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Influence of race and gender on the presentation of eosinophilic esophagitis

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Abstract

Objectives—Eosinophilic esophagitis (EoE) is thought to be more common among males and Caucasians, but little is known about disease presentation among patients with different genders or racial backgrounds. Our aim was to determine the clinical, endoscopic and histologic characteristics of patients with EoE of different genders or racial backgrounds.

Methods—We conducted a retrospective study of the University of North Carolina (UNC) EoE clinicopathologic database between January 2000 and December 2008. Cases of EoE were defined per 2007 consensus guidelines and stratified by race and gender for comparison.

Results—208 incident EoE cases were identified (76% male, mean age 26 years, 82% Caucasian, 12% African American). Caucasians were older at diagnosis than African Americans (27.1 yrs vs. 19.0 yrs, p=0.05), less likely to present with failure-to-thrive (9% vs. 30%, p=0.002), and more likely to have esophageal rings (41% vs. 12%, p=0.005). These findings persisted after stratification by age. A higher proportion of males were diagnosed under the age of 18 as compared with females (48% vs 64%, p=0.05). Males were more likely to report dysphagia and food impaction as symptoms (71% vs. 53%, p=0.02 and 35% vs. 20%, p=0.05, respectively), and these findings also persisted after stratification by age. The remainder of clinical, endoscopic, and histologic features did not differ by either race or gender.

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Conclusions—While age and dysphagia differed by gender and race among EoE patients, the majority of symptoms and findings were not different across groups, even after stratification by age. Clinicians should maintain a high index of suspicion for EoE, regardless of race or gender, and obtain esophageal biopsies to confirm the diagnosis.

Introduction

First described in the literature in 1978, eosinophilic esophagitis (EoE) has become increasingly prevalent over the past decade (1-4). EoE is characterized by symptoms of esophageal dysfunction accompanied by typical histologic findings. Presentations can differ in children and adults. Children often have symptoms of feeding intolerance, regurgitation or vomiting, or failure to thrive while adults usually have symptoms of dysphagia, food impaction, refractory heart burn, or chest pain (5-9). The diagnosis is confirmed by esophageal biopsy showing a prominent esophageal eosinophilic infiltrate in the absence of other clinical causes of eosinophilia (6, 7).

While the epidemiology of EoE is not fully understood, it appears that the incidence of EoE is increasing beyond what would be expected by increased recognition alone (3, 5, 10). Multiple studies have found that EoE is three to four times more common in men than in women, and patients are more likely to be Caucasian than other racial or ethnic groups (7, 8, 11-16). However, the reasons for this are unknown and there is little understanding of the differences in disease presentation among EoE patients of different genders or with different racial backgrounds.

The purpose of this study was to assess the clinical, endoscopic, and histological differences between EoE patients with different racial backgrounds, and between men and women. We hypothesized that a higher proportion of men and Caucasians experienced symptoms such as dysphagia or chest pain and were more likely to have abnormal endoscopic findings.

Methods

We conducted a retrospective study of the University of North Carolina (UNC) EoE clinicopathologic database between January 2000 and December 2008. Details of the development of this database have previously been reported (5). In brief, potential cases were identified by querying our pathology database for every biopsy that included the word “eosinophil” in the report. Charts were then reviewed to confirm the diagnosis of EoE. Cases of EoE were defined per 2007 consensus guidelines (6). Specifically, subjects were required to have clinical symptoms of esophageal dysfunction, ≥ 15 eosinophils in at least one high-power field (eos/hpf), and had other causes of esophageal eosinophilia, including reflux disease, excluded. GERD was excluded in EoE cases by documenting persistent esophageal eosinophilia despite acid suppression at the time of biopsy, by documenting persistent esophageal eosinophilia despite prior symptoms refractory to high-dose acid-suppression, or with negative pH monitoring. Of note, these cases had previously been characterized with confirmation of the diagnosis of EoE (5).

Pertinent data extracted from the chart review included: age; gender; race (as reported either in the general demographic page of the medical record or as recorded in the medical

history); history of atopic disease including allergic rhinitis/sinusitis, asthma, or documented food allergy (demonstrated by either symptomatic evidence of allergy with reintroduction of a food or by testing directed by an Allergist); esophageal symptoms (ie. dysphagia, chest pain, regurgitation/vomiting); clinical indication for esophagogastroduodenoscopy (EGD); endoscopic findings as documented in the previously written procedure note; and dilation during EGD.

Histologic findings were extracted from pathology reports, and then archived pathology slides were re-reviewed by the study pathologist to determine eosinophil counts according to our validated protocol (17). In brief, the maximum eosinophil density (eosinophils/mm^2) was determined after examination of five microscopy fields. For purposes of comparison to previous studies, eosinophil density was then converted to eos/hpf for an assumed hpf size of 0.24 mm^2, the size of an average field as reported in the literature (18, 19).

Descriptive statistics were used to summarize the findings. Because there were so few non-African American EoE patients in other racial groups, we limited our main analysis of race to Caucasians vs African Americans. For bivariate analysis comparing Caucasians to African Americans, and males to females, means were compared using Student's t-test and proportions were compared with chi-square. For variables where data were not normally distributed, medians were compared using the Wilcoxon Rank-sum test. Because the clinical presentation of EoE can vary between adults and children, we also performed a stratified analysis with respect to both race and gender based on patient age at diagnosis (adults ≥ 18 years vs children < 18 years). Multivariate analysis to assess predictors of race and gender was performed with logistic regression, and to further take age of presentation into account. This study was approved by the UNC Institutional Review Board.

Results

Overall, 208 patients with a confirmed diagnosis of EoE were identified. The mean age was 25.7 years, with a range from 6 months to 78 years, and with 50% under the age of 18. Subjects were 76% male. The racial breakdown was as follows: 82% of subjects were Caucasian, 12% were African American, 1% Asian, 1% Native American, 1% Hispanic, and 2% other/unknown.

EoE and race

Table 1 shows the comparison between Caucasian and African American subjects with EoE. Caucasians were significantly older at diagnosis than African American subjects (27 ± 19 yrs vs. 19 ± 19 yrs, p = 0.05), and more likely to report dysphagia as symptom (71% vs. 48%, p=0.02). African Americans were more likely to present with failure-to-thrive than Caucasians (30% vs. 9%, p = 0.002). There was no significant association between race and atopic disease, gender, or any other clinical symptoms.

On endoscopic evaluation (Table 2), Caucasians were significantly more likely to have esophageal rings (41% vs. 12%, p = 0.005) and African Americans were more likely to have normal endoscopic findings (32% vs. 17%) though this relationship was not significant (p =

0.07). There were no other significant associations between race and endoscopic findings, indication, or likelihood of undergoing dilation during the procedure.

The maximum esophageal epithelial eosinophil count in Caucasians and African-Americans was similar (105 ± 100 vs 131 ± 114 eos/hpf, p = 0.24; Table 3). Other histologic findings, including the presence of eosinophil degranulation, eosinophilic microabscesses, or lamina propria fibrosis also did not differ between the groups.

EoE and gender

Male patients with EoE were diagnosed at an younger age than females, but this was not statistically significant (25 ± 19 vs 29 ± 20 yrs; p = 0.19; Table 1). However, a higher proportion of males were diagnosed under the age of 18 in childhood as compared with females (48% vs 36%, p = 0.05). Males were also more likely than females to report dysphagia or food impaction (71% vs. 53%, p = 0.02, and 35% vs. 20%, p = 0.05, respectively), but less likely to report abdominal pain or nausea (17% vs 40%, p = 0.001, and 9% vs 28%, p = 0.002, respectively). There was no significant association between gender and atopic disease, race, or other reported symptoms.

On endoscopic evaluation, there were no significant difference between male and females with EoE; indication for endoscopy, endoscopic findings including rings, linear furrows, white plaques/exudates, or esophageal strictures were similar between the two groups (Table 2).

The maximum esophageal epithelial eosinophil count in males and females was similar (105 ± 96 vs 109 ± 111 eos/hpf, p = 0.80; Table 3). Other histologic findings, including the presence of eosinophil degranulation, eosinophilic microabscesses, or lamina propria fibrosis also did not differ between the groups.

Stratification by age and multivariate analyses

After stratification by age (supplemental Table), the proportion of patients with dysphagia was similar for adult Caucasians and adult African Americans, but in children there was a trend towards more dysphagia in Caucasians (52% vs 27 %, p = 0.07). Failure to thrive remained more common in African American children (40% vs 15%, p = 0.03). The proportion of patients with esophageal rings was greater in Caucasian adults than African American adults (66% vs 30%, p = 0.02), and was also more common in Caucasian children, though this was not significant (11% vs 0%, p = 0.19). On multivariate analysis, odds of failure to thrive were increased for African-Americans (OR 3.48, 95% CI 1.08-11.3), but dysphagia and esophageal rings were not independently associated with race.

For gender (supplemental Table), dysphagia and food impaction were more common in males regardless of age, but this was only statistically significant for adult males with dysphagia (93% vs 68%, p = 0.001). Abdominal pain and nausea were less common in adults males compared with females (6% vs 38%, p < 0.001, and 5% vs 27%, p = 0.004), but there were no differences in these symptoms for children. On multivariate analysis, odds of abdominal pain remained lower for males (OR 0.25, 95% CI 0.09-0.72), and younger age was also independently associated with male gender (OR 1.03, 95% CI 1.01-1.05).

Discussion

Eosinophilic esophagitis (EoE) has become an increasingly prevalent esophageal disease contributing to substantial morbidity among both adults and children (6, 7). Many studies have consistently reported that EoE is far more common in males and Caucasians, but the reasons for this finding are unknown (7, 8, 11-16, 20, 21). As there are few data examining differences in features of EoE by patient race and gender, our aim was to characterize clinical, endoscopic, and histologic findings associated with EoE among Caucasians and African-Americans, as well as among men and women.

Despite some suggestion in the literature of racial and gender differences in EoE, we observed remarkably few differences in features of EoE by either race or gender. With a few exceptions, the clinical presentations were similar, the endoscopic appearances were similar, and the histologic findings and eosinophil counts were similar. This observation would be consistent with preliminary data examining the EoE transcriptome where there did not appear to be differences in gene expression in male vs female EoE patients, though the transcriptome has yet to be analyzed by race (22). However, a younger age at diagnosis was seen both for African Americans and males. This may explain our findings that African-Americans were more likely to present with failure-to-thrive, that Caucasians and males were more likely to report dysphagia and have esophageal rings, and the stratified analysis by age supports this. It is known that symptoms and endoscopic findings of EoE can vary by age (2, 5, 7, 8, 11-16), with failure-to-thrive more common in young patients, and dysphagia and esophageal rings more common in older patients. It is not as clear, however, why age of diagnosis would vary by race. Recent data presented in abstract form corroborate some of our findings and suggest that there might be isolated differences in EoE presentation by race, including a younger age at diagnosis in African-Americans (23), more dysphagia in Caucasians (24-26), and more esophageal rings in Caucasians (26). If differential access to care was important in this disease, and the disease course was the same in African Americans and Caucasians, one might expect African Americans to present at an older age than Caucasians. This presents the interesting possibility that EoE may be a more aggressive disease in African Americans. Of note, in our cohort African Americans did present with a higher mean eosinophil count, and this difference, while not significant, deserves further attention in subsequent studies. Because we found no features apart from failure to thrive in African American children and abdominal and nausea in women that were independently able to predict EoE cases status either by race or by gender, clinicians should maintain a low threshold for taking biopsies in all patients undergoing upper endoscopy when EoE is on the differential.

One issue with these data is that because we do no know the “denominator”, the number of people who are African American or Caucasian and receive their GI health care at our center, the present study design does not allow us to draw conclusions about whether EoE is more frequently seen among Caucasians than African Americans and other racial groups. However, we suggest that this common belief may be an artifact related to the composition of the underlying populations from which the study subjects were drawn. For example, at our center we report 12% of EoE cases are African American, and find that African Americans comprise 14% of the local county, 22% of the state, and 19% of the hospital

population. If studies are compiled that report the racial composition of the EoE populations (4, 12-15, 23-25, 27-31), and this composition is compared to the racial breakdown of the geographic region of study, an interesting trend emerges (Table 4). While not universally true, in many cases (including for the present report) the proportion of African American EoE patients mirrors the proportion of African American residents in the surrounding region (Figure 1). While this comparison is not definitive (importantly, these academic medical centers have wide referral or cachement areas that do not necessarily represent the population of the region), it is provocative. Because no studies of the prevalence of EoE in a general population reflective of the racial make-up of the U.S. have been conducted, we do not know the true distribution by race. However, the fact that some centers report a large number of African-American EoE patients, a rate which approaches the proportion of African-Americans in the general population surrounding those centers (23, 28), calls into question the belief that EoE is a Caucasian-predominant disease. Perhaps the trends reported to date are due to detection, referral, and publication bias?

This study has several strengths and limitations to consider. We report on a large population of patients with a confirmed diagnosis of EoE, and are therefore able to stratify this population by race and by gender. Despite this large sample size, the vast majority of subjects were either Caucasian or African American, and our analysis was limited to these two racial groups. To date, there have been few published cases of EoE in the U.S. Hispanic or Asian-American populations (23, 32). We also fully characterized the patients from a clinical, endoscopic, and histologic standpoint to provide rich descriptive data. However, this was a retrospective, single-center study, so the results might not be generalizable and we were not able to confirm racial status beyond what was in the electronic medical and demographic records.

In summary, we found that while age and dysphagia differed by gender and race among EoE patients, the majority of symptoms, endoscopic findings and all histologic findings were not different across groups. Future studies could investigate whether the earlier presentation of African-American and male patients is due to the pathophysiology of EoE or is otherwise related to social or environmental factors. Clinicians should maintain a high index of suspicion for EoE in the context of appropriate clinical information, regardless of race or gender, and obtain esophageal biopsies to attempt to confirm the diagnosis of EoE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

EGD	esophagogastroduodenoscopy
EoE	eosinophilic esophagitis
eos/hpf	eosinophils per high-power field
GERD	gastroesophageal reflux disease
PPI	proton pump inhibitor
UNC	University of North Carolina

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Study highlights

What is current knowledge?

- Eosinophilic esophagitis (EoE) has been reported to be more common among males and Caucasians.
- Little is known about differences in disease presentation among patients with EoE and different genders or racial backgrounds.

What is new here?

- Caucasians were older at diagnosis with EoE than African Americans, less likely to present with failure-to-thrive, and more likely to have esophageal rings.
- Males were more likely to be diagnosed as children and report dysphagia or food impaction.
- However, the majority of symptoms, endoscopic, and histologic findings were not different across groups.

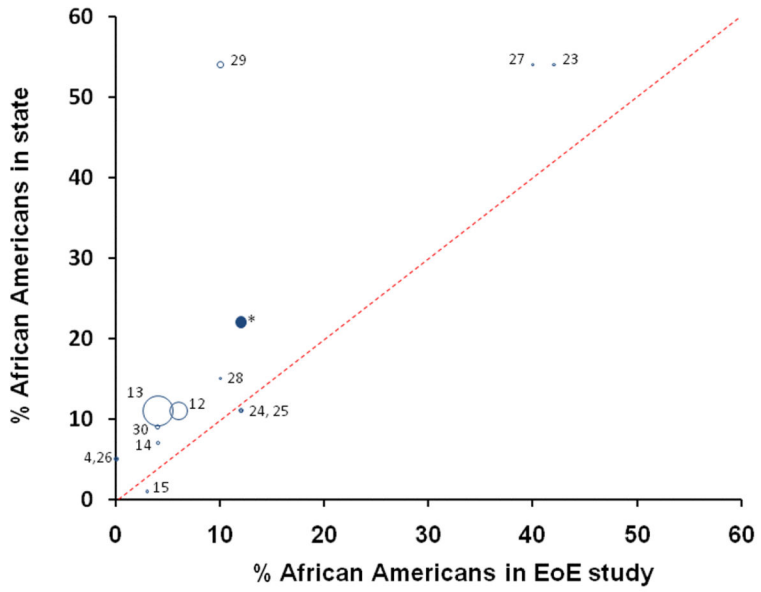

Figure 1.

The proportion of African American patients with EoE in selected studies related to the population proportion of African Americans in the state in which the health care center conducting the study is located. The size of each circle is proportional to the size of the study. The numbers next to the circles represent the reference number of the study. The solid blue circle with the asterisk is the present study. For the correlation between the proportion of African American patients in the studies and in the state, $r = 0.82$ ($p < 0.001$).

Table 1

Patient characteristics

	Caucasian (n=170)	African American (n=25)	p-value†	Male (n=158)	Female (n=50)	p-value†
Mean age at diagnosis/biopsy (years ± SD)	27.1 ± 19.0	19.0 ± 19.4	0.05	24.7 ± 18.9	28.8 ± 20.4	0.19
Age (n, %)						
Child (<18 years)	78 (46)	15 (60)	0.19	82 (52)	18 (36)	0.05
Adult (≥18 years)	92 (54)	10 (40)		76 (48)	32 (64)	
Gender (n, %)						
Male	133 (78)	18 (72)	0.5	--	--	--
Female	37 (22)	7 (28)				
Race (n, %)						
Caucasian	--	--	--	133 (84)	37 (74)	0.5
African American				18 (11)	7 (14)	
Symptoms (n, %)‡						
Dysphagia	118 (71)	12 (48)	0.02	110 (71)	26 (53)	0.02
Food impaction	53 (34)	4 (17)	0.1	49 (35)	9 (20)	0.05
Heartburn	62 (41)	7 (29)	0.27	56 (40)	19 (41)	0.85
Chest pain	12 (8)	0	0.16	9 (7)	4 (9)	0.65
Abdominal pain	37 (24)	3 (13)	0.24	24 (17)	19 (40)	0.001
Nausea	21 (14)	3 (13)	0.9	13 (9)	13 (28)	0.002
Vomiting	36 (24)	8 (35)	0.26	33 (24)	13 (28)	0.61
Failure to thrive	13 (9)	7 (30)	0.002	17 (12)	5 (11)	0.83
Any atopic disease (n, %)	78 (58)	10 (53)	0.65	70 (56)	22 (58)	0.84
Specified atopic diseases (n, %)						
Allergic rhinitis/sinusitis	49 (32)	9 (43)	0.35	46 (33)	12 (35)	0.83
Food allergy	25 (23)	3 (19)	0.73	22 (21)	7 (21)	0.99
Asthma	41 (27)	3 (15)	0.25	34 (25)	12(27)	0.71

† p-values calculated with t-test for continuous variables and with chi-square for categorical variables

‡ patients may have had more than one symptom

Table 2

Endoscopy characteristics

	Caucasian	African American	p-value†	Male	Female	p-value†
Primary EGD indication of dysphagia (n, %)	90 (54)	9 (38)	0.13	83 (54)	21 (43)	0.17
Primary EGD indication of heartburn (n, %)	39 (23)	7 (29)	0.54	38 (25)	11 (22)	0.73
Other EGD indications (n, %)			0.33			0.55
Food impaction alone	7 (4)	2 (8)		7 (5)	2 (4)	
Abdominal pain (any)	20 (12)	2 (8)		13 (11)	11 (23)	
Weight loss/failure to thrive	5 (3)	3 (13)		8 (5)	2 (4)	
Nausea and/or vomiting	7 (4)	1 (4)		6 (4)	2 (4)	
Chest pain	3 (2)	0		2 (1)	1 (2)	
Odynophagia	2 (1)	0		2 (1)	0	
Feeding intolerance	2 (1)	0		2 (1)	0	
EGD findings (n, %)‡						
Normal	28 (17)	8 (32)	0.07	29 (19)	12 (24)	0.42
Rings	69 (41)	3 (12)	0.005	57 (37)	19 (38)	0.88
Stricture	32 (19)	4 (16)	0.71	32 (21)	7 (14)	0.30
Narrowed esophagus	16 (10)	1 (4)	0.36	12 (8)	6 (12)	0.36
Linear furrows	49 (29)	4 (16)	0.16	43 (28)	13 (26)	0.81
“Crepe-paper” mucosa	8 (5)	1 (4)	0.86	7 (5)	3 (6)	0.67
White plaques	20 (12)	5 (20)	0.27	21 (14)	5 (10)	0.51
Erythema	24 (14)	4 (16)	0.83	28 (18)	3 (6)	0.04
Decreased vascularity	12 (7)	3 (12)	0.40	14 (9)	3 (6)	0.50
Erosive esophagitis	53 (32)	6 (24)	0.43	50 (32)	12 (24)	0.27
Hiatal hernia	12 (7)	1 (4)	0.56	7 (4)	7 (14)	0.02
Other findings (n, %)‡*	44 (26)	5 (20)	0.53	41 (26)	11 (22)	0.57
Dilation performed (n, %)	34 (20)	5 (20)	0.96	35 (23)	8 (16)	0.35

† p-values calculated with t-test for continuous variables and with chi-square for categorical variables

‡ patients may have had more than one finding

* examples of other findings include: Schatzki’s ring, nodule, esophageal web.

Table 3

Histology characteristics

	White	Black	p-value†	Male	Female	p-value‡
Maximum eosinophil density (mean eos/mm^2 ± SD)	438 ± 415	545 ± 477	0.24	437 ± 399	454 ± 463	0.80
Maximum eosinophil count (mean eos/hpf ± SD)*	105 ± 100	131 ± 114	0.24	105 ± 96	109 ± 111	0.80
Eosinophil degranulation†	84 (92)	15 (94)	0.84	84 (95)	22 (85)	0.06
Eosinophil microabscesses†	62 (68)	11 (69)	0.96	60 (68)	16 (62)	0.53
Spongiosis present	79 (87)	15 (94)	0.43	79 (90)	22 (85)	0.47
Subepithelial stroma present	73 (80)	14 (88)	0.49	71 (81)	21 (81)	0.99
Lamina propria fibrosis	1 (1)	0	0.66	1 (1)	0	0.58

*The eosinophil count was calculated from the eosinophil density for an assumed hpf size of 0.24 mm^2 with the following equation: eosinophil count (eos/hpf) = eosinophil density (eos/mm^2) × 0.24 mm^2/hpf.

†any seen in biopsy specimen

‡p-values calculated with t-test for continuous variables and with chi-square for categorical variables

Table 4

Race and gender characteristics of EoE studies

Author and publication	Total n in study w/ EoE	Region	African Americans in study (%)	Caucasians in study (%)	African Americans in county/state* (%)	Caucasians in county/state* (%)
*present report	208	UNC hospital-Chapel Hill, NC (Orange county)	12	82	14/22	78/74
Prasad *et al.*, AJG, 2007	33	Mayo Clinic-Rochester, MN (Olmsted county)	0	100	4/5	89/89
Mackenzie *et al.*, Aliment Pharm Ther, 2008	31	University of Utah and Salt Lake Vet Affairs Med Center- Salt Lake City, UT (Salt lake county)	3	97	2/1	90/93
Franciosi *et al.*, CGH, 2009	335	Children's Hospital of Philadelphia-Philadelphia, PN (Philadelphia county)	6	84	44/11	49/85
Prasad *et al.*, CGH, 2009	78	Mayo Clinic-Rochester, MN (Olmsted county)	0	100	4/5	89/89
Veerappan *et al.*, CGH, 2009	25	Walter Reed Army Medical Center-Washington, DC	40	60	54	41
Shah *et al.*, AJG, 2009	30	Children's Memorial Hospital, Northwestern University-Chicago, IL (Cook county)	10	64	26/15	67/79
Spergel *et al.*, J Ped Gastr Nutr, 2009	562	Children's Hospital of Philadelphia-Philadelphia, PN (Philadelphia county)	4	90	44/11	49/85
Dohil *et al.*, Gastro, 2010	24	Rady Children's Hospital, UCSD-San Diego, CA (San Diego County)	4	54	6/7	79/76
Moawad *et al.*, Alim Pharmaco Ther, 2010	127	Walter Reed Army Medical Center-Washington, DC	10	82	54	41
Bohm *et al.*, Gastro, 2011 (abstract)	71	Temple University School of Medicine-Philadelphia, PN (Philadelphia county)	12	82	44/11	49/85
Gupta *et al.*, Gastro, 2011 (abstract)	81	Indiana University School of Medicine-Indianapolis, IN	4	95	26/9	70/88

Author and publication	Total n in study w/ EoE	Region	African Americans in study (%)	Caucasians in study (%)	African Americans in county/state* (%)	Caucasians in county/state* (%)
		(Marion county)				
Sharma *et al.*, J AllerClinImmunol, 2011 (abstract)	50	Children's National Medical Center-Washington, D.C.	42	42	54	41
Zubair Malik, et al., Gastro, 2011 (abstract)	34	Temple University School of Medicine-Philadelphia, PN (Philadelphia county)	12	63	44/11	49/85

* US Census data (http://quickfacts.census.gov)