Mortality and Health Outcomes in North Carolina Communities Located in Close Proximity to Hog Concentrated Animal Feeding Operations

Julia Kravchenko, Sung Han Rhew, Igor Akushevich, Pankaj Agarwal, H. Kim Lyerly

BACKGROUND Life expectancy in southeastern North Carolina communities located in an area with multiple concentrated animal feeding operations (CAFOs) after adjusting for socioeconomic factors remains low. We hypothesized that poor health outcomes in this region may be due to converging demographic, socioeconomic, behavioral, and access-to-care factors and are influenced by the presence of hog CAFOs.

METHODS We studied mortality, hospital admissions, and emergency department (ED) usage for health conditions potentially associated with hog CAFOs—anemia, kidney disease, infectious diseases, and low birth weight (LBW)—in North Carolina communities located in zip codes with hog CAFOs (Study group 1), in zip codes with > 215hogs/km^2 (Study group 2), and without hog CAFOs (Control group). We compared cause-specific age-adjusted rates, the odds ratios (ORs) of events in multivariable analyses (adjusted for 6 co-factors), and the changes of ORs relative to the distance to hog CAFOs.

RESULTS Residents from Study groups 1 and 2 had higher rates of all-cause mortality, infant mortality, mortality of patients with multimorbidity, mortality from anemia, kidney disease, tuberculosis, and septicemia, and higher rates of ED visits and hospital admissions for LBW infants than the residents in the Control group. In zip codes with > 215hogs/km^2, mortality ORs were 1.50 for anemia ($P < 0.0001$), 1.31 for kidney disease ($P < 0.0001$), 2.30 for septicemia ($P < 0.0001$), and 2.22 for tuberculosis ($P = 0.0061$).

LIMITATIONS This study included a lack of individual measurements on environmental contaminants, biomarkers of exposures and co-factors, and differences in residential and occupational locations.

CONCLUSION North Carolina communities located near hog CAFOs had higher all-cause and infant mortality, mortality due to anemia, kidney disease, tuberculosis, septicemia, and higher hospital admissions/ED visits of LBW infants. Although not establishing causality with exposures from hog CAFOs, our findings support the need for future studies to determine factors that influence these outcomes, as well as the need to improve screening and diagnostic strategies for these diseases in North Carolina communities adjacent to hog CAFOs.

Among North Carolina communities, including both high-income and low-income communities, the lowest life expectancy was observed in southeastern North Carolina [1]. Higher risks of chronic kidney disease and low birth weight (LBW) infants have also been reported for this region [2, 3]. These geographic variations in life expectancy and health outcomes have been suggested to correlate with region-specific health behaviors, access to care, and environmental characteristics [1]. One unique environmental characteristic of southeastern North Carolina is the presence of multiple hog concentrated animal feeding operations (CAFOs) [4]. The average number of hogs per farm in North Carolina is much higher than in the areas with hog CAFOs in 2 other US leaders in hog industry—the states of Iowa and Minnesota. Because the population density in southeastern North Carolina is substantially higher than in the areas with hog CAFOs in Iowa and Minnesota, the population of the communities adjacent to hog CAFOs is much greater. Consequently, the proximity of multiple high-density hog CAFOs to a large population makes this region uniquely suited to studying the potential impact of CAFOs on environment and human health.

Previous studies of the potential relationship between health and hog CAFOs were mostly focused on the occupational health risks among CAFO workers [3, 5, 6]. The residents living in close proximity to hog CAFOs may also be at risk as they are chronically exposed to contaminants from land-applied wastes and their overland flows, leaking lagoons, and pit-buried carcasses, as well as airborne emissions, resulting in higher risks of certain diseases [3, 6, 7-20]. In fact, previous survey based studies of residential communities reported significant health risks for residents, including higher risks of bacterial infections, higher frequencies of symptoms of respiratory and neurological disorders, and depression [3, 6, 7, 12, 14, 19, 20-22].

We identified the established health conditions and indicators that were previously used to evaluate community health, including the known medical conditions associated

Electronically published September 10, 2018.

Address correspondence to Julia Kravchenko, DUMC 2850, Durham, NC 27710 (Julia.krauchanka@duke.edu).

N C Med J. 2018;79(5):278-288.
0029-2559/2018/79502

with occupational or residential exposure to CAFOs. These included an increased risk of anemia and kidney disease (which may serve as an indicator of chronic exposure to toxins) [23-26], miscarriage [27], and LBW infants (which may serve as an indicators of maternal and fetal health) [2]. In addition, a higher prevalence and broader spectrum of antibiotic-resistant microorganisms in areas adjacent to hog CAFOs [28-30] has raised concerns about infections in both occupational and residential settings [31]. Therefore, the outcomes of anemia and kidney disease, acute infection (septicemia) and chronic communicable infection (tuberculosis), and LBW infants were analyzed as indicators of health in communities adjacent to hog CAFOs.

We focused our study on assessing the outcomes of these specific disorders in residential communities in southeastern North Carolina. Our objective was to determine whether, or to what extent, poor health outcomes are associated with the additional impact of hog CAFOs beyond disparities associated with demographics, socioeconomic characteristics, behavioral risks factors, or access to medical care. Furthermore, these health conditions served as potential opportunities for interventions if the determined health outcomes were poor.

Materials and Methods

Data. Data on disease-specific mortality were obtained from a publicly available data source at the State Center for Health Statistics for 2007-2013 [32]. Data on emergency department (ED) visits and hospital admissions were obtained from the Healthcare Cost and Utilization Project's (HCUP) State Emergency Department Database (SEDD) [33] and State Inpatient Database (SID) [34] for 2007-2013. The North Carolina analysis represents part of the larger study on health outcomes in the communities adjacent to hog CAFOs that includes other US states with commercial hog production (eg, Iowa and Minnesota). Therefore, we used the HCUP's state-specific database containing the data in a uniform format facilitating multi-state comparisons and analyses of geographic patterns and time trends in health care utilization, access, and outcomes across multiple US states. The SEDD captures discharge information on all ED visits that do not result in an admission and contains more than 100 clinical and non-clinical variables. Information on patients that are initially seen in the ED and then admitted to the hospital is included in SID, which encompasses almost 97% of all US hospital discharges. The SID and SEDD data for North Carolina for the period analyzed in this study had several issues that were addressed in performed analysis. For example, the 2011–2012 North Carolina SEDD included 2 types of erroneous records, such as duplicated records for ED visits that did not result in an admission to the same hospital and records for ED visits that did result in an admission to the same hospital. The SID dataset for North Carolina for 2007-2008 had problems with the coding of discharge disposition. These issues were identified and resolved according to the guidelines provided by the HCUP Data Center.

The list of swine animal operations registered in North Carolina contained information on geographic locations and the number of swine in each CAFO facility. Information was obtained from the North Carolina Division of Water Resources (NC DWR) for the year 2009. The animal operations are defined by General Statute 143-215.10B as feedlots involving 250 or more swine with a liquid waste management system.

Zip-code-level data on median household income (scaled by $10,000) and education level (defined as a percentage of people aged 25+ who attained an educational level higher than a bachelor's degree) were obtained from the 2010-2014 American Community Survey. County level data on the numbers of primary care providers (per 100,000 residents) and the percent of uninsured individuals was obtained from the Area Health Resources Files (AHRF) for 2008 and 2010-2013. County level data on prevalence of current smokers in age-specific groups were obtained from the Behavioral Risk Factor Surveillance System (BRFSS, CDC) for 2008-2013.

Methods. We studied the health outcomes in two study groups. Study group 1 included the residents of North Carolina communities located in zip codes with hog CAFO(s): 221 zip codes with approximately 2,260,000 residents. Study group 2 represented a subset of Study group 1. This group included North Carolina communities located in zip codes with the highest upper quartile of hog density (with > 215hogs/km^2): 56 zip codes with approximately 400,000 residents. North Carolina communities located in zip codes without hog CAFOs represented the Control group: 601 zip codes with approximately 7,200,000 residents. Geographic locations of zip codes for two Study groups and the Control group are shown in Figure 1.

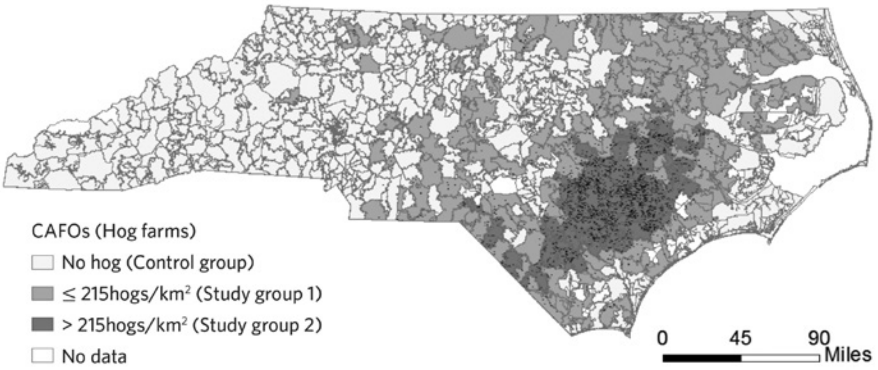
We compared disease-specific mortality, hospital admissions, and ED visits in these groups for the 2007-2013 period. All-cause, infant mortality, and outcomes of anemia, kidney disease, tuberculosis, septicemia, and LBW infants (see Appendix for respective ICD codes) were studied as the health indicators, with disease-specific mortality as primary outcome. The main predictor was the presence of a hog CAFO in a given zip code. Analyses were performed for underlying cause of death/primary diagnosis and for underlying-plus-secondary causes of death/primary-plus-secondary diagnoses. The illustration of the relations in assessment of potential impact factors/outcome associations used in multivariable analysis is shown in Supplemental Figure S1 in the Appendix.

Age-adjusted rates. We empirically estimated disease-

APPENDIX 1.
The International Classification of Diseases (ICD) codes used in the analysis

This appenix is available in its entirety in the online edition of the NCMJ.

FIGURE 1.
Density of Hogs in Zip Codes in Study Group 1 and Study Group 2, Locations of Registered at NC DWR Hog CAFOs in NC, and Locations of Zip Codes without Registered at DWR Hog CAFOs (Control Group), 2009



specific, age-adjusted rates of mortality, hospital admission, and ED visits (per 100,000). 95% confidence intervals (CIs) were estimated based on the approximation suggested by Keyfitz [35]. We compared these rates between Study groups 1 and 2 and the Control group, and additionally to North Carolina and the US average (for mortality rates).

Logistic regression analysis. We used logistic regression analysis (adjusted by age, median household income, education, health insurance coverage, numbers of primary care providers, and smoking prevalence) to evaluate whether a proportion of disease-specific deaths (as well as a proportion of disease-specific hospital admissions and ED visits) among all-cause deaths/all hospital admissions/all ED visits statistically differed between the studied groups. The Control group was a referent group for calculating ORs. This analysis allowed for minimization of potential bias due to uncertainties in population counts in North Carolina zip codes over the study period. SAS Proc Logistic (the SAS 9.4 statistical package; SAS Institute, Cary, NC) was used to evaluate ORs, 95% CIs, and p-values.

The DiSC analysis. We developed and applied an approach we termed the Distance from the Source of potential Contamination (DiSC) analysis to investigate the changes in ORs for all studied health outcomes with closer proximity to the CAFO. The core of this analysis is the new zip-code-specific continuous measure of potential exposures from hog CAFOs constructed using the exact address of each CAFO and the population counts in all census blocks in each zip code. We hypothesized that the risk of mortality (or hospital admission or ED visit) is proportional to the number of hogs in a CAFO, maximal at the location of a CAFO, and decreases with remoteness from a CAFO according to two-dimensional normal distribution (ie, "bell-shaped" distribution) of potential contaminants. Its standard deviation σ is the measure of the distance from the CAFO at which the level of potential contaminants drops 2-fold. The functional form is justified by the theory of diffusion from a point source [36]. The zip-code-specific measures of potential contaminants from CAFOs were modeled by summing the contributions of all census block groups in a given zip code:

$$E_z(\sigma) = \frac{\sum_i p_{iz} \sum_n N_n f(d_{niz}, \sigma)}{\sum_i p_{iz}}$$

where n enumerates all CAFOs; N_n is the number of hogs in the CAFO n; i enumerates all census block groups in a zip code z; p_{iz} is population of census block group i in zip-code z; and

$N_n f(d_{niz}, \sigma)$; where $f(d_{niz}, \sigma) = \frac{1}{\sqrt{2\pi}\sigma} \exp\left(-\frac{d_{niz}^2}{2\sigma^2}\right)$

is the modeled contaminant level from a specific CAFO in a census block group (where d_{niz} is the distance between them). Since there are no direct measurements that allow for estimating σ, we performed radius-specific analyses corresponding to 4 values of σ: ie, at 2, 5, 10, and 20 kilometers (km). A zip-code-specific value of $E_z(\sigma)$ was then used in the logistic regression analysis to evaluate the associations with disease-specific outcomes in multivariable analysis. The evaluated ORs are per a unit of $E_z(\sigma)$. The OR estimates for different σ are comparable because the measures are normalized equally: sums of contaminant levels over all zip-codes equal the total number of hogs in all CAFOs for any σ.

Sensitivity analyses. Because hog CAFOs are predominantly located in rural North Carolina, and access to medical care likely differs in urban and rural areas, we i) excluded zip codes of the cities of Charlotte and Raleigh, and also ii) excluded 18 urbanized areas defined in the US Census Bureau criteria for urban-rural areas as having ≥ 50,000 residents.

FIGURE S1.
Illustration of the Relations in the Assessment of Potential Impact Factors-Outcome Associations

This figure is available in its entirety in the online edition of the NCMJ.

We also used the generalized estimating equation (GEE) method to account for possible correlations between records in specific zip codes.

We used the greedy matching algorithm [37] to perform propensity score-based matching of zip codes from Control group to zip codes in Study group 2 by demographic and socioeconomic characteristics (see Appendix for detailed description of the matched groups and their characteristics presented in Table S1).

Ethics statement. All data analyses were designed and performed in accordance with the ethical standards of a responsible committee on human studies and with the Helsinki Declaration (of 1975, revised in 1983) and have been approved by the Duke University Health System Institutional Review Board.

Results

Demographic and socioeconomic characteristics. The residents of communities adjacent to hog farms were more diverse than the average North Carolina community. There were more African-American (28.8% vs. 19.3%, $P < 0.001$) and American-Indian (2.4% vs. 0.8%, $P < 0.05$) residents in zip codes with hog CAFOs (Study group 1) compared to the Control group (see Supplemental Tables S2 and S3 in Appendix). Study group 1 also had a lower median household income ($39,005 vs. $46,414, $P < 0.001$), fewer college-educated people with bachelor's or higher degrees (16.5% vs. 24.2%, $P < 0.001$), and a lower number of primary care health providers (54 vs. 76 per 100,000 residents, $P < 0.001$). The differences were even more pronounced for the residents of communities located in zip codes with > 215hogs/km^2 (Study group 2): 31.3% ($P < 0.001$) of the residents were African Americans and 4.1% were American Indians ($P < 0.001$). People from Study group 2 had the lowest (among the studied groups) median household income ($36,520, $P < 0.001$), percent of residents with bachelor's or higher degrees (13.7%, $P < 0.001$), and number of primary care providers (51/100,000, $P < 0.001$) (see Supplemental Tables S2 and S3).

TABLE S1.
Characteristics of Matched Group A, Matched Group B, and Study Group 2, NC, 2007-2013

This table is available in its entirety in the online edition of the NCMJ.

[1]Means are evaluated without weights representing zip-code populations.
n/a, non-applicable.

TABLE S2.
Descriptive Table of the 3 Studied Groups of NC Communities with and without Hog Concentrated Feeding Animal Operations (CAFOs): Race-Specific Population Groups, Socioeconomic Characteristics, Smoking Prevalence, and Access-To-Care Characteristics, NC, 2007-2013

This table is available in its entirety in the online edition of the NCMJ.

*$P < 0.05$.
**$P < 0.001$.

TABLE S3.
Person-Years of Observations in Race-Specific Groups of the Residents of NC Communities from the 3 Studied Groups, NC, 2007-2013

This table is available in its entirety in the online edition of the NCMJ.

Mortality rates. Cause-specific mortality rates of all studied diseases were higher in North Carolina communities located in zip codes with > 215hogs/km^2 (Study group 2) compared to the North Carolina and US averages (see Table 1). The all-cause mortality rate in Study group 2 was as high as 934/100,000.

The residents from Study group 2 aged ≤ 24 years old had much higher all-cause mortality rates (92.7/100,000) than mortality rates in North Carolina (69.8/100,000) and the US (62.2/100,000) for this age group (see Table 1). Conditions originating in the perinatal period may have substantially contributed to the differences in mortality at younger ages; the mortality rate among infants under 1 year old in Study group 2 was as high as 495/100,000. This is much higher than both the US average (317/100,000) and the North Carolina average (398/100,000). The groups that contributed the most to increased mortality rates due to perinatal conditions were newborns affected by maternal trauma and by disorders related to length of gestation and fetal growth (see Table 1). The rates of infant death related to maternal trauma were much higher in North Carolina communities located in zip codes with > 215hogs/km^2 (149/100,000) than the United States and North Carolina averages. The rates of death related to the length of gestation and fetal growth were higher in both North Carolina (North Carolina average) and Study group 2 compared to the US average.

Patients from Study group 2 with multimorbid conditions such as co-existing septicemia and kidney disease, septicemia and anemia, or septicemia and kidney disease and anemia had mortality rates 1.5-2.2 times greater than North Carolina and 1.8-1.9 times greater than the US average mortality rates for patients with the same respective co-existing diseases (see Supplemental Figure S2 in Appendix). For all studied diseases, the age-adjusted mortality rates were higher in Study group 1 than in the Control group, but lower than in Study group 2 (see Table 2), except for tuberculosis: its mortality did not significantly differ between Study groups 1 and 2.

To highlight the magnitude of higher mortality in the region, we modeled Study group 2 as an independent geo-

TABLE 1.
Age-Adjusted Mortality Rates (Per 100,000) in NC Communities with > 215hogs/km² (Study Group 2) Compared to the NC and US Average, 2007-2013. (95% Confidence Intervals are Shown in the Parentheses)

Disease	Age and race group	The US average[1]	The NC average[a]	NC communities with > 215hogs/km²
All-cause mortality	All ages, all races	750 (749.5-750.2)	**803**[a] (801.3-805.6)	**934**[ab] (922.7-944.8)
	White, all ages	745 (744.5-745.2)	**780**[a] (777.9-782.6)	**858**[ab] (844.7-871.2)
	AA,[2] all ages	903 (901.6-904.1)	**923**[a] (917.4-928.4)	**969**[ab] (947.9-989.4)
	Age ≤ 24 years old, all races	62.2 (62.0-62.4)	**69.8**[a] (68.7-70.9)	**92.7**[ab] (86.3-99.1)
Conditions of perinatal period	All races, age < 1 year old	317 (314.4-318.6)	**398**[a] **(381.1-408.5)**	**495**[ab] **(420.7-569.5)**
Newborns affected by maternal trauma	All races, age < 1 year old	74.6 (73.6-75.6)	**102**[a] **(95.7-109.1)**	**149**[ab] **(110.6-195.3)**
Disorders related to length of gestation and fetal growth	All races, age < 1 year old	112 (110.6-113.1)	**163**[a] **(154.8-171.8)**	**169**[a] **(128.3-218.4)**
Anemia (underlying cause)	All races, all ages	1.5 (1.5-1.5)	**1.9**[a] (1.8-2.0)	**2.6**[ab] (2.1-3.2)
	AA, all ages	3.0 (2.9-3.0)	**3.6**[a] (3.3-4.0)	**5.3**[ab] (3.9-7.1)
Kidney disease (underlying cause)	All races, all ages	14.6 (14.5-14.6)	**18.3**[a] (18.0-18.6)	**24.8**[ab] (23.0-26.6)
	White, all ages	13.3 (13.3-13.4)	**14.8**[a] (14.5-15.2)	**18.3**[ab] (16.3-20.2)
	AA, all ages	28.1 (27.9-28.3)	**34.9**[a] (33.8-36.0)	**37.7**[a] (33.6-41.8)
Tuberculosis (underlying + secondary cause)	All races, all ages	0.31 (0.30-0.32)	0.30 (0.26-0.35)	**0.63**[ab] (0.32-0.81)
Septicemia (underlying cause)	All ages, all races	10.8 (10.7-10.8)	**13.5**[a] (13.2-13.67)	**16.6**[ab] (15.1-18.1)

[1]Mortality rates are obtained from the Centers for Disease Control and Prevention Multiple Cause of Death data (https://wonder.cdc.gov/mcd.html).
[2]African-American.
[a]Statistically significant difference compared to the US average.
[b]Statistically significant difference compared to NC average.

graphic unit and compared its overall and disease-specific mortality rates to the US states with the highest mortality rates (see Supplemental Table S4 in Appendix). In this model, the geographic area encompassing Study group 2 would be ranked number 4 in the United States for the highest all-cause mortality, number 1 in the United States for mortality from anemia as underlying cause, number 1 for kidney disease, number 2 for septicemia, and number 3 for tuberculosis as underlying-plus-secondary cause.

The rates of hospital admissions and ED visits. For most of the studied diseases, the rates of hospital admissions and ED visits (see Table 2) were higher in Study group 1 than in the Control group, but lower than in Study group 2. Rates did not differ between Study groups 1 and 2 for anemia hospital admissions and ED visits (as primary diagnosis), ED visits for tuberculosis, and LBW hospital admissions (as primary-plus-secondary diagnosis); however, these rates were still higher than in the Control group.

Logistic regression analysis. After adjustment for 6 co-

FIGURE S2.
Mortality Rates among Patients with Co-Existing Anemia, Kidney Disease, and Septicemia: The US Average, NC Average, and NC Communities with > 215hogs/km² (Study Group 2), 2007-2013. (95% Confidence Intervals Are Shown in the Parentheses)

This figure is available in its entirety in the online edition of the NCMJ.

TABLE S4.
Age-Adjusted Mortality Rates (Per 100,000) in NC Communities with > 215hogs/km² (Study Group 2): Ranks of This Area among the US States and District of Columbia with the Highest Mortality, 2007-2013. (95% Confidence Intervals Are Shown in the Parentheses)

This table is available in its entirety in the online edition of the NCMJ.

[a]Mortality rates were calculated using the Multiple Cause of Death data from the Centers for Disease Control and Prevention (https://wonder.cdc.gov/mcd.html).

factors, the ORs for death, hospital admissions, and ED visits for most of the studied diseases in Study group 1 were > 1.0 (see Table 3). The ORs in Study group 2 were significantly higher than in Study group 1 for kidney disease (all 3 outcomes), tuberculosis (hospital admissions), anemia (all 3 outcomes), tuberculosis (ED visits), septicemia (mortality), and LBW (ED visits) (see Table 3).

DiSC analysis. After adjustment for 6 co-factors, the studied outcomes had similar distance-related patterns: the ORs were higher in close proximity to a hog CAFO than in more distant communities (see Table 4). For example, mortality ORs for kidney disease were the highest in communities located within 2 km of a CAFO (OR = 1.14, $P < 0.0001$), then decreased to 1.02 ($P < 0.0001$) at 20 km. For hospital admissions, the OR for kidney disease was 1.22 ($P < 0.0001$) at 2 km, 1.08 at 5 km ($P < 0.0001$), 1.04 at 10 km ($P < 0.0001$), and 1.03 at 20 km ($P < 0.0001$). The most pronounced changes in ORs were observed between 2 km and 5 km from the CAFO.

Sensitivity analysis. After exclusion of urban areas, no significant changes were observed for mortality risks. Slightly lower ORs than in the main analysis were observed for hospital admissions, and slightly higher ORs were observed for ED visits. The results of GEE analysis also confirmed the main study results; one exclusion was some minor changes in hospital admissions.

Locations of matched zip codes are shown in Supplemental Figure S3 (Appendix): compared to "clustered" locations of zip codes with > 215hogs/km^2, non-CAFOs zip codes are sparsely located in different regions of North Carolina. The mortality rates of all studied diseases and hospital admission/ED visit rates of kidney disease, tuberculosis, and LBW were higher in Study group 2 than in matched zip codes

TABLE 2.
Age-Adjusted Rates (per 100,000) of Mortality, Hospital Admissions, and ED Visits in NC Communities with Hog CAFOs (Study Group 1), NC Communities with > 215hogs/km^2 (Study Group 2), and NC Communities without Hog CAFOs (Control Group), 2007-2013. Underlying Cause/Primary Diagnosis and Underlying-Plus-Secondary Cause/Primary-Plus-Secondary Diagnosis. (95% Confidence Intervals Are Shown in the Parentheses)

		Underlying cause/Primary diagnosis			Underlying+secondary cause/ Primary+secondary diagnosis		
Outcome	Disease	Study group 1	Study group 2	Control group	Study group 1	Study group 2	Control group
Mortality	All-cause mortality	**866**[a] (861.1-870.0)	**934**[b] (922.7-944.8)	773 (770.4-775.2)	**866**[a] (861.1-870.0)	**934**[b] (922.7-944.8)	773 (770.4-775.2)
	Anemia	**2.3**[a] (2.1-2.6)	**2.6**[a] (2.1-3.2)	1.7 (1.6-1.8)	**28.4**[a] (27.6-29.2)	**35.5**[ab] (33.4-37.7)	17.0 (16.7-17.4)
	Kidney disease	**21.1**[a] (20.4-21.8)	**24.8**[ab] (23.0-26.6)	17.1 (16.7-17.5)	**101**[a] (99.1-102.1)	**119**[ab] (114.6-122.5)	75.4 (74.7-76.2)
	Tuberculosis	**0.32**[a] (0.21-0.42)	**0.24**[a] (0.04-0.43)	0.13 (0.12-0.14)	**0.52**[a] (0.42-0.61)	**0.63**[a] (0.32-0.81)	0.23 (0.22-0.34)
	Septicemia	**15.5**[a] (14.9-16.1)	**16.6**[a] (15.1-18.1)	12.7 (12.4-13.0)	**67.9**[a] (66.7-69.1)	**75.1**[ab] (71.9-78.2)	50.9 (50.3-51.5)
Hospital admissions	Anemia	**112**[a] (110.7-114.0)	**113**[a] (108.6-116.4)	87.4 (86.6-88.2)	**1,989**[a] (1,982-1,996)	**2,179**[ab] (2,162-2,196)	1,642 (1,638-1,645)
	Kidney disease	**164**[a] (162.3-166.2)	**187**[ab] (181.6-191.4)	128 (126.6-128.6)	**1,809**[a] (1,802-1,815)	**2,031**[ab] (2,015-2,048)	1,369 (1,366-1,372)
	Tuberculosis	**1.8**[a] (1.6-2.0)	**3.1**[ab] (2.4-3.7)	1.0 (0.9-1.1)	**4.0**[a] (3.7-4.3)	**6.2**[ab] (5.3-7.1)	2.4 (2.3-2.6)
	Septicemia	**296**[a] (293.6-298.8)	**313.1**[ab] (306.7-319.5)	239 (237.8-240.4)	**437**[a] (433.9-440.2)	**468**[ab] (460.3-475.9)	344 (342.1-345.2)
	Low birth weight	n/a	n/a	n/a	**2.2**[a] (1.9-2.4)	**2.5**[a] (1.9-3.1)	1.5 (1.4-1.6)
ED visits	Anemia	**84.8**[a] (83.3-86.2)	85.4[a] (81.9-88.9)	71.4 (70.6-72.1)	**605**[a] (600.8-608.4)	**682**[ab] (672.2-691.7)	480 (478.1-481.9)
	Kidney disease	**26.4**[a] (25.6-27.2)	**33.2**[ab] (31.1-35.3)	19.6 (19.2-20.0)	**547**[a] (543.4-550.5)	**643**[ab] (634.0-652.3)	376 (373.9-377.2)
	Tuberculosis	0.22 (0.13-0.32)	0.33 (0.12-0.53)	0.14 (0.11-0.14)	**1.04**[a] (0.8-1.13)	**1.42**[a] (1.03-1.93)	0.72 (0.62-0.74)
	Septicemia	**15.4**[a] (14.8-16.0)	**20.1**[ab] (18.4-21.7)	13.7 (13.4-14.0)	**26.2**[a] (25.4-26.9)	**35.4**[ab] (33.3-37.6)	21.1 (20.7-21.5)
	Low birth weight	n/a	n/a	n/a	**3.0**[a] (2.7-3.3)	**4.7**[ab] (3.9-5.5)	1.6 (1.5-1.7)

[a]Statistically significant difference compared to the Control group.
[b]Statistically significant difference compared to Study group 1.
n/a, non-applicable.

TABLE 3.
Age-Adjusted Rates (per 100,000) of Mortality, Hospital Admissions, and ED Visits in NC Communities with Hog CAFOs (Study Group 1), NC Communities with > 215hogs/km^2 (Study Group 2), and NC Communities without Hog CAFOs (Control Group), 2007-2013. Underlying Cause/Primary Diagnosis and Underlying-Plus-Secondary Cause/Primary-Plus-Secondary Diagnosis. (95% Confidence Intervals Are Shown in the Parentheses)

		Underlying cause/Primary diagnosis		Underlying+secondary cause/ Primary+secondary diagnosis	
Outcome	Disease	Study group 1	Study group 2	Study group 1	Study group 2
Death	Anemia	**1.24** (1.11-1.36), *P* = 0.0012	**1.39** (1.15-1.64), *P* = 0.0077	**1.34** (1.30-1.38), *P* < 0.0001[#]	**1.50**[a] (1.43-1.57), *P* < 0.0001[#]
	Kidney disease	**1.13** (1.09-1.17), *P* < 0.0001[#]	**1.27**[a] (1.19-1.35), *P* < 0.0001[#]	**1.18** (1.16-1.20), *P* < 0.0001[#]	**1.31**[a] (1.27-1.35), *P* < 0.0001[#]
	Tuberculosis	**2.77**[a] (2.33-3.21), *P* < 0.0001[#]	2.12 (1.19-3.04), *P* = 0.1125	**2.23** (1.93-2.54), *P* < 0.0001[#]	**2.22** (1.65-2.79), *P* = 0.0061
	Septicemia	**1.07** (1.02-1.12), *P* = 0.0120	1.08 (0.97-1.17), *P* = 0.1633	**1.18** (1.15-1.20), *P* < 0.0001[#]	**2.30**[a] (2.11-2.48), *P* < 0.0001[#]
Hospital admissions	Anemia	**1.07** (1.05-1.09), *P* < 0.0001[#]	**1.07** (1.03-1.11), *P* = 0.0022	**1.03** (1.03-1.04), *P* < 0.0001[#]	**1.12**[a] (1.11-1.14), *P* < 0.0001[#]
	Kidney disease	**1.09** (1.07-1.11), *P* < 0.0001[#]	**1.21**[a] (1.18-1.24), *P* < 0.0001[#]	**1.15** (1.15-1.16), *P* < 0.0001[#]	**1.33**[a] (1.32-1.34), *P* < 0.0001[#]
	Tuberculosis	**1.48** (1.31-1.64), *P* < 0.0001[#]	**2.81**[a] (2.54-3.08), *P* < 0.0001[#]	**1.39** (1.28-1.50), *P* < 0.0001[#]	**2.30**[a] (2.11-2.48), *P* < 0.0001[#]
	Septicemia	**1.03** (1.02-1.04), *P* < 0.0001[#]	**1.03** (1.00-1.05), *P* = 0.0324	**1.06** (1.05-1.07), *P* < 0.0001[#]	**1.08** (1.06-1.10), *P* < 0.0001[#]
	LBW	n/a	n/a	**1.44** (1.25-1.62), *P* < 0.0001[#]	1.40 (1.04-1.76), *P* = 0.0661
ED visits	Anemia	1.02 (1.00-1.05), *P* = 0.0721	**1.08**[a] (1.03-1.13), *P* = 0.0028	**1.08** (1.07-1.09), *P* < 0.0001[#]	**1.21**[a] (1.19-1.23), *P* < 0.0001[#]
	Kidney disease	**1.05** (1.00-1.09), *P* = 0.0431	**1.26**[a] (1.18-1.34), *P* < 0.0001[#]	**1.23** (1.22-1.24), *P* < 0.0001[#]	**1.43**[a] (1.41-1.45), *P* < 0.0001[#]
	Tuberculosis	1.38 (0.84-1.93), *P* = 0.2451	2.26 (1.33-3.19), *P* = 0.0868	1.24 (1.01-1.47), *P* = 0.0721	**2.22**[a] (1.84-2.61), *P* < 0.0001[#]
	Septicemia	**0.89** (0.82-0.96), *P* = 0.0013	**0.82** (0.69-0.96), *P* = 0.0057	0.98 (0.92-1.03), *P* = 0.3671	0.99 (0.89-1.09), *P* = 0.8742
	LBW	n/a	n/a	**1.53** (1.34-1.73), *P* < 0.0001[#]	**2.45**[a] (2.13-2.76), *P* < 0.0001[#]

[a]Statistically significant difference between the Study groups 1 and 2.
[#]Remains significant under Bonferroni correction.
n/a, non-applicable.

without CAFOs (the results are presented in the Appendix, Table S5).

Discussion

We found that people living in southeastern North Carolina communities located near hog CAFOs had poorer outcomes for a variety of health conditions in different age groups than the residents of North Carolina communities located in zip codes without hog CAFOs; they had higher mortality due to infections, anemia, kidney disease, and perinatal conditions, and higher rates of hospital admissions and ED visits for LBW infants. The observed higher rate of all-cause mortality is consistent with the lower life expectancy in this area [1].

While the precise causes of higher anemia rates observed in our study are unclear, other studies have suggested that exposure to ammonia, hydrogen sulfide, methane, and particulate matters (PMs) near the CAFOs [23, 24], contamination of water and soil with zinc [25], exposure to the antibiotic chloramphenicol previously widely used to treat infections in hogs [26], and inappropriate human use of veterinary medications (certain NSAIDs or antibiotics) [38] cause anemia. Moreover, anemia is an independent risk factor of death in patients with chronic diseases [39, 40], a complication of renal failure [41] and tuberculosis [42], and a risk factor for preterm birth and LBW infants [43].

Earlier studies reported that workers in the swine

FIGURE S3.
Locations of Matched NC Zip Codes without Hog CAFOs (Matched Group A and Matched Group B) and Locations of Zip Codes with > 215hogs/km^2 (Study Group 2)

This figure is available in its entirety in the online edition of the NCMJ.

TABLE 4.
The Distance from the Source of Potential Contamination ("DiSC") Analysis: ORs of Mortality, Hospital Admissions, and ED Visits in NC Communities Located within Different Distances from Hog CAFOs: Underlying-Plus-Secondary Causes of Death/Primary-Plus-Secondary Diagnoses, Logistic Regression, Multivariable Analysis (Adjusted by Age, Income, Education, Health Insurance, Smoking, and Availability of Primary Care Providers), 2007-2013. (95% Confidence Intervals Are Shown in the Parentheses)

		The distance from hog CAFO			
Outcome	**Disease**	**2 km**	**5 km**	**10 km**	**20 km**
Death	Anemia	1.11 (1.05-1.18), $P < 0.0001$	1.05[a] (1.03-1.07), $P < 0.0001$	1.04 (1.03-1.05), $P < 0.0001$	1.03 (1.03-1.04), $P < 0.0001$
	Kidney disease	1.14 (1.11-1.18), $P < 0.0001$	1.06 a (1.05-1.07), $P < 0.0001$	1.03 (1.03-1.04), $P < 0.0001$	1.02 (1.02-1.03), $P < 0.0001$
	Tuberculosis	1.37 (0.95-1.79), $P = 0.1442$	1.12 (0.96-1.27), $P = 0.1621$	1.09 (1.02-1.16), $P = 0.0231$	1.07 (1.03-1.11), $P < 0.0001$
	Septicemia	1.11 (1.06-1.15), $P < 0.0001$	1.04[a] (1.03-1.06), $P < 0.0001$	1.03 (1.02-1.03), $P < 0.0001$	1.02 (1.02-1.09), $P < 0.0001$
Hospital admissions	Anemia	1.06 (91.05-1.07), $P < 0.0001$	1.02[a] (1.02-1.03), $P < 0.0001$	1.01 (1.01-1.02), $P < 0.0001$	1.01 (1.01-1.01), $P < 0.0001$
	Kidney disease	1.22 (1.21-1.23), $P < 0.0001$	1.08[a] (1.08-1.09), $P < 0.0001$	1.04[a] (1.04-1.04), $P < 0.0001$	1.03[a] (1.03-1.03), $P < 0.0001$
	Tuberculosis	1.59 (1.44-1.75), $P < 0.0001$	1.18[a] (1.13-1.24), $P < 0.0001$	1.09[a] (1.06-1.12), $P < 0.0001$	1.06 (1.04-1.07), $P < 0.0001$
	Septicemia	1.10 (1.08-1.11), $P < 0.0001$	1.04[a] (1.03-1.04), $P < 0.0001$	1.02[a] (1.02-1.02), $P < 0.0001$	1.02 (1.01-1.02), $P < 0.0001$
	LBW	1.21 (0.97-1.46), $P = 0.1272$	1.06 (0.97-1.15), $P = 0.1913$	1.04 (0.99-1.08), $P = 0.1112$	1.03 (1.01-1,06), $P = 0.0082$
ED visits	Anemia	1.15 (1.14-1.17), $P < 0.0001$	1.05[a] (1.05-1.06), $P < 0.0001$	1.03[a] (1.02-1.03), $P < 0.0001$	1.02 (1.02-1.02), $P < 0.0001$
	Kidney disease	1.23 (1.21-1.24), $P < 0.0001$	1.08[a] (1.08-1.09), $P < 0.0001$	1.04[a] (1.04-1.05), $P < 0.0001$	1.03[a] (1.03-1.03), $P < 0.0001$
	Tuberculosis	1.99 (1.69-2.29), $P < 0.0001$	1.30[a] (1.19-1.40), $P < 0.0001$	1.13[a] (1.08-1.18), $P < 0.0001$	1.07[a] (1.04-1.10), $P < 0.0001$
	Septicemia	1.14 (1.06-1.22), $P < 0.0001$	1.06[a] (1.03-1.09), $P < 0.0001$	1.03 (1.02-1.04), $P < 0.0001$	1.02 (1.01-1.03), $P < 0.0001$
	LBW	2.28 (2.12-2.44), $P < 0.0001$	1.39[a] (1.34-1.45), $P < 0.0001$	1.20[a] (1.17-1.22), $P < 0.0001$	1.13[a] (1.11-1.14), $P < 0.0001$

[a]Statistically significant difference from the value of the result at shorter vs. longer distances (eg, 5 km vs. 2 km, or 10 km vs. 5 km) within the same row in the table.

industry have a higher risk for tuberculosis; however, this disease has been recently eradicated from US livestock [44]. Our findings on higher rates of tuberculosis likely result from the impact of a combination of factors in this North Carolina region where co-existing medical and social determinants may exacerbate each other [6, 10]. While no information is currently available on potential risk of occurrence of antibiotic-resistant strains of *Mycobacterium tuberculosis* in the communities adjacent to hog CAFOs, this aspect may require detailed analysis. The increased risk of undiagnosed latent tuberculosis that may be present in these communities, which may have a higher number of foreign-born residents [45], also requires attention. Co-existence of factors that may promote tuberculosis from its latent to active form (eg, diabetes, immunosuppression, and other conditions) needs to be accounted for when developing a strategy for improving identification of latent and active cases (ie, through screening) and treatment adherence in patients who require therapy.

Higher mortality rates for infants living in North Carolina zip codes with > 215hogs/km^2 represent an important health issue for this population that requires the immediate attention of public health and health care specialists. Maternal trauma and the length of gestation and fetal growth contribute the most to infant mortality in these North Carolina communities and can be targeted by special programs on maternal and child health. Higher rates of LBW infants in North Carolina communities adjacent to hog CAFOs are an important parameter of maternal and child health, not only because of the immediate medical care needed for such infants, but also because of their increased lifetime risk of chronic diseases (eg, higher risk of development of diabetes mellitus, arterial hypertension, ischemic heart disease, depression, respiratory diseases, and chronic kidney disease) [46]. Targeted programs in North Carolina communities adjacent to hog CAFOs could provide information about health issues related to women's and children's health to women of childbearing potential, as well as supporting mothers and children from pregnancy through birth and beyond.

The DiSC analysis in our study highlighted a potential opportunity for associating residential and occupational exposures in communities located in close proximity to hog CAFOs; poorer health outcomes among the residents of communities located within 2-5 km from CAFOs could be due to additional exposures because of potential employment at CAFOs. That may provide some guidance as to the most efficient use of resources to screen and diagnose diseases/conditions found to be highly prevalent in these communities.

In this study we do not establish causality between exposures from hog CAFOs and higher risk of mortality, hospital admissions, or ED visits for studied diseases in communities adjacent to CAFOs. One interpretation of our findings could be that people who reside in such communities may simultaneously be affected by multiple risk factors including low income and education, higher smoking prevalence, and lower access to medical care. Nonetheless, after adjusting for such co-factors or comparing zip codes with similar co-factors, persistently poorer health outcomes were observed in the communities located in zip codes with hog CAFOs. Furthermore, the DiSC analysis demonstrated a higher risk of poorer health outcomes in closer proximity to the CAFO. Our sensitivity analysis showed that patterns of use of medical care among the residents of these North Carolina communities may also contribute to the differences in health outcomes. For example, residents of rural North Carolina areas (where most of the hog CAFOs are located) are more likely to use EDs when searching for medical assistance and less likely use hospitals (due to problems with access such as transportation issues, problems with medical insurance coverage, or behavioral patterns of preferring EDs to a staying in a hospital).

The limitations of this study include: i) a lack of individual measurements of exposure, co-factors, and potential biomarkers of exposure; ii) potential misclassification of exposure from spray fields, accounting for weather, season and wind direction, exposure to poultry facilities, and coal power plants; iii) limited list of population characteristics in currently available dataset to match the compared population groups; and iv) potentially different residential and occupational locations for the same person. Further studies must address these limitations. The problems of identifying potential causative agents and evaluation of dose-response relationships in hog CAFOs studies are discussed in the literature; it is difficult to account for all required factors in occupational health studies, but the detection of specific exposures and diseases in residential communities is even more challenging due to additional complexities caused by dispersion of environmental agents, different exposure pathways, and variability of individual susceptibility to contaminants [6].

Community based research has been gaining prominence as a source of information for medical decision-making. It has been recognized that detailed individual-level data on co-factors are rarely available in the US; therefore, opportunities for individual-level analyses that account for multiple risk factors are very limited. To obtain information on health outcomes in certain populations, public health specialists and policymakers have begun to shift their attention from an exclusive focus on individual-level studies toward community level analyses. When contributions of specific risk factors to health outcomes in communities can be evaluated, this information can be used for optimization of resource allocation for medical interventions designed to improve health outcomes [47].

TABLE S5.
Age-Adjusted Cause-Specific Rates (per 100,000) of Mortality, Hospital Admissions, and ED Visits in Communities Located in Zip Codes with > 215hogs/km^2 (Study Group 2) and in Communities Located in Zip Codes Matched by Percent of African Americans, Percent of Children and Adults Aged 65+ in Population, and Median Household Income (Matched Group A) and Additionally Matched by Percent of the Residents Aged 25+ with Bachelor or Higher Degree (Matched Group B), NC, 2007-2013. (95% Confidence Intervals Are Shown in the Parentheses)

This table is available in its entirety in the online edition of the NCMJ.

*Statistically significant difference when compared to Study group 2.
n/a, non-applicable.

Conclusion

Southeastern North Carolina communities located in close proximity to hog CAFOs are characterized by poor indicators of health that are not solely due to the impact of converging demographic, socioeconomic, behavioral, and access-to-care factors, but are also due to the additional impact of multiple hog CAFOs located in this area. Although causality with specific exposures from hog CAFOs was not established, our findings suggest research is needed in environmental factors that may influence these outcomes. In addition, these findings suggest an immediate need for improved screening, diagnosis, and intervention for conditions including infant mortality and LBW infants that were found to be overrepresented in these communities. Poor health outcomes in North Carolina communities adjacent to hog CAFOs may also need to be addressed by improving access to medical resources, and future studies to determine the contribution of factors that influence these outcomes are needed. NCMJ

Julia Kravchenko, MD, PhD assistant professor, Environmental Health Scholars Program, Division of Surgical Sciences, Department of Surgery, Duke University School of Medicine, Durham, North Carolina.
Sung Han Rhew, PhD post-doctoral fellow, Environmental Health Scholars Program, Division of Surgical Sciences, Department of Surgery, Duke University School of Medicine, Durham, North Carolina.

Igor Akushevich, PhD associate research professor, The Biodemography of Aging Research Unit, Social Science Research Institute, Duke University, Durham, North Carolina.
Pankaj Agarwal data analyst/bioinformatician, Environmental Health Scholars Program, Division of Surgical Sciences, Department of Surgery, Duke University School of Medicine, Durham, North Carolina.
H. Kim Lyerly, MD director, Environmental Health Scholars Program; George Barth Geller Professor of Cancer Research; professor, Departments of Surgery, Immunology, and Pathology, Duke University School of Medicine, Durham, North Carolina.

Acknowledgments

The authors thank Fred and Alice Stanback for supporting the Environmental Health Scholars Program at the Division of Surgical Sciences, Department of Surgery, Duke University School of Medicine. The authors thank Christine B. Lawson and Amy Keyworth from the North Carolina Department of Environment and Natural Resources, Division of Water Resources, the Animal Feeding Operations Program (Raleigh, North Carolina), and Evan Kane (currently from the Wake County Environmental Services, water Quality Division, Groundwater Protection and Wells Section in Raleigh, North Carolina) for valuable information on regulations and management of hog farms in North Carolina.

Potential conflicts of interest. The authors have no relevant conflicts of interest.

References

1. Chetty R, Stepner M, Abraham S,et al. The association between income and life expectancy in the United States, 2001-2014. JAMA. 2016;315(16):1750-1766.
2. Lackland DT, Bendall HE, Osmond C, Egan BM, Barker DJ. Low birth weights contribute to the high rates of early-onset chronic renal failure in the southeastern United States. Acrch Intern Med. 2000;160(10):1472-1476.
3 Wing S, Wolf S. Intensive livestock operations, health, and quality of life among eastern North Carolina residents. Environ Health Perspect. 2000;108(3):233-238.
4 United States Department of Agricluture Census of Agriculture. 2012 Census Highlights: Hog and Pig Farming – A $22.5 billion industry, up 25 percent since 2007. USDA Census of Agriculture website. https://www.agcensus.usda.gov/Publications/2012/Online_Resources/Highlights/Hog_and_Pig_Farming/. Updated June 2014. Accessed July 19, 2018.
5 Preller L, Heederik D, Boleij J, Vogelzang PF, Tielen MJ: Lung function and chronic respiratory symptoms of pig farmers: focus on exposure to endotoxins and ammonia and use of disinfectants. Occup Environ Med. 1995;52(10):654-660.
6 Cole D, Todd L, Wing S. Concentrated swine feeding operations and public health: a review of occupational and community health effects. Environ Health Perspect. 2000;108(8):685-699.
7 Wing S, Horton RA, Marshall SW, et al. Air pollution and odor in communities near industrial swine operations. Environ Health Perspect. 2008;116(10):1362-1368.
8 Wing S, Freedman S, Band L. The potential impact of flooding on confined animal feeding operations in eastern North Carolina. Environ Health Perspect. 2002;110(4):387-391.
9 Burkholder J, Libra B, Weyer P, et al. Impacts of waste from concentrated animal feeding operations on water quality. Environ Health Perspect. 2007;115(2):308-312.
10 Wing S, Cole D, Grant G. Environmental injustice in North Carolina's hog industry. Environ Health Perspect. 2000;108(3):225-231.
11 Mirabelli MC, Wing S, Marshall SW, Wilcosky TC. Race, poverty, and potential exposure of middle-school students to air emissions from confined swine feeding operations. Environ Health Perspect. 2006;114(4):591-596.
12 Mirabelli MC, Wing S, Marshall SW, Wilcosky TC. Asthma symptoms among adolescents who attend public schools that are located near confined swine feeding operations. Pediatrics. 2006;118(1):e66-75.
13 Wing S, Horton RA, Rose KM. Air pollution from industrial swine operations and blood pressure of neighboring residents. Environ Health Perspect. 2013;121(1):92-96.
14 Schinasi L, Horton RA, Guidry VT, Wing S, Marshall SW, Morland K. Air pollution, lung function, and physical symptoms in communities near concentrated swine feeding operations. Epidemiology. 2011;22(2):208-215.
15 Donham KJ, Wing S, Osterberg D,et al. Community health and socioeconomic issues surrounding concentrated animal feeding operations. Environ Health Perspect. 2007;115(2):317-320.
16 Bullers S. Environmental stressors, perceived control, and health: the case of residents near large-scale hog farms in eastern North Carolina. Human Ecology. 2005;33(1):1-16.
17 Kilburn KH. Exposure to reduced sulfur gases impairs neurobehavioral function. South Med J. 1997;90(10):997-1006.
18 Thu KM. Public health concerns for neighbors of large–scale swine production operations. J Agric Saf Health. 2002;8(2):175-184.
19 Schiffman SS, Walker JM, Dalton P, et al. Potential health effects of odor from animal operations, wastewater treatment, and recycling of byproducts. J Agromedicine. 2004;9(2):397-403.
20 Merchant JA, Naleway AL, Svendsen ER, et al. Asthma and farm exposures in a cohort of rural Iowa children. Environ Health Perspect. 2005;113(3):350-356.
21 Chrischilles E, Ahrens R, Kuehl A, et al. Asthma prevalence and morbidity among rural Iowa schoolchildren. J Allergy Clin Immunol. 2004;113(1):66-71.
22 Kilburn KH. Human impairment from living near confined animal (hog) feeding operations. J Environ Public Health. doi: 10.1155/2012/565690.
23 Hribar C, Schultz M. Understanding Concentrated Animal Feeding Operations and their Impact on Communities. Bowling Green, OH: National Association of Local Boards of Health; 2010.
24 Nikolić M, Nikić D, Stanković A. Effects of air pollution on red blood cells in children. Pol J Environ Stud. 2008;17(28):267-271.
25 Porea TJ, Belmont JW, Mahoney DH. Zinc-induced anemia and neutropenia in an adolescent. J Pediatr. 2000;136(5):688-690.
26 Olsson M, Bensyrd I, Lundh T, Ottosson H, Skerfving S, Oskarsson A. Cadmium in blood and urine – impact of sex, age, dietary intake, iron status, and former smoking – association of renal effects. Environ Health Perspect. 2002;110(12)1185-1190.
27 Kramer MH, Herwaldt BL, Craun GF, Calderon RL, Juranek DD. Surveillance for waterborne-disease outbreaks: United States, 1993-1994. Atlanta, GA: US Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention (CDC); 1996.
28 Rinsky JL, Nadimpalli M, Wing S, et al. Livestock-associated methicillin and multidrug resistant Staphylococcus aureus is present among industrial, not antibiotic-free livestock operation workers in North Carolina. PLoS One. 2013;8(7):e67641.
29 Barton MD. Impact of antibiotic use in the swine industry. Curr Opin Microbiol. 2014;19:9-15.
30 Neyra RC, Frisancho JA, Rinsky JL, et al. Multidrug-resistant and methicillin-resistant Staphylococcus aureus (MRSA) in hog slaughter and processing plant workers and their community in North Carolina (USA). Environ Health Perspect. 2014;122(5):471-477.
31 Woolhouse M, Ward M, van Bunnik B, Farrar J. Antimicrobial resistance in humans, livestock and the wider environment. Philos Trans R Soc Lond B Biol Sci. 2015;370(1670):20140083.
32 North Carolina Provisional Vital Statistics. Raleigh, NC: North Carolina State Center for Health Statistics, North Carolina Department of Health and Human Services; 2007, 2010, 2011, 2013, 2014, 2015; https://schs.dph.ncdhhs.gov/data/vital.cfm. Accessed July 19, 2018.
33 Overview of the State Emergency Departmetn Databases (SEDD). Rockville, MD: Healthcare Cost and Utilization Project (H-CUP); 2007-2013; https://www.hcup-us.ahrq.gov/seddoverview.jsp. Accessed July 19, 2018.
34 Overview of the State Inpatient Databases (SID). Rockville, MD: Healthcare Cost and Utilization Project (H-CUP); 2007-2013; https://www.hcup-us.ahrq.gov/sidoverview.jsp. Accessed July 19, 2018.
35 Keyfitz N. Sampling variance of the standardized mortality rates. Hum Biol. 1966;38:309-317.
36 Bromberg S, Dill K. Molecular Driving Forces. New Yokr, NY: Garland Science; 2002.
37 Austin PC, Chiu M, Ko DT, Goeree R, Tu JV. Propensity score matching for estimating treatment effects. In: Faries DE, Leon AC, Haro JM, Obenchain RL, eds. Analysis of Observational Health Care Data Using SAS. Cary, NC: SAS Institute Inc.; 2010:51-84.
38 Erramouspe J, Adamcik BA, Carlson RK. Veterinarian perception

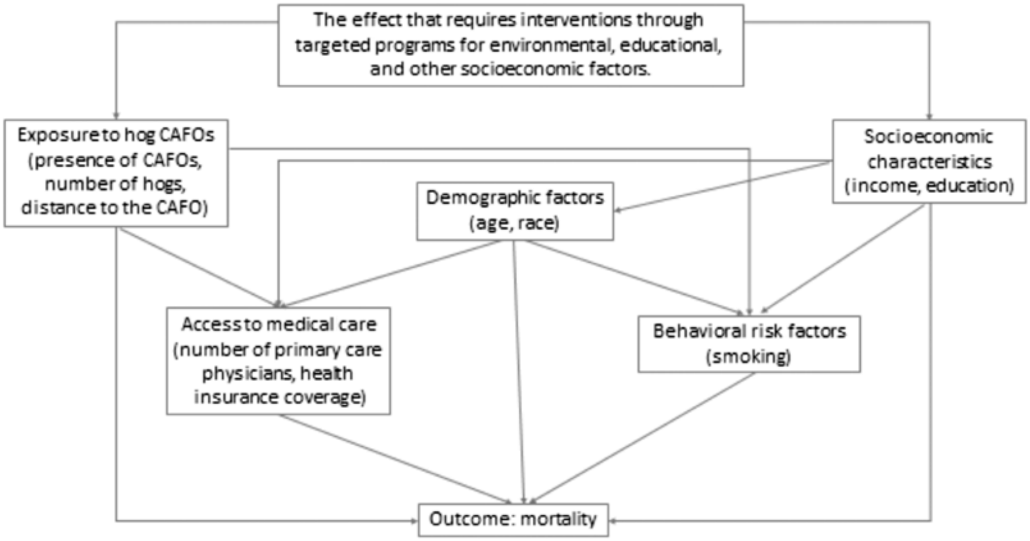
of the intentional misuse of veterinary medications in humans: a preliminary survey of Idaho-licensed practitioners. J Rural Health. 2002;18(2):311-318.
39 Sato Y, Fujimoto S, Konta T, et al. Anemia as a risk factor for all-cause mortality: obscure synergic effect of chronic kidney disease. Clin Exp Nephrol. 2018;22(2):388-394.
40 Del Fabbro P, Luthi JC, Carrera E, Michel P, Burnier M, Burnand B. Anemia and chronic kidney disease are potential risk factors for mortality in stroke patients: a historic cohort study. BMC Nephrol. 2010;11:27.
41 Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. PloS One. 2014;9(1):e84943.
42 Minchella PA, Donkor S, Owolabi O, Sutherland JS, McDermid JM. Complex anemia in tuberculosis: the need to consider causes and timing when designing interventions. Clin Infect Dis. 2014;60(5):764-772.
43 Ren A, Wang J, Ye RW, Li S, Liu JM, Li Z. Low first-trimester hemoglobin and low birth weight, preterm birth and small for gestational age newborns. Int J Gynaecol Obstet. 2007;98(2):124-128.
44 LeJeune J, Kersting A. Zoonoses: an occupational hazard for livestock workers and a public health concern for rural communities. J Agric Saf Health. 2010;16(3):161-179.
45 Malekinejad M, Parriott A, Viitanen AP, Horvath H, Marks SM, Kahn JG. Yield of community-based tuberculosis targeted testing and treatment in foreign-born populations in the United States: A systematic review. PloS One. 2017;12(8):e0180707.
46 Hanson MA, Gluckman PD. Early developmental conditioning of later health and disease: physiology or pathophysiology? Physiol Rev. 2014;94(4):1027-1076.
47 Duke University. Together Duke Advancing Excellence through Community, Academic Strategic Plan. Durham, NC: Duke University; 2017.

APPENDIX 1.
The International Classification of Diseases (ICD) Codes Used in the Analysis

ICD-9 codes (used for analysis of HCUP data)	
280-285	Anemia (includes Iron deficiency anemias, Other deficiency anemias, Hereditary hemolytic anemias, Acquired hemolytic anemias, Aplastic anemia and other bone marrow failure syndromes, Other and unspecified anemias)
580-589	Kidney disease (Nephritis, Nephrotic Syndrome, and Nephrosis)
010-018	Tuberculosis
038	Septicemia, 995.91 – Sepsis
V21.3	Low birth weight
ICD-10 codes (used for analysis of Multiple Cause of Death data)	
D50-D53, D55-D59, D60-D64	Anemia (includes Nutritional anemias, Hemolytic anemias, Aplastic and other anemias and other bone marrow failure syndromes)
N00-N19	Kidney disease (includes Glomerular diseases, Renal tubule-interstitial diseases, Acute kidney failure and chronic kidney disease)
A15-A19	Tuberculosis
A40, A41	Septicemia (includes Streptococcal sepsis, Other sepsis)
P07.1	Low birth weight newborn
P00-P96	Conditions originating in perinatal period
P00-P04	Newborns affected by maternal trauma
P10-P15	Disorders related to length of gestation and fetal growth

79502 APPENDIX 2.

FIGURE S1.
Illustration of the Relations in the Assessment of Potential Impact Factors-Outcome Associations



79502 APPENDIX 3.

APPENDIX 3.
Sensitivity Analysis

2a) Proc Genmod was used for GEE analysis

2b). The propensity score for matching zip codes without CAFO to zip codes with > 215hogs/km^2 (Study group 2) was evaluated using the percent of African Americans, percent of children and people aged 65+ among the residents, as well as median household income, and percent of people with a bachelor's or higher degree. The greedy matching algorithm [37] was used to match zip codes with close propensity scores.

The Matched group A included 56 zip codes that were matched by using the percent of African Americans, percent of children (aged 0-19) and people aged 65+ among the residents, and median household income. The Matched group B included 55 zip codes matched by above listed characteristics of Matched group A and additionally by the percent of people with a bachelor's or higher degree. Characteristics of matched zip codes (i.e., the results on balancing the variables in the matched groups) for the Matched group A and Matched group B are presented in Table S1.

79502 APPENDIX 4.

TABLE S1.
Characteristics of Matched Group A, Matched Group B, and Study Group 2, NC, 2007-2013

Variable	Matching design 1 Mean[1]±SE (95%CI)		Matching design 2 Mean[1]±SE (95%CI)	
	Matched group A	**Study group 2**	**Matched group B**	**Study group 2**
% of African-Americans	28.4±2.9% (22.8%-34.1%)	28.92±1.8% (25.5%-32.4%)	27.1%±3.0% (21.2%-33.0%)	28.9%±1.8% (25.4%-32.4%)
% of children (0-19 years old)	26.8±0.6% (25.7%-27.9%)	27.1±0.4% (26.2%-27.9%)	25.5%±0.6% (24.4%-26.6%)	27.3%±0.4% (26.3%-28.0%)
% of adults (65+ years)	14.0±0.6% (12.9%-15.2%)	14.3±0.4% (13.5%-15.2%)	15.0%±0.6% (13.8%-16.2%)	14.3%±0.4% (13.5%-15.2%)
Median household income (US dollars)	$35,640±$1,118 ($33,450-$37,831)	$36,521±$919 ($34,719-%38,322)	$34,933±$1,161 ($32,658-$37,208)	$36,527±$936 ($34,693-$38,362)
% of people with bachelor or higher degree education among those aged 25+ years	n/a	n/a	9.16%±0.8% (7.7%-10.7%)	11.1%±0.5% (10.2%-12.0%)

[1]Means are evaluated without weights representing zip-code populations.
n/a, non-applicable.

Then, age-adjusted total mortality rate and cause-specific rates of mortality, hospital admissions, and ED visits were compared between Matched group A and B and Study group 2 for underlying cause of death or primary diagnosis and for underlying-plus-secondary cause of death or primary-plus-secondary diagnosis. As shown in Table S5, mortality rates for total mortality and anemia and kidney as underlying causes were higher in Study group 2 than in Matched group A and B. Also, mortality rates of anemia, kidney disease, tuberculosis, and septicemia were higher in Study group 2 than in both matched groups for these diseases as underlying-plus-secondary causes of death. Hospital admission and ED visit rates were higher in Study group 2 than in Matched group A and B for kidney disease and tuberculosis (for primary diagnoses and for primary-plus-secondary diagnoses). ED visits rate for children with LBW also was higher in Study group 2 than in both matched groups (for primary-plus-secondary diagnosis).

TABLE S2.
Descriptive Table of the 3 Studied Groups of NC Communities with and without the Hog Concentrated Feeding Animal Operations (CAFOs): Race-Specific Population Groups, Socioeconomic Characteristics, Smoking Prevalence, and Access-To-Care Characteristics, NC, 2007-2013

Characteristics	NC communities with hog CAFOs (Study group 1)	NC communities with > 215hogs/km^2 (Study group 2)	NC communities without hog CAFOs (Control group)
Race (%):			
White	63.9%**	58.3%**	73.7%
African-American (AA)	28.8%*	31.3%**	19.3%
American Indian	2.4%*	4.1%**	0.8%
Asian	0.8%**	0.3%**	2.5%
Other	4.1%	6.0%**	3.7%
Median household income	$39,005**	$36,520**	$46,414
Bachelor or higher degree education	16.5%**	13.7%**	24.2%
Availability of primary care providers (per 100,000 population)	54**	51**	76
Percent of uninsured individuals	18.2%	18.5%	17.8%
Smokers prevalence among those aged 24+ years old	24.4%	25.9%**	24.0%

*$P < 0.05$.
**$P < 0.001$.

79502 APPENDIX 6.

TABLE S3.
Person-Years of Observations in Race-Specific Groups of the Residents of NC Communities from the 3 Studied Groups, NC, 2007-2013

Race	NC communities with hog CAFOs (Study group 1)	NC communities with > 215hogs/km^2 (Study group 2)	NC communities without hog CAFOs (Control group)
White	10,054,073	1,588,477	36,675,276
African-American (AA)	4,528,375	851,839	9,593,021
American Indian	370,901	111,226	411,900
Asian	129,901	8,574	1,242,243
Other	642,425	162,896	1,870,849

FIGURE S2.
Mortality Rates among Patients with Co-Existing Anemia, Kidney Disease, and Septicemia: The US Average, NC Average, and NC Communities with > 215hogs/km² (Study Group 2), 2007-2013. (95% Confidence Intervals Are Shown in the Parentheses)

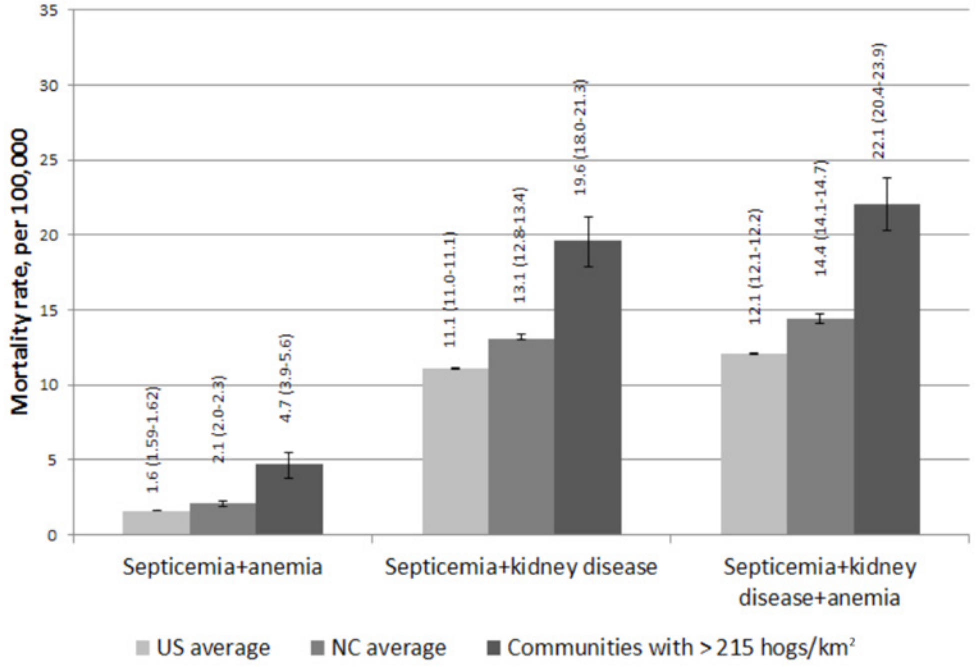


TABLE S4.
Age-Adjusted Mortality Rates (per 100,000) in NC Communities with > 215hogs/km^2 (Study Group 2): Ranks of This Area among the US States and District of Columbia with the Highest Mortality, 2007-2013. (95% Confidence Intervals Are Shown in the Parentheses)

Disease, cause of mortality	NC communities with > 215hogs/km^2	Rank of the area with > 215hogs/km^2 among the US states with the highest mortality	The US states (with their current respective ranks)[a] with mortality rates closest to the rates of the area with > 215hogs/km^2	
All-cause mortality	934 (922.7-944.8)	#4	#3 Alabama	940 (936.7-943.1)
Anemia:				
• as underlying cause,	2.6 (2.1-3.2)	#1	#1 Mississippi	2.3 (2.1-2.5)
• as underlying+secondary cause	**35.5** (33.4-37.7)	#1	#1 West Virginia	24.4 (23.7-25.2)
Kidney disease:				
• as underlying cause,	24.8 (23.0-26.6)	#2	#1 Louisiana	26.2 (25.7-26.8)
• as underlying+secondary cause	**119** (114.6-122.5)	#1	#1 West Virginia	96.2 (94.7-97.7)
Tuberculosis:				
• as underlying+secondary cause	0.63 (0.32-0.81)	#3	#2 District of Columbia	0.73 (0.49-1.04)
Septicemia:				
• as underlying cause,	16.6 (15.1-18.1)	#7	#6 Alabama	17.0 (16.6-17.4)
• as underlying+secondary cause	75.1 (71.9-78.2)	#2	#1 District of Columbia	83.6 (80.7-86.4)

[a]Mortality rates were calculated using the Multiple Cause of Death data from the Centers for Disease Control and Prevention (https://wonder.cdc.gov/mcd.html).

79502 APPENDIX 9.

FIGURE S3.
Locations of Matched NC Zip Codes without Hog CAFOs (Matched Group A and Matched Group B) and Locations of Zip Codes with > 215hogs/km^2 (Study Group 2)

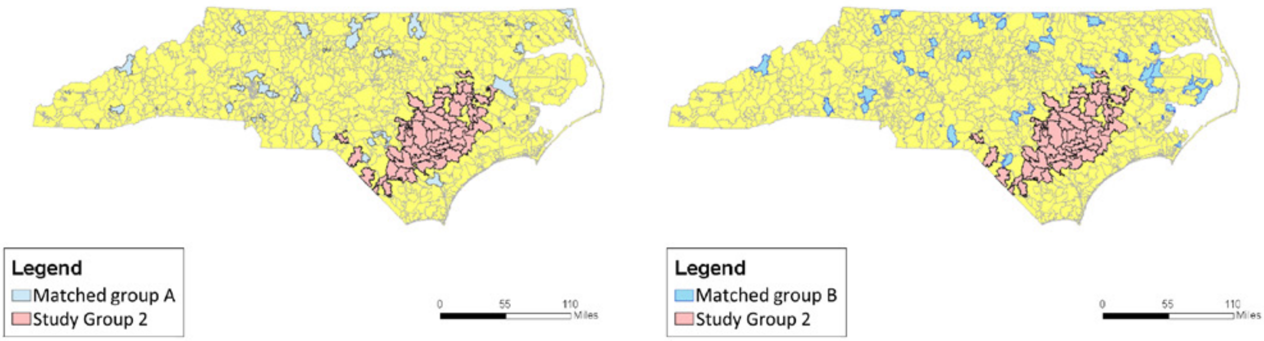


TABLE S5.
Age-Adjusted Cause-Specific Rates (per 100,000) of Mortality, Hospital Admissions, and ED Visits in Communities Located in Zip Codes with > 215hogs/km^2 (Study Group 2) and in Communities Located in Zip Codes Matched by Percent of African Americans, Percent of Children and Adults Aged 65+ in Population, and Median Household Income (Matched Group A) and Additionally Matched by Percent of the Residents Aged 25+ with Bachelor or Higher Degree (Matched Group B), NC, 2007-2013. (95% Confidence Intervals Are Shown in the Parentheses)

		Underlying cause/Primary diagnosis			Underlying+secondary cause/ Primary+secondary diagnosis		
Outcome	**Disease**	**Study group 2**	**Matched group A**	**Matched group B**	**Study group 2**	**Matched group A**	**Matched group B**
Mortality	Total mortality	**934** (922.7-944.8)	**867*** (857.9-875.3)	**920*** (908.6-930.8)	**934** (922.7-944.8)	**867*** (857.9-875.3)	**920*** (908.6-930.8)
	Anemia	**2.65** (2.2-3.2)	**2.1*** (1.6-2.5)	**1.8*** (1.3-2.2)	**35.5** (33.4-37.7)	**20.6*** (19.2-21.9)	**24.1*** (22.3-25.9)
	Kidney disease	**24.8** (23.0-26.6)	**20.9*** (19.6-22.3)	**22.5*** (20.7-24.2)	**119** (114.6-122.5)	**90.1*** (87.2-92.9)	**107*** (103.3-110.9)
	Tuberculosis	0.21 (0.04-0.38)	0.11 (0.01-0.20)	**0.04*** (0.04-0.13)	**0.55** (0.28-0.82)	**0.25*** (0.10-0.40)	**0.24*** (0.06-0.42)
	Septicemia	16.6 (15.1-18.1)	15.9 (14.7-17.1)	16.7 (15.2-18.2)	**75.1** (72.0-78.2)	**62.7*** (60.3-65.0)	**67.6*** (64.6-70.6)
Hospital	Anemia	113 (108.6-116.4)	116 (112.3-118.6)	**141*** (136.3-145.3)	2,179 (2,162-2,196)	**1,867*** (1,854-1,880)	2,165 (2,148-2,183)
	Kidney disease	**187** (181.6-191.4)	**152*** (148.5-155.8)	**175*** (170.4-180.1)	**2,031** (2,015-1,2048)	**1,713*** (1,701-1,725)	**1,864*** (1,848-1,880)
	Tuberculosis	**3.1** (2.4-3.7)	**1.7*** (1.4-2.1)	**0.86*** (0.51-1.21)	**6.2** (5.3-7.2)	**3.7*** (3.2-4.3)	**2.4*** (1.9-3.0)
	Sepsis	313.1 (306.7-319.5)	**272*** (267.4-277.2)	**324*** (317.2-330.4)	468 (460.3-475.9)	**396*** (390.4-402.2)	466 (458.4-474.3)
	Low birth weight	n/a	n/a	n/a	2.5 (1.9-3.1)	**1.5*** (1.2-1.9)	2.3 (1.7-2.9)
ED visits	Anemia	85.4 (81.9-88.9)	88.5 (85.8-91.3)	**115*** (111.0-119.3)	682 (672.2-691.7)	**570*** (563.0-577.0)	**729*** (718.6-739.0)
	Kidney disease	**33.2** (31.1-35.3)	**25.1*** (23.6-26.6)	31.7 (29.6-33.8)	643 (634.0-652.3)	**517*** (510.7-524.2)	633 (623.7-642.3)
	Tuberculosis	**0.32** (0.11-0.53)	**0.15*** (0.04-0.25)	**0.08*** (0.03-0.18)	**1.4** (1.0-1.9)	**0.89*** (0.62-1.17)	**0.61*** (0.32-0.90)
	Sepsis	20.1 (18.5-21.7)	**12.1*** (11.1-13.2)	21.3 (19.6-23.0)	35.5 (33.3-37.6)	**20.1*** (18.7-21.4)	33.1 (31.0-35.2)
	Low birth weight	n/a	n/a	n/a	**4.7** (3.9-5.5)	**1.04*** (0.74-1.34)	**1.9*** (1.4-2.5)

*Statistically significant difference when compared to Study group 2.
n/a, non-applicable.