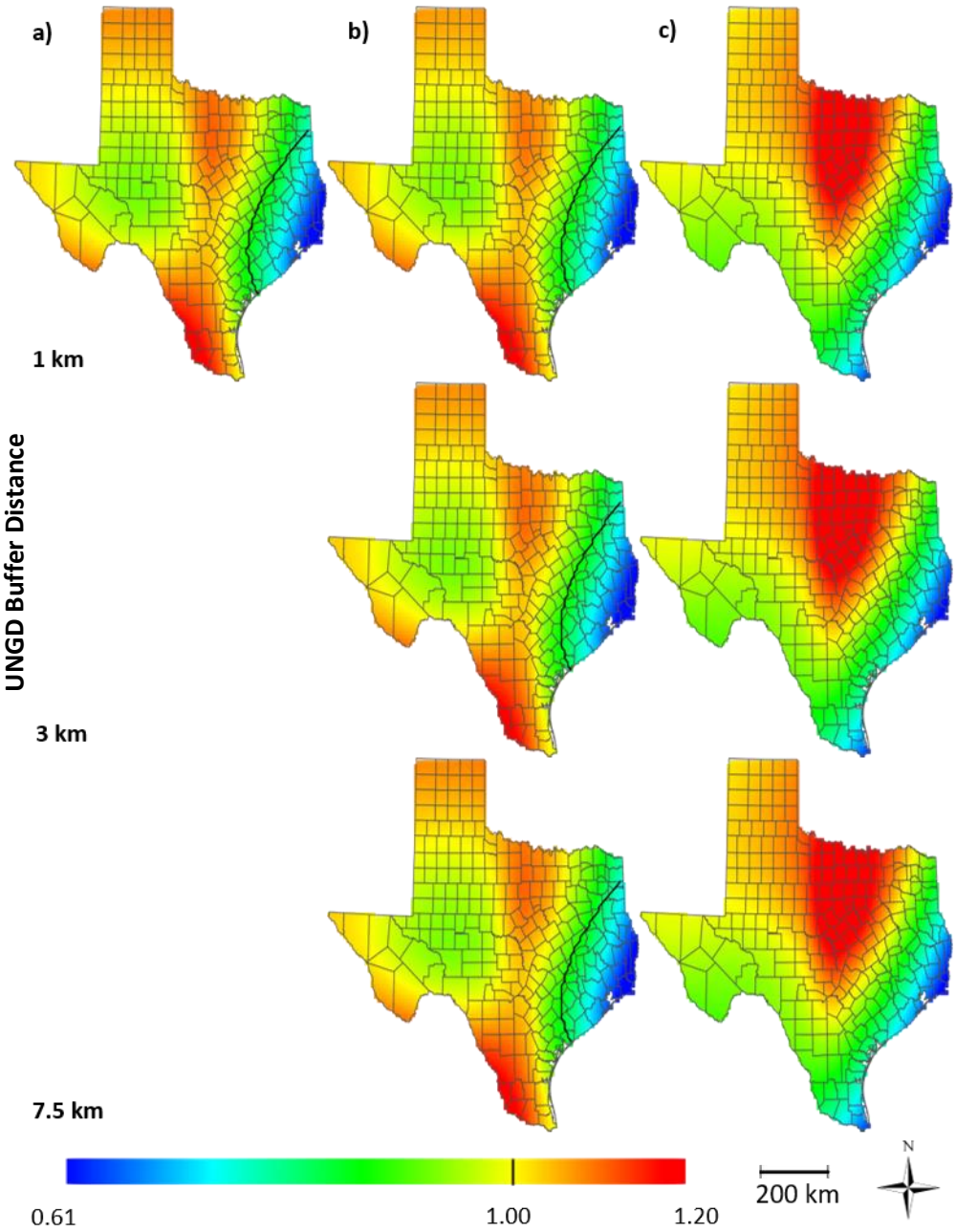


Appendix Figure C.37: Sensitivity analysis: diabetes and geographic patterns of anencephaly and unconventional natural gas developments (UNGD) buffer radii among Texas Births, 2009-2011.

(a) model 1: crude model with only location and diabetes percentage, (b) model 2: adjusted model with UNGD density, (c) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.

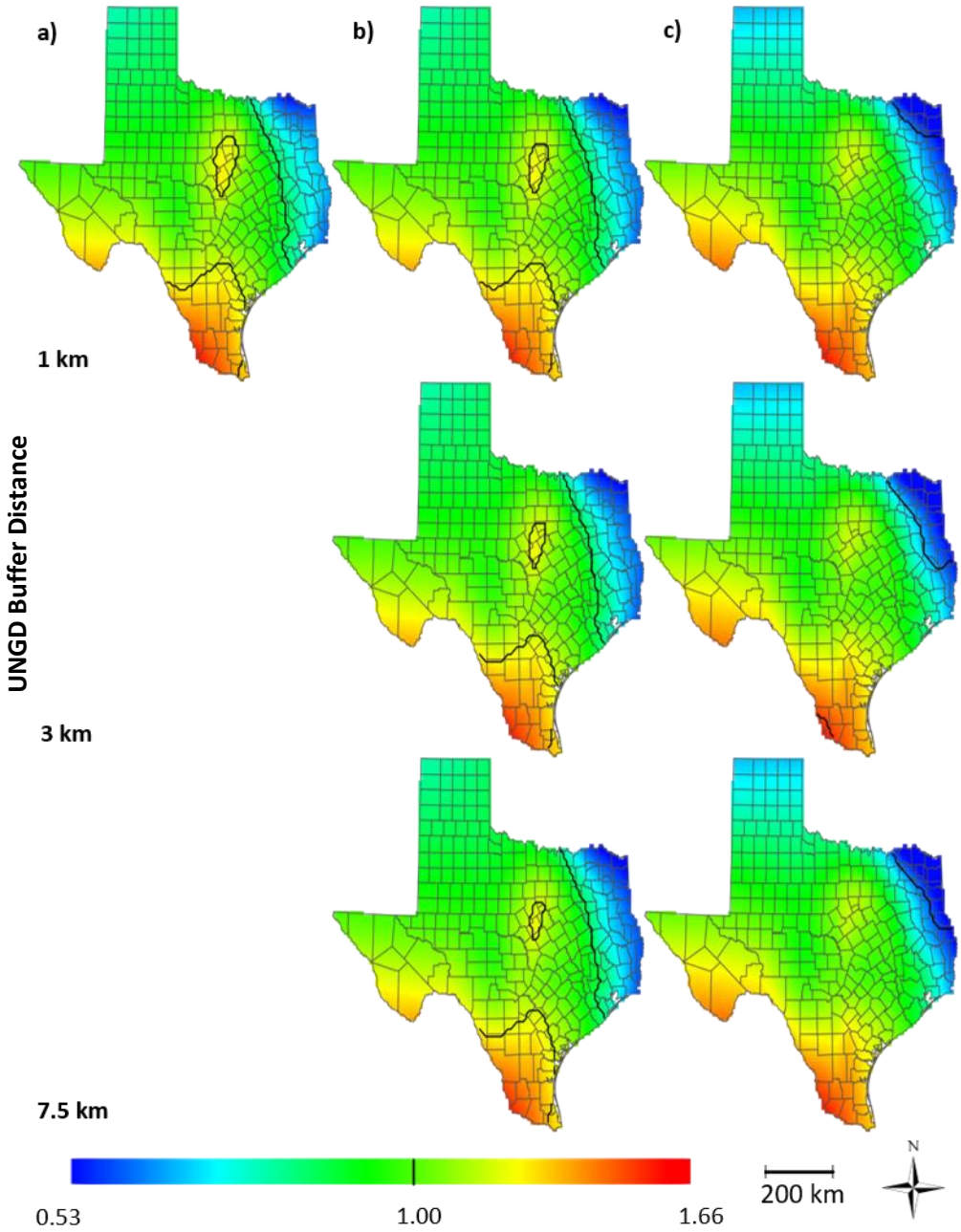


Appendix Figure C.38: Sensitivity analysis: uninsured and geographic patterns of anencephaly and unconventional natural gas developments (UNGD) buffer radii among Texas Births, 2009-2011. (a) model 1: crude model with only location and uninsured percent, (b) model 2: adjusted model with UNGD density, (c) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.

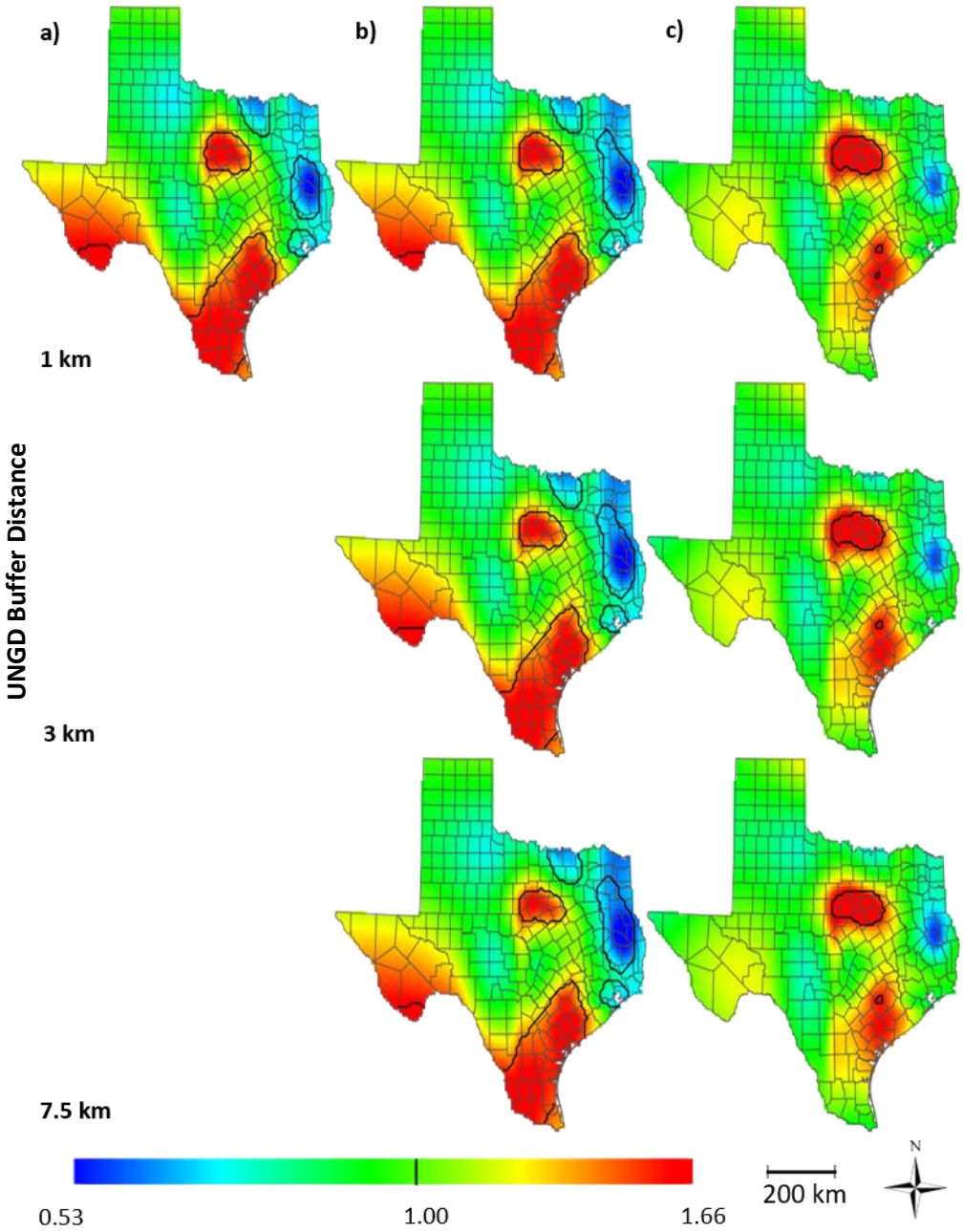


Appendix Figure C.39: Sensitivity analysis: opioid and geographic patterns of anencephaly and unconventional natural gas developments (UNGD) buffer radii among Texas Births, 2009-2011.

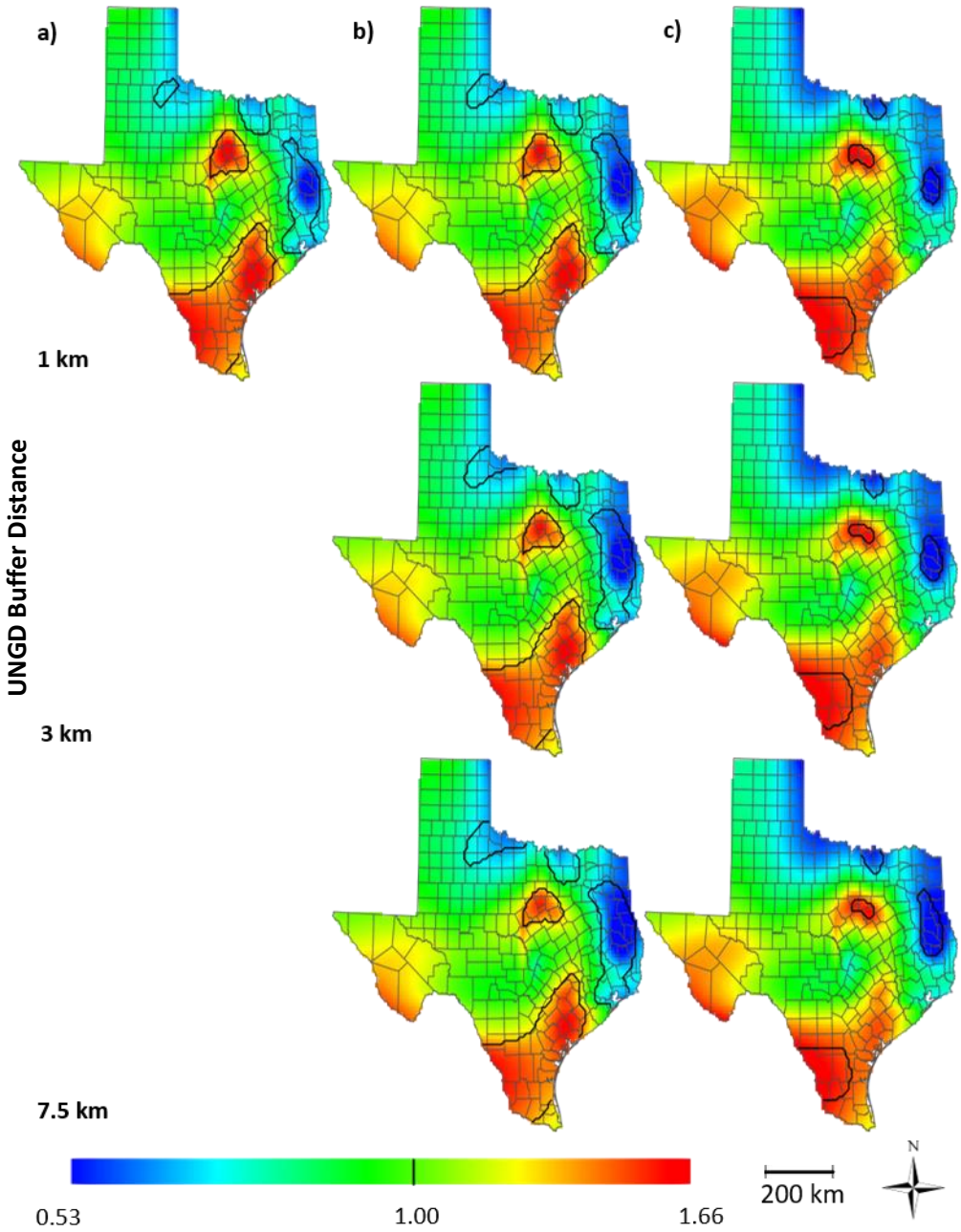
(a) model 1: crude model with only location and opioid prescription rates, (b) model 2: adjusted model with UNGD density, (c) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



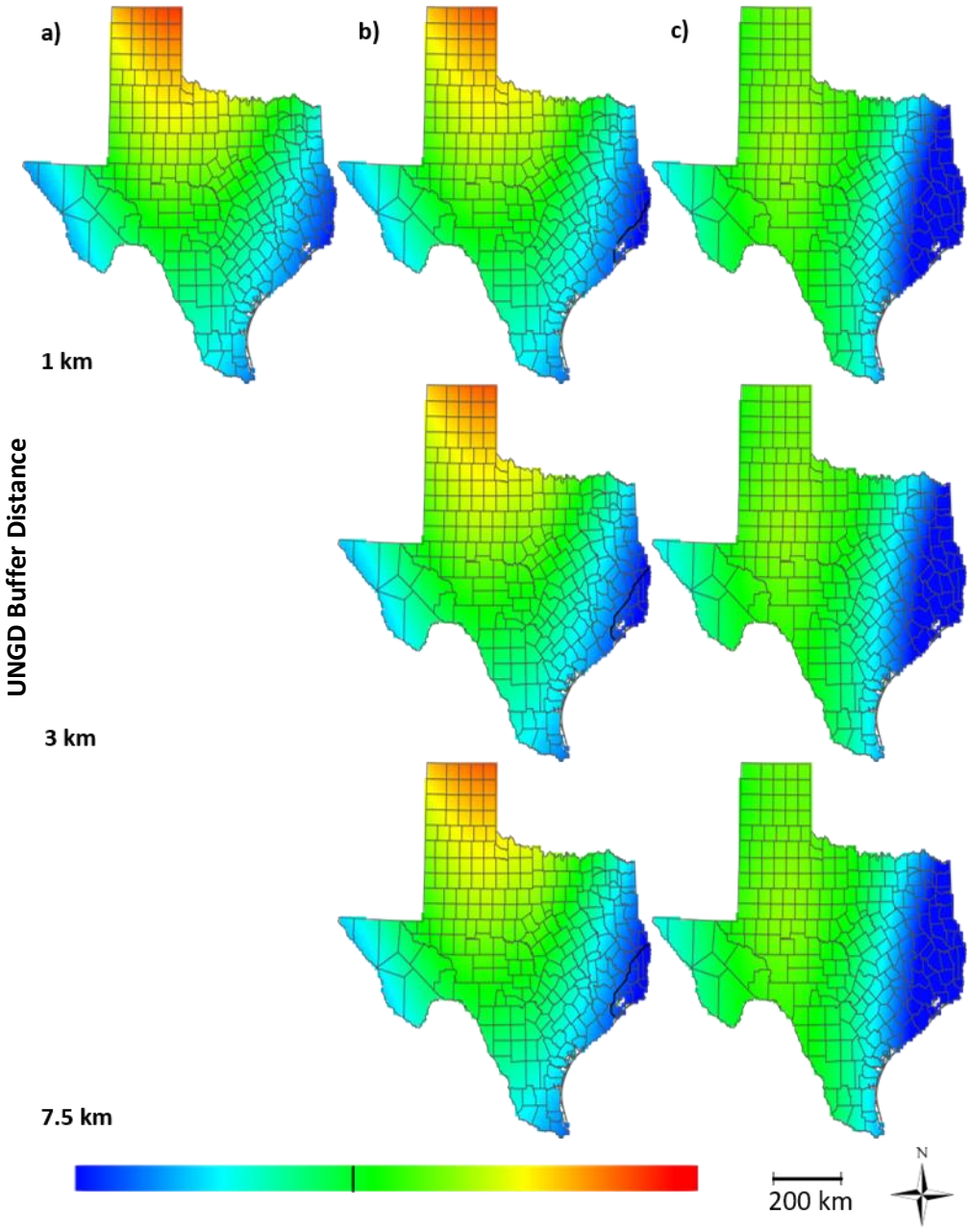
Appendix Figure C.40: Sensitivity analysis: diabetes and geographic patterns of aortic valve stenosis (AVS) and unconventional natural gas developments (UNGD) buffer radii among Texas Births, 2009-2011. (a) model 1: crude model with only location and diabetes percentage, (b) model 2: adjusted model with UNGD density, (c) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



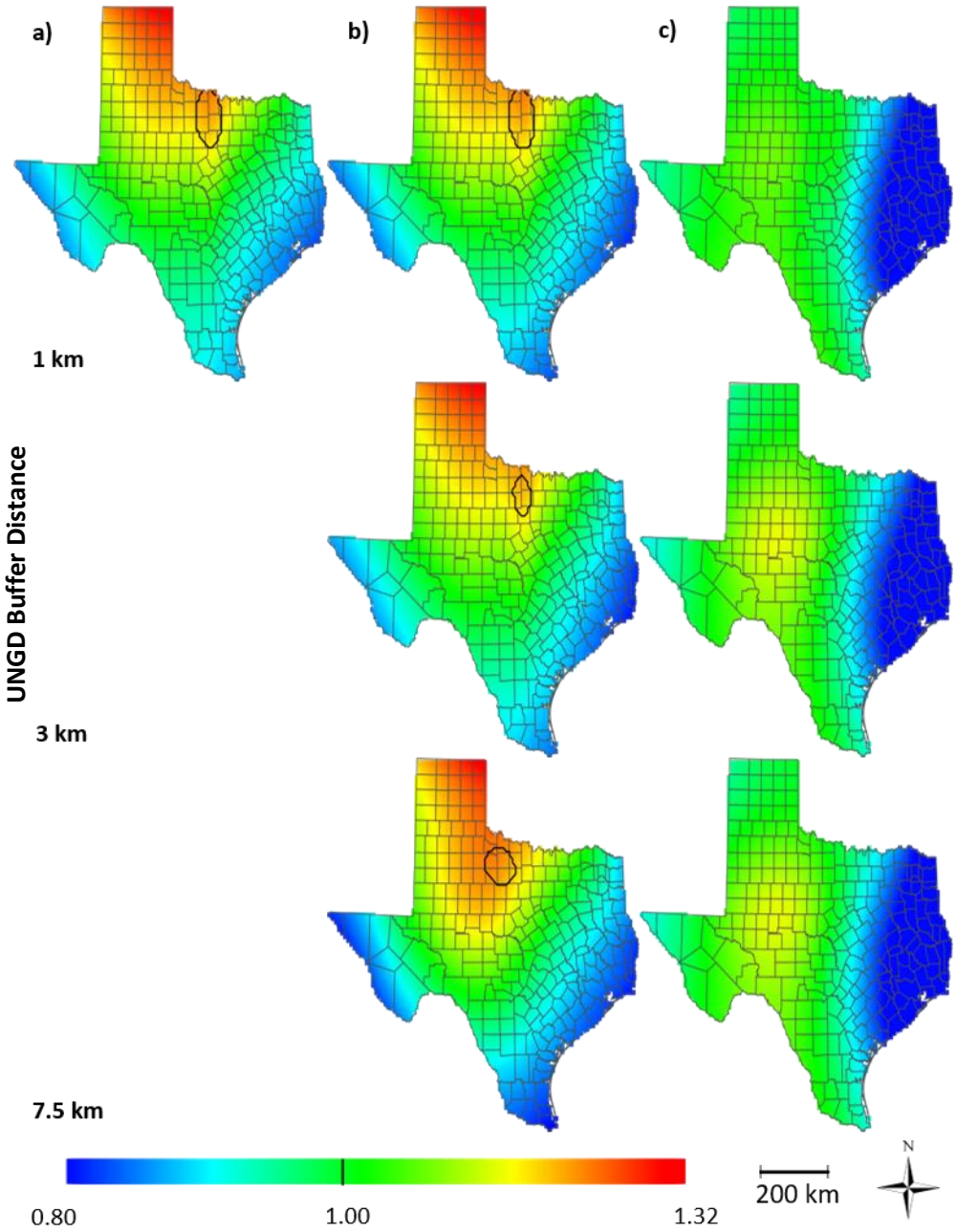
Appendix Figure C.41: Sensitivity analysis: uninsured and geographic patterns of aortic valve stenosis (AVS) and unconventional natural gas developments (UNGD) buffer radii among Texas Births, 2009-2011. (a) model 1: crude model with only location and uninsured percentage, (b) model 2: adjusted model with UNGD density, (c) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



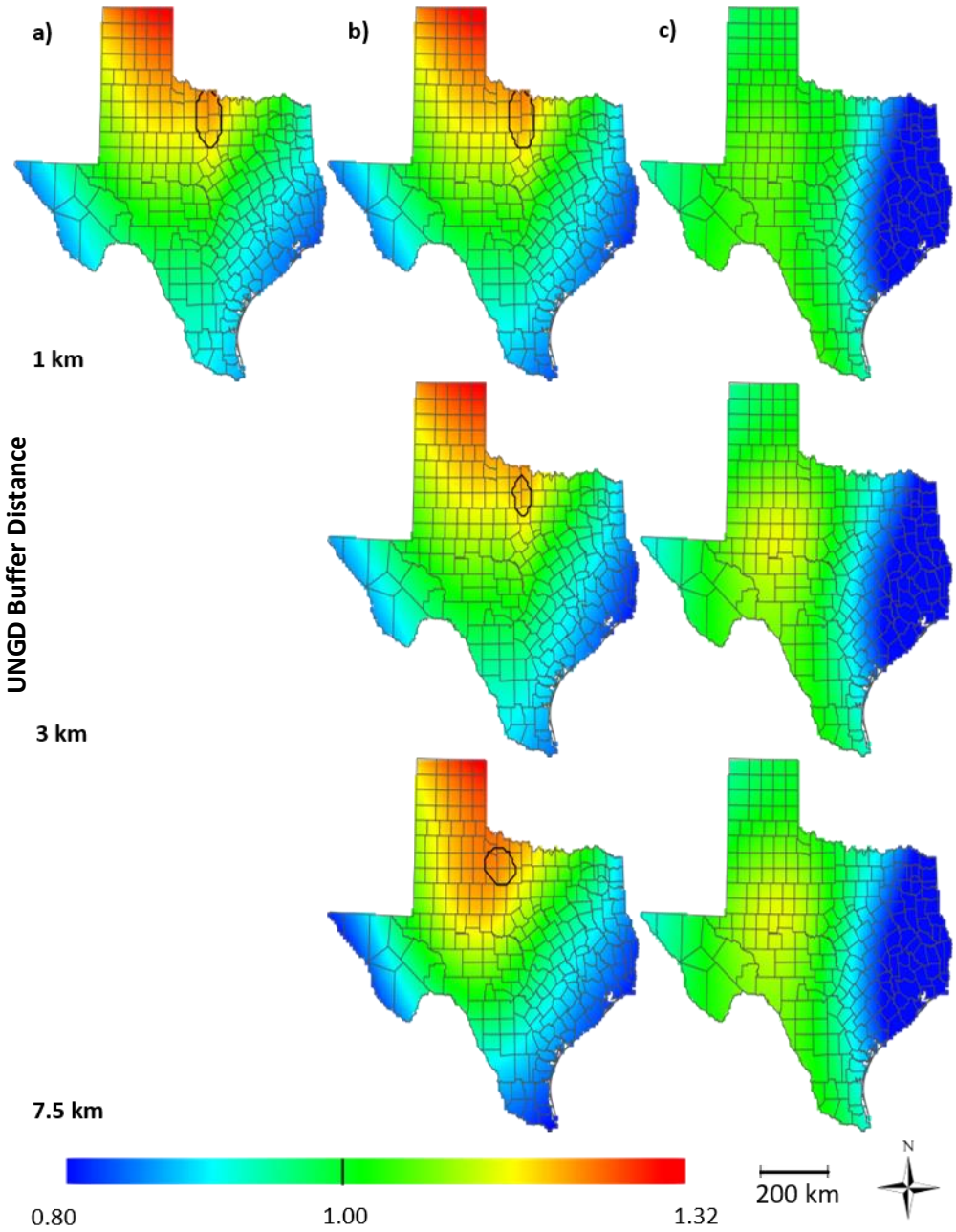
Appendix Figure C.42: Sensitivity analysis: opioid and geographic patterns of aortic valve stenosis (AVS) and unconventional natural gas developments (UNGD) buffer radii among Texas Births, 2009-2011. (a) model 1: crude model with only location and opioid prescription rates, (b) model 2: adjusted model with UNGD density, (c) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



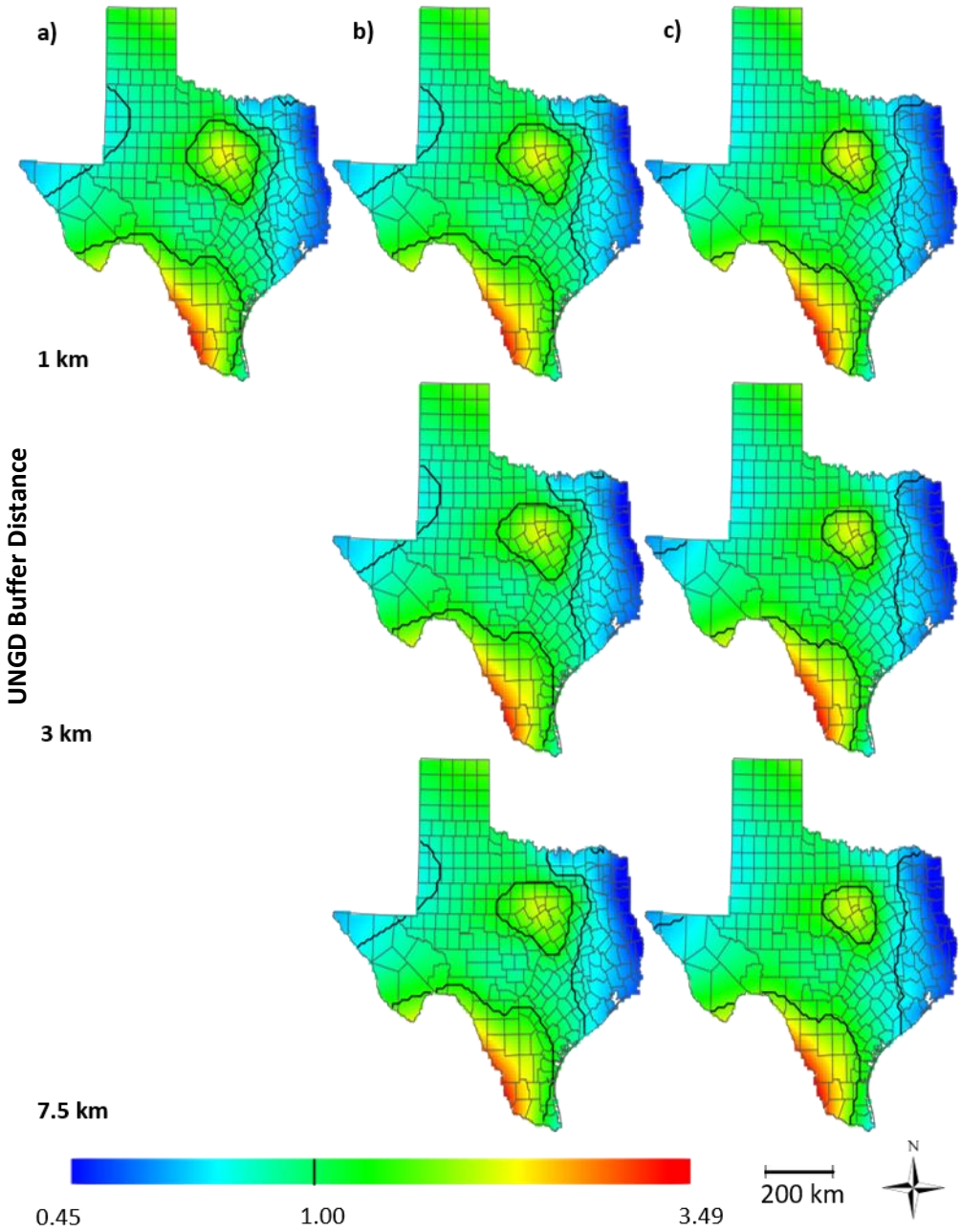
Appendix Figure C.43: Sensitivity analysis: diabetes and geographic patterns of hypoplastic left heart syndrome (HLHS) and unconventional natural gas developments (UNGD) buffer radii among Texas Births, 2009-2011. (a) model 1: crude model with only location and diabetes percentage, (b) model 2: adjusted model with UNGD density, (c) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



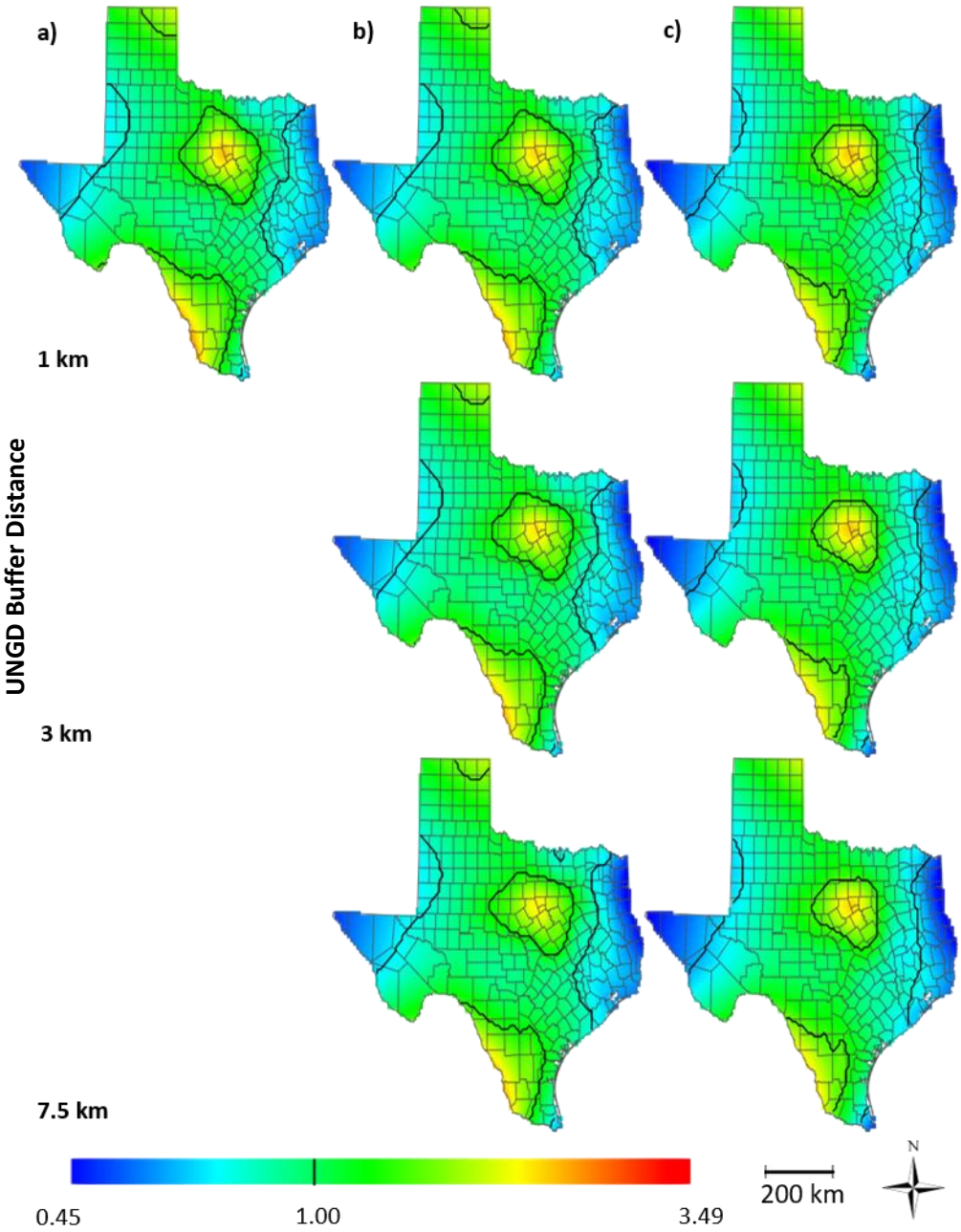
Appendix Figure C.44: Sensitivity analysis: uninsured and geographic patterns of hypoplastic left heart syndrome (HLHS) and unconventional natural gas developments (UNGD) buffer radii among Texas Births, 2009-2011. (a) model 1: crude model with only location and uninsured percentage, (b) model 2: adjusted model with UNGD density, (c) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



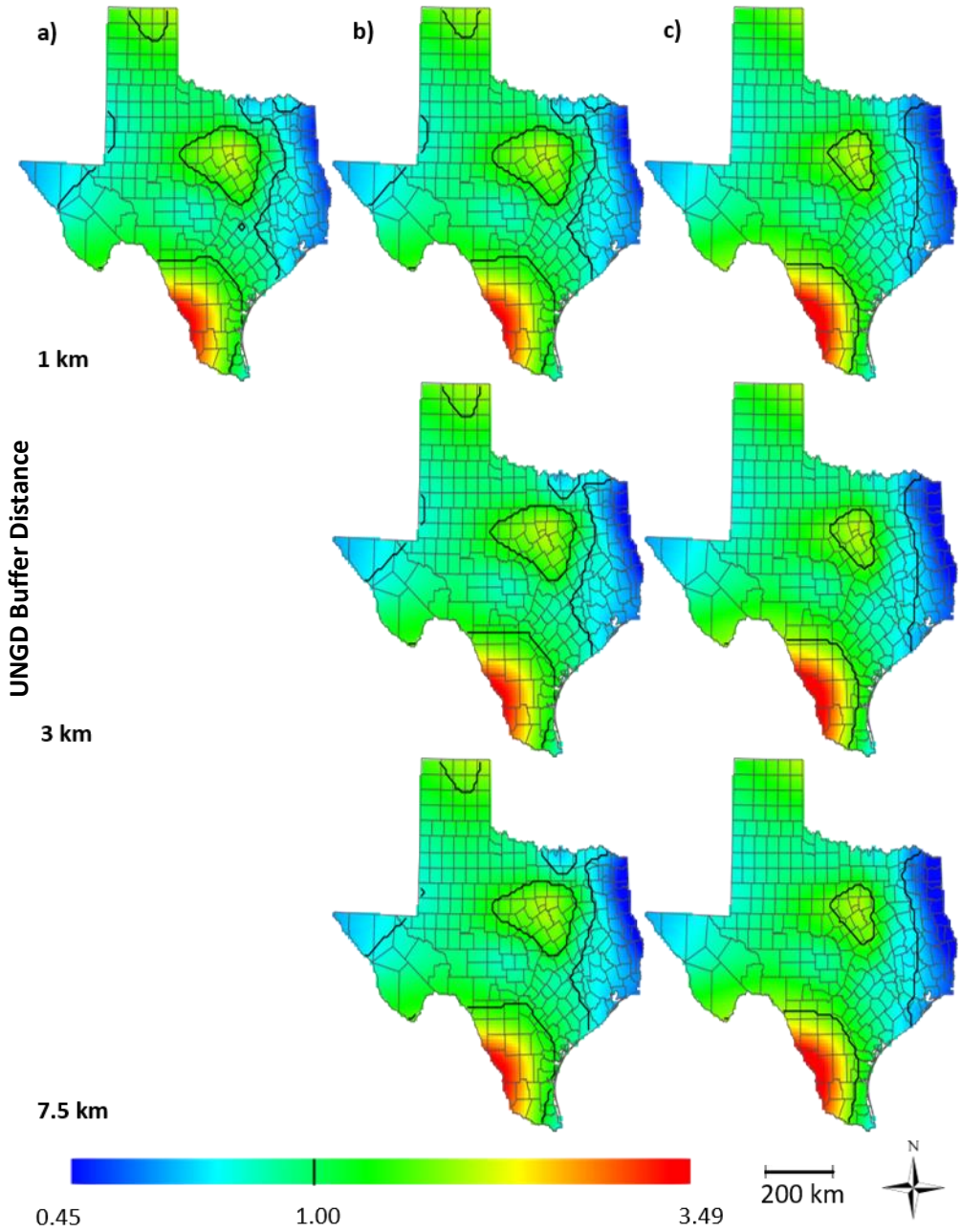
Appendix Figure C.45: Sensitivity analysis: opioid and geographic patterns of hypoplastic left heart syndrome (HLHS) and unconventional natural gas developments (UNGD) buffer radii among Texas Births, 2009-2011. (a) model 1: crude model with only location and opioid prescription rates, (b) model 2: adjusted model with UNGD density, (c) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



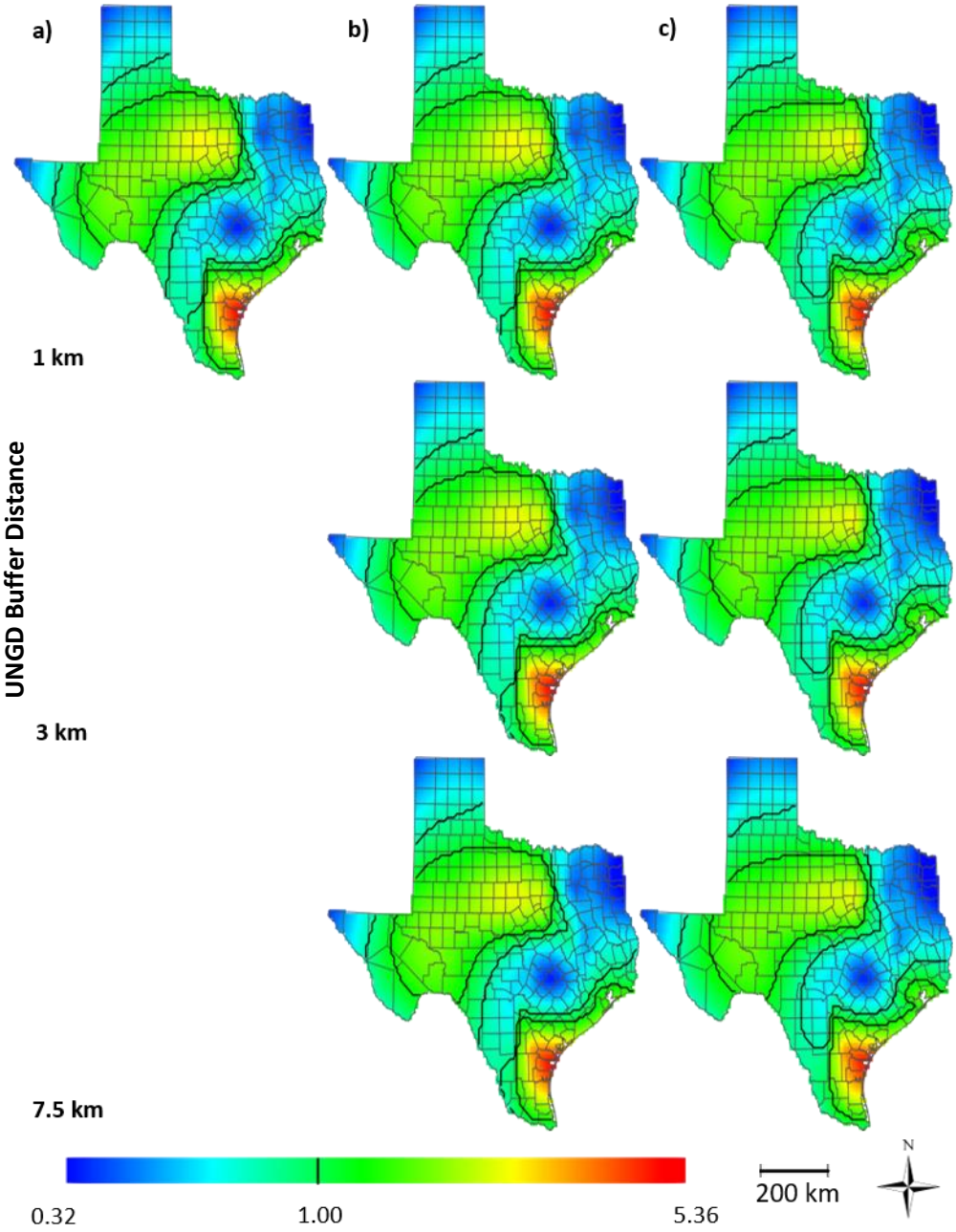
Appendix Figure C.46: Sensitivity analysis: diabetes and geographic patterns of pulmonary valve atresia/stenosis (PVAS) and unconventional natural gas developments (UNGD) buffer radii among Texas Births, 2009-2011. (a) model 1: crude model with only location and diabetes percentage, (b) model 2: adjusted model with UNGD density, (c) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



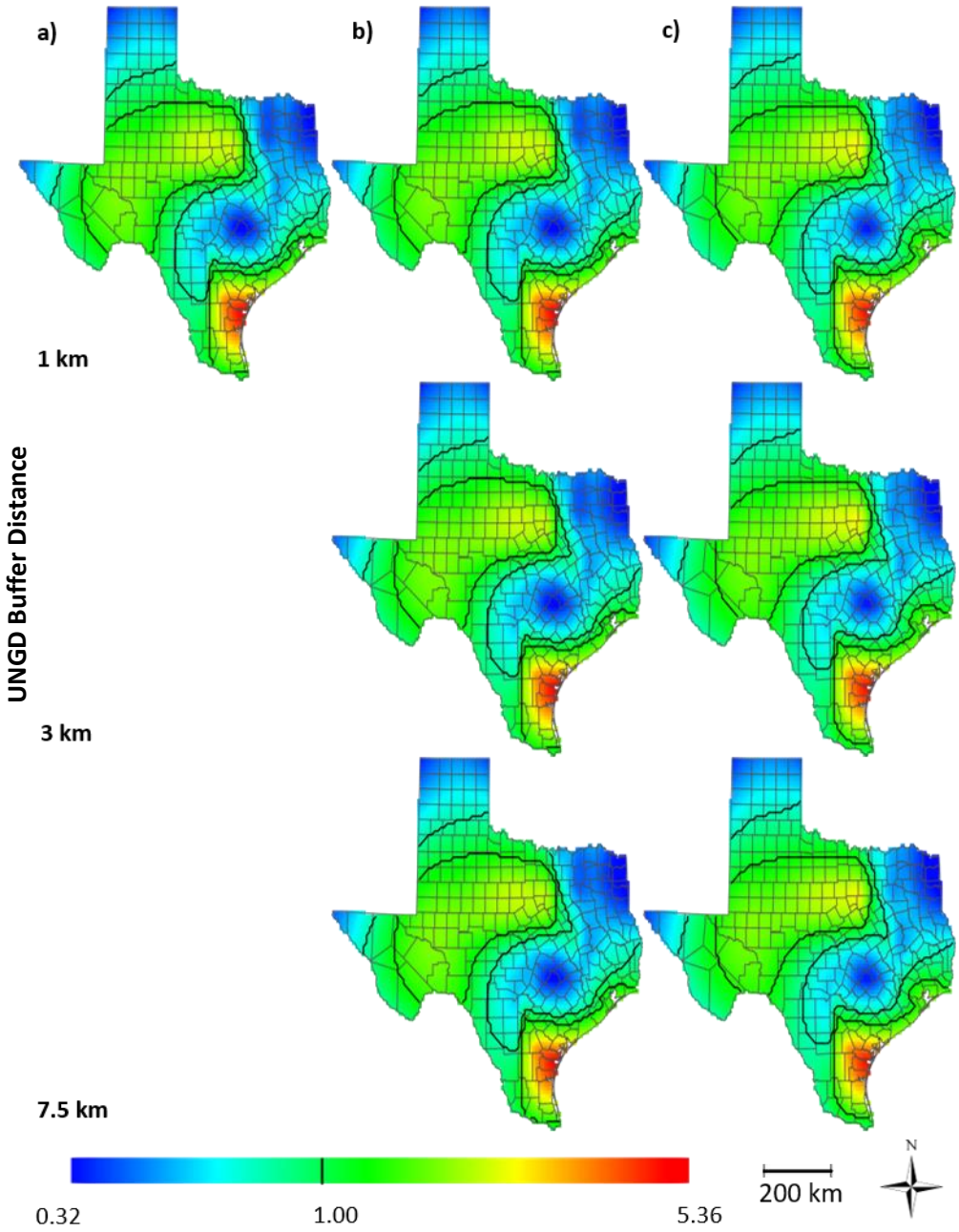
Appendix Figure C.47: Sensitivity analysis: uninsured and geographic patterns of pulmonary valve atresia/stenosis (PVAS) and unconventional natural gas developments (UNGD) buffer radii among Texas Births, 2009-2011. (a) model 1: crude model with only location and uninsured percentage, (b) model 2: adjusted model with UNGD density, (c) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



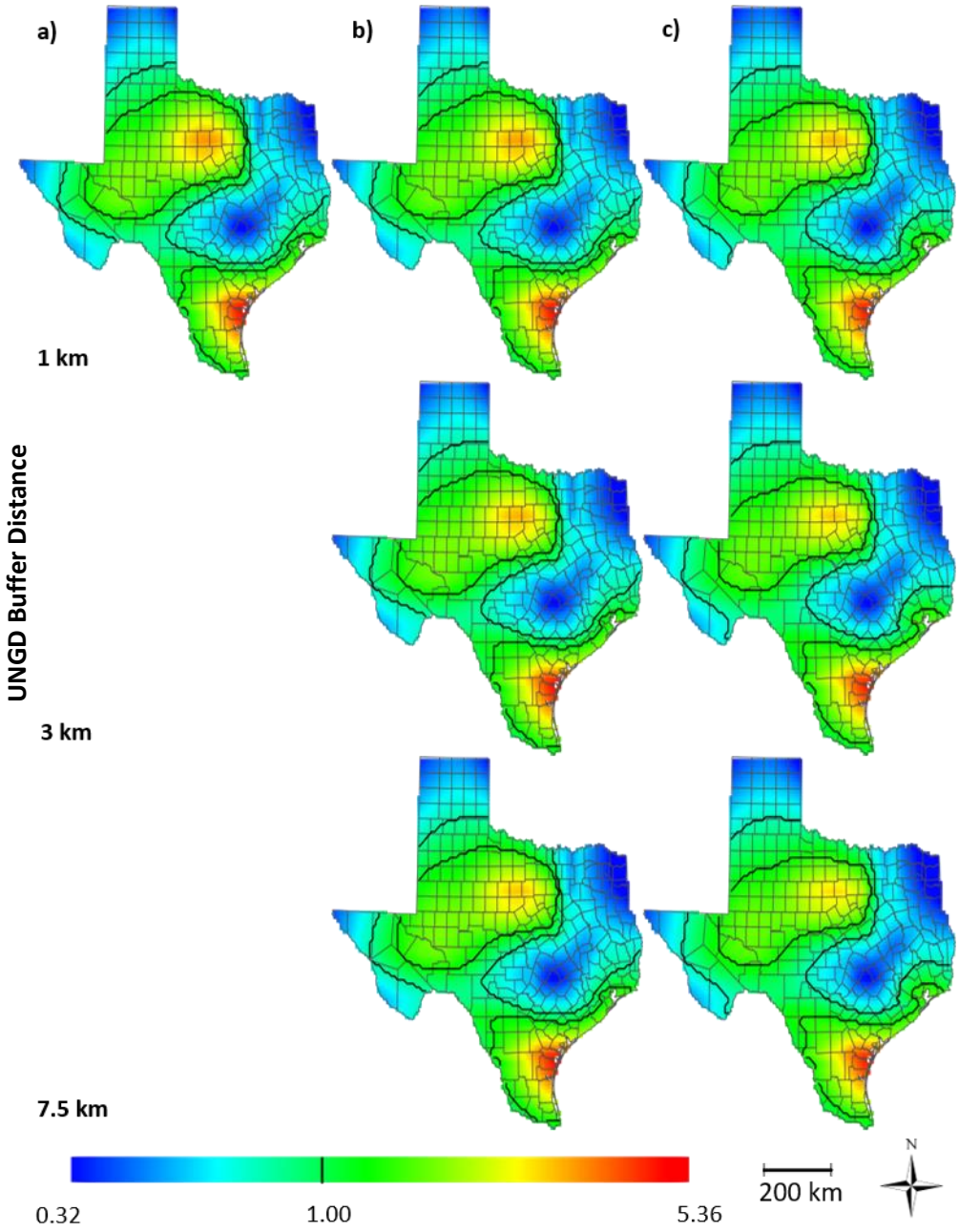
Appendix Figure C.48: Sensitivity analysis: opioid and geographic patterns of pulmonary valve atresia/stenosis (PVAS) and unconventional natural gas developments (UNGD) buffer radii among Texas Births, 2009-2011. (a) model 1: crude model with only location and opioid prescription rates, (b) model 2: adjusted model with UNGD density, (c) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



Appendix Figure C.49: Sensitivity analysis: diabetes and geographic patterns of atrial septal defects (ASD) and unconventional natural gas developments (UNGD) buffer radii among Texas Births, 2007-2009: (a) model 1: crude model with only location and diabetes percentage, (b) model 2: adjusted model with UNGD density, (c) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



Appendix Figure C.50: Sensitivity analysis: uninsured and geographic patterns of atrial septal defects (ASD) and unconventional natural gas developments (UNGD) buffer radii among Texas Births, 2007-2009: (a) model 1: crude model with only location and opioid prescription rates, (b) model 2: adjusted model with UNGD density, (c) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.



Appendix Figure C.51: Sensitivity analysis: opioid and geographic patterns of atrial septal defects (ASD) and unconventional natural gas developments (UNGD) buffer radii among Texas Births, 2007-2009: (a) model 1: crude model with only location and opioid prescription rates, (b) model 2: adjusted model with UNGD density, (c) model 4: fully adjusted model that also includes median income, urban indicator, and average daily vehicle miles traveled for trucks by county. Black contour lines indicate statistically significant areas of increased or decreased risks.