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Evaluating Disparities in Recurrent *Clostridioides difficile* Infection (CDI) and Fecal Microbiota Transplant (FMT) Treatment using Geospatial and Social Vulnerability Analytic Tools

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B.S., Towson University, 2021

Thesis Committee Chair: Scott Fridkin, MD

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Abstract

Evaluating Disparities in Recurrent *Clostridioides difficile* Infection (CDI) and Fecal Microbiota Transplant (FMT) Treatment using Geospatial and Social Vulnerability Analytic Tools

By Keighly Little

Recurrence of *Clostridioides difficile* infection (CDI) occurs in 20-30% of patients and is associated with increased risk of complications and mortality. Fecal microbiota transplantation (FMT) is the most definitive treatment for recurrent CDI. Predictors of recurrent CDI have identified patient race as important, but disparities of CDI incidence and subsequent health outcomes are more complicated than just race alone. We aimed to estimate the magnitude of any racial disparities in the incidence of recurrent CDI and treatment with FMT and determine if specific metrics of social vulnerability better predict these events than race alone. The study population consisted of patients ages 18+ located within Health District 3 with at least one incident episode of CDI between 2016 and 2019. Although black race was found to be protective of patients developing multiple recurrences of CDI, the only SVI theme that was predictive of any recurrence was housing type & transportation. Black race, as well as all SVI themes were significant predictors of FMT receipt in a univariate logistic regression, with leading themes including socioeconomic status and racial & ethnic minority status. Adjusting for age, gender, and racial & ethnic minority status, patients located in vulnerable census tracts were 44% less likely to receive an FMT compared to the rest of the study population (p-value = 0.002). Geospatial analysis comparing the number of FMTs and rCDI rates by census tract suggests disproportionate use of FMTs in HD3.

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Background

Clostridioides difficile infection (CDI) is the most common healthcare-associated infection in the United States, affecting 500,000 Americans a year (1,2). The crude incidence of CDI in the U.S. is 101.3 per 100,000 persons, per the surveillance conducted at the Emerging Infections Program (EIP) in 2020 (3). Additionally, CDI is estimated to have caused 12,800 deaths in 2017; CDI has been labeled as an urgent threat by the Centers for Disease Control and Prevention (CDC) (1).

Clostridioides difficile is a spore- and toxin- producing bacterium first identified in 1935 within the flora of healthy infants (4). After the discovery of its contribution to human disease in the 1970s, increases in cases of CDI has been a cause of concern. Surges of this infection are largely attributed to the introduction of antibiotics, which is now known to cause patients to have a 7-10-fold increase in risk due to the disruption of the microbiome (5,6). Antibiotic resistance has thus caused CDI to become increasingly harder to treat.

Transmission of *C. difficile* occurs via the oral-fecal route, often person-to-person or through a contaminated environment. In the past, incident cases were largely healthcare-associated, but the bacterium has become increasingly recognized within the community (4). The EIP found in 2020 that about 50% of all cases were estimated to be community-associated, but general studies of the ribotypes of both strains suggest a common source of *C. difficile* for both settings (3,4).

Symptoms of CDI vary depending on the severity of illness; it can often present asymptomatically, through mild bouts of diarrhea, or even as severe disease involving colitis and toxic megacolon (7). The overall presentation of the infection and its severity is highly dependent on the characteristics of the patient; age, prior medication use, and underlying

comorbidities are likely to influence this (4). CDI can have serious effects on health and overall quality of life (2).

As mentioned previously, the use of antibiotics is a known risk factor for CDI. The severity of infection can be influenced by different factors of the antibiotic use, including which ones were taken, the dosage, and how long the course was (4). Other risk factors include a recent stay at a hospital or other healthcare facility, and this risk increases with longer stay. Older age (>65 years) also puts an individual at risk for CDI, increased severity of the infection, and mortality (5). A weakened immune system and/or underlying comorbidities have also been found to be associated with increased CDI risk (2,4). Current treatments for CDI include antibiotics – metronidazole, vancomycin, fidaxomicin are among the most recommended for treatment of mild- to moderate CDI. For more severe cases, surgical therapies are considered (4).

CDI most commonly affects whites, females, and those of advanced age (>65 years). Argamany, Delgado and Reveles found in a retrospective analysis that while incidence of CDI was 57% higher among white patients compared to black patients, mortality and severity of CDI outcomes were significantly poorer for black patients (8). This was the first study to associate worse health outcomes in CDI with race. In contrast, in a uniform subpopulation with little differences in healthcare access and exposure probability, Mao, Kelly and Machan reported no racial differences in CDI rates, suggesting that differential CDI outcomes could be influenced by a variety of environmental factors, including health-insurance, health-related behaviors, and access to care, rather than race itself (9).

Several studies have been done on the relationship between social determinants and incident CDI. Hudspeth, Qeadan and Phipps assessed differences in socioeconomic and ethnic factors among community-associated CDI (CA-CDI) patients; this study was also done using

EIP data, specifically from the New Mexico program. Results showed that CA-CDI risk was higher in census tracts with lower health insurance coverage, lower educational attainment, higher percentages of households with individuals ≥65 years of age, and ≥1.5 people per room, though the last two were not significant (10). Skrobarcek et al corroborates previous research, finding higher CA-CDI incidence present in communities with lower socioeconomic status (SES). Specifically, they looked at communities with high numbers of residents with low income, below poverty level, unemployed, on public health insurance, who are foreign-born or speak less English at home, and with crowding in the home (11). As previously mentioned, Mao, Kelly and Machan suggest disproportionate risk in CDI likely due to healthcare access and/or utilization after finding that higher SES is associated with increased risk for CDI (9). The cause of these differences, in that those with higher SES have increased risk for any CDI, but lower SES are at risk for specifically CA-CDI, are unknown. CA-CDI cases are without clear links to healthcare, so these disparities could be caused by certain populations being missed in routine surveillance.

A patient with incident CDI has a 15-25% chance of recurrent infection within 8 weeks of the first, and the risk increases up to 65% as the number of previous recurrences increases (4). Every year, recurrent CDI accounts for tens of thousands of additional CDI cases. It is due to the patient having a heavily depleted microbiota and has long-term effects on quality of life (2). Known risk factors of rCDI are similar to incident cases, including impaired immune response, advanced age, concomitant antibiotics, and increased severity of prior episodes (4). Freedberg et al found that black race was associated with increased risk for recurrence, but little other research has been done on racial or socioeconomic factors and rCDI (12).

The fecal microbiota transplantation (FMT) procedure is the most definitive treatment for rCDI. It was first documented during the Dong Lin Dynasty between 284 and 364 BC and first performed in modern medicine in 1958. In 1983, it was first performed in a patient with CDI, and its usage as a therapy has increased in the last decade as it becomes increasingly accessible (5,13,14). FMTs utilize the feces from healthy donors and then infuses it in patients with rCDI; the healthy microbiota prevents the overgrowth of *C. difficile* bacterium (13,14). Among all other treatments, FMT has the highest rate of prevention of additional recurrences at 94% (14). While who receives FMTs is not standardized across healthcare systems, it is generally thought that patients with >2 recurrences are eligible, when the efficacy of antibiotic treatment is only 30% (4).

Currently, there is a gap in the literature between eligibility of FMT and receipt of FMTs. Jamot et al is one of the few to investigate this, but only looked at once factor: race. They reported that black patients in their study were significantly under-represented in FMT receipt, despite previous literature showing that they are also more likely to experience increased severity of CDI, mortality, and recurrent CDI (13).

The Social Vulnerability Index (SVI) is a collaboration between the CDC and the Agency for Toxic Substances and Disease Registry (ATSDR); the tool was created from U.S. census data to assess the vulnerability of a community. Census tract data was used because it is a common way to collect government and public health data for policy and planning; additionally, they are made to be “demographically homogeneous”, and allows for patterns of vulnerability to be revealed using smaller populations (15). This tool was created for and is primary used for disaster management to assess a groups’ potential for preparedness and response, but recently

has been used to assess the impact of vulnerability on disease outcomes, including COVID-19, coronary heart disease, and obesity (16–18).

The SVI contains four domains: socioeconomic status, household characteristics, racial and ethnic minority status, and housing type and transportation (19). Table 1 summarizes the four domains of the SVI and each of their corresponding variables.

Socioeconomic status comprises the following variables: the percentage of persons below 150% poverty level, percentage of persons 16+ that are unemployed, percentage of housing cost burden (defined as the percentage of households that spend 30% or more of annual income on housing), percentage of persons 25+ with no high school diploma, and the percentage of uninsured (19). SES is an important factor in disease outcomes, as poverty and high incidence of infectious diseases is a known fact; this is likely due to the lack of medical access and low educational attainment (10). Additionally, those who lack health insurance or are underinsured are more likely to seek treatment at emergency rooms, which have increased risk for *C. difficle* transmission. This is a result of the high density of patients, which is especially dangerous among the elderly populations (10,11,20). SES also influences one's ability to finish antibiotic courses, which also increases risk of rCDI (21). On the other hand, those from lower SES groups might be less likely to access healthcare services due to a lack of insurance and/or education and thus have a protective effect for CDI (10).

The household characteristics domain includes the percentage of persons aged 65 and older, percentage of persons 17 and younger, percentage of civilians noninstitutionalized with a disability, percentage of single-parent households consisting of children under 18, and percentage of persons 5+ who speak English "less than well" (19). As aforementioned, advanced age is a risk factor for both CDI and rCDI, which suggests increased vulnerability of this

population to infection (5). Additionally, those with limited English proficiency are overall less insured compared to those who speak only English; thus, making them more likely to utilize emergency rooms where increased transmission of CDI occurs (10,22).

The third domain, racial and ethnic minority status, consists of the following variables: percentage Hispanic or Latino (of any race); Black or African American; Asian; American Indian or Alaska Native; Native Hawaiian or Pacific Islander, Two or More Races, and Other Races (19). This is a critical theme when looking into health outcomes, as all populations are not equally impacted by social determinants of health. Racial and ethnic minority groups are heavily marginalized in this society, thus influencing their access to healthcare, economic stability, environment, and educational attainment, leading to differential health outcomes (23). When pertaining to CDI, Argamany, Delgado and Reveles reported that in their study, blacks were overall more uninsured compared to their white counterparts, thus more likely to utilize emergency rooms which have increased risk of transmission. Blacks were also more likely to be readmitted to the hospital, further increasing that risk. Additionally, this group had a higher number of preexisting conditions, which likely influenced mortality and/or severity of CDI (8).

The final domain, housing type and transportation, includes the percentage of housing with 10 or more units within the same structure, percentage of mobile homes, percentage of households with more people than rooms, percentage of households with no vehicle, and percentage of persons living in group quarters (19). This domain is heavily entwined with wealth; therefore, it can have a strong impact on infectious disease, similarly to socioeconomic status (15). Primarily, the lack of resources, such as transportation to follow-up appointments, can contribute to rCDI (21). Another variable in this theme, overcrowding, is also linked to increased infectious disease susceptibility; specifically, several studies have investigated the

association between crowding and diarrheal or gastrointestinal diseases, and found positive associations (24).

The goal of this study is to 1) explore disparities of social vulnerability metrics among those who receive FMT treatment versus those who do not, and 2) estimate the differences of the social vulnerability metrics between those with recurrent CDI to those without.

Argamany et al. suggests that such disparities of CDI incidence and subsequent health outcomes are more complicated than just race itself, and could be influenced by a variety of factors, including health insurance, health-related behaviors, and access to care (8). This specific research will allow us to see if certain vulnerabilities can represent drivers of inequities rather than race alone. Additionally, the SVI as a predictor for both rCDI and FMT receipt can help locate primarily vulnerable communities for these events, and thus efficiently target efforts for control and prevention.

Recurrence occurs in ~30% of patients; additionally, there is increased odds of hospital readmission among those living in disadvantaged neighborhoods, and among those with dual Medicare-Medicaid enrollment (21). This is a significantly large group that is disproportionately affected by CDI and rCDI, where little work has been done to see the effect of SES and other vulnerabilities on recurrent CDI. Furthermore, increases in rCDI in the past few years, and the risk of mortality and additional complications with recurrence, suggests a need for this research (2).

Methods

Study Population

The Georgia Emerging Infections Program (GA EIP) conducts active surveillance for *C. difficile* in Health District 3 (HD3), which comprises Clayton, Cobb, Dekalb, Douglas, Fulton,

Gwinnett, Newton, and Rockdale counties. The study population consisted of patients ages 18-99 located within HD3 with at least one incident episode of CDI between 2016 and 2019. This study was reviewed and approved by both the Emory University and Georgia Department of Public Health Institutional Review Board.

GA EIP defines an incident case of *C. difficile* as a positive toxin assay or molecular assay from an HD3 resident with no prior positive result in the last 8 weeks. In this study, we defined an episode as any incident or recurrent case within the study period. We defined a sole incident case of CDI as a single episode, and recurrent CDI was defined as rapidly recurrent CDI (rrCDI when sequential episodes occurred <365 days from the previous CDI episode). The CDI episodes immediately preceding the date of FMT were designated as CDI episodes receiving FMT for the analysis. In this patient-level study, each participant was classified into three groups: single incident episode, single recurrent episode, or multiple (2 or more) recurrent episodes.

Data Sources

The primary data used for this research was a patient-level dataset of *C. difficile* surveillance data from the GA EIP. All positive *C. difficile* laboratory results from residents in HD3 are reported to GA EIP and are included in this dataset. Patient data is limited to demographics, name, and residence. The GA EIP was not involved in the analyses presented in this thesis. A second data source was a line list of patients having received an FMT during this time period. Prior evaluation of FMT procedures performed in HD3 identified 85% of FMTs were performed by two major health systems, both of which shared patient identifiers to link to our surveillance data.

Social Vulnerability Index

The Social Vulnerability Index data was accessed from the CDC/ATSDR SVI Data and Documentation Download database (19). Georgia census tract-level data from 2020 was used. The process used to obtain the numerical data was as follows: each of the variables mentioned in Table 1 were ranked across all census tracts in Georgia, and then assigned a corresponding percentile rank (percentile rank = (rank-1) / (n-1). The sum of the percentile ranks of each variable within each domain were used in this analysis, as well as a composite theme that included the overall rank for the census tract that incorporates all themes (19).

Merging of datasets

ArcGIS Online was used to geocode the addresses from each patient's first episode within the study period. 2020 census tract shapefiles were used to geocode and match 2020 SVI data. Two observations were homeless and did not have an address to be used for geocoding and were removed from the dataset. 15 observations had pending counties and addresses and were removed from the analysis.

The geocoding process assigned each patient a FIPS code, which is a unique 11-digit number specific to each census tract in the U.S. Each FIPS code contains a 2-digit state code, 3-digit county code, and 6-digit tract code. The patient-level dataset was then merged with the census-level SVI data by the FIPS code, successfully assigning each patient with a unique set of values for each theme. The FIPS codes obtained from geocoding for 23 observations did not match with the SVI data; the FFIEC Geocoding/Mapping System was used to obtain 2022 FIPS codes for these addresses and then re-matched with the SVI data. The final dataset contained 13,835 observations.

Statistical Analyses

Patient demographics and characterization, stratified by CDI history

Patient demographics were summarized using counts (percentages) for each categorical variable, and mean (standard deviation) for age, the only continuous variable. For each categorical variable, risk ratios were calculated using log binomial logistic regression, comparing each level of the variable to the reference category. The first comparison was between single episodes of CDI and single rrCDI, and the second comparison being between single episodes of CDI and multiple (two or more) rrCDI. County-level data was compared using a global chi-square test and the test.

Univariate analysis predicting rrCDI

Each SVI theme and composite variable was then assessed as a predictor for rrCDI using logistic regression. The RR, 95% CI, and p-values were reported. rrCDI was defined as any recurrence within 365 days of the incident episode. The upper quartile, or 75th percentile of the entire dataset was defined for each SVI theme and the composite variable and used as a cutoff point for this analysis. A binary variable was used where any observations at or above the 75th percentile was given a 1, and the rest of the observations given a 0. We decided on utilizing this format of the SVI themes rather than the continuous variables as it is easier to interpret from an outside perspective.

Patient demographics and characterization, stratified by FMT receipt

Similar summarizations to the analysis stratified by CDI history were conducted comparing observations with no FMT to any FMT receipt over the study period. For each categorical variable, counts (percentages) were summarized and for the continuous age variable, the mean (standard deviation) was summarized. Risk ratios were calculated using log binomial logistic regression that compared each level of the variable to the reference category for categorical variables. The global chi-square test was used to find the significance of county-level

data. One variable summarized the time between a patients' first two episodes and was thus restricted to patients with at least a single rrCDI episode.

Univariate analysis predicting FMT receipt

An ordinal variable was created for all SVI themes and the composite variable by gathering the quartile cutoff values to assess differences in FMT receipt at different vulnerability levels. Counts and percentages are presented as well as a risk ratio comparing each level of the variable to the reference category (below 25th percentile), using log binomial logistic regression. This analysis was restricted to FMT eligible patients (at least one rrCDI episode), which is consistent with the prior research using this data source. Additionally, 45 patients who were not considered "FMT eligible" received an FMT during the study period and were therefore excluded from this analysis.

Multivariate analysis

A forward stepwise selection process was conducted for both prediction of rCDI and FMT receipt. Though we first included race in the model (Table 6), due to a large percentage of missingness (~25.6%), we decided to maximize the number of observations able to be used in the model and remove race completely when examining the final models with the SVI themes. While race is linked to the patient, and the SVI themes are linked to an entire group, using the themes in place of race again allows us to maximize the data and provide more robust results.

A forward stepwise logistic regression was used to assess the most significant predictors of rCDI and FMT receipt from the following variables: age, gender, socioeconomic status, housing characteristics, racial & ethnic minority status, and housing type & transportation. A p-value threshold of 0.05 was used to assess eligibility for entry into the model. The multivariate analysis predicting FMT receipt was restricted to patients those FMT eligible with at least one

rapid recurrent episode and utilized the SVI themes comparing the patients at or above 75th percentile to the rest of the study population.

Additionally, we assessed FMT receipt utilizing a model that included the uninsured variable of the socioeconomic status theme. A forward stepwise logistic regression was used to assess if the health insurance variable would be eligible for the model along with age, gender, and racial & ethnic minority status. A p-value threshold of 0.05 was used to assess eligibility, and the analysis was restricted to FMT eligible patients with at least one rapid recurrent episode.

Geographical Analysis

ArcGIS Online was again used to create maps illustrating the geographical distribution of the study data. A spot map was created, where the size of the symbol represents the number of FMTs in that specific census tract. Additionally, two choropleth maps were created to show the number of CDI episodes per 100,000 persons by census tract, and the number of rCDI episodes per 100,000 persons by census tract. The distribution for the spot map utilized the Jenks natural breaks classification method, and both choropleth maps utilized the quantile method. These three maps contrast the geographical patterns of FMT receipt and CDI/rCDI episodes.

Supplemental maps

Six additional choropleth maps were created to supplement this research. A choropleth map for each SVI theme and the composite variable illustrates the geographical distribution of each theme in HD3 by census tract. The continuous variables of each SVI theme were used for this analysis; 0 represents the least vulnerable, 1 represents the most vulnerable. An additional choropleth map was created to show the predominant SVI theme by census tract in HD3. The continuous variables for each theme were utilized for this map as well.

Results

Recurrent CDI

13,835 cases of *C. difficile* detected in Health District 3 from 2016-2019 were analyzed in this study. Among the 13,835 patients, 3,038 (22.0%) had recurrent CDI and 250 (1.8%) had an FMT procedure during the study period. Of the 3,038 recurrent CDI patients, 2,055 (67.6%) had single recurrence and 983 (32.4%) had multiple (two or more) recurrent episodes. Majority of the cohort was white, female, and middle age (Table 2).

There was no significant difference in the distribution of sex between single episodes of CDI and recurrent CDI (Table 2). As age increased, the risk of rCDI increased between 19 and 41 percent for single rrCDI, and 16 and 35 percent for multiple (two or more) rrCDI. No significant difference was found in race and 1 rrCDI. Blacks and the "Other" category (American Indian/Alaska Native, Asian, and Pacific Islander) were 15 and 28 percent less likely to have multiple (two or more) rrCDI, respectfully. No significant differences in the distribution of cases by county were found when comparing single episodes of CDI to single rrCDI, but there was a significant finding when comparing single episodes of CDI to multiple (two or more) rrCDI (p-value=0.003).

A univariate analysis found the only significant SVI predictor for recurrent CDI was housing type and transportation; patients at or above the 75th percentile of this variable were 11% more likely to have recurrence compared to those below the 75th percentile (p-value=0.005). All other SVI themes and the composite variable were insignificant when looking at recurrence (Table 3).

Consistent with the previous analysis, a forward stepwise logistic regression identified the only significant variable in the assessment of recurrent CDI was housing type and

transportation. When adjusted for age and gender, patients at the 75th percentile or higher had 1.13 times the odds of recurrent CDI compared to those under the 75th percentile (p-value=0.009).

FMT Receipt

As shown in Table 4, males were 51% less likely to get an FMT. As age increased, the likelihood of an FMT decreased between 9 and 17 percent. Blacks and the "Other" category (American Indian/Alaska Native, Asian, and Pacific Islander) were 55 and 80 percent less likely to have an FMT, respectfully. Minor differences in the frequency of FMT was observed between counties. Patients with a single rrCDI and multiple (2 or more) rrCDI were 5.68 and 32.26 times more likely to get an FMT, respectfully, compared to patients with no recurrence. No significant relationship was found when looking at the time between the first two episodes of CDI and FMT receipt (Table 4).

The likelihood of receiving an FMT decreased as the quartile of vulnerability increased for all SVI themes (Table 5). The most significant differences in FMT receipt existed for the socioeconomic status and racial and ethnic minority status themes. Patients above the 75th percentile of the socioeconomic status theme were 51% less likely to receive an FMT compared to those below the 25th percentile. Patients above the 75th percentile of the racial and ethnic minority status theme were 47% less likely to receive an FMT compared to those below the 25th percentile. The composite theme seems to be driven by these two themes and had similar results (Table 5).

In a regression model with only age, gender, and race, race was found to be extremely significant in the assessment of FMT receipt (p-value=<.0001; Table 6). When introducing the SVI themes, all themes except household characteristics were found to be significant before race

was entered into the model. When race was introduced, all themes became insignificant, as shown in table 7, but roughly 25% of observations were dropped due to missing race. Maximizing observations used, we focused our forward stepwise logistic regression without evaluating medical-record derived race, and identified SVI defined racial and ethnic minority ranking as the only significant SVI variable in the assessment of FMT receipt (Table 8). Socioeconomic ranking was also significant (p-value=0.0108), but once racial and ethnic minority ranking entered the model, it became insignificant (p-value=0.1508). When adjusted for age and gender, patients at the 75th percentile or higher for racial and ethnic minority status were 44% less likely to receive an FMT compared to those under the 75th percentile (p-value=0.002). When the specific uninsured variable ranking was introduced to this model, it was significant (p-value=0.05); increases in this variable is associated with a decrease in the odds of FMT receipt, when adjusted for age, gender, and racial and ethnic minority status (Table 9).

Geographical Analysis

FMTs were clustered in Cobb, Dekalb, Fulton, and Gwinnett counties (Figure 1). CDI episodes per 100,000 persons were relatively distributed across HD3, with some heavier clustering in Cobb and Dekalb counties (Figure 2a). Similarly, when looking at recurrent CDI episodes per 100,000 persons, clustering appears in Cobb, Dekalb, and Newton counties (Figure 2b).

Supplemental maps

The most vulnerable census tracts related to the socioeconomic status theme appears to be centered in Fulton, Clayton, Dekalb, and Newton counties (Figure 3a). Vulnerability regarding the household characteristic and housing type and transportation themes appear to be more equally distributed; with slightly more vulnerable tracts in Fulton, Clayton, and Dekalb

counties (Figure 3b, 3d). The racial and ethnic minority status theme has the most distinct differences compared to the other themes; heavy clustering of the most vulnerable tracts occurs in Fulton, Clayton, and Dekalb counties (Figure 3c). Again, the composite theme seems to be driven the most by socioeconomic status and racial and ethnic minority status, with the most vulnerable census tracts centered around Fulton, Clayton, and Dekalb counties (Figure 4). Figure 5 indicates that most predominant theme with the most vulnerability throughout HD3 is racial ethnic and minority status, which is consistent with Figure 4. The least predominant theme throughout HD3 is socioeconomic status.

Discussion

The patient demographics and characteristics measured in this study are consistent with previous literature. Increased incidence of CDI among patients who are female, white, and/or of advanced age (≥65) was observed, which Argamany et al also observed in 2016 (8). A county-level analysis among this population in HD3 appears to be insufficient, as only minor differences in rCDI and FMT receipt were observed across counties. This is likely due to larger variations on the county-level and suggests a need for census tract-level research.

Advanced age (≥65) and prior CDI episodes increased risk for recurrent CDI, again consistent with prior analyses on this topic. As one ages, they are more likely to undergo increased health system exposure and antibiotic usage, as well as have an impaired immune system, all making them more susceptible to infection (25). The risk for recurrence is known to increase as the number of previous recurrences increases, which is likely due to depleted microbiome (2).

No significant differences in recurrence risk based on sex was observed, despite females being largely impacted by CDI overall, and previous research suggesting females are at increased

risk for rCDI (26). Black patients and those in the "Other" category, including American Indian/Alaska Native, Asian, and Pacific Islander, while less likely to experience multiple recurrent episodes, were slightly more likely to have single recurrence, although not significant. This is not consistent with previous literature, that found black race to be associated with increased risk for recurrence (12). This discrepancy can be due to the missingness of our data, or slight differences within our own surveillance area.

When assessing the SVI themes as a predictor for recurrent CDI, only the housing type and transportation theme was found to be associated with increased risk. This was consistent in both the univariate and multivariate analyses. This is unsurprising, due to this themes' ties to wealth overall. Homes with overcrowding and lack of transportation has been associated with increased infectious disease in several studies (21,24). We did expect the other themes, especially socioeconomic status and racial and ethnic minority status, to also be significant, due to their known ties to disproportionate health outcomes. Since this outcome was defined as rapidly recurrent CDI, different results are possible if overall recurrence over the study period was used instead.

Among this study population, females and younger individuals were significantly more likely to receive an FMT. It is unclear as to why there are clear distinctions in sex, but it is hypothesized that despite older individuals being at an increased risk for recurrence, the FMT administration procedure, i.e., a colonoscopy, does pose a risk for complication that increases in older individuals and those with more underlying illness (such as men with hypertension); therefore the procedure may be preferentially favored for younger persons and women who tend to have fewer complicating conditions. No association was observed when looking at the relationship between FMT receipt and the time between the first two CDI episodes; we expected

to see higher FMT receipt among those with shorter time between episodes, which we hypothesized to be a marker for disease severity and failure of primary treatments.

Black patients and those in the "Other" category, including American Indian/Alaska Native, Asian, and Pacific Islander, were 55% and 80% less likely to receive an FMT, respectfully, compared to their white counterparts. This is consistent with one of the few studies on eligibility and receipt of FMTs, where it was observed that black individuals with recurrent CDI were "significantly under-represented" among patients who received FMT (13). This suggests disproportionate access to FMT treatment. However, the Jamot et al study was carried out in a single center with a very small black population, suggesting poor internal validity (13). In comparison, our research has better generalizability; it was conducted in HD3, a much more diverse population compared to other studies, and included patient data across several centers.

In a univariate analysis predicting FMT receipt utilizing the SVI themes, all themes were found to be significantly negatively associated with FMT receipt. The two main drivers appear to be socioeconomic status and racial and ethnic minority status, which is consistent with what we expected. Since a large number of FMTs in the surveillance area are self-referrals, it was hypothesized that more affluent patients with health insurance, likely white in this area, were more likely to do so and have the FMT procedure. The composite theme had similar results to both socioeconomic status and racial and ethnic minority status themes, which suggests they are likely related to one another and together drive results of the composite theme.

In the multivariate analysis predicting FMT receipt, the age, gender, and race variables were all found to be statistically significant in a model with one another. When the four SVI themes were introduced in this same model, all themes became insignificant. This suggests race is a complicated variable, and likely has immense influence within all social vulnerability

metrics. To observe the relationships of the SVI themes on FMT receipt, we removed the race variable to assess if any themes would be significant. Both racial & ethnic minority status and socioeconomic status were found to be significant, but once the racial theme entered, the socioeconomic status variable became insignificant. Again, this suggests a strong relationship between these two themes, with racial & ethnic minority status being the most important metric in FMT receipt.

Prior analyses suggest access to healthcare is a leading factor in FMT receipt, as mentioned previously, many of the FMTs done in the Atlanta metropolitan area are self-referrals. They are currently not a standard of care, so patients with adequate health insurance and an awareness of the treatment are likely more likely to receive it. We thus decided to assess whether the percent uninsured variable alone would be eligible for entry into the model along with age, gender, and racial and ethnic minority status. The variable was found to be significant, suggesting its importance in the relationship between FMT eligibility and FMT receipt, and a need for more research on this topic.

The number of FMTs by census tract do not appear to be related to the distribution of CDI and rCDI cases per 100,000 persons by census tract. The CDI and rCDI rates appear to be distributed across the counties, with only slight clustering, while the FMTs appear to be clustered in Cobb, Fulton, and Dekalb counties. This suggests disproportionate access to FMTs in HD3. While portions of Newton, Gwinnett, and Fulton counties have higher CDI and rCDI rates, they have little to no FMTs done. The supplemental maps of the overall distribution of the SVI themes by census tract also suggest the composite theme is driven by both socioeconomic status and racial & ethnic minority status, as both choropleth maps appear similar, with comparable distributions of the themes among all three.

This study is one of the few to assess SES and its relationship with rCDI and FMT receipt; this is significant, as prior research on the impact of SES and similar metrics on infectious disease has suggested a need for this research. Specifically, we looked at a variety of vulnerability metrics using the Social Vulnerability Index, which is unprecedented. Since the SVI is flexible, with a broad range of variables, it can be applied to different events (15). It is particularly useful as many of the variables included in this data influence disease control. Census tract-level data also allows for a deeper dive compared to county-level and can allow for more focused targeting of potential interventions.

This research also has several limitations. First, ~25.6% of the entire dataset had missing race classification, making it possible that the participants in this study do not properly represent the larger population and limits generalizability. On the other hand, when SVI themes are used instead of race, race isn't needed and we could still maximize the observations utilized in each analysis. The line list of FMTs from the two health systems also is not inclusive of all procedures done in the surveillance area, which could have led to misclassification of observations as non-FMT received when they have received them; however, a prior analysis suggests we captured 90% of FMTs in HD3. As mentioned previously, a large number of the FMTs in the Atlanta metropolitan area are self-referrals; thus, the distribution of FMTs is heavily influenced by a self-awareness pattern, where those who advocate for the treatment are more likely to receive it. It is not a standard of care, which likely explains the geographical differences in FMTs versus increased rCDI rates. Additionally, regarding census tract-level analyses, there is always the possibility of significant variation of certain variables within each tract that cannot be assessed. Using census tract-level data rather than individual vulnerabilities also might not provide the full story. Lastly, there was no definitive answer on how to dichotomize the SVI themes for the

analyses. Further research should be done on how to best represent the variables in research such as this.

Conclusion

Using census tract summary data, we successfully estimated the association between SVI metrics and rCDI. More novel, we estimated that the likelihood of receiving an FMT was roughly 50% lower among persons residing in more vulnerable communities defined by A, and B. our study captured patients from more than 20 hospitals and many community settings, suggesting these findings are generalizable and actionable. Specifically, as FMT options become more common and easier to administer, providers of FMT may need to be pro-active in education and outreach to area providers to minimize the existing disparities in FMT use we documented in our study. Additionally, similar research to this study can be conducted in different populations post COVID-19 pandemic to see if findings are consistent or persistent.

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Tables

Table 1. Summary of Social Vulnerability Index (SVI) themes.

Themes	Variables Included
Socioeconomic Status	Below 150% Poverty Level
	Unemployed
	Housing Cost Burden
	No High School Diploma
	No Health Insurance
Household Characteristics	Aged 65 & Older
	Aged 17 & Younger
	Civilian with a Disability
	Single-Parent Households
	English Language Proficiency
Racial & Ethnic Minority Status	Hispanic or Latino (of any race)
	Black or African American, Not Hispanic or Latino
	Asian, Not Hispanic or Latino
	American Indian or Alaska Native, Not Hispanic or Latino
	Native Hawaiian or Pacific Islander, Not Hispanic or Latino
	Two or More Races, Not Hispanic or Latino
	Other Races, Not Hispanic or Latino
Housing Type & Transportation	Multi-Unit Structures
	Mobile Homes
	Crowding
	No Vehicle
	Group Quarters

Table 2. Characteristics of overall study population by CDI history.

Characteristics	No. (%)		RR (95% CI)[3]	No. (%)	RR (95% CI)[3]
	Single episode (n=10797)	1 rrCDI[1] (n=2055)	1 rrCDI/single	2+ rrCDI[2] (n=983)	2+ rrCDI/single
Sex					
Female, n=8264	6427 (77.8%)	1233 (12.9%)	REF	604 (7.3%)	REF
Male, n=5571	4370 (78.4%)	822 (14.8%)	0.98 (0.91, 1.07)	379 (6.8%)	0.93 (0.82, 1.05)
Age, years, mean (SD)	60.2 (18.7)	63.1 (17.8)		62.5 (17.7)	
Age group					
18-49, n=3639	3005 (82.6%)	413 (11.4%)	REF	221 (6.1%)	REF
50-64, n=3705	2868 (77.4%)	581 (15.7%)	1.19 (1.13, 1.25)	256 (6.9%)	1.16 (1.08, 1.25)
≥65, n=6491	4924 (75.9%)	1061 (16.4%)	1.41 (1.28, 1.56)	506 (7.8%)	1.35 (1.17, 1.57)
Race					
White, n=5508	4221 (76.6%)	824 (15.0%)	REF	463 (8.4%)	REF
Black, n=4456	3431 (77.0%)	704 (15.8%)	1.01 (0.93, 1.10)	321 (7.2%)	**0.85 (0.75, 0.96)**
Other[4], n=323	261 (80.8%)	44 (13.6%)	1.02 (0.87, 1.20)	18 (5.6%)	**0.72 (0.57, 0.92)**
Unknown, n=3548					
County			**Chi-Square (p-value)**		**Chi-Square (p-value)**
Clayton, n=684	562 (82.2%)	88 (12.9%)		34 (5.0%)	
Cobb, n=3003	2336 (77.8%)	445 (14.8%)		222 (7.4%)	
Dekalb, n=2844	2171 (76.3%)	446 (15.7%)		227 (8.0%)	
Douglas, n=480	388 (80.8%)	74 (15.4%)	11.58 (0.115)	18 (3.8%)	21.52 (0.003)
Fulton, n=3680	2836 (77.1%)	569 (15.5%)		275 (7.5%)	
Gwinnett, n=2491	1993 (80.0%)	336 (13.5%)		162 (6.5%)	
Newton, n=343	262 (76.4%)	55 (16.0%)		26 (7.6%)	
Rockdale, n=310	249 (80.3%)	42 (13.6%)		19 (6.1%)	

Reported as n (%) unless otherwise specified.

[1]1 rrCDI refers to rapid recurrent CDI, with sequential episodes occurring <365 days from the first.

[2]2+ rrCDI refers to at least 2 recurrent episodes occurring within one year from the first.

[3]Univariate analysis using log binomial logistic regression.

[4]Includes American Indian/Alaska Native, Asian, and Pacific Islander.

Table 3. Social Vulnerability Index (SVI) themes as a predictor for rrCDI[1]

SVI Theme[3]	RR (95% CI)[2]	P-value
Socioeconomic Status	1.01 (0.94, 1.08)	0.86
Household Characteristics	1.04 (0.96, 1.11)	0.34
Racial & Ethnic Minority Status	1.03 (0.96, 1.10)	0.46
Housing Type & Transportation	1.11 (1.03, 1.19)	0.005
Composite Theme	1.02 (0.95, 1.10)	0.51

[1]rrCDI refers to sequential episodes occurring <365 days from the first.
[2]Univariate analysis using log binomial logistic regression.
[3]Comparing patients in 75th percentile to the rest of the study population.

Table 4. Characteristics of overall study population, by FMT receipt.

Characteristics	No. (%)		RR (95% CI)[4]
	No FMT n=13585	Any FMT n=250	Any FMT/No FMT
Sex			
Female, n=8264	8076 (97.7%)	188 (2.3%)	REF
Male, n=5571	5509 (98.9%)	62 (1.1%)	0.49 (0.37, 0.65)
Age (years), mean (SD)	60.8 (18.5)	59.0 (19.2)	
Age (categorized)			
18-49, n=3639	3567 (98.0%)	72 (2.0%)	REF
50-64, n=3705	3634 (98.1%)	71 (1.9%)	0.91 (0.79, 1.05)
≥65, n=6491	6384 (98.4%)	107 (1.7%)	0.83 (0.62, 1.11)
Race			
White, n=5508	5363 (97.4%)	145 (2.6%)	REF
Black, n=4456	4409 (99.0%)	47 (1.1%)	0.45 (0.33, 0.60)
Other[5], n=323	319 (98.8%)	4 (1.2%)	0.20 (0.11, 0.36)
Unknown, n=3548			
County			**Chi-Square (p-value)**
Clayton, n=684	679 (99.3%)	5 (0.7%)	19.52 (0.007)
Cobb, n=3003	2953 (98.3%)	50 (1.7%)	
Dekalb, n=2844	2801 (98.5%)	43 (1.5%)	
Douglas, n=480	475 (99.0%)	5 (1.0%)	
Fulton, n=3680	3589 (97.5%)	91 (2.5%)	
Gwinnett, n=2491	2449 (98.3%)	42 (1.7%)	
Newton, n=343	338 (98.5%)	5 (1.5%)	
Rockdale, n=310	301 (97.1%)	9 (2.9%)	
Recurrence			
0 rrCDI, n=10797	10752 (99.6%)	45 (0.4%)	REF
1 rrCDI, n=2055	1992 (96.9%)	63 (3.1%)	5.68 (4.88, 6.61)
2+ rrCDI, n=983	841 (85.6%)	142 (14.5%)	32.26 (23.85, 43.64)
Time between first two episodes[3]	n=2833	n=205	
>6 months	415 (93.9%)	27 (6.1%)	REF
2-6 months	708 (92.7%)	56 (7.3%)	1.01 (0.84, 1.21)
<2 months	1710 (93.3%)	122 (6.7%)	1.02 (0.71, 1.47)

Reported as n (%) unless otherwise specified.
[1]1 rrCDI refers to rapid recurrent CDI, with sequential episodes occurring <365 days from the first.
[2]2+ rrCDI refers to at least 2 recurrent episodes occurring within one year from the first.
[3]Restricted to patients with at least 1 rrCDI.
[4]Univariate analysis using log binomial logistic regression.
[5]Includes American Indian/Alaska Native, Asian, and Pacific Islander.

Table 5. Distribution of SVI themes, stratified by FMT receipt. Restricted to patients with at least one rapid recurrent episode (FMT eligible).

Socioeconomic Status	FMT Receipt		Total	RR (95% CI)
	No	Yes		Any FMT/No FMT
Below 25th percentile	682 (91.2%)	66 (8.8%)	748	REF
25th-50th percentile	711 (92.1%)	61 (7.9%)	772	0.79 (0.71, 0.88)
50th-75th percentile	713 (94.6%)	41 (5.4%)	754	0.62 (0.50, 0.78)
Above 75th percentile	727 (95.2%)	37 (4.8%)	764	0.49 (0.35, 0.69)
Total	2833 (93.3%)	205 (6.7%)	3038	

Household Characteristics	FMT Receipt		Total	RR (95% CI)
	No	Yes		Any FMT/No FMT
Below 25th percentile	687 (90.9%)	69 (9.1%)	756	REF
25th-50th percentile	702 (94.0%)	45 (6.0%)	747	0.91 (0.82, 1.02)
50th-75th percentile	711 (94.2%)	44 (5.8%)	755	0.83 (0.66, 1.03)
Above 75th percentile	733 (94.0%)	47 (6.0%)	780	0.75 (0.54, 1.05)
Total	2833 (93.3%)	205 (6.7%)	3038	

Racial & Ethnic Minority Status	FMT Receipt		Total	RR (95% CI)
	No	Yes		Any FMT/No FMT
Below 25th percentile	710 (91.8%)	63 (8.2%)	773	REF
25th-50th percentile	688 (92.1%)	59 (7.9%)	747	0.81 (0.72, 0.91)
50th-75th percentile	693 (93.5%)	48 (6.5%)	741	0.66 (0.52, 0.82)
Above 75th percentile	742 (95.5%)	35 (4.5%)	777	0.53 (0.38, 0.74)
Total	2833	205	3038	

Housing Type & Transportation	FMT Receipt		Total	RR (95% CI)
	No	Yes		Any FMT/No FMT
Below 25th percentile	658 (91.6%)	60 (8.4%)	718	REF
25th-50th percentile	670 (92.0%)	58 (8.0%)	728	0.87 (0.78, 0.98)
50th-75th percentile	728 (94.5%)	42 (5.5%)	770	0.76 (0.61, 0.95)
Above 75th percentile	777 (94.5%)	45 (5.5%)	822	0.67 (0.48, 0.93)
Total	2833	205	3038	

Composite Theme	FMT Receipt		Total	RR (95% CI)
	No	Yes		Any FMT/No FMT
Below 25th percentile	645 (90.7%)	66 (9.3%)	711	REF
25th-50th percentile	735 (92.7%)	58 (7.3%)	793	0.80 (0.72, 0.90)
50th-75th percentile	714 (94.1%)	45 (5.9%)	759	0.65 (0.52, 0.81)
Above 75th percentile	739 (95.4%)	36 (4.6%)	775	0.52 (0.37, 0.73)
Total	2833	205	3038	

Table 6. Multivariate analysis predicting FMT receipt. Restricted to patients with at least one rapid recurrent episode (FMT eligible). n=2374

Dependent Variable	Adjusted Odds Ratio (95% CI)	P-value
Age	0.61 (0.50, 0.74)	<.0001
Gender	0.44 (0.30, 0.63)	<.0001
Race[1]	0.40 (0.28, 0.56)	<.0001

[1]Race variable is coded as 0=white, 1=black. Race categorized as "other" set to missing.

Table 7. Statistical Significance of each SVI Theme as an independent predictor[1] of FMT receipt in forward selection process by scenario with and without including Race as an eligible predictor. Restricted to patients with at least one rapid recurrent episode (FMT eligible); n=23742

Dependent Variable	Without Race (p-value)	With Race (p-value)
Socioeconomic Status	0.003	0.104
Household Characteristics	0.28	0.57
Racial & Ethnic Minority Status	<0.001	0.27
Housing Type & Transportation	0.041	0.20

[1]Comparing patients in the 75th percentile to the rest of the study population.
[2]Race variable is coded as 0=white, 1=black. Race categorized as "other" set to missing.

Table 8. Multivariate analysis predicting FMT receipt. Restricted to patients with at least one rapid recurrent episode (FMT eligible). n=3038

Dependent Variable	Adjusted Odds Ratio (95% CI)	P-value
Age	0.72 (0.61, 0.86)	0.0002
Gender	0.49 (0.36, 0.68)	<.0001
Racial & Ethnic Minority Status[1]	0.56 (0.38, 0.81)	0.002

[1]Comparing patients in the 75th percentile to the rest of the study population.

Table 9. Multivariate analysis including uninsured variable predicting FMT receipt. Restricted to patients with at least one rapid recurrent episode (FMT eligible). n=3038

Dependent Variable	Adjusted Odds Ratio (95% CI)	P-value
Age	0.71 (0.60, 0.85)	0.0001
Gender	0.49 (0.36, 0.68)	<.0001
Racial & Ethnic Minority Status[1]	0.63 (0.42, 0.93)	0.02
% No Health Insurance[2]	0.61 (0.37, 1.00)	0.05

[1]Comparing patients in the 75th percentile to the rest of the study population.
[2]Continuous variable.

Figures

Figure 1. Spot map of number of Fecal Microbiota Transplantation (FMTs) by census tract of recipients residence; HD3, 2016-2019

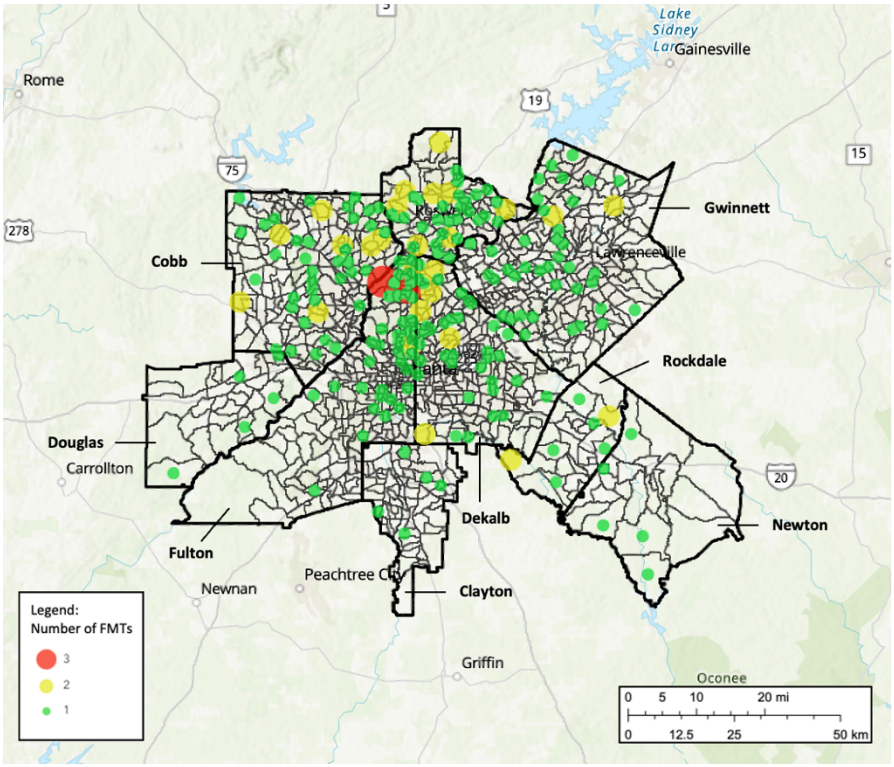
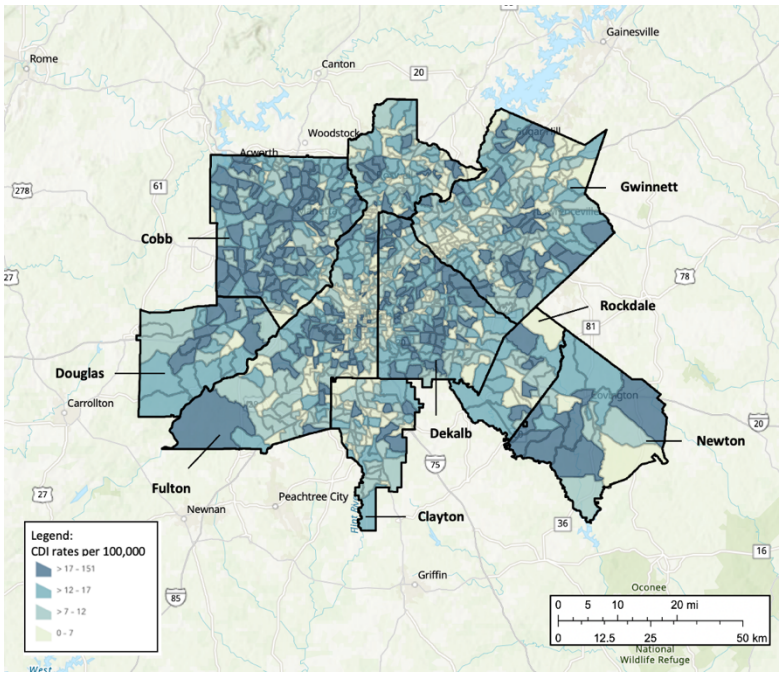


Figure 2. Choropleth map of (A) CDI rate (episodes of CDI per 100,000 persons) and (B) recurrent CDI rate (recurrent CDI episodes per 100,000 persons) by census tract; HD3, 2016-2019

a)



b)

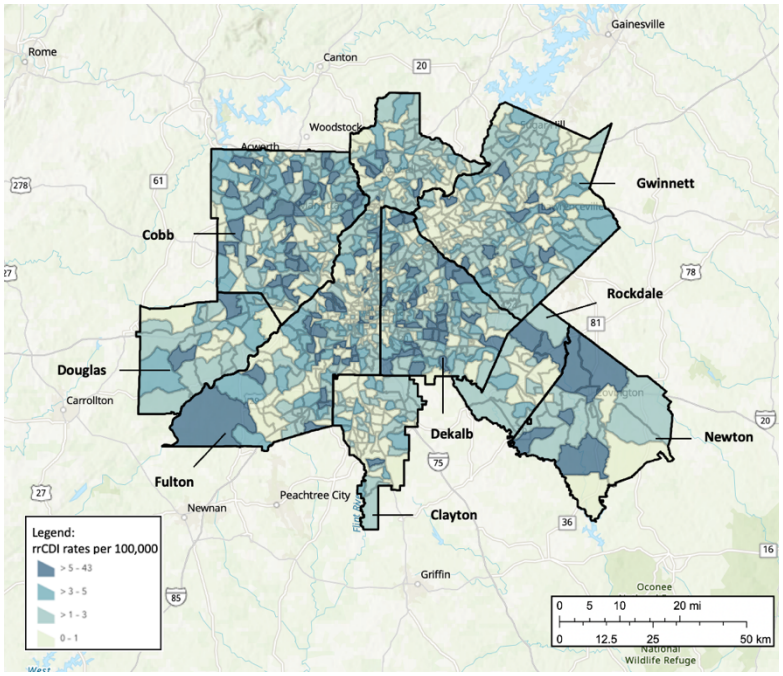
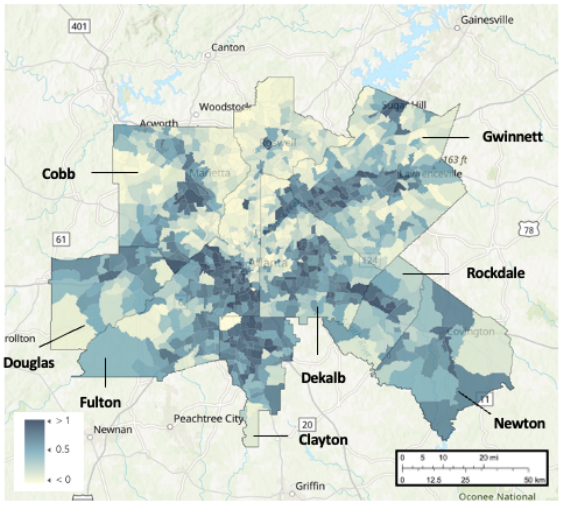
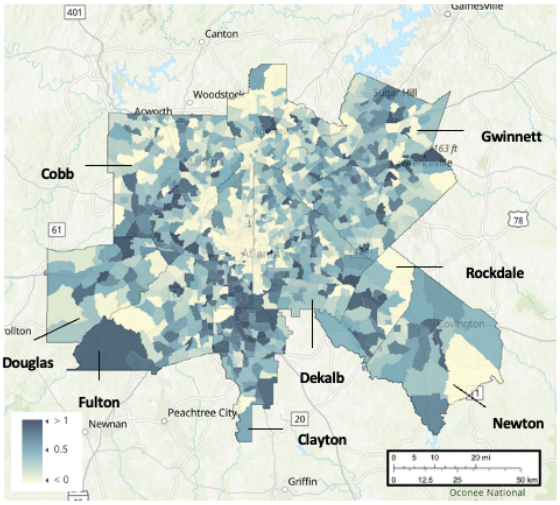


Figure 3. Geographical distribution of each SVI theme in HD3 by census tract. 0=least vulnerable, 1=most vulnerable.

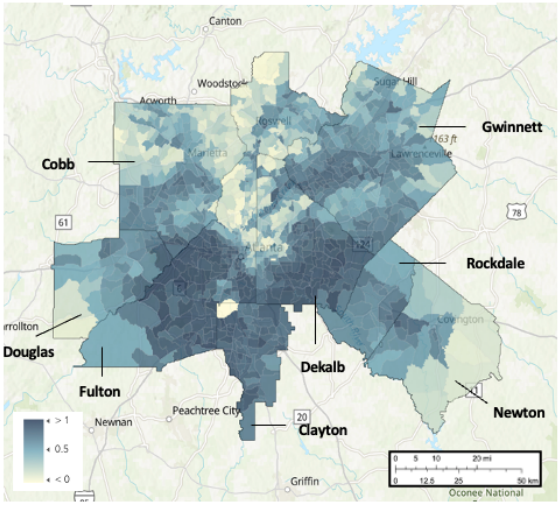
a) Socioeconomic Status



b) Household Characteristics



c) Racial & Ethnic Minority Status



d) Housing Type & Transportation

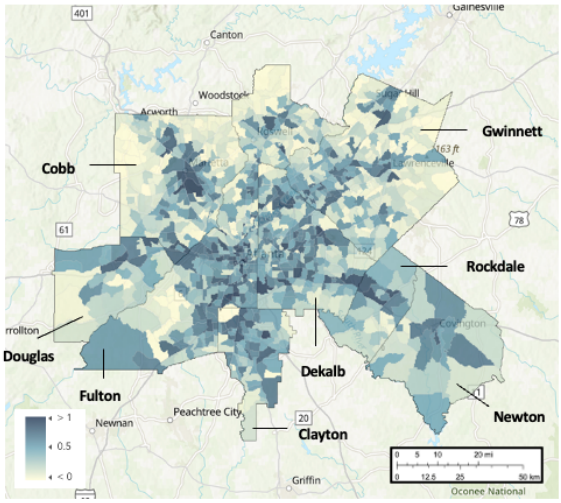


Figure 4. Geographical distribution of the composite SVI theme in HD3 by census tract. 0=least vulnerable, 1=most vulnerable.

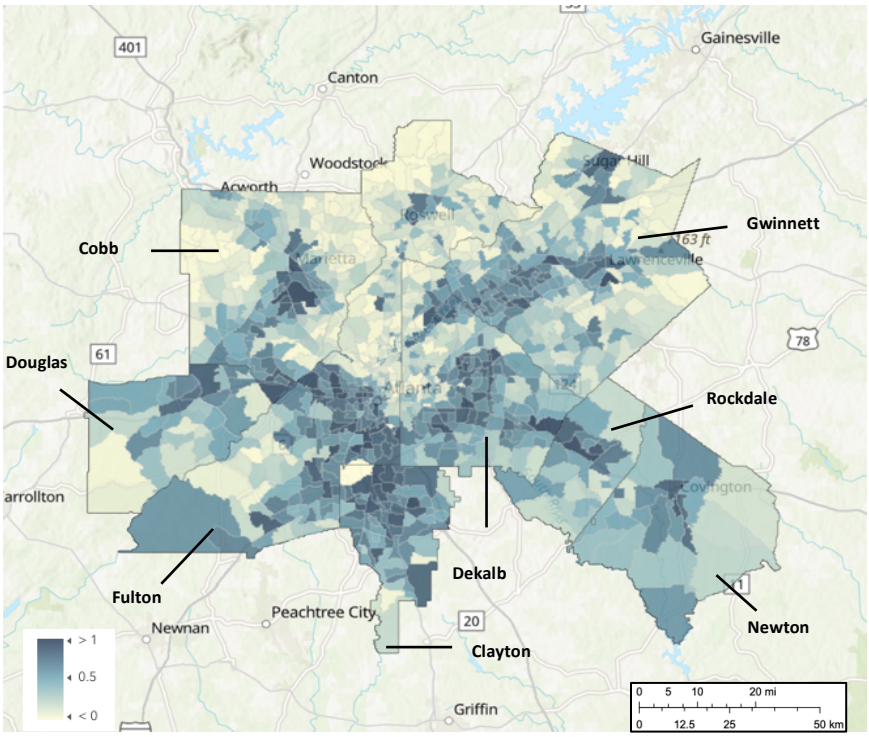


Figure 5. Predominant SVI theme by census tract in HD3.