Proximity to Swine Farming Operations as a Risk Factor for Eosinophilic Esophagitis

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Abstract: We aimed to determine whether residential proximity to permitted swine facilities was associated with an increased risk of eosinophilic esophagitis (EoE) by conducting a case-control study using 2 complementary data sources: 1 from a tertiary care center (n = 401 cases and 1805 controls) and 1 from a large pathology group (n = 904 cases and 4074 controls). Addresses of the subjects and swine facilities were geocoded, and adjusted odds of EoE relative to proximity to and density of swine facilities were calculated. We observed a positive association between proximity to a permitted swine facility (<1 mile) and odds of EoE (adjusted odds ratio R, 2.56; 95% CI, 1.33–4.95) in the tertiary center data; density of farms (>10 farms/census tract) was also positively associated (adjusted odds ratio, 2.76; 95% CI, 1.30–5.84). However, this association was not observed in the pathology database. Though proximity to and density of swine operations were associated with EoE, associations were sensitive to the database used.

Key Words: eosinophilic esophagitis, risk factors, farms, etiology

What Is Known?

- The increasing incidence of eosinophilic esophagitis (EoE) suggests changing environmental factors play a role in its etiology.
- We have previously shown that EoE may be more likely in rural areas, but the reasons for this are unknown.

What Is New?

- In this case-control study using both tertiary care data and data from a large pathology database, we examined proximity to commercial swine farms as a possible risk factor for EoE.
- We found that EoE was associated with both proximity to swine facilities and with the density of farms in the tertiary center data, though the association was not observed when evaluating subjects from the pathology database.

INTRODUCTION

The increasing incidence and prevalence of eosinophilic esophagitis (EoE) suggest that changing environmental factors, potentially interacting with esophageal barrier defects, drive EoE pathogenesis (1). A number of environmental exposures have been associated with EoE. We previously found relationships between low population density, poor water quality, and EoE prevalence (2,3), but these are likely proxies for other specific factors impacting disease development. For example, large-scale animal feeding operations are more common in areas of low population density, may impact water sources, and have been associated with increased exposure to immune-modifying compounds as well as several diseases in humans (4–6). However, proximity to these has never been assessed as a risk factor for EoE. Therefore, we aimed to determine whether residential proximity to permitted swine facilities was associated with an increased risk of EoE.

METHODS

We performed a case-control study of patients who had undergone upper endoscopy and biopsy using 2 complementary data sources from 2008 to 2015. The first was an EoE and endoscopy database from the University of North Carolina (UNC), a tertiary care center. The second was a national pathology database from Inform Diagnostics (previously called Miraca LifeSciences), restricted to data obtained from residents of NC only and reflective of a general practice setting. Details related to the creation of both databases, as well as histopathologic examination protocols, have been previously reported (2,3,7–9). Cases from UNC were newly diagnosed with EoE per consensus guidelines available at the time of diagnosis (10). Cases from the pathology database had active esophageal eosinophilia ≥15 eos/hpf (hpf area = 0.237mm^2), with other pathologic or clinical causes of eosinophilia on available records excluded. The primary control group was patients who underwent upper endoscopy and had no indication of any esophageal pathology. We used a second control group of patients with Barrett's esophagus (BE) for sensitivity analyses to test the

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robustness of results, given the potential for selection bias from differences in specialty referral patterns for those with and without a more significant disease presentation.

The exposures of interest were proximity to and density of permitted swine facilities (typically housing ≥250 pigs), which were determined using data obtained from the NC Division of Water Resources, Animal Feeding Branch. Residential addresses of the subjects from both data sources and swine facility locations were geocoded using ArcGIS (Version 10.0). For analysis, we used generalized linear models (logit link; binomial distribution) to estimate the adjusted odds ratio (aOR; adjusted for age, sex, race, and population density) of EoE relative to each exposure. The study was approved by the UNC Institutional Review Board.

RESULTS

The tertiary center assessment identified 401 cases and 1852 endoscopy-based controls, whereas the pathology database yielded 904 cases and 4074 endoscopy-based controls. Cases were generally younger, and a higher proportion were male, compared with controls (Table 1); 6.3% of patients were <18 years old in the tertiary database, whereas 0.9% were <18 years old in the pathology data. We observed a positive association between proximity to a permitted swine facility (<1 mile distance) and odds of EoE (aOR, 2.56; 95% CI, 1.33–4.95) compared with endoscopy-based controls in the tertiary center data; density of farms (>10 farms/census tract) was also positively associated with EoE (aOR, 2.76; 95% CI, 1.30–5.84) (Table 2). However, this association was not observed when evaluating subjects from the pathology database (Table 2).

In sensitivity analyses, we identified 432 BE controls from the tertiary care center and 1853 BE controls from the pathology database (Table 1). In the tertiary center data, we found a similar magnitude of association with swine operation density (aOR, 2.27; 95% CI, 0.96–5.33), but an attenuation of association with proximity (aOR. 1.80; 95% CI, 0.59–5.48) (Table 2). In the pathology database, there was no association observed between swine operations and EoE when using BE controls (Table 2).

DISCUSSION

The rapidly evolving epidemiology of EoE strongly suggests etiologic environmental factors. In this study, we extended our prior work on exposure patterns previously observed for increased odds of EoE in rural areas and related to poor water quality (2,3). To do this, we focused on data from North Carolina, where we could examine granular data from a single referral center and complimentary information from a pathology database. We found increased odds of EoE with closer proximity to and a higher density of commercial swine farms, when considering the tertiary center data and endoscopy controls, though this was not confirmed in the pathology database, and the relationship was less prominent with BE controls, highlighting potential referral bias. Nevertheless, this study is an example where a general association (increased EoE in rural areas or with poor water quality) leads to a more detailed etiologic exposure (commercial farms).

Prior research has demonstrated increased health risks across multiple diseases by proximity to swine farms (4–6). However, it is not clear if these risks are from waste byproducts in the groundwater, chemicals involved in the farming process or airborne contaminants, other features of the farms themselves, or if they are proxy measures for some other exposure within the same area. Future research will

TABLE 1. Characteristics of the study populations

	Tertiary center data source			Pathology database source		
	EoE cases (n = 401)	Endoscopy controls (n = 1852)	BE controls (n = 432)	EoE cases (n = 904)	Endoscopy controls (n = 4074)	BE controls (n = 1858)
Age (mean years ± SD)	28.0 ± 19.4	51.4 ± 17.6	57.6 ± 28.5	45.4 ± 14.7	53.5 ± 15.3	61.2 ± 12
Male (n, %)*	283 (70.6)	650 (35.1)	159 (64.9)	534 (59.1)	1183 (29.1)	1251 (67.4)
White (n, %)	309 (77.1)	1346 (72.7)	231 (94.3)	-	-	-
White (mean proportion ± SD)†	-	-	-	72.9 ± 17.0	67.2 ± 20.3	69.9 ± 18.5
Population density (mean persons/square mile ± SD‡	1391 ± 1418	1189 ± 1375	962 ± 1115	998 ± 1126	1065 ± 1192	944 ± 1075
Distance to farm (n, %)						
<1 mile	14 (3.5)	28 (1.5)	5 (1.2)	29 (3.2)	151 (3.7)	48 (2.6)
1–5 miles	77 (19.2)	288 (15.6)	51 (11.8)	247 (27.3)	1120 (27.5)	541 (29.1)
5–10 miles	110 (27.4)	474 (25.6)	131 (30.3)	272 (30.1)	1386 (34.0)	570 (30.7)
>10 miles	200 (49.9)	1062 (57.3)	245 (56.7)	356 (39.4)	1417 (34.8)	699 (37.6)
Farm density in census tract (n, %)						
0 farms	345 (86.0)	1665 (89.9)	216 (50.0)	734 (81.2)	3300 (81.0)	1496 (80.5)
0–5 farms	35 (8.7)	131 (7.1)	16 (3.7)	116 (12.8)	517 (12.7)	263 (14.2)
5–10 farms	7 (1.7)	25 (1.3)	6 (1.4)	37 (4.1)	133 (3.3)	53 (2.9)
>10 farms§	14 (3.5)	31 (1.7)	7 (1.6)	16 (1.8)	124 (3.0)	46 (2.5)

BE = Barrett's esophagus; EOE = eosinophilic esophagitis.
*5 patients were missing sex information in the tertiary center data, and 4 were missing sex information in the pathology database.
†Proportion of residents with white race in census tract of residence for the pathology database.
‡Obtained from linkage to 2010 US Census data, with density determined by zip code.
§Maximum 125 farms.

TABLE 2. Associations between farm distance or farm density and EoE

	Tertiary center data source		Pathology database source	
	EoE vs endoscopy controls	EoE vs BE controls	Esophageal eosinophilia vs endoscopy controls	Esophageal eosinophilia vs BE controls
	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Distance to farm				
<1 mile	2.56 (1.33–4.95)	1.80 (0.59–5.48)	0.89 (0.58–1.38)	1.73 (0.95–3.18)
1–5 miles	1.15 (0.79–1.69)	1.25 (0.74–2.11)	0.97 (0.79–1.19)	1.01 (0.78–1.30)
5–10 miles	1.07 (0.78–1.47)	1.03 (0.65–1.63)	0.88 (0.74–1.06)	1.03 (0.81–1.32)
>10 miles	Ref.	Ref.	Ref.	Ref.
Farm density in the census tract				
0 farms	Ref.	Ref.	Ref.	Ref.
1–5 farms	1.27 (0.78–2.07)	2.33 (1.09–4.99)	0.96 (0.73–1.26)	1.00 (0.71–1.40)
6–10 farms	1.39 (0.57–3.39)	1.09 (0.31–3.87)	1.10 (0.80–1.52)	1.84 (1.01–3.09)
>10 farms	2.76 (1.30–5.84)	2.27 (0.96–5.33)	0.72 (0.39–1.32)	0.90 (0.44–1.83)

Multivariable logistic regression models adjusted for age, sex, race, and population density. aOR = adjusted odds ratio; BE = Barrett's esophagus; CI = cofidence interval; EOE = eosinophilic esophagitis.

need to delve into these specific factors with measures taken directly from patient samples and should also be powered to assess for any effect in children. Limitations of this study include the retrospective design with limited data elements available (eg, symptom duration; time of exposure farm; atopy; histologic fibrosis; and EoE severity), that associations are ecologic, that we are not able to determine causality, and that findings were not consistent between databases. However, we have used 2 complementary databases that yielded cases and controls throughout NC and assessed 2 different control groups in sensitivity analyses.

In conclusion, while we observed a positive association between proximity to and density of swine operations in relation to EoE, associations were sensitive to the database used and the selection of controls. While not formally evaluated, bias resulting from variation in referral patterns may contribute to the differences in estimates observed between the tertiary center and pathology databases. Additional studies with well-characterized cases and appropriately selected controls with biosamples available to more accurately measure exposures may build on the evidence provided.

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