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Urban–rural residence and birth defects prevalence in Texas: a phenome-wide association study

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BACKGROUND: Some assessments indicate the prevalence of certain birth defects varies by urban–rural status. We evaluated associations between urban–rural residence and a spectrum of birth defects, using a phenome-wide association study approach in Texas, a state with large urban centers and expansive rural areas.

METHODS: Data for birth defects and livebirths during 1999–2015 were obtained from the Texas Birth Defects Registry and the Center for Health Statistics. Maternal residence was classified as urban or rural, and prevalence ratios (PR) and 95% confidence intervals (CI) were calculated for any defect and 140 specific defects by Poisson regression.

RESULTS: Overall, birth defects were less frequent in rural compared to urban counties (PR = 0.88, 95% CI: 0.87–0.89). Twelve specific defects were less prevalent in rural counties, including ventricular septal defects (VSDs; PR = 0.76, 95% CI: 0.73–0.79) and hypospadias (PR = 0.86, 95% CI: 0.82–0.89). For some birth defects, including VSDs, there was evidence of decreasing prevalence with decreasing population size.

CONCLUSIONS: In our large population-based assessment, we demonstrated that several birth defects were less prevalent in rural counties, suggesting that characteristics of urban settings may be relevant to their etiologies, diagnosis, or surveillance. Further research is needed to identify specific exposures underlying these associations.

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IMPACT:

- There are few studies of birth defects prevalence in urban versus rural settings. To address this, we investigated a comprehensive range of birth defects, including several rare defects that have not been previously studied, in a large and diverse population.
- We identified 12 structural birth defects that were less prevalent in rural areas.
- Findings suggest possible differential exposures among urban and rural women, and/or possible underdiagnosis of certain birth defects in rural areas.
- Findings highlight the need for further study of geographically referenced risk factors for birth defects, and of the completeness of birth defects ascertainment in rural areas.

INTRODUCTION

In the United States (US), birth defects affect ~3% of births each year and account for 20% of infant deaths.[1] Common birth defects include neural tube defects, congenital heart defects, and cleft lip with or without cleft palate.[1] Birth defects can develop in any stage of pregnancy; however, most develop during the first trimester.[2] More than 70% of cases are considered multifactorial, involving both genetic and environmental factors.[3]

There is some evidence that certain birth defects are associated with urban–rural residence.[4–10] For example, Langlois et al. compared different measures of urban–rural residence, and found that the prevalence of atrial septal heart defects was higher in counties with greater percentage cropland; mild cases of ventricular septal defect (VSD) but not severe cases were less prevalent in rural areas.[5] Defects including neural tube defects, cleft lip, and cleft palate, as well as other adverse pregnancy outcomes, have also been evaluated in relation to urban–rural residence.[7,8,11] These and other studies investigating the associations between urban–rural residence and birth defects have included relatively few cases or have investigated only a few specific birth defects in detail. Notably, urban–rural residence can serve as a proxy for various exposures, including pesticides, air pollution, water quality, differential access to health and social services, and variations in clinical practice. Therefore, evaluating

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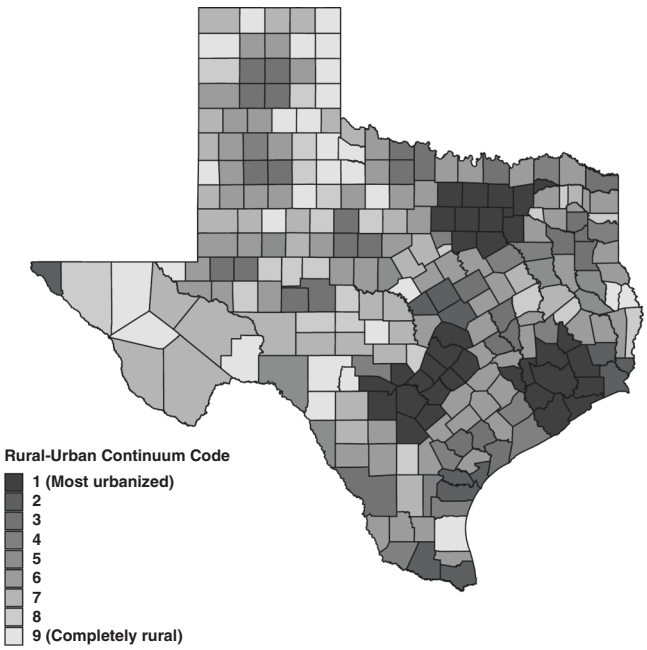

Fig. 1 2003 United States Department of Agriculture Economic Research Service Rural-Urban Continuum Codes (RUCC) for Texas counties. Lower scores (darker colors) indicate a greater degree of urbanization. In dichotomous analyses of urban vs. rural residence, urban counties were defined as those with RUCC ≤3 and rural counties were defined as those with RUCC ≥4.

the impact of urban–rural status may be informative when attempting to identify novel risk factors for birth defects.

Population-based birth defects registries collect information on birth defect cases in a defined geographic area using multiple sources, such as birth and fetal death certificates, and records from hospitals and clinics. These registries represent an underutilized resource for studying birth defects etiology. Building on this evidence and these resources, our objective was to systematically characterize the associations between urban–rural residence and a comprehensive spectrum of structural birth defects, using a phenome-wide association study (pheWAS) approach.[12–14] We conducted our assessment in Texas, a state characterized by large urban centers and expansive rural areas, which is also home to the Texas Birth Defects Registry (TBDR), one of the world's largest population-based, active birth defects surveillance systems.

METHODS

Birth defect ascertainment

Our analysis included all birth defects recorded by the TBDR that were diagnosed before delivery or within the first year of life, regardless of pregnancy outcome, from January 1, 1999 through December 31, 2015. The TBDR is an active surveillance, statewide registry, which ascertains cases from multiple sources, and records diagnoses from hospitals and other facilities where affected children are born or treated. The information is abstracted into case records that are subject to review by registry staff. TBDR links records to birth and fetal death certificates, resulting in >95% of cases being linked to their vital records.

The TBDR classifies birth defects using Centers for Disease Control (CDC)-modified British Pediatric Association (BPA) six-digit codes. These original six-digit codes were collapsed to their respective first four digits (i.e., BPA4 codes) for comparability to the International Classification of Disease, Ninth Revision (ICD-9). Exceptions to this include spina bifida (collapsed to the first three digits to combine spina bifida with and without hydrocephaly); cleft lip alone (749.1) and cleft lip with cleft palate (749.2), which were both assigned 749.1, and cleft lip with or without cleft palate; omphalocele (756.700) which was assigned 756.70; and gastroschisis (756.710), which was assigned 756.71. In addition, a dummy BPA4 code ("888.8") was created, indicating diagnosis of any monitored birth defect. The full list of birth defects included in this analysis is provided in Supplemental Table 1. Cases with two or more of the same BPA4 code were de-duplicated to ensure that they had a maximum of one of each code. Any diagnoses that were flagged as "possible" or "probable" based on qualifiers found in the medical record (~4%) were excluded from our analyses. The birth prevalence denominators were obtained from the Texas Department of State Health Services Center for Health Statistics (CHS) and consisted of all livebirths, in Texas and among Texas residents for the same time period (January 1, 1999 through December 31, 2015).

Urban–rural residence

US Department of Agriculture Rural–Urban Continuum Codes (RUCC) are defined as a multilevel county classification used to measure rurality, and assess the economic and social diversity of nonmetro areas in the US.[15] Maternal county of residence at delivery was obtained primarily from vital records and was categorized by TBDR and CHS staff as either urban or rural based on the 2003 RUCC.[16]

The 2003 RUCC use 2000 U.S. Census data to divide counties into metropolitan areas, nonmetropolitan areas, and completely rural areas (Fig. 1). Specifically, urban counties are classified as those in metropolitan areas with populations ranging from over 1 million to <250,000.[16] Rural counties are defined as an open countryside, a rural town with a population <2500 people, or an urban area with a population ranging from 2500 to 49,999, that are not part of metropolitan areas.[15] Rural counties were further divided in expanded analyses. First, we classified counties into four categories based on population density: (1) metropolitan counties; (2) nonmetropolitan counties with a population of ≥20,000; (3) nonmetropolitan counties with a population between 2500 and 19,999; and (4) completely rural counties with a population <2500. Second, we grouped counties into three categories based on their proximity to metropolitan counties: (1) metropolitan counties; (2) counties adjacent to a metropolitan county; and (3) counties not adjacent to a metropolitan county. The rationale for this approach, and its possible implications, are described in detail in the "Discussion" section.

Covariates

We obtained data on infant sex, maternal age, maternal race/ethnicity, maternal education, number of previous livebirths, and county of residence from birth and fetal death certificates. Maternal age was grouped into six categories (<20, 20–24, 25–29, 30–34, 35–39, and ≥40 years). Maternal race/ethnicity was classified as Hispanic, non-Hispanic White, non-Hispanic Black, and other. Maternal education was classified as less than high school, high school, or greater than high school. Number of previous livebirths were grouped into four categories (0, 1, 2, or ≥3).

Statistical analysis

Distributions of maternal characteristics among cases and all livebirths were summarized using counts and percentages. Birth prevalence per 10,000 livebirths was estimated for each birth defect (i.e., each BPA4 code) among offspring by urban–rural residence.

We computed crude and multivariable Poisson models to estimate the prevalence ratio (PR) and 95% confidence intervals (CI) for the index birth defect among offspring by urban–rural residence. All multivariable models were adjusted for the following potential confounders: maternal age, maternal race/ethnicity, maternal education, and number of previous livebirths, as these factors are associated with either birth defect prevalence or urban–rural residence.[6,17] Only those BPA4 coded structural birth defects (BPA4 codes 740.0–759.9) with ≥50 total cases and ≥10 cases born to women residing in rural areas were included in our analyses.

Prior to analysis, data were randomly divided into a discovery partition, including 60% of the data, and a replication partition, which included the remaining 40% of the data. Models were first computed in the discovery partition and statistical significance was evaluated using a Bonferroni-adjusted threshold of $p < 3.55 \times 10^{-4}$. This was derived by dividing the desired family-wise error rate of $\alpha = 0.05$ by the number of association tests to be performed (i.e., the number of included birth defects; $n = 141$). Birth defects identified as candidates in the discovery partition were re-evaluated in the replication partition and declared statistically significant if they were associated with urban–rural residence at $p < 0.05$, and the direction of effect was the same. This two-stage modeling approach reduces the possibility of type I errors. For these birth defects, we present PRs and 95% CIs estimated in the pooled dataset. For replicated birth

Table 1. Demographic characteristics of livebirths and birth defect cases in Texas, 1999–2015.

	Total livebirths (*N* = 6,543,387) (%)	Birth defects cases (*N* = 304,621) (%)
Maternal age (yrs)		
10–19	831,365 (12.7)	36,245 (11.9)
20–24	1,769,279 (27.0)	77,171 (25.3)
25–29	1,784,385 (27.3)	79,903 (26.2)
30–34	1,387,169 (21.2)	66,081 (21.7)
35–39	632,649 (9.7)	35,202 (11.6)
≥40	138,010 (2.1)	9997 (3.3)
Maternal race/ethnicity		
Hispanic	3,165,219 (48.4)	144,452 (47.5)
Non-Hispanic White	2,328,963 (35.6)	112,837 (37.1)
Non-Hispanic Black	738,796 (11.3)	33,733 (11.1)
Other	302,756 (4.6)	13,385 (4.4)
Maternal education		
<High school	1,841,020 (28.3)	85,824 (28.8)
High school	1,809,367 (27.8)	79,841 (26.8)
>High school	2,849,877 (43.8)	132,471 (44.4)
Previous livebirths		
0	2,490,880 (38.6)	120,918 (40.8)
1	2,007,439 (31.1)	86,992 (29.3)
2	1,165,476 (18.1)	51,358 (17.3)
≥3	786,727 (12.2)	37,387 (12.6)
Birth year		
1999–2004	2,208,758 (33.8)	80,212 (26.3)
2005–2009	1,999,140 (30.6)	90,870 (29.8)
2010–2015	2,335,489 (35.7)	133,539 (43.8)
County of residence		
Urban	5,846,046 (89.3)	276,374 (90.7)
Rural	697,341 (10.7)	28,247 (9.3)
Population size		
Metropolitan counties	5,846,046 (89.3)	276,374 (90.7)
Nonmetro with population of ≥20,00	251,673 (3.8)	10,196 (3.3)
Nonmetro with pop between 2500–19,999	405,310 (6.2)	16,561 (5.4)
Nonmetro with ≤2500	40,358 (0.6)	1490 (0.5)
Adjacency to metropolitan counties		
Metropolitan counties	5,846,046 (89.3)	276,374 (90.7)
Counties adjacent to metro counties	478,045 (7.3)	20,318 (6.7)
Counties not adjacent to metro counties	219,296 (3.4)	7929 (2.6)

defects, we performed additional analyses based on population size and proximity to metropolitan counties. All analyses were performed in R v.3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

This study was approved by the Baylor College of Medicine and Texas Department of State Health Services Institutional Review Boards (IRB), IRB numbers H-31777 and 18-046, respectively, and performed in accordance with the principles of the Declaration of Helsinki. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines were followed.[18]

RESULTS

Our assessment included 6,543,397 livebirths and 964,054 birth defects diagnosed in 304,621 offspring (Table 1 and Supplemental Table 2). Among the total population, 5,846,046 (89.3%) children were born to mothers residing in urban counties and 697,341 (10.7%) were born to mothers in rural counties. Among case mothers, 276,374 (90.7%) resided in urban counties, whereas 28,247 (9.3%) resided in rural counties.

Birth defects prevalence according to urban versus rural residence

In the discovery partition, among the 141 phenotypes evaluated, urban–rural residence was associated with 18 birth defects at the Bonferroni threshold of $p < 3.55 \times 10^{-4}$ (Fig. 2, upper panel, and Supplemental Table 1). Increased prevalence of cleft lip without cleft palate and conjoined twins were observed for children born to mothers residing in rural compared to urban counties (PR = 1.21, Bonferroni-adjusted CI: 1.03–1.43; PR = 2.54, Bonferroni-adjusted CI: 1.02–6.34, respectively). Prevalence estimates for the remaining 16 birth defects associated with urban–rural residence were lower for children born in rural counties, ranging from 0.61 (Bonferroni-adjusted CI: 0.48-0.78) for anomalies of the cervix, vagina, and external female genitalia to 0.89 (Bonferroni-adjusted CI: 0.84–0.94) for ostium secundum type atrial septal defects (ASDs).

Replication and pooled analyses

Thirteen of 18 phenotypes identified in the discovery partition, including any monitored birth defect, were associated with urban–rural residence in the same direction at $p < 0.05$ in the replication partition (Fig. 2, lower panel, and Supplemental Table 3). Any monitored birth defect was less prevalent in rural compared to urban counties (PR = 0.87, 95% CI: 0.86–0.89). In addition, the 12 specific structural birth defects that replicated were less likely to occur among children born to mothers residing in rural counties compared to urban counties. The observed PRs ranged from 0.71 (95% CI: 0.66–0.76) for anomalies of the skull, face, and jaw (e.g., depressions in the skull and congenital deviation of the nasal septum) to 0.91 (95% CI: 0.88–0.95) for ostium secundum type ASD.

To maximize precision, PRs and 95% CIs were calculated for birth defects that replicated in the pooled dataset. Adjusted PRs and 95% CIs for the 13 replicated phenotypes are presented in Table 2. These results were similar to the replication analysis but with improved precision. The PR of any monitored birth defect was 0.88 (95% CI: 0.87–0.89) for children born to mothers residing in rural compared to urban counties. Similar to the replication analysis, all birth defects associated with urban–rural residence were less prevalent in rural compared to urban counties. The strongest association observed was for anomalies of the cervix, vagina, and external female genitalia (PR = 0.66, 95% CI: 0.60–0.73).

Birth defects prevalence according to population size and proximity to metropolitan areas

For replicated birth defects, we also performed two additional analyses in the pooled data to determine whether birth defect prevalence varied by county population size or adjacency to metropolitan counties. In the analysis based on population size, we found that the prevalence of certain birth defects (e.g., ostium secundum type ASD and patent ductus arteriosus) decreased with decreasing county population while others, such as microcephalus and anomalies of the skin increased with decreasing population (Table 3). In the analysis based on adjacency to metropolitan counties, we found that birth defects prevalence decreased as

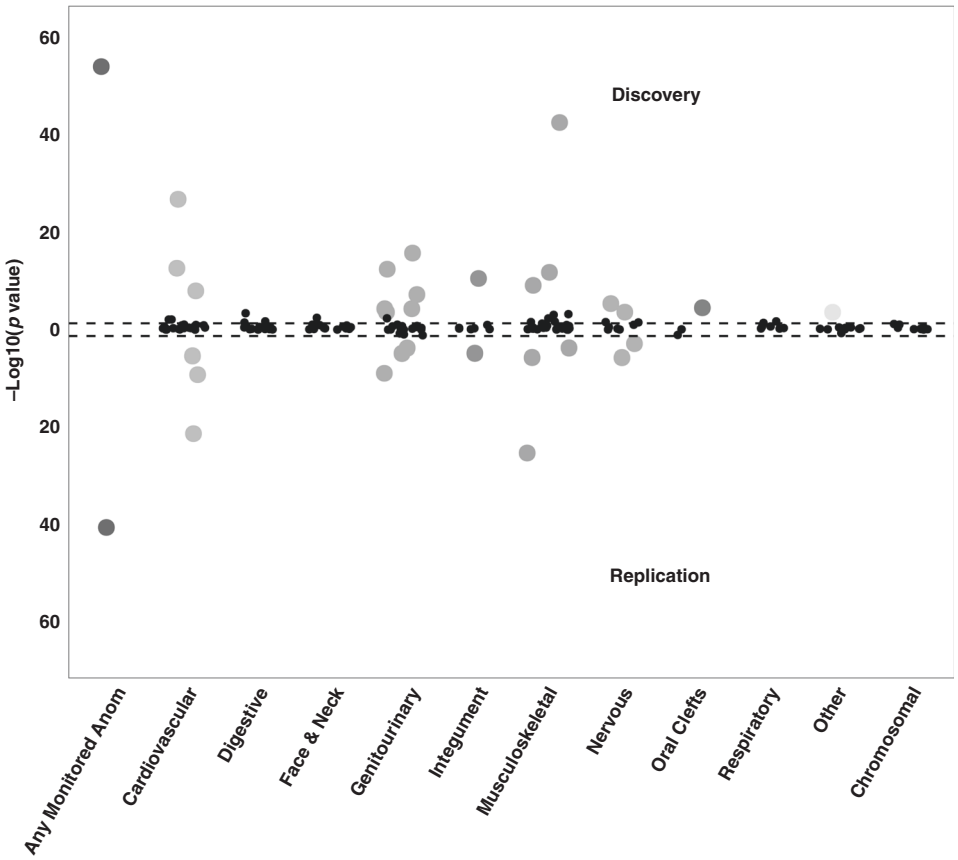

Fig. 2 Associations between urban–rural residence and birth defects. Birth defects associated with urban–rural residence at $p < 3.55 \times 10^{-4}$ in discovery (upper panel; $n = 18$) were retested in replication (Fig. 2, lower panel). Those associated with urban–rural residence in replication at $p < 0.05$ were declared significant ($n = 13$).

Table 2. Adjusted prevalence ratios and 95% confidence intervals for the associations between maternal rural compared to urban residence and replicated birth defects, estimated among all study subjects in Texas from 1999 to 2015.

BPA4 code	Birth defect	Urban cases	Rural cases	PR (95% CI)[a]
742.1	Microcephalus	7175	684	0.82 (0.76, 0.89)
742.4	Other specified anomalies of the brain	10,646	1003	0.80 (0.75, 0.86)
745.4	Ventricular septal defect	35,048	3053	0.76 (0.73, 0.79)
745.5	Ostium secundum type atrial septal defect	69,737	7244	0.90 (0.88, 0.92)
747.0	Patent ductus arteriosus (PDA)	34,850	3388	0.86 (0.83, 0.89)
752.4	Anomalies of cervix, vagina, and external female genitalia	5611	415	0.66 (0.60, 0.73)
752.6	Hypospadias, epispadias, and congenital chordee	22,244	2245	0.86 (0.82, 0.89)
753.2	Obstructive defects of renal pelvis and ureter	26,176	2426	0.80 (0.77, 0.84)
754.0	Certain anomalies of skull, face, and jaw	31,477	2522	0.70 (0.67, 0.73)
755.6	Other anomalies of lower limb, including pelvic girdle	11,308	1007	0.79 (0.74, 0.84)
756.8	Other specified anomalies of muscle, tendon, and connective tissue	9725	842	0.74 (0.69, 0.79)
757.3	Other specified anomalies of skin	5680	438	0.67 (0.61, 0.74)
888.8	Any monitored birth defect	276,374	28,247	0.88 (0.87, 0.89)

[a]Adjusted for maternal age, race/ethnicity, education, and number of previous livebirths.
PR prevalence ratio.

distance to a metropolitan area increased, with the exception of anomalies of the lower limb (Table 4).

Isolated versus non-isolated birth defects

In addition, we investigated replicated birth defects separately among isolated versus non-isolated cases in the pooled dataset. Among isolated cases, all replicated birth defects remained associated with urban–rural residence at $p < 0.05$ (Supplemental Table 4). In non-isolated cases, all replicated birth defects except for microcephalus were significant at $p < 0.05$ and showed the same direction of effect (Supplemental Table 5).

Table 3. Prevalence ratios for birth defects associated with urban–rural residence, in Texas from 1999 to 2015, by population size (relative to metropolitan counties).

BPA4 code	Birth defect	Nonmetropolitan counties with a population of 20,000 or more adjusted PR (95% CI)[a]	Nonmetropolitan counties with a population between 2500 and 19,999 adjusted PR (95% CI)[a]	Completely rural counties with a population <2500 adjusted PR (95% CI)[a]
742.1	Microcephalus	0.76 (0.67, 0.87)	0.85 (0.77, 0.94)	0.98 (0.73, 1.31)
742.4	Other specified anomalies of the brain	0.73 (0.65, 0.81)	0.84 (0.78, 0.92)	0.86 (0.68, 1.10)
745.4	Ventricular septal defect	0.75 (0.71, 0.80)	0.77 (0.74, 0.81)	0.66 (0.56, 0.78)
745.5	Ostium secundum type atrial septal defect	0.95 (0.91, 0.99)	0.88 (0.86, 0.91)	0.71 (0.64, 0.79)
747.0	Patent ductus arteriosus (PDA)	0.87 (0.83, 0.93)	0.86 (0.82, 0.90)	0.75 (0.65, 0.88)
752.4	Anomalies of the cervix, vagina, and external female genitalia	0.60 (0.51, 0.71)	0.70 (0.61, 0.79)	0.74 (0.50, 1.11)
752.6	Hypospadias, epispadias, and congenital chordee	0.89 (0.83, 0.96)	0.82 (0.78, 0.87)	0.93 (0.80, 1.09)
753.2	Obstructive defects of renal pelvis and ureter	0.81 (0.76, 0.87)	0.79 (0.75, 0.84)	0.86 (0.73, 1.01)
754.0	Certain anomalies of skull, face, and jaw	0.69 (0.64, 0.73)	0.72 (0.68, 0.75)	0.57 (0.48, 0.69)
755.6	Other anomalies of lower limb, including pelvic girdle	0.79 (0.71, 0.88)	0.79 (0.72, 0.85)	0.84 (0.65, 1.07)
756.8	Other specified anomalies of muscle, tendon, and conn tissue	0.76 (0.67, 0.85)	0.75 (0.68, 0.82)	0.49 (0.35, 0.69)
757.3	Other specified anomalies of skin	0.64 (0.55, 0.75)	0.68 (0.60, 0.77)	0.87 (0.61, 1.23)
888.8	Any monitored congenital anomaly	0.88 (0.86, 0.90)	0.89 (0.87, 0.90)	0.80 (0.76, 0.84)

[a]Adjusted for maternal age, race/ethnicity, education, and number of previous livebirths.
PR prevalence ratio.

DISCUSSION

This study investigated a comprehensive range of birth defects in relation to mother's urban–rural residence. Overall, we found that several birth defects were associated with urban–rural residence. A range of factors, including social, structural, environmental, or any combination thereof, could influence the observed differences. The pheWAS approach allowed us to confirm previous reported associations and identify novel ones. Our findings provide evidence of decreased prevalence of certain birth defects among offspring born to mothers residing in rural counties compared to urban counties. In particular, we observed lower prevalence estimates for most replicated birth defects in counties that did not border major urban areas. Several studies evaluated the role of urban–rural residence on the prevalence of birth defects. For example, Langlois et al. studied the occurrence of septal heart defects using TBDR data for 1999–2003, which were also included in our study, and found that VSDs (particularly mild cases) were less prevalent in rural areas (PR = 0.85, 95% CI: 0.76–0.94) compared to metropolitan areas,[5] which is consistent with our findings. However, we also found that ostium secundum type ASDs were less prevalent in rural counties compared to urban counties (PR = 0.90, 95% CI: 0.88–0.92), which was not reported in the study by Langlois et al. This could be in part to the larger sample size of our study. In another assessment by Luben et al., investigators found that encephalocele (a neural tube defect) was more frequent in rural areas.[8] While this association was not seen in our assessment, we found microcephalus was less prevalent in offspring of mothers residing in rural counties compared to urban counties.

One consistent finding in our assessment was the lower prevalence of certain birth defects in rural counties, including congenital heart defects and limb defects, that have been implicated in studies of urban air pollution and birth defects.[19–22] Rural counties experience fewer unhealthy air quality days compared to metropolitan counties.[19] This is likely because of the abundance of particulate matter (PM), nitrogen dioxide, and ozone present in urban areas.[19,23] Greater concentrations of several pollutants associated with birth defects have been demonstrated in urban settings compared to rural areas. For instance, sulfur dioxide exposure has been found to increase the risk of VSDs and PM_{10} exposure has been associated with increased risk of ASDs.[24] A meta-analysis conducted in 2020 found similar associations between pollutant exposure, including PM_{10} and ozone, and the increased risk of ASDs.[20] In addition, a case–control study in Taiwan found an association between exposure to sulfur dioxide in outdoor air during the first trimester of pregnancy and specific limb reductions, such as reduction deformities of limbs.[9] This is consistent with our finding related to anomalies of the lower limb.

In our study, we found a lower prevalence of male genitourinary defects (e.g., hypospadias) in rural compared to urban counties. Although hypospadias was rated as having low diagnostic heterogeneity in a survey of clinical geneticists,[25] differences in diagnosis and reporting for hypospadias, or other genitourinary defects, between urban and rural counties may explain our finding. In addition, exposure to endocrine disrupting chemicals, such as pesticides, in utero have been evaluated in several studies of hypospadias.[22,26–28] Rocheleau et al. conducted a meta-analysis and found an increased risk of hypospadias associated with both maternal and paternal occupational exposure to pesticides or agricultural work (36 and 19% increased risk, respectively).[26] Compared to agricultural areas, which are typically rural, urban areas see a higher frequency of insecticides and herbicides in streams and shallow ground water, both from current and past use.[29] There are multiple pesticide exposure pathways in the urban environment, as pesticides are used for maintenance of roadsides and lawns, esthetic values of sports fields, and indoor pest control.[29,30] Pesticide exposure among urban women may be important in the etiology of male genitourinary defects, although further research will be required to evaluate this hypothesis.

Table 4. Prevalence ratios for birth defects associated with urban–rural residence, in nonmetropolitan counties adjacent versus not adjacent to metropolitan counties, Texas, 1999–2015.

BPA4 code	Birth defect	Counties adjacent to metropolitan counties adjusted PR (95% CI)[a]	Counties not adjacent to metropolitan counties adjusted PR (95% CI)[a]
742.1	Microcephalus	0.85 (0.78, 0.94)	0.75 (0.65, 0.87)
742.4	Other specified anomalies of the brain	0.84 (0.78, 0.90)	0.73 (0.65, 0.82)
745.4	Ventricular septal defect	0.82 (0.79, 0.86)	0.63 (0.58, 0.67)
745.5	Ostium secundum type atrial septal defect	0.97 (0.94, 0.99)	0.76 (0.72, 0.79)
747.0	Patent ductus arteriosus (PDA)	0.92 (0.89, 0.96)	0.72 (0.68, 0.77)
752.4	Anomalies of the cervix, vagina, and external female genitalia	0.69 (0.61, 0.77)	0.62 (0.52, 0.74)
752.6	Hypospadias, epispadias, and congenital chordee	0.89 (0.85, 0.94)	0.77 (0.71, 0.83)
753.2	Obstructive defects of renal pelvis and ureter	0.85 (0.81, 0.89)	0.71 (0.66, 0.77)
754.0	Certain anomalies of skull, face, and jaw	0.74 (0.71, 0.78)	0.60 (0.56, 0.65)
755.6	Other anomalies of lower limb, including pelvic girdle	0.78 (0.82, 0.84)	0.81 (0.73, 0.91)
756.8	Other specified anomalies of muscle, tendon, and conn tissue	0.81 (0.75, 0.88)	0.56 (0.49, 0.65)
757.3	Other specified anomalies of skin	0.78 (0.70, 0.87)	0.45 (0.37, 0.55)
888.8	Any monitored congenital anomaly	0.92 (0.90, 0.93)	0.79 (0.77, 0.81)

[a]Adjusted for maternal age, race/ethnicity, education, and number of previous livebirths.
PR prevalence ratio.

Rurality is difficult to define as it is a multifaceted concept with no universal meaning, and it can be defined differently based upon which definition of rurality is used and for the purpose of its use.[31] The proximity of a rural county to a larger metropolitan area may influence the health of its residentnonmetro s. To account for this, we evaluated replicated birth defects in nonmetropolitan counties adjacent versus not adjacent to metropolitan counties (Table 4). We found that the prevalence of the replicated birth defects tended to decrease among counties not adjacent to a metropolitan county.

Some of these results may be explained by differences in access to or quality of healthcare for women in urban versus rural counties. For example, limited access to prenatal care among women in rural counties may lead to increased birth defects prevalence if it is associated with, for example, lower rates of folic acid supplementation or poorer management of chronic health conditions, such as diabetes or hypertension. Conversely, it is possible that there could be less extensive prenatal testing, or underdiagnosis/under recording of certain defects in rural hospitals and birthing facilities, which may lack capacity to diagnose or treat birth defects. Such differences may result in lower prevalence estimates among offspring of women living in rural counties.

However, we reported significant associations for some birth defects that were broadly classified by clinical geneticists as having low diagnostic variability, including anomalies of the lower limbs and hypospadias, epispadias, and congenital chordee.[25] Findings for those defects are therefore unlikely to be explained by differential diagnosis or reporting in rural settings. Underdiagnosis of certain birth defects is concerning for public health practice as delayed treatment for children with these defects can affect their health outcomes and quality of life.

The definition of an urban versus rural county is central to the present study. Different measures can be used; typically, these include RUCC, Rural–Urban Commuting Areas (RUCA), and Urban Influence Codes (UIC). RUCA uses a census tract-based classification system to subdivide a county into different levels of rurality, while UIC distinguishes metropolitan counties by population size and nonmetropolitan counties by size of the largest city and proximity to metro and micropolitan areas. As counties in Texas can be large and some areas in a given county may be more heavily urbanized than others, any county-based classification of urban or rural may not accurately reflect a pregnant individual's exposure history. Nonetheless, we opted to use RUCC opposed to RUCA as >10% of subjects were missing census tract information, while we had appropriate data to assign RUCC for all subjects. UIC was not used as previous literature shows it is more useful to consider how geographic context affects economic development and that RUCC tends to be more informative.[6,32] RUCC are updated every ten years. Our study solely used 2003 RUCC, as they were closest in time to the majority of livebirths. Conceivably, access to healthcare may have increased for residents of counties that urbanized during the study period, and exposures in the physical environment (i.e., air and water) may also have changed. This could lead to an increase in birth defects prevalence, due to increased diagnosis and reporting, true increases in prevalence related to changing exposures among the population, or both. Conversely, in counties in which the population decreased, access to prenatal and neonatal care may have become more limited, leading to a drop in reported birth defects prevalence. As <5% of Texas counties changed from urban to rural, or vice versa, when comparing 2003 and 2013 RUCC scores, we anticipate that exposure misclassification related to the exclusive use of 2003 RUCC was minimal.

A key strength of this study is its large and diverse sample. This allowed us to investigate associations between urban–rural residence and a comprehensive range of birth defects, including several rare defects, which has not been done before. Texas has both large urban and rural populations that are racially, ethnically, and geographically diverse and covered by a single active population-based surveillance system. Rural areas in Texas are diverse with respect to geography, primary industry, race/

ethnicity, and other key factors. Further research will be required to identify specific county-level factors associated with birth defects prevalence. We therefore expect our findings to be generalizable to the US population. Another strength is the use of RUCC, which are used to classify all counties in the US,[16] and which was available for all births and cases in the analysis. Therefore, we were able to maximize sample size and retain rare birth defects in our analysis, which may have been dropped otherwise.

Our study should be interpreted in light of its limitations. We collapsed CDC-BPA codes to BPA4 codes for comparability with ICD-9 codes, to reduce multiple testing burden, and to allow the inclusion of rare phenotypes. However, we acknowledge this approach may increase heterogeneity, as it often aggregated data on multiple defects. In addition, we do not know how long a mother has resided at their current address prior to delivery; therefore, we cannot be assured that address at delivery reflects residence during critical developmental periods. However, research in Texas indicates maternal residential mobility among cases and controls is similar and within short distances; thus, it is highly unlikely that women moved between counties during their pregnancy or that residential mobility would have been differential in nature so this likely did not bias our findings.[33] Finally, although we adjusted for several demographic characteristics, there may be remaining differences between urban and rural populations for which we did not adjust.

CONCLUSION

This study investigated a comprehensive range of birth defects in relation to mother's residence. In this large population-based assessment, we identified 12 structural birth defects that were less prevalent in rural areas, some of which have not been reported previously. As compared to urban women, rural women may experience differential access to, utilization of, or quality of healthcare. Our findings suggest possible underdiagnosis of certain birth defects in rural areas, or differences in access to healthcare resources, which are of concern for rural mothers and children. In addition, differential physical environmental exposures, such as air and water quality, are possible explanations. Additional research into whether differences in birth defects prevalence may be explained by differences in the healthcare experience of rural women and their offspring, or differences in the physical environment in rural counties is warranted. In addition, comparing different measures (RUCC, RUCA, and UIC) in the same analysis can help better understand how the choice of measure influences results. Such research could inform public health policy, as well as birth defects surveillance, diagnosis, and treatment.

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AUTHOR CONTRIBUTIONS

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COMPETING INTERESTS

The authors declare no competing interests.

CONSENT STATEMENT

Patient consent was not required.

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