#### **ORIGINAL ARTICLE**



# Going the distance: Associations between adverse birth outcomes and obstetric provider distances for adolescent pregnancies in South Carolina

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#### Abstract

**Purpose:** Distances to obstetric care providers are a persistent concern, especially for rural pregnant adolescents. Births to adolescents are disproportionately affected by adverse birth outcomes (ABOs), yet little is known regarding how driving distances may impact ABOs. This study examines the association between driving distances to obstetric providers and ABOs among adolescent mothers in South Carolina.

**Methods:** This retrospective cross-sectional study derived ZIP Code-level birth statistics from mothers aged 10–19 in South Carolina using 2013–2017 statewide birth certificate data. ABOs included preterm birth and/or low birthweight. Provider distance was calculated between an obstetric provider's ZIP Code tabulated area (ZCTA) centroid and a maternal resident's ZCTA centroid. Descriptive statistics and weighted generalized linear regression were conducted.

**Results:** Mean provider distances to obstetric providers were similar between urban (11.76 miles) and rural adolescent mothers (12.04 miles). An increase in provider distance, on average, was associated with a decrease in ABO rates (-0.79, p=.0038); however, rural–urban differences were found. Living in a rural ZCTA was associated with a decrease in ABOs (4.94%, p=.0043). Urban ZCTAs showed a U-shaped association with provider distance, with ABO rates decreasing until approximately 17 miles away from a provider and then increasing.

**Conclusion:** Rural adolescent mothers with greater distance to providers had lower ABO rates, while, in urban ZCTAs, provider distance over 17 miles was associated with higher ABO rates. Understanding what mitigates the effects of driving distance on ABOs in rural South Carolina would help inform future policy planning in underserved communities.

#### **KEYWORDS**

adverse birth outcomes, provider distance, South Carolina

Adverse birth outcomes (ABOs) are a leading cause of infant mortality in South Carolina (SC). While 11.7% of overall births in SC in 2010 were preterm (i.e., born at  $\leq$ 36 weeks), 67% of infants who died that year were preterm births. In addition to increased risk

for mortality, ABOs, defined as low birthweight (i.e., <2500 grams at birth) or preterm birth, can also greatly increase the risk for cerebral palsy, intellectual disabilities, impaired vision, and poor dental health. $^{2-5}$ 



In 2017, the birth rate in the United States (US) for all ages was 11.8 births per 1000 women aged 15–44.<sup>6</sup> The birth rate in adolescents was 18.8 births per 1000 women aged 15–19, and 5% of all US births were to adolescent mothers.<sup>6</sup> Despite decreasing national trends in infant mortality, there remain persistent age-based disparities, with 5.8 infant deaths per 1000 live births in mothers 15–44 compared to 9.0 deaths per 1000 live births in births to adolescent mothers.<sup>7,8</sup> In SC, the adolescent birth rate in 2017 was 21.7 births per 1000 women aged 15–19—a rate that was nearly double the general birth rate among all SC women (11.4 births per 1000 women).<sup>6</sup> The state faces significant challenges related to birth outcomes; while SC ranks 19th in the nation for adolescent births, it ranks fifth for low birthweight and seventh for preterm births.<sup>9</sup> From 2010 to 2015, 28.3% of adolescent births.<sup>10</sup>

Understanding the drivers behind high ABOs among adolescent mothers in SC is an essential step to develop effective policy measures. The state is largely rural with a medically underserved population. Over 70% of communities in SC are designated as rural, and 43 out of 46 counties are fully designated as health provider shortage areas (HPSAs), with two additional counties comprising primarily census tracts that are HPSAs. 11,12 While a shortage area designation does not exist yet for obstetric providers, there is also a low number of obstetric providers in the state, with approximately one provider for every 2250 women of childbearing age. 10 Midwives must be overseen by a licensed medical provider, and their practice is significantly restricted by strict regulations. Thus, most births are attended to and prenatal care is given by obstetric providers. Fewer obstetric providers mean longer travel distances for obstetric care, including prenatal care. 13 Having fewer than five prenatal visits during a pregnancy is linked to ABOs, infant mortality, and maternal mortality, 14,15

Adolescent mothers are more likely to receive inadequate prenatal care for a number of reasons. Adolescents often realize they are pregnant later in their pregnancy than older mothers, may not understand the necessity of prenatal care, and are more likely to have difficulties with transportation to appointments. 16-18 While a previous study in SC found no significant relationship between the distance to a delivery hospital and infant mortality, rural women and women from low socioeconomic status (SES) are more likely to face longer travel times to hospitals; in rural British Columbia, greater distance to an obstetric provider has been found to be associated with a higher likelihood of ABOs. 19-21 Only 64.8% of SC residents live within 30 miles of an obstetric provider; therefore, rural adolescents may face increased barriers to obstetric care and thus greater risk for ABOs. No research, to our knowledge, has examined the relationship between driving distance to an obstetric provider and ABOs in adolescent mothers in SC or the US.

Sociodemographic, socioeconomic, and clinical factors have also been identified as important predictors of ABOs in the US. 22,23 Mother's age is associated with risk for ABOs, with adolescent mothers more likely to experience an ABO than nonadolescent mothers. 24,25 In particular, adolescent women who are from low SES and those from racial and ethnic minority groups have a greater likelihood of experiencing ABOs; in addition, adolescent women with certain health condi-

tions, including those who are obese or overweight, are also at greater risk for ABOs.  $^{26,27}$  In the US, Black adolescents, regardless of rurality or SES, have been shown in multiple studies to have a higher risk of ABOs, with one study finding 2.4 times greater risk of ABO when compared to infants born to White mothers.  $^{28}$  There is mixed evidence on the impact of rural residence on ABOs.  $^{22,23,29,30}$  Women without a local obstetric provider who have to travel outside their community do have an increased rate of ABOs and maternal adverse outcomes.  $^{31,32}$  However, from 2013 to 2017, 34.8% (N = 6395) of adolescent births in SC were to rural mothers, so it is important to understand what role rurality plays in health outcomes.

This study aims to determine whether provider distance is associated with ABOs for adolescent mothers in SC, while controlling for important potential covariates, such as race, ethnicity, SES, and prenatal care.

#### **METHODS**

## **Data sources**

Statewide residential ZIP Code tabulated area (ZCTA)-level birth certificate data from 2013 to 2017 were retrieved from the South Carolina Community Assessment Network (SCAN)-an interactive vital records data system created and managed by the SC Department of Health and Environmental Control. 10 We extracted infant characteristics for all preterm births (i.e., born at ≤36 weeks of gestation), births with low birthweight (i.e., ≤2500 grams at birth), and births that were preterm and low birthweight; maternal demographic variables of race, ethnicity, age, and insurance payor; and maternal health characteristics of inadequate prenatal care (i.e., fewer than five prenatal visits), weight (i.e., overweight or obese before pregnancy based on body mass index), smoking status (i.e., ever used tobacco during pregnancy), and occurrence of gestational diabetes. These covariates were chosen because they have been shown to either impact ABOs, are correlated with rural residence, or are impacted by provider distance. 26,27,32-34 To control for community-level SES, we used percent of children aged 18 or younger at the ZCTA-level under the poverty threshold from the 2017 American Community Survey 5-year estimates. 35 We calculated ABOs and covariates aside from SES by dividing the total for each variable per ZCTA by the number of all births to adolescent mothers per ZCTA.

Information on licensed health care providers was obtained from SK&A Physician Licensure files (IQVIA, Irvine, CA); specifically, we retrieved data for 672 physicians—obstetricians and family physicians—who had an active license in SC at any time from 2013 to 2017. This data source includes both primary and secondary places of practice; the primary site was used for analysis.

Provider distance between ZCTA centroids was calculated with the MapQuest API (MapQuest, Inc., Denver, CO) as the shortest road distance in miles. Each ZCTA with adolescent births was matched to the closest ZCTA with a licensed obstetric provider. This approach for deriving distance has been used previously in cancer research, rural-urban obstetric care research, and in ABO research in Canada when

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**TABLE 1** Mean percent births with adverse outcomes, live births to women aged 10–19 in SC, 2013–2017

		Rurality, as def	fined byrural-urban commutin	g area codes
	Total	Urban (N = 263)	Rural (N = 115)	
	Mean (SD)	Mea	an (SD)	p values <sup>a</sup>
Percent births with adverse outcomes <sup>b</sup>	23.56 (54.63)	25.75 (50.46)	19.59 (60.66)	.0112
Percent low birthweight	9.21 (23.31)	10.31 (22.18)	7.21 (24.13)	.0092
Percent preterm birth	9.09 (24.78)	9.75 (24.33)	7.90 (25.31)	.0501
Percent low birthweight and preterm birth	5.26 (16.90)	5.69 (16.27)	4.48 (17.98)	.0390

<sup>&</sup>lt;sup>a</sup>This was calculated using a standard two-sample *t*-test. Bolded values indicate significance.

patient addresses were not available. <sup>20,21,36,37</sup> While not an exact distance to the patient's provider, studies have shown that this method is an acceptable alternative.

Rural-Urban Commuting Area (RUCA) codes (version 3.1) were used to signify rurality at the ZCTA level, with primary codes 1, 2, and 3 designated as urban and all other codes designated as rural.  $^{38}$ 

### Statistical analyses

Two-sample t-tests were used to examine the differences in maternal characteristics and birth outcomes by rurality. Generalized linear regression was performed using the percentage of ZCTA-level ABOs as the dependent variable and provider distance from each ZCTA centroid to the nearest obstetric provider as the independent variable. adjusting for other maternal demographic and clinical factors, rurality, and community-level SES. To estimate a potential U-shaped association between provider distance and ABOs, we also included provider distance as a quadratic variable. The model originally included an interaction between provider distance and rurality; this was not significant and was ultimately removed. Analyses were weighted by the percent of adolescents who had births out of all female adolescents per ZCTA from 2013 to 2017. All models were evaluated using variance inflation factors (VIFs) to address for potential multicollinearity; all variables had VIF<4. Predictive probabilities of ABOs were calculated for each ZCTA using the full model, stratified by rurality. Additional sensitivity analysis was conducted to include only ZCTAs with at least 10 annual births to ensure that ZCTAs had ABO rates stable enough for meaningful comparisons. All analyses were conducted with SAS 9.4 (SAS Institute Inc., Cary, NC).

#### **RESULTS**

From 2013 to 2017, a total of 24,782 births occurred to adolescent women (aged 10–19) in SC, with these births occurring in 369 out of 378 ZCTAs. Out of these births, 7015 (28.31%) experienced ABOs, with ABOs occurring in 323 ZCTAs. Among the 7015 ABO births,

38.65% were preterm, 37.13% were low birthweight, and 24.22% were both low birthweight and preterm. Rates of ABOs varied substantially across all ZCTAs, ranging from 0% to 100%. Mean rates of ABOs were higher in urban areas (25.75%) when compared to rural areas (19.59%) (p=.0112; Table 1). Across ABO type, urban areas had higher rates of low birthweight (10.31%) compared to rural areas (7.21%; p=.0092) as well as births with both low birthweight and preterm birth (5.69% vs. 4.48%; p=.0390). There was no significant difference in preterm birth between urban and rural areas.

Shown in Table 2, the mean provider distance was 11.86 miles (range, 0–42.91 miles). Provider distance was not significantly different between rural (11.76 miles) and urban ZCTAs (12.04 miles, p=0.0958). The majority (83.28%) of births were paid by Medicaid, and rural births (86.46%) to adolescent mothers were more likely to be covered by Medicaid than urban births (81.51%; p=0.0071). The mean level of child poverty was higher in urban ZCTAs (33.39% compared to 29.99%; p=0.0106). Few births (7.67%) had inadequate prenatal care, with no significant differences between rural or urban ZCTAs. Weight, tobacco use, and gestational diabetes were also not significantly different between urban and rural ZCTAs.

In terms of maternal demographic characteristics, only percentages of births to Hispanic mothers were significantly different between rural and urban ZCTAs. Specifically, births to Hispanic adolescents were more common in urban ZCTAs (6.7%) than in rural ZCTAs (3.9%; p < .0001).

The unadjusted analysis of ABOs by provider distance showed an inverse association between provider distance and ABOs (Table 3). An increase of 1 mile in provider distance was associated with a decrease in ABO by 1.05% (CI: -1.58 to -0.52, p=.0001). A U-shaped relationship was found, where an increase of 1 mile (squared) was associated first with a decrease in ABO until approximately 17 miles and then an increase in ABO of 0.3% (CI: 0.01-0.05, p=.0032).

After controlling for maternal characteristics, inadequate prenatal care and rurality were significantly associated with ABO rates among births to adolescent mothers (Table 3). Inadequate prenatal care (defined as < five prenatal visits) was associated with an increased ABO by 0.42% (CI: 0.23–0.62, p < .0001). Births in a rural area had a lower ABO of 4.94% (CI: –8.41 to –1.58, p = .0043) compared to those

<sup>&</sup>lt;sup>b</sup>Low birthweight is defined as <2500 grams at birth. Preterm birth are infants born at 36 weeks of a pregnancy or earlier.

 TABLE 2
 ZCTA-level characteristics by rurality, live births to women aged 10-19 in SC, 2013-2017

		Rurality, as defined	Rurality, as defined byrural-urban commuting area codes	
	Total	Urban (N = 263)	Rural (N = 115)	
	Mean (SD)	Mean (SD)	SD)	p values <sup>a</sup>
Mean percent of ZCTA-level teen pregnancies by maternal characteristics:	teristics:			
Inadequate prenatal care	7.67 (28.38)	8.00 (22.18)	7.08 (38.96)	.3409
Overweight or obese	39.03 (55.91)	38.00 (47.16)	40.89 (71.66)	.4562
Used tobacco during pregnancy	13.68 (55.07)	12.36 (30.47)	16.07 (87.93)	.8196
Gestational diabetes	1.86 (12.16)	2.07 (12.24)	1.48 (11.90)	.4288
Insurance coverage:				
Private insurance	11.87 (41.10)	12.83 (39.50)	10.13 (44.00)	.0814
Self-pay	2.12 (13.24)	2.26 (12.70)	1.86 (14.40)	.2408
Medicaid	83.28 (50.78)	81.51 (51.09)	86.46 (48.13)	.0071
Race				
White	56.01 (94.05)	57.37 (90.83)	53.53 (100.78)	.0587
Black	42.91 (93.93)	41.70 (91.08)	45.09 (100.02)	.0742
Other	1.06 (10.14)	0.89 (6.51)	1.36 (15.48)	.4353
Ethnicity				
Non-Hispanic	94.27 (28.04)	93.27 (29.27)	96.10 (23.72)	<.0001
Hispanic	5.70 (27.97)	6.69 (29.20)	3.90 (23.72)	<.0001
Percent of children in poverty	32.18 (64.55)	33.39 (61.45)	29.99 (70.71)	.0106
Average road mile distance to provider $^{\mathrm{b},\mathrm{c}}$	11.86 (28.96)	11.76 (28.64)	12.04 (29.79)	.0958

<sup>a</sup>This was calculated using a standard two-sample t-test. Bolded values indicate significance.

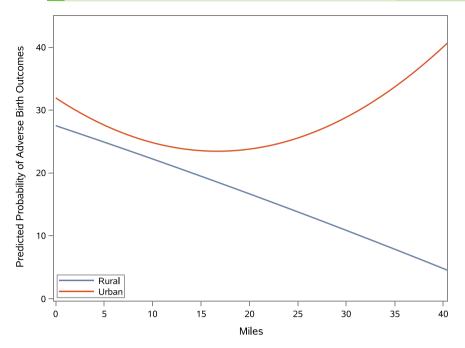
 $<sup>^{\</sup>mathrm{b}}$  Distance is calculated by using residential road miles from ZCTA centroid of patient to closest ZCTA centroid of a provider.  $^{\mathrm{c}}$  This includes all obstetric and family medicine physicians who had a license during the study.

NRHA

TABLE 3 Bivariate and multivariable linear regression of births with adverse outcomes, live births to women aged 10-19 in SC, 2013-2017<sup>a</sup>

	Unadjusted		Adjusted	
	Percent difference in ABO rate		Percent difference in ABO rate	
	Estimate (confidence interval)	<i>p</i> value <sup>b</sup>	Estimate (confidence interval)	<i>p</i> value <sup>b</sup>
Average road mile distance to provider	-1.05 (-1.58 to -0.52)	.0001	-0.79 (-1.32 to -0.26)	.0038
Average distance squared	0.03 (0.01-0.05)	.0032	0.02 (0.0003-0.04)	.0469
Inadequate prenatal care			0.42 (0.23-0.62)	<.0001
Overweight or obese			-0.05 (-0.16 to 0.06)	.3615
Used tobacco during pregnancy			-0.12 (-0.25 to 0.01)	.0638
Gestational diabetes			0.16 (-0.29 to 0.61)	.4869
Insurance coverage:				
Private insurance			REF	
Self-pay			-0.12 (-0.57 to 0.33)	.6032
Medicaid			0.01 (-0.11 to 0.12)	.9116
Race				
White			REF	
Black			0.04 (-0.03 to 0.12)	.2703
Other			-0.13 (-0.66 to 0.40)	.6257
Ethnicity				
Non-Hispanic			REF	
Hispanic			0.05 (-0.18 to 0.27)	.6810
Percent children in poverty			-0.05 (-0.14 to 0.04)	.2559
Rurality <sup>c</sup>				
Urban			REF	
Rural			-4.94 (-8.41 to -1.58)	.0043
Intercept	29.90 (26.58-33.22)	< .0001	30.16 (18.56 to 41.77)	<.0001

 $<sup>^</sup>a$  Reference: White, non-Hispanic, private pay, and urban.  $^b$  Bolded values indicate significance.  $^c$  Rurality is defined as a dichotomous variable, with rural ZCTAs marked 1.



**FIGURE 1** Predicted probability of ABO by rurality in road miles

*Note*: The full model from Table 3 was used to calculate these predicted values, stratified by rurality.

in urban areas. An increase of 1 mile in provider distance was associated with a decrease in ABO by 0.79% (CI: -1.32 to -0.26, p=.0038), and a smaller U-shaped relationship was found: an increase of 1 mile (squared) was associated with a 0.02% decrease in ABO at first and then an increase in ABO at approximately 17 miles (CI: 0.0003–0.04, p=.0469).

The predicted probability of ABO (Figure 1) shows a distinct difference based on maternal rurality. As miles to a provider increase, the probability of ABOs in rural ZCTAs decreases. The probability of ABOs in urban ZCTAs shows a U-shaped relationship: ABOs initially decrease as miles to a provider increase until approximately 17 miles, at which point the probability of an ABO begins to increase.

The sensitivity analysis limiting only ZCTAs with at least 10 annual births showed consistent results—a U-shaped distance-outcome relationship—in urban ZCTAs; however, in rural ZCTAs, we found a U-shaped distance-outcome relationship among these 38 rural ZCTAs with 10 or more annual births (online Appendix Figure 1). These results demonstrate that teen pregnant women in urban and rural ZCTAs that had to travel more than 13 miles to reach the nearest obstetric providers would have higher ABO rates with farther distances.

# DISCUSSION

This study examined the relationship between ABOs and provider distance for adolescent births in SC from 2013 to 2017. Counterintuitively, in rural ZCTAs, residing farther from an obstetric provider was associated with lower ABO rates. In urban ZCTAs, the relationship followed a U-shaped curve with closer areas associated with a decrease in ABOs and areas past 17 miles associated with an increase in ABOs. Urban areas also had significantly higher percentages of ABOs over-

all, specifically births with low birthweight and both preterm and low birthweight.

The inverse relationship between provider distance and ABOs in rural areas is contrary to previous findings among mothers of all ages in the literature and thus requires close consideration. <sup>30,33</sup> In this analysis, living farther away from a provider in rural areas was associated with lower ABO percentages. Simply living in a rural area of SC was associated with a 5% decrease in ABOs when all other variables were held constant. There are two possible reasons for this. First, rural adolescents were more likely to rely on Medicaid, and therefore, those mothers may have been able to access earlier and/or more care throughout their pregnancies, as seen in Sonchak's<sup>39</sup> work; however, there was not a significant difference in the percentage of mothers with inadequate prenatal care—defined as fewer than five prenatal visits between rural and urban ZCTAs.<sup>39</sup> Future studies may wish to employ expanded measures of prenatal care (i.e., both quantity and quality) in order to examine whether this finding may be explained by differences in timing, amount, and/or content of care. Second, while there are adolescent pregnancy programs in both urban and rural areas in SC, there are a number of programs that focus on rural SC, including Healthy Start and Fact Forward. Healthy Start is a federally funded locally based program that enrolls pregnant women and guides them through their pregnancies, providing women with in-home visits, education, housing assistance, transportation to medical appointments, and post-birth support with breastfeeding and nutrition education.<sup>40</sup> In SC, they are primarily located in the PeeDee region, in the northeast area of the state. 40 Fact Forward trains providers and educators to talk with adolescents about sexual health and pregnancy prevention throughout SC, primarily in rural areas.<sup>41</sup>

Urban findings differed significantly. In urban ZCTAs, after a provider was approximately 17 miles away from the mother, ABO rates began to increase. This urban "disadvantage" has been identified for



other health conditions. For instance, Spees and associates found that urban cancer patients over 15 miles from a provider were less likely to start their treatment than those with a close provider, while rural patients were more likely to start and finish treatment. This is not directly comparable as there was not a significant difference between urban and rural ZCTAs regarding prenatal care, but it nonetheless highlights that travel distance may impact urban residents differently than rural residents. In rural states like SC, urban access has not been widely studied, and it would be worthwhile to see if rural interventions could be replicated in urban underserved areas, like perinatal care regionalization, Rural Maternity and Obstetrics Management Strategies, Healthy Start, and Home Visiting programs. Further research is needed to elucidate what burdens urban adolescents face in accessing a provider and to identify other ABO determinants.

In the adjusted regression, inadequate prenatal care was the only other covariate to be significantly associated with ABOs. Specifically, we found that every 1% increase in inadequate prenatal care in a ZCTA was associated with a 0.4 absolute percentage increase in ABOs. Inadequate prenatal care has been found to be a strong predictor of ABOs in both adult and adolescent births, so this finding, while a relatively small association, adds further support that receiving a minimal threshold of prenatal care is important to achieve successful birth outcomes. 22,25,26,42,43 Along with prenatal care, race and income level are shown in the literature to be important predictors of ABOs. 15,28,30,43 Household income data were not available for this ZCTA-level study; however, most of the births analyzed in the current study were paid through Medicaid. Thus, the majority of mothers included in the sample are likely to have come from low SES backgrounds. Insurance payer was not associated with ABOs in the regression—possibly due to a homogenous sample or the use of this proxy measure of income. In terms of racial differences, the percent of White or Black mothers was not significantly different across the state. Race itself was not statistically significant in the regression, possibly because there was a similar proportion of adolescent births to Black women between rural and urban SC. Importantly, this analysis was conducted at the ZCTA-level; use of individual-level data may yield more understanding of the relationship between individual factors (e.g., care received, sociodemographic variables, and SES) to ABOs. Comparing the results of low-income mothers in high- or mid-income ZCTAs or counties could also be an avenue for future research.

Current findings make at least two distinct contributions to the current literature. In SC, adolescents in rural ZCTAs that are farther from providers are a logical target for policies or programs that aim to reduce ABOs. Rural programs that seek to improve access to care and reduce transportation burdens may be warranted, such as providing reliable Medicaid transportation or increasing use of telehealth services when appropriate. Policies that incentivize providers to increase Medicaid patients' return visits may also be useful, since the use of Medicaid was higher among mothers in rural ZCTAs. Second, adolescent mothers in urban ZCTAs were more likely to reside in areas with higher child poverty—a proxy for community SES. Adolescent mothers in low-income, urban areas may face unique challenges that impact their care and later birth outcomes. Public transportation is limited in

SC, even in many urban centers. Therefore, even urban adolescents may experience transportation challenges, such as having to rely on others with an automobile. While child poverty was not a significant factor in the adjusted model, community SES could impact the ability of urban residents who live far from providers to travel to receive frequent care. Again though, inadequate prenatal care had only a small effect on ABOs in the current study, and more in-depth research is needed on ABOs among urban adolescent mothers.

#### Limitations

This study has some limitations. Because this is aggregate data, addresses for patients were unavailable, and distance to the closest provider could in fact be either shorter or longer than calculated using ZCTA centroids. Yet, we do not think this would affect the study findings as this measurement error would be expected to be randomly distributed across urban and rural communities. Additionally, the analysis only looked at the closest provider, rather than the distance to the specific provider a patient used. Patients choose providers based on myriad factors, not just distance from their office. 44,45 Thus, future studies that are able to link providers and their documented patients would be a useful extension. Finally, choice of covariates was limited due to information collected and presented in SCAN; adding more covariates could explain more of the variation in the model.

## **CONCLUSION**

While longer provider distance was associated with lower ABO rates overall, this study revealed some important differences in ABOs for adolescent mothers in rural versus urban ZCTAs. Adolescents in urban ZCTAs in SC appear to be more at risk for ABOs when provider distance is greater than 17 miles, while other unobservable factors might drive the fact that adolescent mothers in rural ZCTAs with a higher travel burden had lower ABO rates. This association needs to be further studied to ascertain what programs in rural ZCTAs could positively impact birth outcomes among adolescents in urban areas and to understand the counterintuitive direction of the association between provider distance and ABOs in rural SC births.

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#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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