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Prevalence and Geographic Distribution of Pediatric Eosinophilic Esophagitis in the 2012 U.S. Medicaid Population

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Eosinophilic esophagitis (EoE) is estimated to affect 34.4/100,000 individuals,(1) and the incidence appears to be increasing.(2) However, previous prevalence studies used administrative data that did not include those insured by Medicaid, a federally-funded program available to low-income Americans. Furthermore, while disparities in asthma morbidity(3) and food allergy (4) have been seen by socioeconomic status, our understanding of the association between EoE, poverty, and urbanization is poor. Our objective was to estimate the overall prevalence of EoE among children enrolled in Medicaid, and to examine this prevalence by gender, race/ethnicity, urban/rural status, and neighborhood-level poverty.

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Clinical Implications: Among 18,452,886 children enrolled in Medicaid in 2012, children living in areas with higher neighborhood-level poverty were less likely to be diagnosed with EoE. Whether this is due to unique environmental exposures or under-diagnosis and under-treatment remains unknown.

This was a cross-sectional study of individuals aged 0–17 years enrolled in Medicaid in 2012. Individuals were included if they were enrolled for the full 12-month period. EoE was defined as having at least one inpatient or outpatient visit with an International Classification of Diseases, Ninth Revision (ICD-9) code for EoE (530.13) during the 12-month period. Period prevalence was estimated by dividing the number of EoE cases by the total number of included individuals. Prevalence estimates were stratified by age, race/ethnicity, gender, rural/urban classifications, and poverty status. Multivariable logistic regression, adjusted for the above covariates and state of residence, was used to assess the relationship between poverty, urban/rural status, and EoE. Further details regarding the study methodology can be found in the Online Repository Text and Figure E1.

A total of 18,452,886 individuals were included. Population characteristics and EoE prevalence estimates are presented in Table E1. Among this population, 4,836 cases of EoE were identified, for an overall prevalence of 26.21/100,000. The prevalence estimates were highest among males (35.68/100,000), those with self-reported “White” (43.97/100,000) and “Unknown” (62.85/100,000) race/ethnicity, those living in large fringe-metro (suburban) areas (32.03/100,000) and those living in ZCTAs with 0–5% of the population below the poverty level (42.91/100,000). The five states with the highest prevalence of EoE were New Hampshire, West Virginia, Tennessee, Utah, and Arizona (Figure 1).

In unadjusted models, children living in large-central metro areas had the lowest odds of EoE (Table 1). However, when adjusting for potential confounders, this relationship changed, and living in rural areas was protective for EoE diagnosis when compared to large-central metro areas (small metro: OR 0.78; 95% CI 0.69–0.88); micropolitan: OR 0.79; 95% CI 0.70–0.89; non-core (rural): OR 0.68; 95% CI 0.59–0.78, all p<0.001). This inversion appeared to be driven by adjustment for race/ethnicity rather than age or neighborhood-level poverty (Table E2). There was also a negative relationship between poverty and EoE diagnosis, with less neighborhood poverty conveying a significantly higher odds of EoE diagnosis (OR 3.09; 95% CI 2.69–3.54; p<0.001), which persisted in adjusted models (Table 1). These results did not change in a sensitivity analysis including states that were previously excluded due to missing data on race/ethnicity (Table E3).

In this study of 18,452,886 children enrolled in Medicaid in 2012, we found that the overall prevalence of EoE was 26.21/100,000. In addition, we found that living in rural areas (compared to large-central metro) and in areas with more neighborhood poverty were associated with a lower odds of being diagnosed with EoE. Finally, we found that there was notable spatial variation in the prevalence of EoE, with some states (i.e. NH, WV, and TN) showing markedly higher rates than others (CA, ND, and TX), (Figure 1). Future research should explore environmental factors that may explain these differences, such as exposure to fine and coarse particulate matter.

Previous studies examining the association between EoE and urbanization have yielded conflicting results. Using a national pathology database, Jensen *et al* found that the odds of having esophageal eosinophilia was higher among individuals living in areas with low population density.(5) While we found similar results in unadjusted models, when we adjusted for potential confounders, the odds of being diagnosed with EoE was lower in rural areas. This inversion is likely due to confounding by race/ethnicity, as the proportion of non-Hispanic Whites living in rural areas is high (>40%), and the prevalence of EoE is higher among this population (Table E1). (7)It is also possible that the discrepancy in our findings and that of Jensen *et al* may be due differences in the definition of urbanization or the age of the study populations. as <3% of the biopsies in the previous study were from pediatric patients. Further research into whether there are unique protective factors in rural environments, and whether the determinants of EoE are different among children and adults, is clearly needed.

While disparities in asthma morbidity and food allergy diagnosis by poverty have been seen, (3, 4) very little is known about the effect of poverty on EoE. One previous case-control study found that individuals with EoE were more affluent and more educated than control populations, but this association did not persist when adjusting for race/ethnicity, and the study was limited by selection bias.(6) Using a cohort in Southern California, Kim *et al,* demonstrated that EoE was more prevalent among households with higher annual income, however this study did not assess whether this was due to confounding by gender or race/ethnicity.(7) In our study examining a broader U.S. population, we similarly found that children living in areas with more neighborhood poverty were less likely to be diagnosed with EoE, despite adjusting for potential confounders. Whether this is due to unique environmental exposures that are protective for the development of EoE, under-diagnosis and/or under-perception of EoE, or lack of access to care in impoverished populations is unknown and warrants further study.

This study is primarily limited by the utilization of ICD-9 coding to define EoE, which has been shown to be specific (99%), but not sensitive (60%),(8) for identifying patients with EoE. Furthermore, this data was collected prior to the revised EoE diagnosis guidelines,(9) and thus the ICD-9 code may have been reserved for individuals who completed a PPI trial. Thus, it is possible that the prevalence of EoE was underestimated in this population. This study is further limited by the lack of individual-level data on income, potentially leading to residual confounding and ecological fallacy. In addition, a large number of individuals with EoE had “Unknown” race/ethnicity, which limits our ability to make meaningful conclusions about the differences in EoE prevalence by race/ethnicity. Finally, the results of this study may not be generalizable to all socioeconomic groups. These limitations, however, are balanced by the fact that this study included over 18 million children enrolled in a nationwide database, which enables us to identify associations with low-income children across the U.S., rather than relying on a specific geographic region. Furthermore, this is the first study to examine the association between neighborhood-level poverty and EoE.

In summary, our findings suggest that EoE is less prevalent among children living in impoverished areas. Whether the prevalence of EoE is truly lower in this population, and if so, whether this is due to unique environmental exposures or under-diagnosis and under-treatment remains unknown and warrants further study.

Online Repository Text

Participants

As previously described, the data were centrally compiled and cleaned by the Research Data Assistance Center (ResDAC, University of Minnesota, Minneapolis, MN)(3) and obtained by the authors in August 2018. Medicaid data were collected and aggregated on the state level and then processed by the Centers for Medicare and Medicaid into the Medicaid Analytic Extract (MAX), with individuals grouped by zip-code tabulation area (ZCTA). All individuals aged 0–17 who were enrolled for the entirety of 2012 were eligible for inclusion in these analyses. The ZCTA data was then linked to the 2013 NCHS Urban-Rural Classification scheme for Counties, based on the containing county, and the 2011 American Community Survey. Use of the data was approved by the Johns Hopkins School of Medicine Institutional Review Board, and all analyses were performed in R.

Three states were excluded from the analysis because of concerns about data quality: Maine, which had incomplete utilization data, and Idaho and Rhode Island, which had abnormally low levels of enrollment (<1000 individuals). In addition, five states were excluded because greater than 15% of subjects had missing data for race/ethnicity: Colorado (n=241,722), Iowa (n=178,524), Massachusetts (n=356,927), Vermont (n=42,066), and Washington (n=489,916). This data linkage and exclusion process is depicted in Figure E1.

Definition of Covariates

Urbanization was categorized according to this scheme as “large central metro,” “large fringe metro (suburban)” “medium metro” (250,000–999.999 population), “small metro” (50,000 –249,999 population), “micropolitan” (10,000 – 49,999 population, and “noncore” (rural, <10,000 population). Neighborhood-level poverty was defined as the proportion of families at or below the poverty level in the ZCTA. Race/ethnicity was defined by self-report, and categories included “White,” “Black,” “Asian,” “Hispanic,” “North American Native,” “>1 race (Hispanic), >1 race (non-Hispanic), Hawaiian, and “Unknown.” For the purpose of analysis, “Native American/Alaskan,” “>1 race (Hispanic), “>1 race (non-Hispanic),” and “Hawaiian” were combined into “Grouped.”

Statistical Analysis

Age, race, gender, ZCTA-level poverty, and county urban-rural code were all treated as categorical variables in the multivariable logistic regression models. In addition to the analyses described in the main manuscript, sensitivity analyses were performed to a) examine whether the inversion of the association between urban/rural status and EoE diagnosis was due to confounding by race/ethnicity or neighborhood-level poverty and to b) assess whether the exclusion of States due to missing data on race/ethnicity influenced the overall results. In order to graphically depict the prevalence of EoE, county-level estimates were plotted and adjusted for the statewide average (“smoothed”) in order to account for differences in the number of enrollees in each county. In all analyses, correlation within zip-code tabulation area (ZCTA) was accounted for using generalized estimating equations.

Supplemental Results

In order to further examine whether the inversion of the association between urban/rural status and EoE diagnosis was due to confounding by race/ethnicity or neighborhood-level poverty, we first adjusted the analyses for only gender and age (Table E2, Model 1), and the results did not change. We then adjusted the model for gender, age, and race/ethnicity, and the results were similar to the inversion seen in the full model (Table E2, Model 2). Finally, we then further adjusted for neighborhood-level poverty (Table E2, Final Model), and the results were unchanged. In the sensitivity analysis examining the exclusion of States with missing data, the trends and conclusions depicted in the main manuscript did not change (Table E3).

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Appendix

Table E1:

EoE Prevalence by Demographic Characteristics

	Overall Medicaid Population	EOE Cases	EOE Prevalence (per 100,000)
Overall	18,452,886	4,836	26.21
Gender			
Male	9,439,267 (51%)	3,368	35.68
Female	9,013,619 (49%)	1,468	16.29
Age Categories			
0–2 y	2,869,959 (16%)	751	26.17
3–5 y	4,084,601 (22%)	1,059	25.93
6–8 y	3,463,024 (19%)	911	26.31
9–11 y	3,173,084 (17%)	890	28.05
12–14 y	2,796,751 (15%)	745	26.64
15–17 y	2,065,467 (11%)	480	23.24
Race/Ethnicity			
White	6,531,027 (35%)	2,872	43.97
Black	4,775,776 (26%)	748	15.66
Asian	483,620 (3%)	64	13.22
Hispanic	4,261,405 (23%)	369	8.66
Grouped[§]	1,492,556 (8%)	212	14.20
Unknown	908,502 (5%)	571	62.85
Urban/Rural			
Large Central Metro	6,603,911 (36%)	1,308	19.81
Large Fringe Metro	3,327,678 (18%)	1,066	32.03
Medium Metro	3,976,658 (22%)	1,147	28.84
Small Metro	1,588,802 (9%)	456	28.70

	Overall Medicaid Population	EOE Cases	EOE Prevalence (per 100,000)
Micropolitan	1,733,698 (9%)	531	30.63
Noncore (rural)	1,222,139 (7%)	328	26.84
ZCTA-Level Poverty			
0 – 5%	1,931,817 (11%)	829	42.91
6 – 10%	4,057,501 (22%)	1,458	35.93
11 – 15%	4,235,865 (23%)	1,180	27.86
16 – 20%	3,151,910 (17%)	657	20.84
21 – 25%	1,977,825 (11%)	281	14.21
26 – 100%	3,097,968 (17%)	431	13.91

Values expressed as n (%)

§Defined as the combination of "Native American/Alaskan," ">1 race (Hispanic), ">1 race (non-Hispanic)," and "Hawaiian"ZCTA: Zip-code tabulation area 60

Table E2:

Association Between ZCTA-Level Poverty, Urban/Rural Status and EoE

	Model #1	95% CI	Model #2	95% CI	Final Model	95% CI
Urban/Rural Status						
Large Central Metro	REF		REF		REF	
Large Fringe Metro	1.42	1.29 – 1.56	1.07	0.98 – 1.18	0.93	0.84 – 1.02
Medium Metro	1.32	1.19 – 1.46	1.01	0.92 – 1.12	0.95	0.86 – 1.05
Small Metro	1.16	1.02 – 1.32	0.82	0.73 – 0.93	0.78	0.69 – 0.88
Micropolitan	1.22	1.08 – 1.37	0.81	0.72 – 0.92	0.79	0.70 – 0.89
Noncore (rural)	1.03	0.89 – 1.19	0.68	0.59 – 0.78	0.68	0.59 – 0.78

Model #1: Adjusted for state, gender, and age

Model #2: Adjusted for state, gender, age, and race/ethnicity

Final Model: Adjusted for state, gender, age, race/ethnicity, and neighborhood-level poverty

Table E3:

Sensitivity Analysis including States previously excluded due to missing data

	Model #1	95% CI	Model #2	95% CI
Gender				
Female	REF		REF	
Male	2.14	2.01 – 2.27	2.08	1.98 – 2.23
Age Categories				
0–2 y	REF		REF	
3–5 y	0.99	0.90 – 1.09	0.99	0.90 – 1.08
6–8 y	0.99	0.89 – 1.09	1.01	0.92 – 1.11
9–11 y	1.03	0.94 – 1.14	1.05	0.96 – 1.16
12–14 y	0.98	0.89 – 1.09	1.01	0.92 – 1.12
15–17 y	0.87	0.77 – 0.98	0.90	0.81 – 1.01
Race/Ethnicity				
White	REF		REF	

	Model #1	95% CI	Model #2	95% CI
Black	0.41	0.38 – 0.45	0.41	0.38 – 0.45
Asian	0.37	0.28 – 0.49	0.38	0.29 – 0.49
Hispanic	0.31	0.27 – 0.35	0.31	0.27 – 0.35
Grouped[§]	0.40	0.34 – 0.47	0.45	0.39 – 0.52
Unknown	1.64	1.48 – 1.80	1.43	1.30 – 1.58
Urban/Rural Status				
Large Central Metro	REF		REF	
Large Fringe Metro	0.93	0.84 – 1.02	0.97	0.89 – 1.07
Medium Metro	0.95	0.87 – 1.05	0.97	0.88 – 1.06
Small Metro	0.78	0.69 – 0.88	0.76	0.68 – 0.86
Micropolitan	0.79	0.70 – 0.89	0.80	0.71 – 0.90
Noncore (rural)	0.68	0.59 – 0.78	0.67	0.59 – 0.77
ZCTA-Level Poverty				
< 5%	2.00	1.75 – 2.28	1.98	1.74 – 2.26
6 – 10%	1.78	1.57 – 2.00	1.78	1.58 – 2.00
11 – 15%	1.50	1.33 – 1.69	1.52	1.34 – 1.71
16 – 20%	1.30	1.14 – 1.49	1.34	1.17 – 1.52
21 – 25%	0.99	0.84 – 1.16	1.00	0.86 – 1.17
26 – 100%	REF		REF	

Values expressed as odds ratios (OR) and 95% CIs

[*] Model #1 is the final adjusted model defined in the manuscript, excluding States with >15% missing data for race/ethnicity

[*] Model #2 is the final adjusted model defined in the manuscript, including States with >15% missing data for race/ethnicity

[§] Defined as the combination of "Native American/Alaskan," ">1 race (Hispanic), ">1 race (non-Hispanic)," and "Hawaiian" ZCTA: Zip-code tabulation area

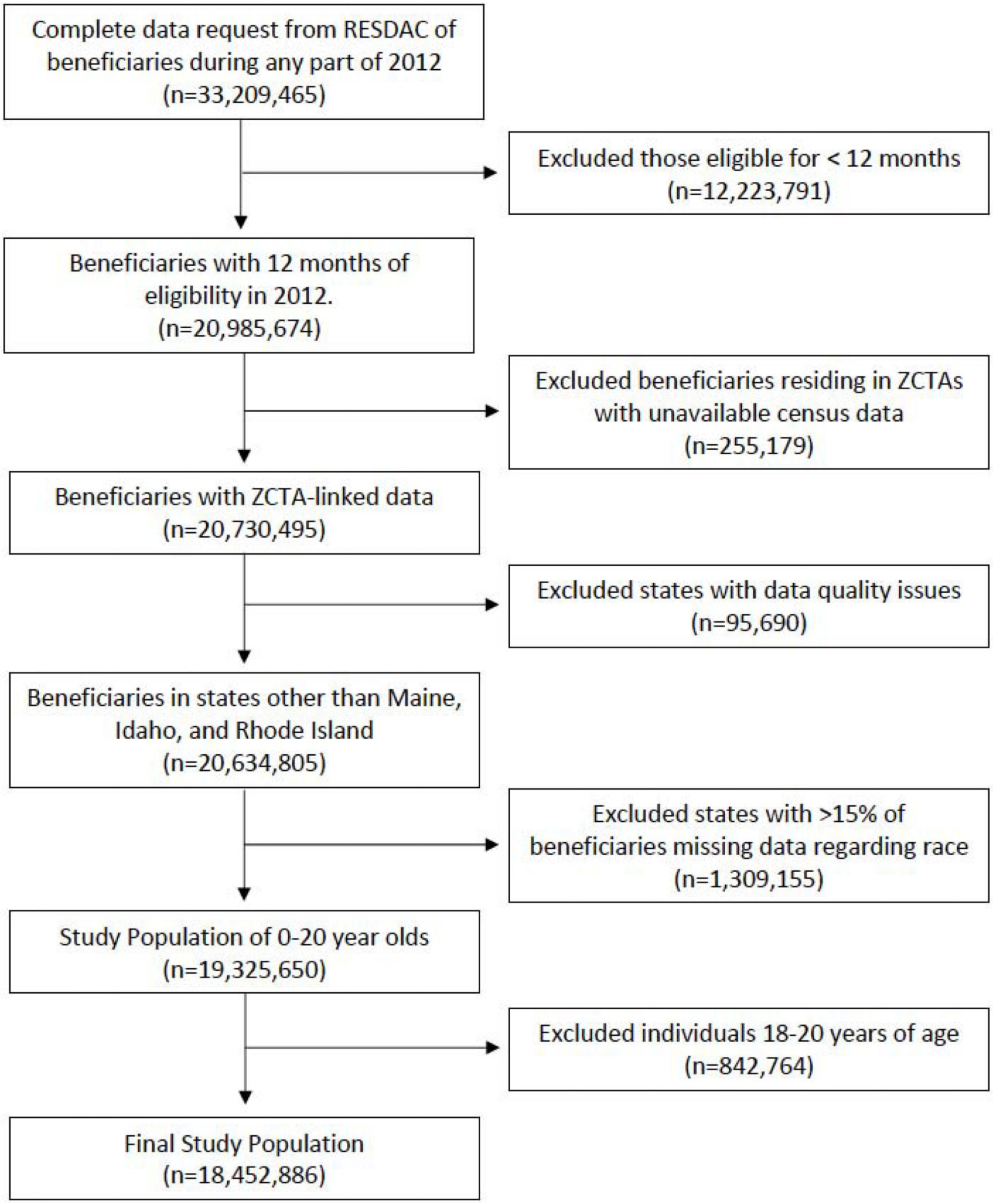

Figure E1:
Flow Diagram of Medicaid 2012 Beneficiaries Included in Study

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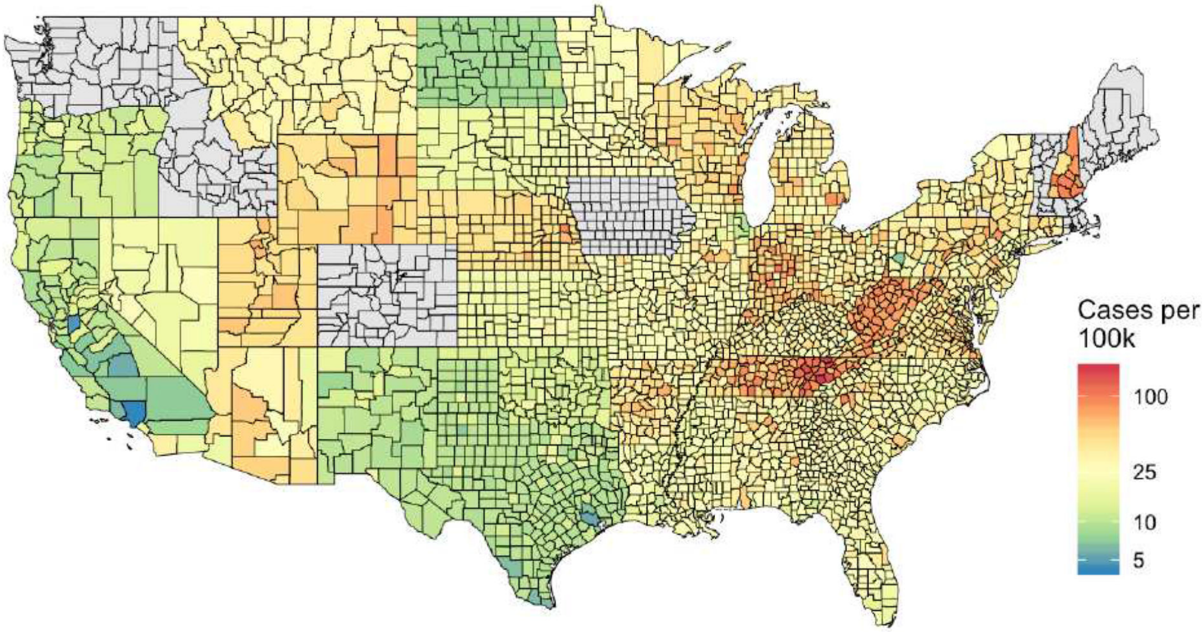

Figure 1.

County-level prevalence estimates of EoE among 2012 enrollees in the U.S., smoothed within state. States in gray were excluded from all analyses due to concerns about data quality (ME, ID, RI) or ≥ 15% missing data for race/ethnicity (CO, IA, MA, VT, WA).

Table 1:

Association Between ZCTA-Level Poverty, Urban/Rural Status and EoE

	Crude OR	95% CI	Adjusted OR*	95% CI
Gender				
Female	REF		REF	
Male	2.19	2.06 – 2.33	2.14	2.01 – 2.27
Age Categories				
0–2 y	REF		REF	
3–5 y	0.99	0.90 – 1.09	0.99	0.90 – 1.09
6–8 y	1.00	0.91 – 1.11	0.99	0.89 – 1.09
9–11 y	1.07	0.97 – 1.18	1.03	0.94 – 1.14
12–14 y	1.02	0.92 – 1.13	0.98	0.89 – 1.09
15–17 y	0.89	0.79 – 1.00	0.87	0.77 – 0.98
Race/Ethnicity				
White	REF		REF	
Black	0.36	0.33 – 0.39	0.41	0.38 – 0.45
Asian	0.30	0.23 – 0.39	0.37	0.28 – 0.49
Hispanic	0.20	0.18 – 0.22	0.31	0.27 – 0.35
Grouped§	0.32	0.28 – 0.37	0.40	0.34 – 0.47
Unknown	1.43	1.30 – 1.57	1.64	1.48 – 1.80
Urban/Rural Status				
Large Central Metro	REF		REF	
Large Fringe Metro	1.62	1.47 – 1.79	0.93	0.84 – 1.02
Medium Metro	1.46	1.32 – 1.61	0.95	0.87 – 1.05
Small Metro	1.45	1.28 – 1.64	0.78	0.69 – 0.88
Micropolitan	1.55	1.37 – 1.74	0.79	0.70 – 0.89
Noncore (rural)	1.36	1.18 – 1.55	0.68	0.59 – 0.78
ZCTA-Level Poverty				
< 5%	3.09	2.69 – 3.54	2.00	1.75 – 2.28
6 – 10%	2.58	2.27 – 2.94	1.78	1.57 – 2.00
11 – 15%	2.00	1.75 – 2.29	1.50	1.33 – 1.69
16 – 20%	1.49	1.29 – 1.74	1.30	1.14 – 1.49
21 – 25%	1.02	0.86 – 1.21	0.99	0.84 – 1.16
26 – 100%	REF		REF	

Values expressed as odds ratios (OR) and 95% CIs

*Models adjusted for gender, age, race/ethnicity, urban/rural status, state of residence, and ZCTA-level poverty

§Defined as the combination of “Native American/Alaskan,” “>1 race (Hispanic), “>1 race (non-Hispanic),” and “Hawaiian” 147 ZCTA: Zip-code tabulation area