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Geospatial Analysis of Population-based Incidence of Multiple Myeloma in the United States

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Abstract

Background: We investigated the spatial patterns of multiple myeloma (MM) incidence in the United States (US) between 2013 and 2017 to improve understanding of potential environmental risk factors for MM.

Methods: We analyzed the average county-level age-adjusted incidence rates ("ASR") of MM between 2013 and 2017 in 50 states and the District of Columbia using the U.S. Cancer Statistics Public Use Databases. We firstly divided the ASR into quintiles and described spatial patterns using a choropleth map. To identify global and local clusters of the ASR, we performed the Spatial Autocorrelation (Global Moran's I) analysis and the Anselin's Local Indicator of Spatial Autocorrelation (LISA) analysis. We compared the means of selected demographic and socioeconomic factors between the clusters and counties of the whole US using Welch one-sided t-test.

Results: We identified distinct spatial dichotomy of the ASR across counties. High ASR were observed in counties in the Southeast of the US as well as the Capital District (metropolitan areas surrounding Albany) and New York City in the state of New York, while low ASR were observed in counties in the Southwest and West of the US. The ASR showed a significant positive spatial autocorrelation. We identified two major high-high local clusters of the ASR in Georgia and Southern Carolina and five major low-low local clusters of the ASR in Alabama, Arizona, New Hampshire, Ohio, Oregon, and Tennessee. The racial population distribution may partly explain the spatial distribution of MM incidence in the US.

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Authorship Contribution Statement

J.C. and B.C. designed the study; J.C. conducted analysis and drafted the manuscript; W.Z. helped interpret the results; B.C. obtained data and provided oversight; all authors reviewed and approved the final manuscript.

Conflict of Interest Statement

The authors have no relevant financial or non-financial interests to disclose.

Conclusion: Findings from this study showed distinct spatial distribution of MM in the US and two high-high and five low-low local clusters. The non-random distribution of MM suggests that environmental exposures in certain regions may be important for the risk of MM.

Keywords

Multiple myeloma; Spatial analysis; Environmental exposure

Introduction

Multiple myeloma (MM) is a malignancy characterized by clonal expansion of malignant plasma cells in the bone marrow, with a median survival of about 6 years [1, 2]. It is the second most common hematologic malignancies in the United States (US), affecting 32,270 estimated new cases and 12,830 estimated deaths in 2022 [3]. MM is more common in males than females, and is twice as common in Blacks than Whites [1]. MM remains mostly incurable, highlighting a critical need to identify risk factors for appropriate prevention.

Despite extensive epidemiology research in the past two decades, including works from the International Lymphoma Epidemiology Consortium (InterLymph) Myeloma Working Group, risk factors for MM, and racial/ethnic disparities in particular, remain poorly understood [4]. To date, known risk factors for MM include genetic susceptibility, a family history of MM [5, 6], older age [7], monoclonal gammopathy of undetermined significance (MGUS) [8, 9], and obesity [10, 11]. Findings are inconsistent on risk factors such as occupational exposure to ionizing radiation [12], pesticides [13–16], and occupations such as firefighter, hairdresser and metal processer [17, 18]. Importantly, these risk factors do not fully explain the excess risk of MM in Blacks.

To improve our understanding of potential environmental risk factors for MM, we conducted a geospatial analysis of population-based MM incidence between 2013 and 2017 in the US. We hypothesized that the distribution of MM incidence in the US is not random. Our goal is to identify both global clusters and local outliers of MM incidence that could provide insights on etiologic factors.

Methods

Data

We obtained the United States Cancer Statistics (USCS) Public Use Databases from the Centers for Disease Control and Prevention (CDC) (https://www.cdc.gov/cancer/uscs/public-use/index.htm), which included de-identified cancer incidence data reported to the CDC's National Program of Cancer Registries and the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) Program. The public-use Cancer Statistics database provided average county-level age-adjusted incidence rates ("ASR") of MM between 2013 and 2017 in all 50 states and the District of Columbia. The 2000 US standard population is used in the dataset [19, 20]. In accordance with the USCS publication criteria, the incidence rate data in a county is suppressed in the database if fewer than 16 cases were reported in a specific category (e.g., the cancer type, race, or county). By

excluding the suppressed data (shown as “No Data” in our study), 1202 counties were included in our analysis. The total number of people with MM among the included counties was 118,627, with an average age-adjusted MM incidence rate of 7.2 out of 100,000. The average age-adjusted MM incidence rates for Blacks and Whites among the included counties were 15.0 and 6.4 out of 100,000. The most recent available US county-level mean males/females ratio (2013–2017), blacks/whites ratio (2020), mean percent of population below poverty level (2015–2019), and mean percent of population that earned a bachelor’s degree (2015–2019) were retrieved from US Department of Agriculture (USDA) Economic Research Service and *R* package *tidycensus* which returns tidy data frames from the US Census Bureau API [21–24].

Statistical Analyses

We conducted a three-step analytical process to identify the spatial pattern of the ASR. First, we divided the ASR into quintiles. The spatial distribution of the ASR quintiles was illustrated using a choropleth map to identify distinct spatial patterns.

Next, we performed the spatial autocorrelation (Global Moran’s I) analysis of the ASR across each county. The Global Moran’s I identifies the presence of global spatial autocorrelation by evaluating both feature locations and feature values. The Moran’s I is then computed to determine to what extent the spatial pattern is clustered, dispersed, or random. The Moran’s I ranges from −1 (perfect dispersion) to 1 (perfect clustering). In this analysis, we defined the neighbor relationship as Queen’s case adjacency, which denotes that all county boundaries sharing at least a corner are considered neighbors. The Global Moran’s I statistics for spatial autocorrelation are given as:

$$I = \frac{N}{s_0}\sum_i \sum_j W_{ij}\frac{(x_i-\mu)(x_j-\mu)}{\sum_i (x_i-\mu)^2} \text{[25]}$$

where N is the total number of counties, w_{ij} is the element in the spatial-weight matrix corresponding to the counties i and j; and x_i and x_j are the ASR for counties i and j with the mean μ; and

$$S_0 = \sum_i \sum_j w_{ij}$$

Third, we performed the Anselin’s Local Indicator of Spatial Autocorrelation (LISA) analysis of the ASR across each county. LISA indicates the local spatial association that measures whether the ASR for one county is closer to the value of a neighboring county or the average value of the study area. The significance of such associations was tested using a Monte Carlo permutation approach. The permutation assumes that the likelihood for the ASR of the investigated county is equal at any location under randomization, so the observed values are randomly shuffled over a defined spatial unit. The LISA is then re-computed for each permutation. A sufficiently large number of the permutations would then generate a reference distribution and allow the algorithm to return the statistical significance of the LISA. In this analysis, the value 9999 was used for the number of permutations. We defined the neighbor relationship as Queen’s case adjacency, which describes that all

county boundaries sharing at least a corner are considered neighbors. The analysis identifies hot spots, cold spots, and spatial outliers by yielding five categories: “high-high (HH)”, “low-low (LL)”, “high-low (HL)”, “low-high (LH)”, and “not significant (NS)”. The HH county or LL county indicates a county with a cluster of high ASR or low ASR. A HL county represents a county with a high ASR adjacent to a county with a low ASR and vice versa for a LH county. A NS county means that no statistically significant spatial autocorrelation of the ASR is observed in that county. The Local Moran’s I statistic of spatial autocorrelation in our study is given as:

$$I_i = \frac{x_i - \overline{x}}{s_i^2} \sum_{j=1, j \neq 1}^{n} w_{i,j}(x_j - \overline{X}) \quad [26]$$

where n is the total number of counties, x_i is the ASR for the county i, $\overline{x}$ is the mean of the ASR across counties, $w_{i,j}$ is the spatial weight between the county and i and j, and

$$S_i^2 = \frac{\sum_{j=1,j11}^{n}(x_j - \overline{X})^2}{n\text{-}1}$$

The spatial analysis was conducted in *ArcGIS Pro* version 3.0.3 [27].

To evaluate the potential roles of demographic and socioeconomic status within the counties in the spatial distribution of MM incidence, we compared the most recent available US county-level mean males/females ratio, blacks/whites ratio, mean percent of population below poverty level, and mean percent of population that earned a bachelor’s degree between the identified clusters and counties of the whole US. We conducted Welch two-sample one-sided t-test to determine whether means are significantly different. We conducted the analysis in *R* version 4.2.1 [28].

Results

Fig. 1 shows the spatial distribution of the ASR of MM across each county. We found a distinct spatial dichotomy of the ASR between counties in the US. High ASR, defined as incidence rates at the top quintile, were observed in counties in the Southeast of the US. Specifically, high ASR were observed in counties in Florida, Georgia, North Carolina, Southern Carolina, and Texas. We also found high ASR in counties in the Capital District (metropolitan areas surrounding Albany) and New York City in the state of New York. Low ASR, defined as incidence rates at the bottom quintile, were observed in counties in the Southwest and West of the US, including several counties in Arizona, California, Oregon, and Washington.

Table 1 presents the result of the spatial autocorrelation (Global Moran’s I) analysis of the ASRs across each county. It shows that the ASR was significantly clustered globally, with a Moran’s Index of 0.31 ($p<0.001$) indicating a significant positive spatial autocorrelation. Given the z-score of 10.3, there is less than a 1% likelihood ($p<0.01$) that such a positive spatial autocorrelation results from the theoretical random pattern represented by the null hypothesis.

Fig. 2 shows the result of the Anselin's Local Indicator of Spatial Autocorrelation (LISA) analysis of the ASR across each county. We identified two major HH clusters and five major LL clusters of the ASRs across the counties. As shown in Fig. 2, the two notable HH clusters were in Georgia and Southern Carolina, while the five LL clusters were in Alabama, Arizona, New Hampshire, Ohio, Oregon, and Tennessee.

Next, we evaluated the potential roles of demographic and socioeconomic status within the counties in the spatial distribution of MM incidence (Table 2). We found that Blacks/Whites ratio within counties correlated with the observed clusters of MM incidence. On the other hand, other selected demographic and socioeconomic factors, such as males/females ratio, percent of population below poverty level, and percent of population that earned a bachelor's degree do not correlate with the clusters of MM incidence.

Discussion

To the best of our knowledge, no study has comprehensively evaluated the spatial patterns of MM incidence in the US. We identified a distinct spatial dichotomy of the MM ASR across counties in the US. High MM ASR were observed in counties in the Southeast of the US as well as the Capital District (metropolitan areas surrounding Albany) and New York City, while low MM ASR were observed in counties in the Southwest and West of the US. Our global Moran's I analysis suggests that the MM ASR in the US were highly clustered. The LISA analysis identified two major local HH clusters and five major local LL clusters.

Our findings of significant association between the Blacks/Whites ratio within counties and the observed clusters of MM incidence suggest that the racial population distribution may partly explain the spatial distribution of MM incidence in the US. We also found that demographic and socioeconomic factors such as males/females ratio, percent of population under poverty line, and education levels do not correlate with the spatial distribution of MM incidence. Taken together, these findings suggest that clustering of MM incidence may be multifaceted resulting from complex interplay of a broad spectrum of demographic, genetic, personal/lifestyle, and environmental risk factors.

Previous studies investigating the geographic disparities in cancer incidence have linked geographic patterns with environmental factors such as air pollution [29] and pesticides [30, 31]. For instance, a large cluster of high lung cancer incidence was found in locations with high air toxics estimates modeled by the National Air Toxics Assessment Program [29]. A higher colon cancer rate was also found in locations that have higher exposure to pesticides [30, 31]. Thus, it is possible that the identified clustering of MM may also be associated with environmental exposures in certain regions. For example, we found HH clusters of the MM in Georgia and Southern Carolina where a high concentration of ambient benzene has been reported [32]. A positive association between benzene exposure and incidence of MM has been reported [33]. The 2014 National Air Toxics Assessment (NATA) also showed a high concentration of formaldehyde in Georgia and Southern Carolina [34], while exposure to formaldehyde has been suggested as a risk factor for MM [35].

In the current report, we found high ASR of MM in the Southeast of the US and the Capital District (metropolitan areas surrounding Albany) and New York City in the state of New York. These findings may reflect the geographic pattern of the dioxin-emitting facilities in these regions [36]. Dioxin and dioxin-like compounds have been associated with MM risk in previous studies [37–39]. Furthermore, high MM ASR in these two highly urban areas suggest air pollution may be important for MM. Studies in India and Iran found positive associations between the risk of MM and urban areas which have more air toxicant, more ionizing radiation, and an obesogenic food environment [40, 41]. Living in urban areas may also be associated with certain lifestyle factors (e.g., diet, physical activity, stress, etc.) that impact the risk of MM. For example, obesity, a risk factor for MM [10, 11, 42], is more prevalent in metropolitan areas that have a large share of convenience store and fast-food restaurant [43]. However, other highly urban areas such as Los Angeles in our analysis showed significantly low MM ASR. Explanations for the discrepancies are not clear. Because the incidence of MM is 2 to 3 times higher in African Americans than Caucasians, it is possible that these findings reflect different compositions of populations in these urban cities. For example, in 2015, New York City's population was about 43% Whites and 25% Blacks or African Americans, whereas the corresponding numbers were 53% and 9%, respectively, in Los Angeles [44].

Interestingly, the 2020 National Precipitation Rank Map showed spatial patterns of precipitation in the US similar to the spatial dichotomy of MM in that high precipitations were observed in HH clusters and low precipitations were observed in LL clusters [45]. High precipitation and cold climate zone has been linked to higher incidence of invasive cancer in the US in an ecological study, even after controlling for county-level demographic and socioeconomic variables [46]. High precipitation may be associated with higher amounts of organic pollutants such as pesticides in surface soils, water, and air, where exposure to pesticides has been suggested as a possible risk factor for MM [47, 48]. Nevertheless, it remains to be determined if pollutants due to precipitation may explain clustering of MM.

A major strength of this study is the use of high-quality population-based MM incidence data collected by the CDC and NCI's SEER program. There was also limitation. The incidence data in a county is suppressed in the database if fewer than 16 cases were reported in a specific category (e.g., the cancer type, race, or county). These counties are likely in sparsely populated remote or rural areas, which may have unique environmental or occupational exposures that may be important for MM risk. Nevertheless, because of low case count, exclusion of these counties is unlikely to bias the estimates of the MM clusters. This study has generated hypotheses that warrant a comprehensive analysis of MM incidence and certain suggestive environmental risk factors in the future studies.

Conclusion

The geospatial analysis suggests that the spatial distribution of MM incidence in the US is not random. We found that MM in the US was highly clustered and there were 2 high-high and 5 low-low local clusters. These patterns provide insights into putative environmental exposures for MM and may help explain the excess risk of MM in Blacks. Future studies with individual-level data are warranted to evaluate the relationship between MM risk, the

built environments, toxicant emissions such as ambient benzene, dioxin and dioxin-like compounds, and air toxins that have been reported in some high MM clusters identified in the current report.

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Abbreviations

ASR	age-adjusted incidence rates
CDC	Centers for Disease Control and Prevention
InterLymph	International Lymphoma Epidemiology Consortium
LISA	Anselin's Local Indicator of Spatial Autocorrelation
MGUS	monoclonal gammopathy of undetermined significance
MM	multiple myeloma
NCI	National Cancer Institute
USCS	United States Cancer Statistics

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Highlights

- A distinct spatial dichotomy of the MM ASR across counties in the US was present.
- The MM ASR showed a significant positive spatial autocorrelation.
- 2 major local high-high clusters and 5 major local low-low clusters were identified.
- The racial population distribution may partly explain the spatial distribution of MM incidence in the US.

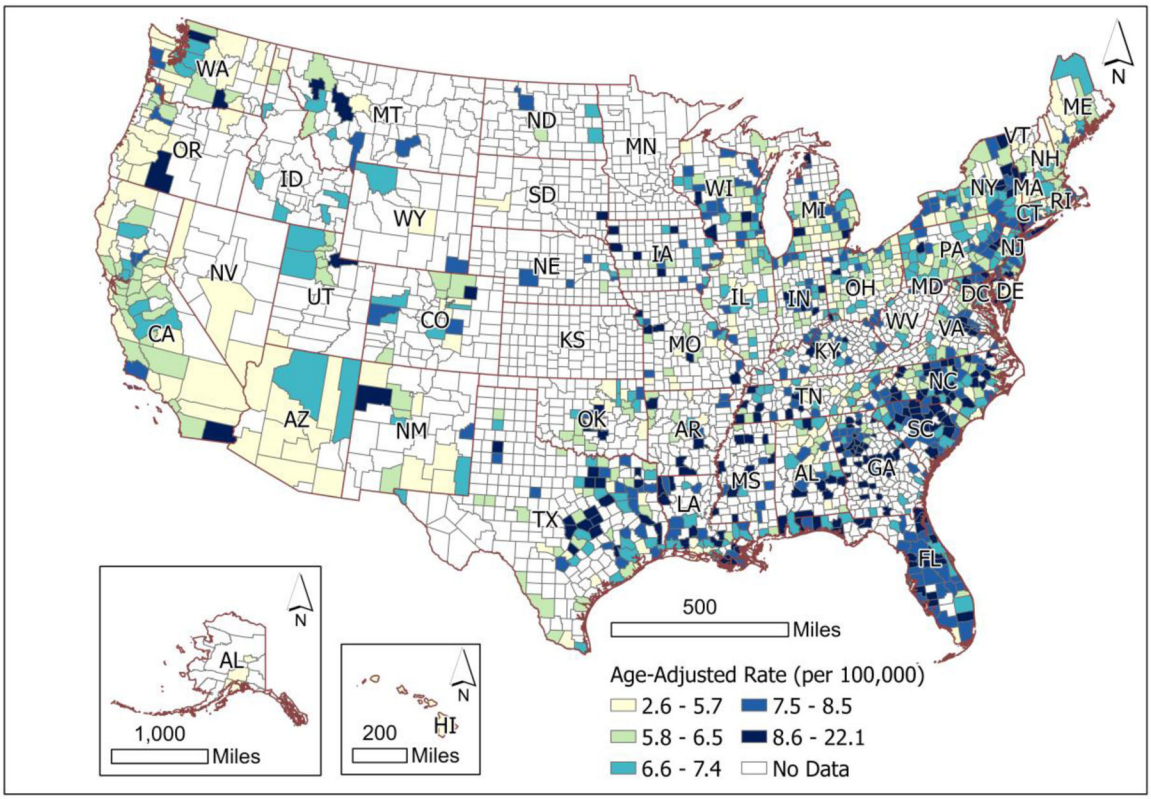

Fig 1.

Choropleth map of the average county-level age-adjusted rates of multiple myeloma incidence in quintiles between 2013 and 2017 in the United States.

Note: [1] AL = Alabama, AK = Alaska, AZ = Arizona, AR = Arkansas, CA = California, CZ = Canal Zone, CO = Colorado, CT = Connecticut, DE = Delaware, DC = District of Columbia, FL = Florida, GA = Georgia, GU = Guam, HI = Hawaii, ID = Idaho, IL = Illinois, IN = Indiana, IA = IOWA, KS = Kansas, KY = Kentucky, LA = Louisiana, ME = Maine, MD = Maryland, MA = Massachusetts, MI = Michigan, MN = Minnesota, MS = Mississippi, MO = Missouri, MT = Montana, NE = Nebraska, NV = Nevada, NH = New Hampshire, NJ = New Jersey, NM = New Mexico, NY = New York, NC = North Carolina, ND = North Dakota, OH = Ohio, OK = Oklahoma, OR = Oregon, PA = Pennsylvania, PR = Puerto Rico, RI = Rhode Island, SC = South Carolina, SD = South Dakota, TN = Tennessee, TX = Texas, UT = Utah, VT = Vermont, VI = Virgin Islands, VA = Virginia, WA = Washington, WV = West Virginia, WI = Wisconsin, WY = Wyoming. [2] The maps presented in this paper were in Lambert Conformal Conic (single parallel) projection with −96.0 Central Meridian and 40.0 Latitude of Origin for the continental US, −141.0 Central Meridian and 65.0 Latitude of Origin for Alaska, and −157.0 Central Meridian and 20.0 Latitude of Origin for Hawaii.

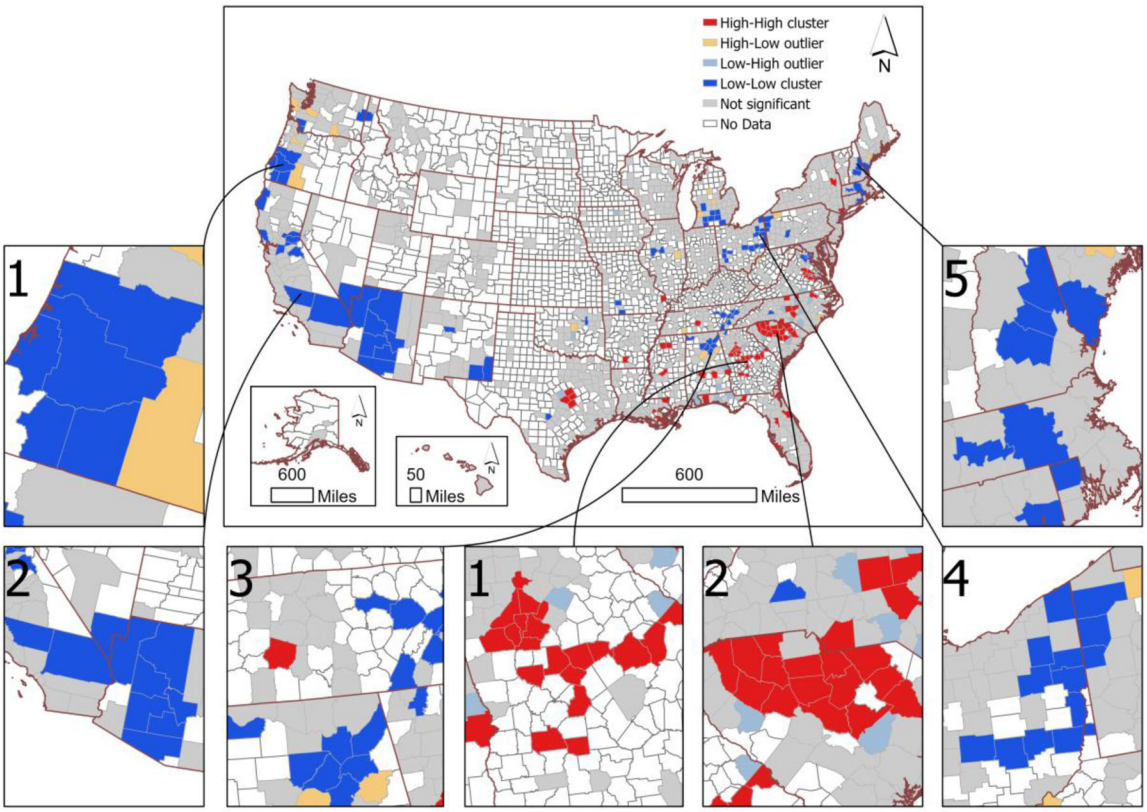

Fig 2.

Anselin's Local Indicator of Spatial Autocorrelation (LISA) analysis of the average county-level age-adjusted rates of multiple myeloma incidence between 2013 and 2017 in the United States.

Note: The maps presented in this paper were in Lambert Conformal Conic (single parallel) projection with −96.0 Central Meridian and 40.0 Latitude of Origin for the continental US, −141.0 Central Meridian and 65.0 Latitude of Origin for Alaska, and −157.0 Central Meridian and 20.0 Latitude of Origin for Hawaii.

Table 1.

Spatial autocorrelation (Global Moran's I) analysis of the average county-level age-adjusted rates of multiple myeloma incidence between 2013 and 2017 in the United States.

	Moran's Index	Z-Score	p-value
Parameter	0.31	10.3	<.001

Table 2.

Comparison of mean demographic and socioeconomic factors between clusters and the whole United States using Welch two-sample one-sided t-test.

	Mean (Cluster)	Mean (United States)	t Statistics	One-sided p-value
Males/Females ratio (number of males per 100 women)				
H-H Cluster 1	93.516	100.917	−7.604	1
H-H Cluster 2	93.619	100.917	−10.071	1
L-L Cluster 1	96.340	100.917	−9.003	<0.001
L-L Cluster 2	100.040	100.917	−0.650	0.266
L-L Cluster 3	96.119	100.917	−8.245	<0.001
L-L Cluster 4	96.657	100.917	−4.612	<0.001
L-L Cluster 5	96.088	100.917	−3.524	0.004
Blacks/Whites ratio				
H-H Cluster 1	1.291	0.181	3.355	0.002
H-H Cluster 2	0.563	0.181	4.473	<0.001
L-L Cluster 1	0.008	0.181	−19.877	<0.001
L-L Cluster 2	0.095	0.181	−2.700	0.011
L-L Cluster 3	0.073	0.181	−4.962	<0.001
L-L Cluster 4	0.057	0.181	−8.247	<0.001
L-L Cluster 5	0.045	0.181	−7.295	<0.001
% Population under poverty line				
H-H Cluster 1	17.729	15.430	1.135	0.138
H-H Cluster 2	16.967	15.430	1.525	0.074
L-L Cluster 1	16.400	15.430	1.472	0.897
L-L Cluster 2	16.310	15.430	0.888	0.802
L-L Cluster 3	15.750	15.430	0.422	0.661
L-L Cluster 4	14.843	15.430	−0.746	0.234
L-L Cluster 5	10.133	15.430	−4.024	0.005
% Population that earned a bachelor's degree				
H-H Cluster 1	25.184	21.972	1.194	0.876
H-H Cluster 2	21.431	21.972	−0.246	0.405
L-L Cluster 1	22.180	21.972	0.072	0.473
L-L Cluster 2	24.020	21.972	0.836	0.212
L-L Cluster 3	20.469	21.972	−0.852	0.796
L-L Cluster 4	20.893	21.972	−0.705	0.754
L-L Cluster 5	35.250	21.972	6.527	<0.001