

RESEARCH ARTICLE

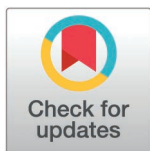
Environmental risk and Alpha-gal Syndrome (AGS) in the Mid-Atlantic United States

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Data availability statement: In accordance with institutional regulations, deidentified individual data that supports the results will be shared provided the investigator who proposes to use the data has approval from an Institutional Review Board (IRB), Independent Ethics Committee (IEC), or Research Ethics Board (REB), as applicable, and executes

Abstract

Alpha-gal syndrome (AGS), commonly referred to as the tick bite red meat allergy, has been reported worldwide with the number of suspected cases in the United States increasing from 24 in 2009 to over 34,000 in 2019. Within the US, AGS is associated with the bite of two tick species, *Amblyomma americanum* and *Ixodes scapularis*, and has particularly high incidence rates in the mid-Atlantic region. Because AGS is associated with tick bites, the risk of developing AGS is affected by the environment individuals visit. Despite this, as well as the numerous studies associating the environment with *Am. americanum*, no work to-date has evaluated AGS risk factors associated with the surrounding landscape. We test the hypothesis that AGS risk is associated with habitat fragmentation typically seen in areas classified as open space and low intensity development that are suitable for human-tick interactions, using a combination of generalized linear modeling (GLM), boosted regression trees (BRT), and Maximum Entropy (MaxEnt). We qualitatively compare results from the models, as well as their predictions within the mid-Atlantic region. We found that models mostly agree when determining important environmental variables, with open space development and population density being highly predictive across all models. BRT and GLM predicted a strong east to west gradient of risk across the mid-Atlantic, which largely mirrors the environmental transition from mountains to coastal plains. MaxEnt predicted a much patchier distribution across the region with no discernable patterns. These results provide evidence that AGS is associated with land uses that are associated with habitat fragmentation, the preferred habitat of *Am. americanum*. This information can be used to inform future education programs aimed at reducing AGS incidence in the region.

a data use/sharing agreement with UNC.

The Principal Investigator should submit a request to the UNC Industry Contracting team (OSPContracting@unc.edu) to initiate the data use/sharing agreement.

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Introduction

Alpha-gal syndrome (AGS) is a food allergy caused by an immunoglobulin E (IgE) antibody specific response to galactose- α -1,3-galactose (alpha-gal), which is most commonly found in mammalian meat products. AGS is triggered by consumption of mammalian meat or other products containing alpha-gal, with symptoms including gastrointestinal issues (e.g., cramping, vomiting, diarrhea), hives/itching, joint pain/arthritis, and anaphylaxis [1–3]. Increasing epidemiological evidence suggests AGS is triggered by ticks, and within the United States (US), with the repeated bites from lone star ticks (*Amblyomma americanum*) considered the primary cause [1,2], although laboratory-based work has also suggested Black-legged ticks (*Ixodes scapularis*) could be implicated [4].

Since 2007, AGS, commonly referred to as the red meat allergy, has been reported throughout North America, Australia, Europe, and Asia [1,5,6]. Tick-associated red meat allergies were first described in Australia between 2004 and 2007 [7]. Since the first documented case in the southeastern US in 2009 [5,8], diagnoses of AGS have increased rapidly, with reported cases increasing from 24 in 2009 to over 34,000 in 2019 [5,6]. AGS is the leading cause of adult-onset allergies in the US [9], with test positivity rates of 30.5% [10]. Increased awareness and testing, along with the publication [11] of standard case definitions in 2022, has improved AGS reporting: with positive tests increasing from 1,110 in 2011 [1] to 18,885 in 2021 [10] within the US. Increases in AGS diagnoses, and tickborne disease (TBD) diagnoses overall, have been linked to environmental factors (e.g., warmer surface temperatures, longer summers) [12–14] and human factors including increased travel and reforestation of previously developed areas [15], resulting in an increase in suitable habitat for ticks. *Am. americanum*, the tick primarily associated with development of AGS, is associated with the presence of white-tailed deer, and is present throughout the southeastern [1] and midwestern United States [16,17], where AGS incidence is high.

Relatively little is known about the ecology of AGS, due to its recent description [5]. Studies have begun to describe individual risk factors, both in humans [18,19] and ticks [20], and the peridomestic environment [21], but no work has been done to establish risk factors associated with the surrounding landscape. This is likely due to its association with *Am. americanum* whose environmental preferences are well studied. However, the distribution of alpha-gal cases throughout the United States [10] does not perfectly align with the known distribution of *Am. americanum* [17,22,23] suggesting potential environmental confounders and/or ascertainment bias. Estimating incidence and the geographic distribution of AGS is further complicated by 1) limited case reporting as the disease is generally not reportable at the state or federal level in the United States [1] and 2) 77% of health care providers self-reporting they were unaware of AGS or not confident in their ability to diagnose it [24]. AGS incidence, like all TBD, is largely driven by human behaviors that increase human-tick interactions, e.g., land use change, as opposed to tick population dynamics [25]. Anthropogenic land use change, such as forest fragmentation and urbanization in particular, have been linked to increased TBD risk [26]. As low-intensity development has continued throughout the US, humans have encroached on tick habitat, while tick ranges have expanded due to climate change [12,27,28].

To identify potential environmental drivers of AGS risk, we developed species distribution models of AGS. Specifically, we hypothesized that AGS risk would be strongly correlated with habitat fragmentation typically seen in areas classified as open space and low intensity development that are suitable for human-tick interactions [29]. Using a dataset of 462 laboratory-confirmed cases of AGS from UNC Health, we fit generalized linear models (GLM), maximum entropy models (MaxEnt), and boosted regression trees (BRT) of AGS risk based on environmental variables (e.g., landcover and topography). Here, we present a qualitative

comparison of these model fits and predictions to determine environmental correlates for, and the distribution of, AGS risk across North Carolina, South Carolina, and Virginia.

Methods

Data

Anonymized patient records were collected from UNC hospitals, including individual's home address. Individuals were included if: 1) they were seen in the UNC Allergy & Immunology Clinic from 2010–2021, 2) their clinical history was consistent with AGS diagnosis, 3) they were IgE positive for alpha-gal (>0.1 IU/mL), 4) their symptoms improved on an AGS-appropriate avoidance diet, and 5) they resided within 200 miles of UNC Health. Patient records were accessed on May 17th – May 21st, 2021, with 536 patients meeting clinical criteria. 74 individuals were excluded due to either distance from UNC Health or only having a PO Box provided. This included 7 individuals in North Carolina, 3 in South Carolina, and 14 in Virginia. 462 patient records met all inclusion criteria. Only patients' home addresses were extracted as part of this study and were converted to latitude and longitude for analysis. Fig 1 shows the approximate location of individuals included in this study. Pseudo-absence data ($n=500$) were added to the dataset for models that require presence-absence data (GLM, BRT), which is commonly done when modeling the distribution of rare events since random points are unlikely to contain a positive event.

Information on dominant landcover was obtained from the National Land Cover Database (NLCD) for 2011 and 2019 [30] and estimates of human population and population density based on the 2010 census tract data were obtained from ESRI. Dominant landcover was aggregated within 1km of each observation to describe types of environments that individuals would be most likely to experience. In addition, the change in dominant landcover between 2011 and 2019 was used as a measure of urbanization or reforestation. Data extraction and aggregation was performed in ArcGIS [31].

Species distribution modeling

Species distribution models use species occurrence data to estimate environmental suitability, which we use here as a measure of risk. Three classes of species distribution models were fit to the dataset and qualitatively compared; binomial GLM [32], MaxEnt [33,34], and BRT [35] models. Qualitative comparison of species distribution models is common as the models have varying assumptions, often produce slightly different results, and there is no consensus on which is most appropriate [36]. All models used the patient's residence as the event's location, due to lack of information on location of exposure. Models were fit in R [37] using the "sdm" [38], "dismo" [39], and "gbm" [40] packages. Model performance was determined based on the Area Under the Curve (AUC) metric from the Receiver Operating Characteristics (ROC) curve from 100 model fits using an 80–20 split of training to test data. Additionally, for GLMs, backwards model selection was performed to reduce collinearity and overfitting, and model assumptions were visually checked using the "performance" package [41].

The predicted relative risk for AGS experienced at a location was calculated based on each model. While included for model fitting, distance to UNC Hospital was excluded since it is indicative of care-seeking behavior, and thus an individual-level risk factor, rather than a predictor of AGS risk at the location itself. For ease of comparison, predicted risk was standardized between 0 (no risk predicted) and 1 (highest predicted risk) for each model. Predictions were then qualitatively compared across maps as low, medium, or high. AGS risk was defined in two ways: (1) individual-level risk (an individual's risk of developing AGS) and (2) population-level risk (where AGS cases are likely located), calculated as individual-level risk multiplied by population density.

All code associated with this manuscript is available at https://github.com/bdhollin/alpha_gal_sdm.

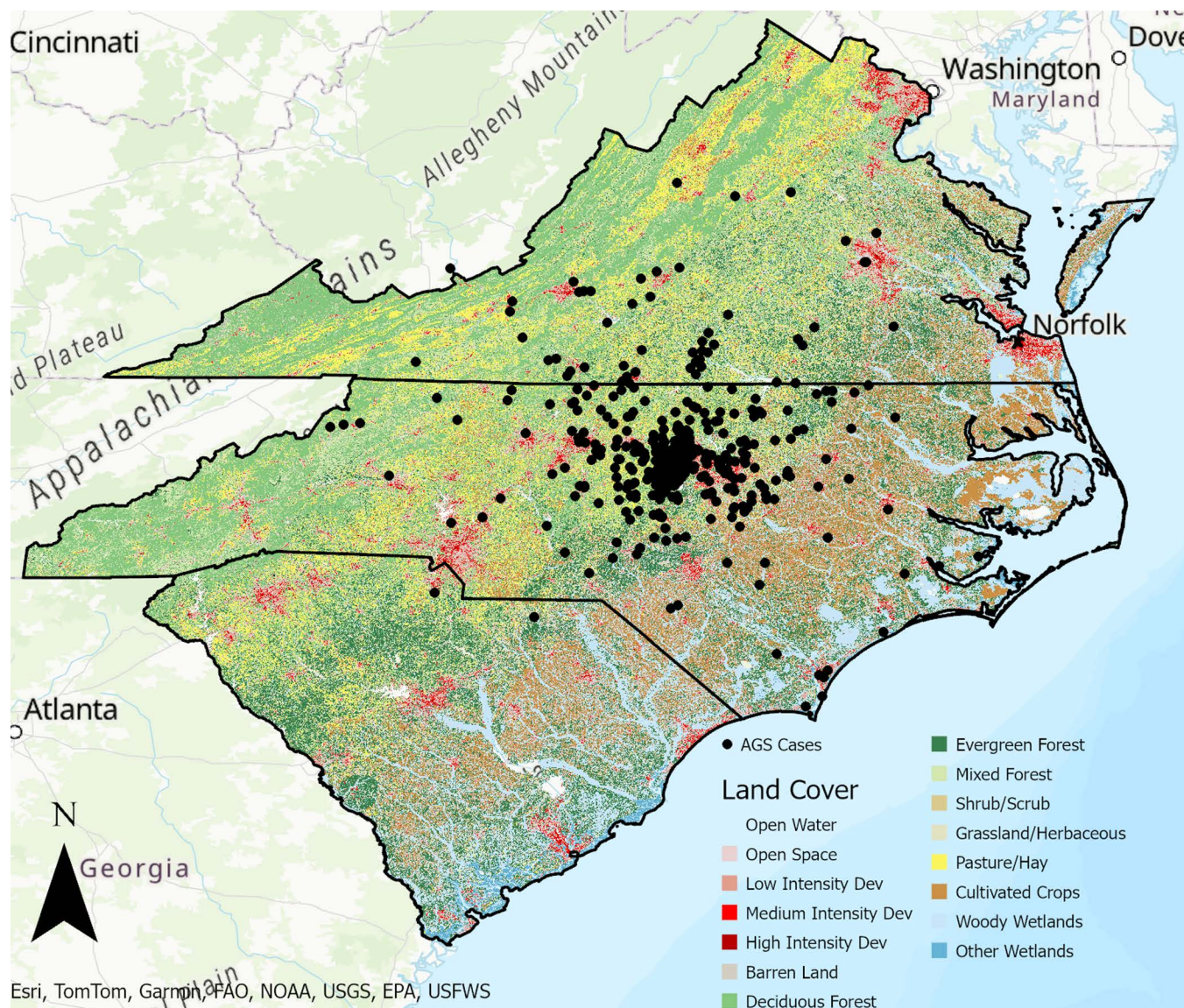


Fig 1. AGS cases and land use in North Carolina, South Carolina, and Virginia (2019). (Base map: ESRI <https://www.arcgis.com/home/item.html?id=6e850093c837475e8c23d905ac43b7d0>, Land Cover: MRLC mrlc.gov/data, State Boundaries: ESRI <https://www.arcgis.com/home/item.html?id=540003aa59b047d7a1f465f7b1df1950>).

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Ethical approvals

Ethical approval was provided by the institutional review boards of the University of North Carolina at Chapel Hill (18-3451).

Results

Risk factors

The best fit GLM found that AGS risk, defined as the likelihood of a confirmed case, was significantly and positively associated with the proportion of open space development (aRR=1.067, $p<0.001$) and proportion of mixed forest (aRR=1.034, $p=0.014$) within the buffer

region and significantly negatively associated with population density (aRR=0.999, $p<0.001$). Additionally, the probability of a case was negatively associated with the distance to UNC Hospital (aRR=0.967, $p<0.001$), which relates to the UNC Allergy & Immunology Clinic's catchment area. (Table 1)

MaxEnt and BRT are not capable of calculating an adjusted risk ratio (aRR), so we instead report variable importance based on AUC to determine which variables are important for model predictions (Table 2). All models found distance to UNC Health, population density, and open space development to be the most important variables. In addition, MaxEnt found low intensity development, medium density development, evergreen forests, mixed forests, and cultivated cropland to impact predictions, while the BRT found change in open space development, change in medium density development, change in grasslands, change in deciduous forests, change in evergreen forests, and mixed forest cover to impact predictions.

Individual and population-based level AGS risk maps

Individual- and population-level AGS risk maps were produced for the mid-Atlantic region (South Carolina, North Carolina, and Virginia) after controlling for distance to UNC Health (Figs 2 and 3, respectively). The GLM and BRT predicted the largest amount of spatial variation in AGS

Table 1. Variable names, adjusted relative risks, 95% confidence intervals, and p-values of GLM.

Variable Name	Adjusted Risk Ratio	95% Confidence Interval (CI)	p-value
Open space development ^a	1.067	(1.036, 1.099)	<0.001*
Change in open space development ^b	1.361	(0.860, 2.153)	0.189
Low intensity development ^a	1.014	(0.976, 1.053)	0.469
Change in low intensity development ^b	0.800	(0.468, 1.368)	0.415
Medium intensity development ^a	0.991	(0.941, 1.044)	0.737
Change in medium density development ^b	1.344	(0.776, 2.328)	0.292
Grassland/herbaceous land ^a	1.038	(0.955, 1.128)	0.378
Change in grassland/herbaceous land ^b	1.124	(0.785, 1.608)	0.524
Shrub/Scrubs land ^a	1.086	(0.982, 1.201)	0.107
Change in Shrub/Scrub land ^b	1.097	(0.756, 1.591)	0.625
Deciduous forest cover ^a	1.003	(0.984, 1.024)	0.736
Change in deciduous forest cover ^b	1.109	(0.775, 1.589)	0.571
Evergreen forest cover ^a	0.999	(0.972, 1.028)	0.959
Change in evergreen forest cover ^b	1.180	(0.823, 1.692)	0.367
Mixed forest cover ^a	1.034	(1.007, 1.061)	0.014*
Change in mixed forest cover ^b	0.993	(0.671, 1.470)	0.973
Pasture/hay land ^a	1.016	(0.994, 1.039)	0.149
Change in pasture/hay land ^b	1.095	(0.728, 1.647)	0.663
Cultivated cropland ^a	0.988	(0.961, 1.016)	0.382
Change in cultivated cropland ^b	1.388	(0.892, 2.159)	0.146
Population density (persons per sq. mi.)	0.999	(0.999, 1.000)	<0.001*
Distance to UNC hospital (miles)	0.967	(0.962, 0.971)	<0.001*

*Significant at $\alpha = 0.05$ level

^a% Coverage

^bChange in % coverage 2011-2019

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Table 2. Variable importance for GLM, MaxEnt, and BRT. Based on AUC measure.

Variable Name	GLM	MaxEnt	BRT
Open space development (% coverage)	8.2%	7.9%	2.0%
Change in open space development	1.3%	0.1%	0.1%
Low intensity development (% coverage)	0.5%	2.5%	0.2%
Change in low intensity development	0.6%	0.1%	0.1%
Medium intensity development (% coverage)	0.3%	1.3%	0.0%
Change in medium density development	2.6%	0.2%	0.0%
Grassland/herbaceous land (% coverage)	0.2%	0.2%	0.0%
Change in grassland/herbaceous land	2.6%	0.1%	0.0%
Shrub/Scrubs land	0.8%	0.1%	0.1%
Change in Shrub/Scrub land	1.7%	0.1%	0.0%
Deciduous forest cover (% coverage)	0.2%	0.7%	0.4%
Change in deciduous forest cover (% coverage change 2011–2019)	1.3%	0.0%	0.1%
Evergreen forest cover (% coverage)	0.1%	2.0%	0.0%
Change in evergreen forest cover	3.5%	0.2%	0.0%
Mixed forest cover (% coverage)	1.5%	1.3%	0.5%
Change in mixed forest cover	0.1%	0.1%	0.0%
Pasture/hay land (% coverage)	0.7%	0.8%	0.1%
Change in pasture/hay land	0.1%	0.1%	0.0%
Cultivated cropland (% coverage)	0.3%	2.2%	0.8%
Change in cultivated cropland	0.8%	0.2%	0.1%
Population density (persons per sq. mi.)	3.9%	8.3%	2.6%
Distance to UNC hospital (miles)	64.3%	63.5%	67.0%

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risk, with risk concentrated in the western, mountainous, part of the region into the piedmont, with lowest risk along the coast. MaxEnt predicted patchy individual-level risk throughout the piedmont and mountain regions with slightly lower risk in the coastal region. This distribution matches the known distribution of *Am. americanum* in the region [17,22,23], providing further support for its bites being the primary cause of AGS. Predictions of population-level risk did not differ between modeling approaches models and predicted areas around population centers to have the highest risk of AGS cases, likely due to the large disparity in population density and ease of access to specialists (e.g., allergists) between urban and rural areas.

Model cross-validation

Cross-validation suggests that all models had roughly similar predictive ability. MaxEnt (mean AUC = 0.905) performed marginally better than the GLM (mean AUC = 0.902) and BRT (mean AUC = 0.898), but all models had high predictive ability (Fig 4).

Discussion

Based on species distribution models of AGS risk, we found that land use patterns often associated with fringe areas, namely open space development, low density development, and mixed forest were associated with AGS. Open space and mixed forests are likely associated

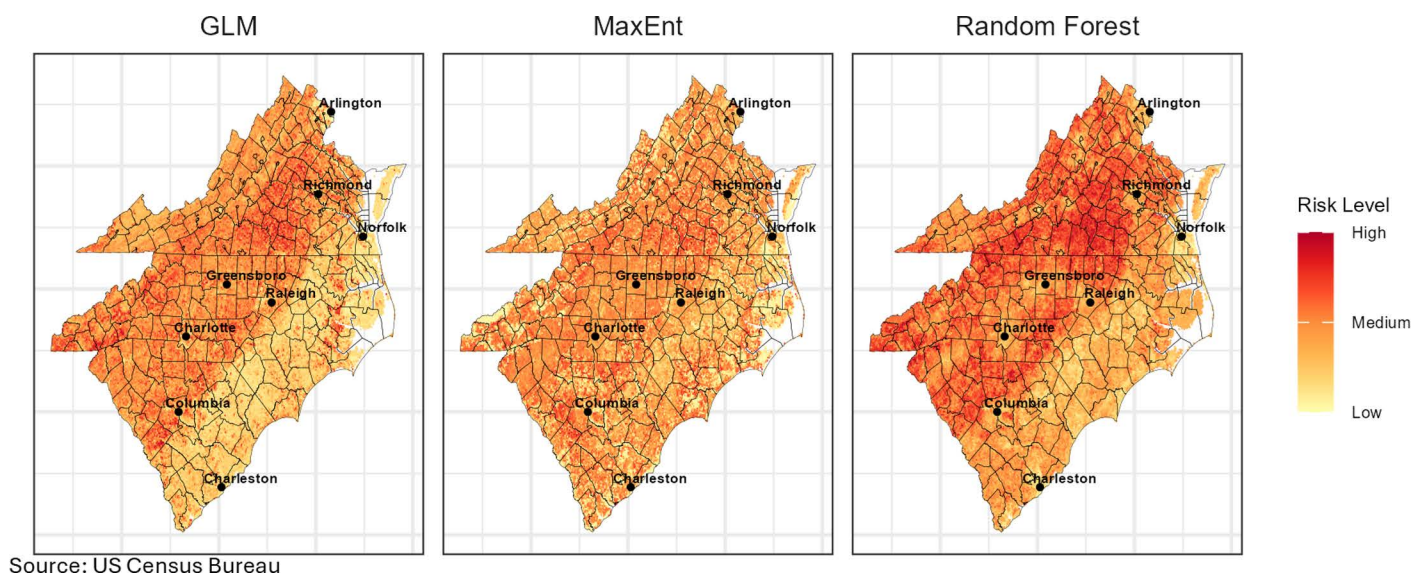


Fig 2. Predicted Individual-level AGS risk for the mid-Atlantic region from GLM, MaxEnt, and BRT. GLM and BRT predict highest risk within the mountainous eastern sides of the region, with lower risk occurring along the eastern coastline. However, BRT predicts a steeper change in risk between regions than the GLM. MaxEnt predicts patchy risk across most of the region. (County Boundaries: US Census Bureau https://services2.arcgis.com/FiaPA4ga0iQKduv3/arcgis/rest/services/TIGERweb_Counties_v1/FeatureServer).

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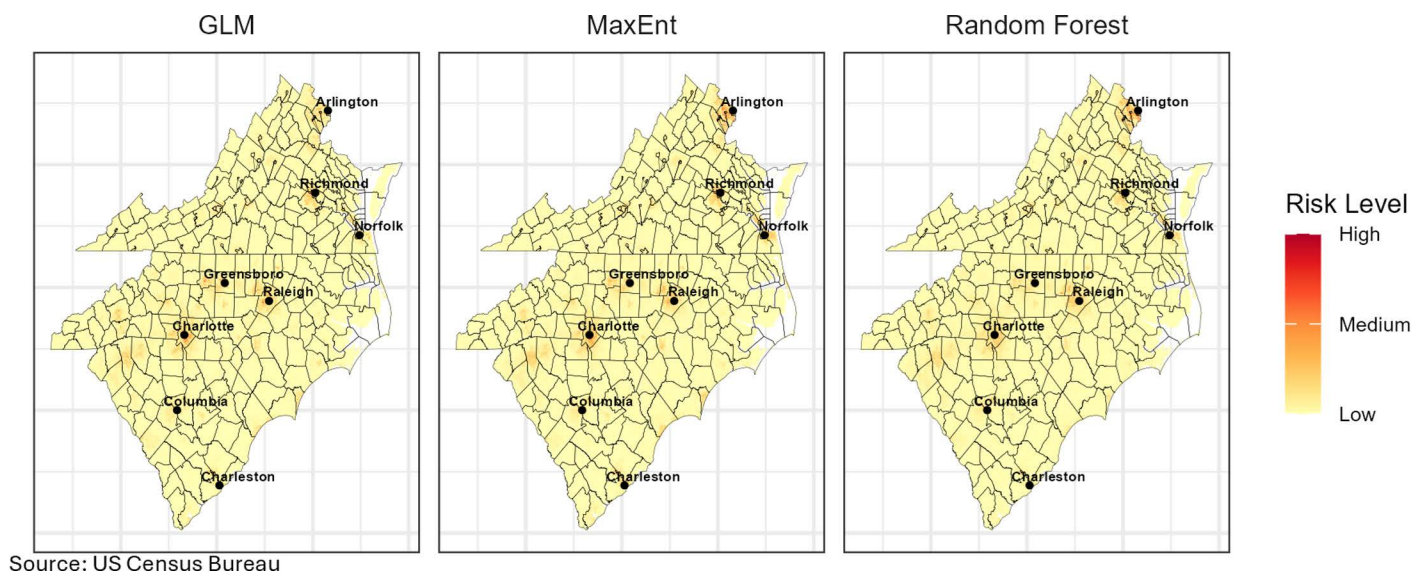


Fig 3. Predicted Population-level AGS risk for the mid-Atlantic region from GLM, MaxEnt, and BRT. All models predict areas around population centers to have the highest risk of AGS cases, likely due to the large disparity in population density and ease of access to specialists (e.g., allergists) between urban and rural areas. (County Boundaries: US Census Bureau https://services2.arcgis.com/FiaPA4ga0iQKduv3/arcgis/rest/services/TIGERweb_Counties_v1/FeatureServer).

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with forest fragmentation and edge habitat as they are defined as areas having a mixture of constructed materials and vegetation, with <20% impervious surface, and having a mixture of vegetation >5 feet and <5 feet tall, respectively [30]. These predictors were found to be important across all models, supporting our hypothesis that edge habitat and fragmented forest near a person's residence may be an important driver of AGS risk.

Reports of AGS have grown rapidly since its first report in 2009 [5,8] and are likely to continue to increase as awareness of AGS and incidence of tick-borne disease more broadly increases [24]. These increases are likely to be exacerbated by shifts in land use, resulting in more human-tick interactions throughout the southeastern US [26]. While clinical and laboratory diagnostics for AGS are becoming more readily available, the epidemiology of AGS, and tick-borne disease in general, apart from Lyme disease, is not well described. Understanding environmental risk factors associated with AGS diagnosis is a critical first step for determining at-risk populations, and here we show evidence supporting the hypothesis that AGS is associated with landcovers often correlated with the presence of *Am. americanum*. This information provides a starting point for education, prevention, and control efforts, which – to date – are not well-established, especially for *Am. americanum* ticks [42]. This is of added importance as very little work has been done to evaluate tick control measures in the region, especially related to epidemiological endpoints [42]. Edge habitat has long been associated with tick interactions and tick-borne disease risk [29]. This work highlights that this is also true of AGS risk and that the presence of open space development and mixed forested lands posed the highest risk [29]. Given the lack of research on the effectiveness of environmental acaricides in the region [42], our work suggests the need for personal protection measures for individuals residing in, or entering, these areas.

While this paper contributes to research surrounding land use factors affecting AGS risk, it is not without limitations. Importantly, the reported patient address was used as an estimate of where tick exposure occurred, since knowing the precise location is not possible. While we include a buffer region around the residence to account for some of this uncertainty, a travel history was not reported. Additionally, there is likely bias in AGS reporting – those with the time and resources are more likely to seek out testing. Therefore, older individuals with higher incomes who tend to live in suburban and lower intensity developed areas are likely over-represented in our dataset. Further, tick-borne disease is underreported in the mid-Atlantic [43,44] and given the relative novelty of AGS and that it is not a reportable disease in Virginia, North Carolina, South Carolina nor at the national level, the issue is likely exacerbated.

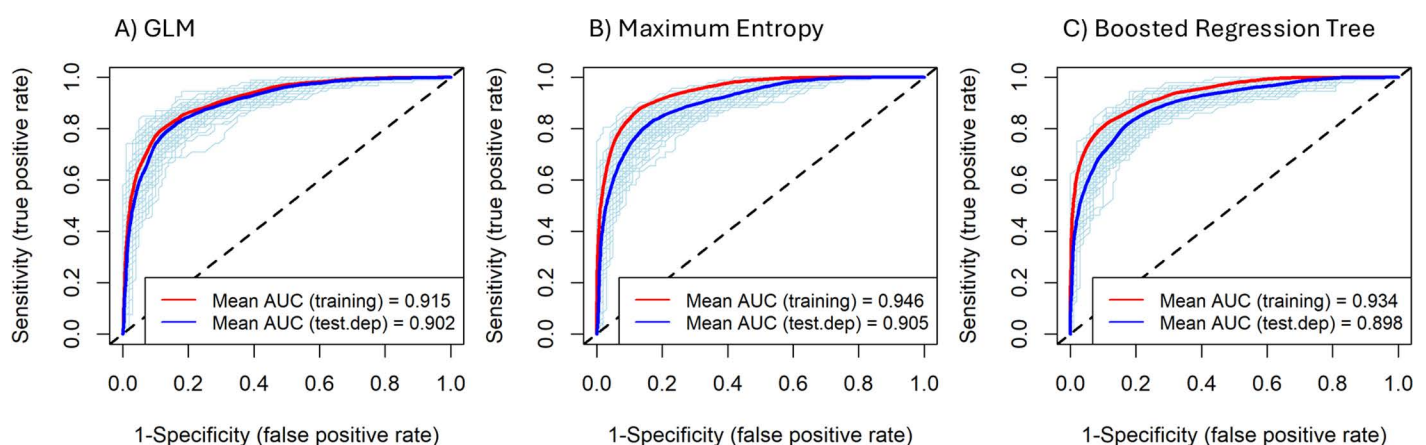


Fig 4. Receiver Operating Characteristics (ROC) curves for GLM, MaxEnt, and BRT.

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Species distribution models assume that the distribution is stable. While reports of AGS are rapidly increasing in more areas, it is likely partially due to greater awareness and diagnostics in regions where *Am. americanum* are established [45]. However, given the recent description of AGS and its limited range within the US compared to *Am. americanum*, the area in which individuals are at risk of AGS is likely still expanding. A comparison of *Am. americanum* ticks and seroprevalence surveys between areas is needed to determine if this is the case. Finally, we relied on pseudo-absence data for risk mapping as to date no geo-referenced seroprevalence survey has been performed.

Conclusion

Understanding environmental factors affecting AGS risk is important for identifying at-risk populations for intervention strategies (e.g., educational campaigns and diagnostic testing). While little is currently known about risk factors associated with AGS, beyond tick exposure, the spatial distribution of cases, along with a priori knowledge of the habitat preferences of *Am. americanum*, allow us to begin to understand how local environments affect AGS risk. Here, we leveraged a unique dataset of AGS patients acquired from the UNC Allergy & Immunology clinic to examine environmental factors near patient residences. Our modeling results support the hypothesis that the presence of edge and fragmented habitat, which is known to be associated with *Am. americanum*, are positively associated with AGS risk. Further, risk mapping based on environmental factors allows us to begin to understand where risk within the region is highest. Given the paucity of research on the effectiveness of environmental acaricides, this highlights the importance of personal protection measures for individuals entering or residing in these areas.

Author contributions

Conceptualization: Brandon D. Hollingsworth, Margaret Wiener, Scott P Commins, Ross M Boyce.

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Resources: Dana A Giandomenico.

Supervision: Ross M Boyce.

Validation: Brandon D. Hollingsworth.

Visualization: Brandon D. Hollingsworth, Margaret Wiener.

Writing – original draft: Brandon D. Hollingsworth, Margaret Wiener, Dana A Giandomenico, Scott P Commins, Ross M Boyce.

Writing – review & editing: Brandon D. Hollingsworth, Margaret Wiener, Dana A Giandomenico, Scott P Commins, Ross M Boyce.

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