

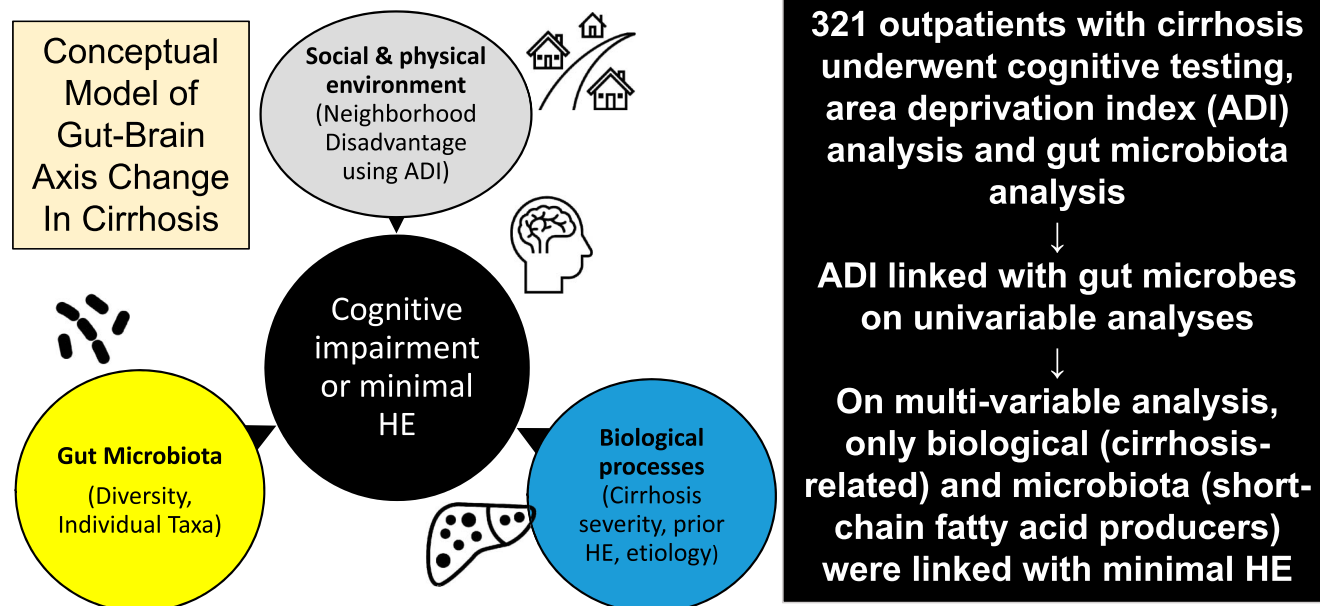
# Area Deprivation Index and Gut-Brain Axis in Cirrhosis

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**INTRODUCTION:** Neighborhood deprivation has been associated with chronic diseases and with gut microbial alterations. Although cirrhosis is associated with gut microbiome changes and hepatic encephalopathy (HE), their association is unclear.

**METHODS:** Demographics and cirrhosis details (model for end-stage liver disease [MELD], prior HE, and medications) were recorded from outpatients with cirrhosis. Area deprivation index (ADI), which ranks neighborhoods by socioeconomic disadvantage, was recorded as state decile and national percentile (high = worse for both) and dichotomized on the median. Patients underwent cognitive testing to diagnose minimal HE (MHE). Stool microbiota was analyzed using 16S ribosomal RNA for  $\alpha/\beta$ -diversity. Multivariable analysis was used to evaluate the factors independently associated with MHE.

## Area Deprivation Index and Gut-Brain Axis in Cirrhosis



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**RESULTS:** A total of 321 people with cirrhosis (60 years, 78% men, 75% non-Hispanic White, 24% non-Hispanic African American, 4% Hispanic) were included. 45% had prior HE and 56% MHE. For ADI, the national percentile was  $49.1 \pm 21.8$  while the state decile was  $6.1 \pm 2.3$ . ADI was not associated with race, ethnicity, MELD, or HE-related variables on regression. Regarding microbiota,  $\alpha$ -diversity was lower in MHE and prior HE patients but similar across ADI rankings. Low vs high ADIs were associated with different  $\beta$ -diversity in univariable but not multivariable analyses. Multivariable analyses showed positive associations with MELD, prior HE, and lactate producers (*Lactobacillus* and *Lactocaseibacillus*) and negative associations with short-chain fatty acid producers (*Blautia*, *Lachnospirillum*, and *Anaerobutyricum*) with MHE.

**DISCUSSION:** Cirrhosis-related variables may be more influential in determining gut microbiome composition and cognitive impairment than ADI. Therefore, the focus should be on improving cirrhosis care, regardless of ADI, but studies evaluating other measures of social determinants are needed in cirrhosis.

**SUPPLEMENTARY MATERIAL** accompanies this paper at <http://links.lww.com/CTG/A809>

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## INTRODUCTION

Social determinants of health are the environmental contributors to health outcomes. These may include components of the built environment, access to education and health care, and economic stability, among others (1,2). Area deprivation index (ADI) is a multidimensional measure of the socioeconomic conditions in a neighborhood, which extends beyond individual socioeconomic status and has been linked to health outcomes (3–7). The ADI is based on a measure created by the Health Resources and Services Administration and then validated by the census block group (3). The ADI is calculated using 17 indicators based on income, education, employment, and housing conditions and determines the areas of deprivation and affluence within a community. The ADI serves as a surrogate measure for actual determinants of income, education, employment, and housing quality. Similarly, the microbiome is shaped by the environment, including sociopolitical and economic factors, and is a potential mediator between social determinants and health inequities (8–10). However, the role of ADI and microbiome changes in determining health outcomes needs to be better studied in the context of cirrhosis.

There are several reasons to believe that cirrhosis-related cognitive impairment or minimal hepatic encephalopathy (MHE) may be mediated through a pathway through alterations of the gut microbiota and also to neighborhood disadvantage. Cirrhosis is an established cause of altered gut microbial structure and function (11–14). The most common causes of cirrhosis include obesity, viral hepatitis, and alcohol misuse, which disproportionately affect people with socioeconomic disadvantage (4,15–20). Furthermore, an altered gut-brain axis (21) is inherent in the causation of MHE that affects daily function, progression to the overt stage, and survival (22,23). Thus, we propose a conceptual model wherein ADI, microbiome, and other social and individual level factors influence MHE in cirrhosis.

Understanding how ADI and alterations of the gut microbiota interact to affect health outcomes for patients with cirrhosis may improve prognostication and generate individualized therapeutic strategies. Our aim was to study the associations of ADI and gut microbial changes with MHE in a large cohort of outpatients with cirrhosis. We hypothesized that ADI is associated with gut microbiota composition and with cognitive dysfunction in patients with cirrhosis.

## METHODS

We included outpatients with cirrhosis older than 18 years who were able to consent, provide stool samples, and perform cognitive testing using psychometric HE scores (PHES). Cirrhosis was diagnosed using liver biopsy, radiological or endoscopic evidence of portal hypertension in patients with chronic liver disease, evidence of decompensation, or using elastography. We excluded patients in whom the diagnosis of cirrhosis was unclear; those with recent or active alcohol or illegal substance misuse; and those unable to provide consent and samples or perform complete cognitive testing.

### Data collection

Data regarding demographics, including self-identified race (White, African American, or Asian based on Census bureau definitions) and ethnicity (Hispanic or not) on interview, years of education, current and all addresses lived at within the past 5 years were recorded. Cirrhosis severity; complications of cirrhosis; and medications that affect the microbiota, such as proton pump inhibitors (PPIs), lactulose, rifaximin, and other antibiotics, were also collected from the medical record.

We used patient-reported addresses to calculate ADIs for each patient for the address at the time of sample collection and testing. ADIs were calculated along with the state (decile) and national (percentile) levels using census blocks (3).

PHES is a validated 5-test paper-pencil battery which tests visuomotor coordination, psychomotor speed, and reaction time (24). It consists of the number connection test A, number connection test B, digit symbol test, serial dotting test, and line tracing test (has 2 components: time and errors). Based on population control values, the SDs are calculated for each subtest and the total is added to give 1 value (21). A low score indicates better cognition. We used adjusted norms to determine MHE when the total score was  $\leq -4$  SD (25). Since these norms were based on some measures (educational status) that were also collinear with determining the ADI, we also performed analyses of individual tests for national and state ADI rankings.

### Microbial analysis

Stool was collected using Para-Pak collection kits. DNA was extracted using published methods. The V1 and V2 variable regions of the bacterial 16S ribosomal RNA gene were sequenced

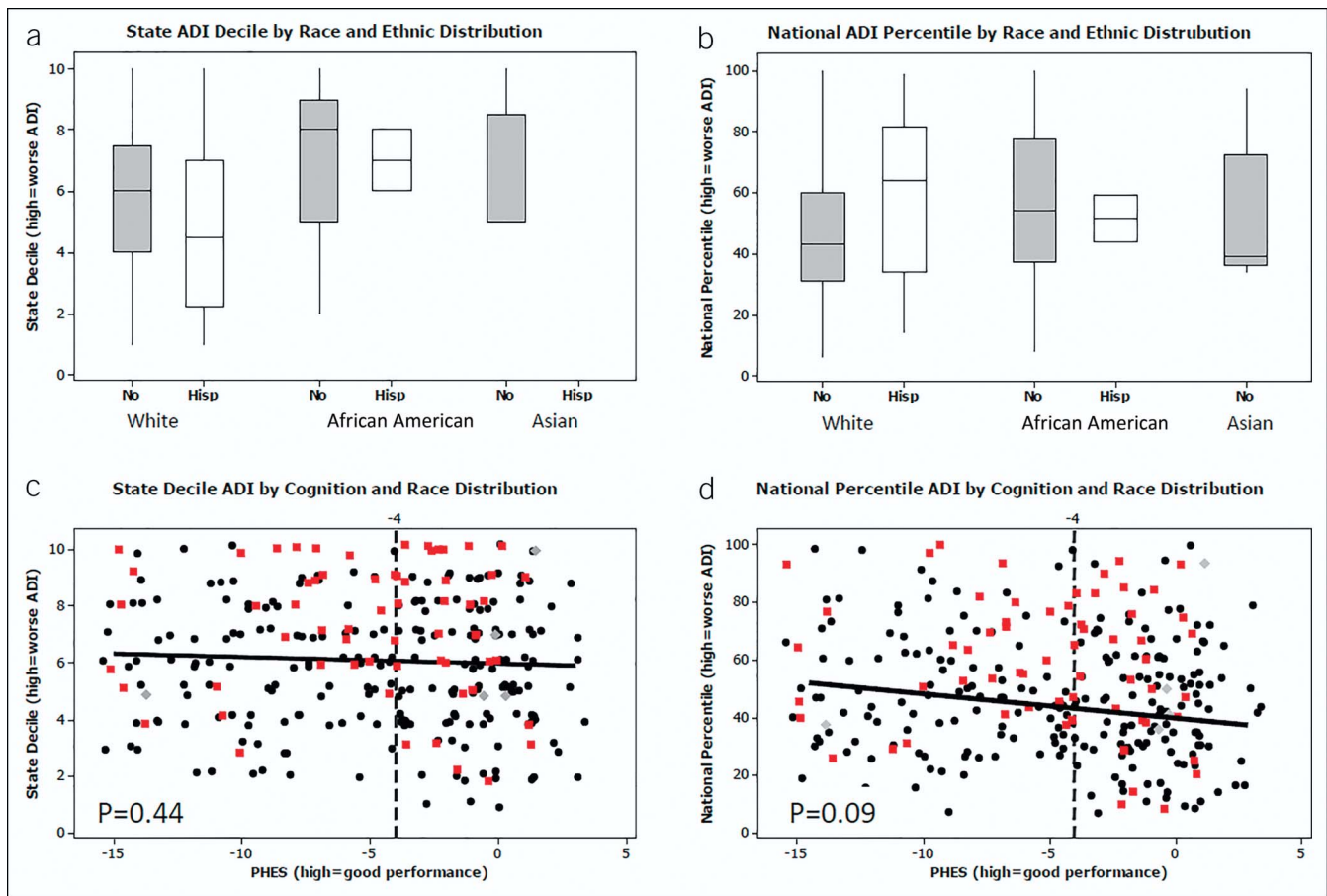
using Multitag fusion primers and sequenced on an Ion Torrent PGM next-generation sequencer (see Supplementary Methods, Supplementary Digital Content 1, <http://links.lww.com/CTG/A809>). Data from each pooled sample were “deconvoluted” by sorting the sequences into bins based on the barcodes using custom PERL scripts. Thus, we were able to normalize each sample by the total number of reads from each barcode. We used a local installation of the RDP 11.5 Classifier to produce the taxonomic relative abundance tables used by BiomMiner (26).

### Statistical and bioinformatics analyses

Patients with high vs low ADI were compared for demographics, race, ethnicity, cirrhosis severity, medications, and cognitive performance. Because the total PHES and MHE classification is age, sex, and education-adjusted but individual test results are not, we also compared the individual results between groups. Associations between ADI (continuous) and demographics, model for end-stage liver disease (MELD) score, and total PHES were also assessed using Pearson correlations.

**Microbiota.** Analyses were conducted at the bacterial genus level and measures of alpha and beta-diversity were calculated. DESeq2 was used to compare taxa between MHE-positive and negative patients and between those with high and low ADI (50th percentile/decile) rankings at state and national levels (27). PERMANOVA analyses of Bray-Curtis distance were performed between low/high ADIs, and *t* tests comparing Shannon diversity were performed between groups, including between those with/without prior HE and MHE. Shannon diversity was correlated with PHES, MELD score, and ADI state and national rankings.

Separate linear regression models were created, modeling PHES and then state and national ADI rankings as dependent variables. Demographics, race, ethnicity, cirrhosis details, and medications were independent variables. The model for MHE included ADI as a continuous variable, whereas the ADI model included PHES as a continuous variable. Finally, we created models using MAAsLin2 to evaluate the contribution of demographics, cirrhosis severity, concurrent medications, and microbiota toward neighborhood disadvantage and on MHE (28).



**Figure 1.** Relationship of the area deprivation index (ADI) with demographics and cognitive performance. No: not Hispanic; Hisp: Hispanic. **(a)** The decile of state ADI rankings based on race (White, African American, and Asian) and Hispanic ethnicity showed no differences between groups. No significant differences were observed between different races and ethnicities for ADI rankings. Higher ranking indicates higher disadvantage. **(b)** The percentile of national ADI rankings based on race (White, African American, and Asian) and Hispanic ethnicity showed no differences between groups. No significant differences were observed between different races and ethnicities for ADI rankings. Higher ranking indicates higher disadvantage. **(c)** State ADI decile according to psychometric hepatic encephalopathy score (PHES) shows no significant correlation ( $P = 0.44$ ) without any consistent relationship with race.  $-4$  SD or lower indicates minimal hepatic encephalopathy (MHE). Black: White; red: African American; gray: Hispanic; and patients to the left of the dotted line have MHE. Higher ranking indicates higher disadvantage. **(d)** National ADI percentile according to PHES shows no significant correlation ( $P = 0.09$ ) without any consistent relationship with race.  $-4$  SD or lower indicates MHE. Black: White; red: African American; gray: Hispanic; and patients to the left of the dotted line have MHE. Higher ranking indicates higher disadvantage.

**Table 1.** Comparison of clinical and demographic variables depending on area deprivation index rankings

Area deprivation index 50th decile/percentile division	State decile upper/lower half			National percentile upper/lower half		
	Lower disadvantage (n = 137)	Higher disadvantage (n = 184)	P value	Lower disadvantage (n = 179)	Higher disadvantage (n = 142)	P value
Age (yr)	59.5 ± 8.1	61.6 ± 7.7	0.02	60.2 ± 7.9	61.3 ± 7.9	0.25
Male sex	97 (71)	152 (91)	0.012	128 (71)	121 (85)	0.003
White/AA/Asian	114/20/3	127/55/2	0.004	144/32/3	97/43/2	0.03
Hispanic ethnicity	7 (5)	7 (4)	0.57	6 (3)	8 (6)	0.32
Education (yr)	13.9 ± 2.4	13.3 ± 2.4	0.02	13.8 ± 2.3	13.1 ± 2.5	0.01
Diabetes	59 (43)	81 (44)	0.86	75 (42)	65 (46)	0.49
MELD	12.8 ± 6.0	12.3 ± 6.1	0.48	12.3 ± 5.3	12.9 ± 7.0	0.40
Alcohol-related etiology	44 (32)	68 (37)	0.31	61 (34)	51 (36)	0.89
Prior HE	66 (48)	81 (44)	0.10	89 (50)	58 (41)	0.48
Lactulose	53 (39)	65 (35)	0.54	70 (39)	48 (34)	0.33
Rifaximin	39 (28)	55 (30)	0.78	53 (30)	41 (29)	0.89
Proton pump inhibitors	72 (53)	102 (55)	0.61	96 (53)	80 (56)	0.63
PHES	-4.45 ± 5.01	-4.96 ± 4.80	0.39	-4.63 ± 4.98	-4.91 ± 4.77	0.63
MHE	75 (55)	106 (58)	0.61	101 (56)	80 (56)	0.98
NCT-A (s)	45.3 ± 22.7	53.2 ± 52.0	0.08	49.5 ± 48.1	50.2 ± 33.2	0.88
NCT-B (s)	127.0 ± 102.0	139.6 ± 96.5	0.28	130.0 ± 104.0	139.9 ± 91.6	0.37
DST (raw score)	47.7 ± 17.9	44.2 ± 16.4	0.08	46.4 ± 17.8	44.8 ± 16.1	0.41
SDT (raw score)	76.5 ± 34.2	80.7 ± 37.9	0.31	79.3 ± 37.6	78.4 ± 34.9	0.83
LTtE (raw score)	36.9 ± 35.4	38.5 ± 26.3	0.66	36.1 ± 33.0	40.1 ± 26.9	0.25
LTTt (s)	109.5 ± 54.2	111.1 ± 66.2	0.82	116.1 ± 64.9	103.1 ± 55.6	0.07

Data are presented as mean ± SD or n (%).

A high PHES indicates good cognition. High scores on NCT-A, NCT-B, LTtE, LTTt, and SDT and low scores on DST indicate good performance. All Hispanic patients were White.

AA, African American; DST, digit symbol test; HE, hepatic encephalopathy; LTtE, errors on line tracing test; LTTt, time to complete line tracing test; MELD, model for end-stage liver disease; MHE, minimal hepatic encephalopathy; NCT-A, number connection test A; NCT-B, number connection test B; PHES, psychometric hepatic encephalopathy score; SDT, serial dotting test; SES, socioeconomic status.

A *P* value of <0.05 with a *q* value of <0.05 was considered significant on MAAsLin2.

## RESULTS

We enrolled 321 patients with cirrhosis with a mean age of 60.1 ± 7.9 years and an educational level of 13.5 ± 2.4 years with mostly men (*n* = 249, 78%). Most patients (*N* = 241, 75%) self-identified as non-Hispanic White while 23% (*n* = 75) self-identified as non-Hispanic African American, 5 patients (1%) as Asian, and 14 (4%) as being of Hispanic ethnicity, all of whom had Latin American ancestry. The average national percentile of ADI was 49.08 ± 21.77 (range 6–100, with higher scores indicating higher disadvantage), and the mean state decile was 6.1 ± 2.3 (range 1–10, with 10 indicating the most neighborhood disadvantage). Approximately half of the patients fell below the national (44%, *n* = 142) and state (57%, *n* = 184) mean ADIs. Only 10 patients had moved to an area within the past 5 years that would have changed their state and national ADIs; remaining had stable addresses within that period.

Alcohol-related etiology was found in 112 patients (36%). Forty-five percent of the patients (*n* = 145) had prior HE, most of whom were on lactulose (*n* = 112) or rifaximin (*n* = 87). The

mean MELD score was 12.5 ± 6.1, and most patients were on PPI therapy (*n* = 169, 53%). The mean PHES adjusted for age, sex, and education was -4.75 ± 4.89, with 181 patients (56%) diagnosed with MHE according to our norms.

### Relationship between ADIs and patient characteristics

The individual education level was significantly, inversely correlated with state and national ADI deciles (both *R* = -0.20, *P* < 0.0001; Figure 1). However, no other liver-related and demographic characteristics were correlated with ADI (Table 1, Figure 1, see Supplementary Figure S1a,b, Supplementary Digital Content 1, <http://links.lww.com/CTG/A809>). Self-identified non-Hispanic White people with cirrhosis had a lower state ADI decile (5.8 ± 2.2) compared with non-Hispanic African American people (7.1 ± 2.4, *P* < 0.0001). Similarly, the national percentile was also lower in non-Hispanic White (46.5 ± 20.5) compared with non-Hispanic African American (57.1 ± 23.8, *P* = 0.001) patients. The state ADI decile (Hispanic 5.1 ± 2.7 vs non-Hispanic 6.1 ± 2.3, *P* = 0.2) and national ADI percentile (Hispanic 58.7 ± 26.0 vs non-Hispanic 48.6 ± 21.5, *P* = 0.18) were statistically similar between those who self-identified as Hispanic versus the rest. Because PHES and MHE are adjusted, we

**Table 2.** Correlations between area deprivation rankings and clinical variables

	State decile		National percentile	
	R	P value	R	P value
MELD score	-0.07	0.23	0.05	0.36
PHES	-0.05	0.44	-0.11	0.06
NCT-A (s)	0.05	0.41	0.07	0.22
NCT-B (s)	0.06	0.30	0.10	0.07
DST (raw score)	-0.09	0.13	-0.08	0.09
SDT (raw score)	-0.01	0.99	0.06	0.28
LTTe (raw score)	0.06	0.28	0.09	0.12
LTTt (s)	-0.08	0.19	-0.06	0.29

A high PHES score indicates good cognition. High scores on NCT-A, NCT-B, LTTe, LTTt, and SDT and low scores on DST indicate good performance. Higher area deprivation ranking is associated with higher neighborhood deprivation.

DST, digit symbol test; HE, hepatic encephalopathy; LTTe, errors on line tracing test; LTTt, time to complete line tracing test; MELD, model for end-stage liver disease; MHE, minimal hepatic encephalopathy; NCT-A, number connection test A; NCT-B, number connection test B; PHES, psychometric hepatic encephalopathy score; SDT, serial dotting test.

also studied raw scores of the 6 subtests, which were again not significantly correlated with ADI (Table 2).

### Microbiota composition

**HE-related comparisons.** Shannon diversity was lower in those with MHE ( $2.08 \pm 0.6$  vs  $2.21 \pm 0.49$ ,  $0.03$ ) and prior HE patients ( $1.99 \pm 0.60$  vs  $2.25 \pm 0.53$ ,  $P < 0.0001$ ) vs. the rest. Shannon diversity was negatively correlated with the MELD score ( $r = -0.4$ ,  $P < 0.0001$ ) and PHES ( $r = -0.4$ ,  $P < 0.0001$ ). There was also a significant separation on PCoA using PERMANOVA (Figure 2a). Patients with MHE had a greater log fold change of genera belonging to Lactobacillaceae (*Pediococcus*, *Lacticaseibacillus*, and *Lactobacillus*) and potential pathobionts (*Enterococcus*, *Klebsiella*, *Escherichia-Shigella*, *Pseudomonas*) compared with those without MHE (Figure 2b).

**ADI-related comparisons.** There was a significant separation between groups with high versus low ADI at both state and national levels on PERMANOVA (Figures 3a and 4a). In the state comparison, high ADI (high disadvantage) was associated with *Lactobacillus* (*Pediococcus*, *Leuconostoc*, and *Weissella*) and other lactate producers (*Fournierella*) with Proteobacteria members (*Desulfovibrio*, *Phytobacter*, and *Raoultella*), whereas *Enterococcus* and *Enterobacter* were lower on fold changes (Figure 3b).

On the national comparison, log<sub>2</sub> fold change in those with low ADI (low disadvantage) was greater for short-chain fatty acid (SCFA)-producing taxa (*Faecalibacterium*, *Roseburia*, *Alistipes*, and *Lachnospiraceae*) while also higher for gram-negative taxa (Figure 4b). There was a very low correlation between Shannon diversity at the genus level and state decile ( $r = 0.15$ ,  $P = 0.007$ ; Figure 3c) and national percentile ( $r = 0.10$ ,  $P = 0.09$ ; Figure 4c).

### Multivariable analyses

Linear regression analyses were performed using PHES and state and national deciles as dependent variables using clinical data. National ADI was significantly, inversely associated with education ( $t$  value  $-3.31$ ,  $P = 0.001$ ) and positively associated with African American self-identification ( $2.73$ ,  $P = 0.007$ ), diabetes ( $2.4$ ,  $P = 0.02$ ), Hispanic ethnicity ( $2.1$ ,  $P = 0.03$ ), prior HE ( $-1.5$ ,  $P = 0.13$ ),

and male sex ( $1.7$ ,  $P = 0.09$ ). The decile of state ADI was inversely associated with education ( $-3.56$ ,  $P < 0.001$ ) and positively associated with identifying as African American ( $3.83$ ,  $P < 0.001$ ), higher age ( $2.11$ ,  $P = 0.036$ ), and diabetes ( $1.45$ ,  $P = 0.15$ ).

Factors significantly associated with higher PHES (noting that higher score indicates better performance) for included prior HE ( $t$  value  $-2.20$ ,  $P = 0.005$ ), MELD ( $-0.17$ ,  $P < 0.0001$ ), education ( $0.38$ ,  $P < 0.001$ ), PPI use ( $-1.06$ ,  $P = 0.04$ ), and male sex ( $-1.40$ ,  $P = 0.03$ ). ADI was not significantly associated with PHES in multivariable models.

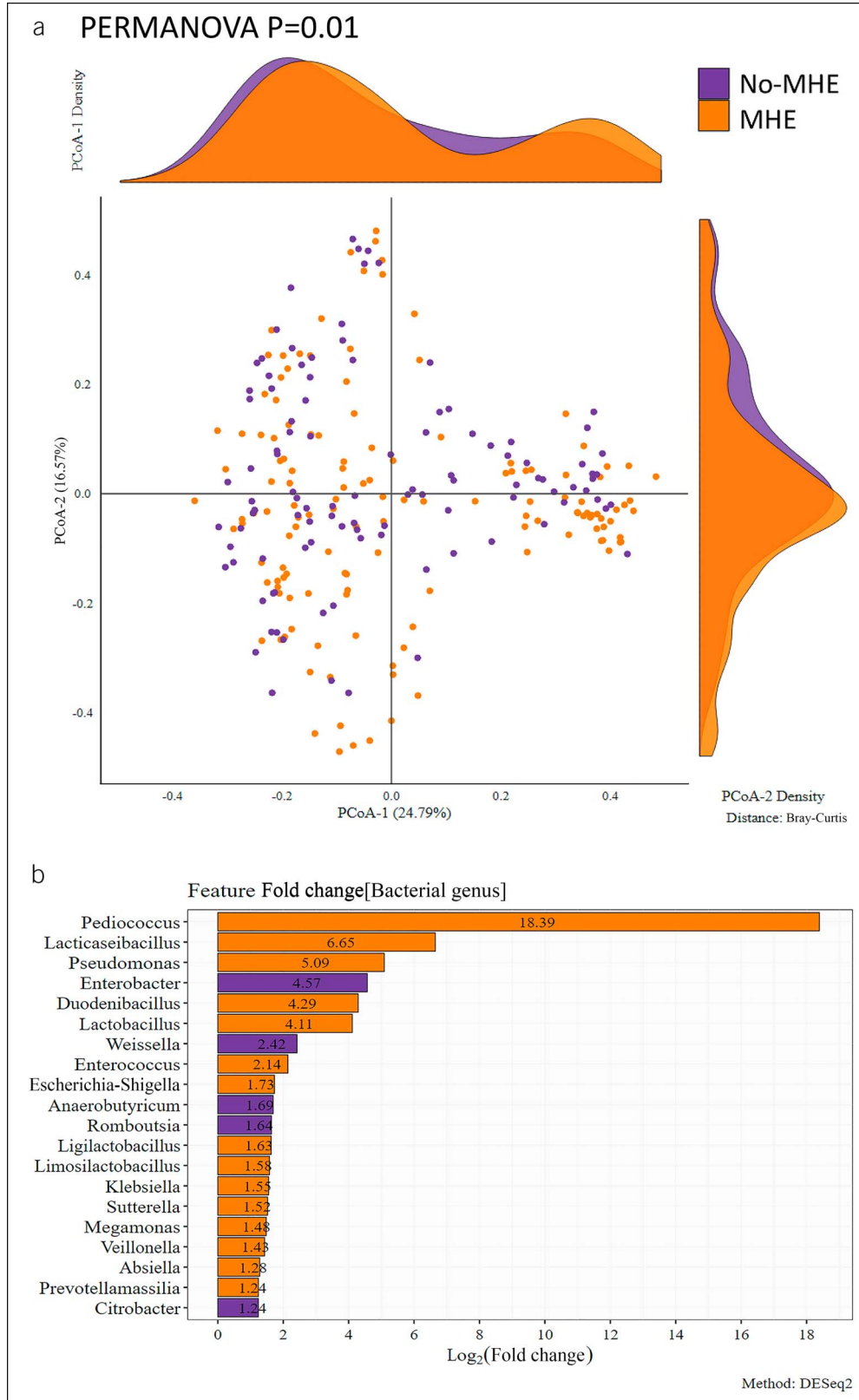
Neither state nor national ADIs were significantly associated with MHE on MAAsLin2. A higher national ADI percentile was associated with MHE with  $P = 0.09$ , which did not pass FDR ( $q$  value  $0.69$ ). Similarly, the state decile of ADI was associated with MHE with  $0.41$  and a  $q$  value of  $0.99$ . As presented in Table 3, liver-related factors were significantly related to MHE. In addition, bacterial genera associated with SCFA production (*Blautia*, *Lachnoclostridium*, and *Mediterraneibacter*) were protective against while lactate producers (*Lactobacillus* and *Lacticaseibacillus*) were associated with MHE.

Using the 50th percentile/decile of the ADI rankings as the outcome (modeling high vs low ADI), none of the clinical or microbiota-related features were significant after FDR correction (see Supplementary Tables 1 and 2, Supplementary Digital Content 1, <http://links.lww.com/CTG/A809>).

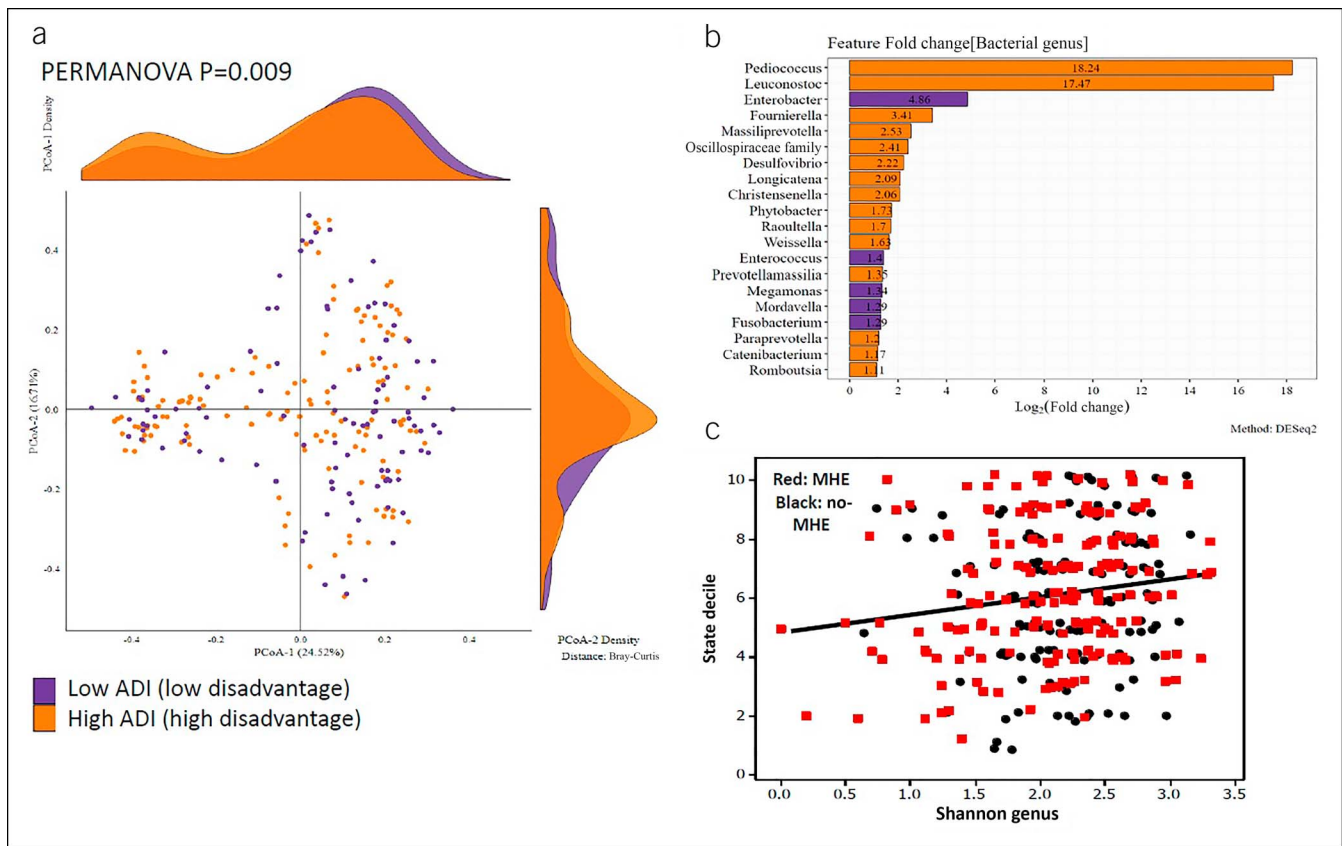
### DISCUSSION

ADI was associated with gut microbial composition alterations in patients with cirrhosis on univariate analysis. However, when traditional cirrhosis-related risk factors such as HE and MELD scores were considered, ADI was not associated with gut microbiota composition or cognitive performance on multivariable analysis.

The focus of our study was to determine whether ADI was associated with microbiota composition and with cognitive impairment in the complex chronic disease setting of cirrhosis. The hypothesis was that cognitive impairment with cirrhosis would be related to higher ADI as a surrogate for socioeconomic and health disparities and to gut bacterial dysbiosis. This is relevant because



**Figure 2.** Microbial comparisons between patients with and without minimal hepatic encephalopathy (MHE) at the genus level. **(a)** Principal coordinate analysis of MHE (orange) vs no-MHE (purple) with PERMANOVA ( $P = 0.01$ ) using Bray-Curtis distance. **(b)** Log<sub>2</sub> fold change differences between MHE (orange) and no-MHE (purple).



**Figure 3.** Microbial comparisons of area deprivation index (ADI) rankings at the state level. (a) Principal coordinate analysis of low ADI (purple) vs high ADI (orange) with PERMANOVA using Bray-Curtis distance; higher ranking indicates higher disadvantage. (b) Log<sub>2</sub> fold change differences between low ADI (purple) vs high ADI (orange); higher ranking indicates higher disadvantage. (c) Correlation between state decile and Shannon diversity (red: minimal hepatic encephalopathy [MHE], black: no-MHE). MHE was significant, but coefficient was <0.1.

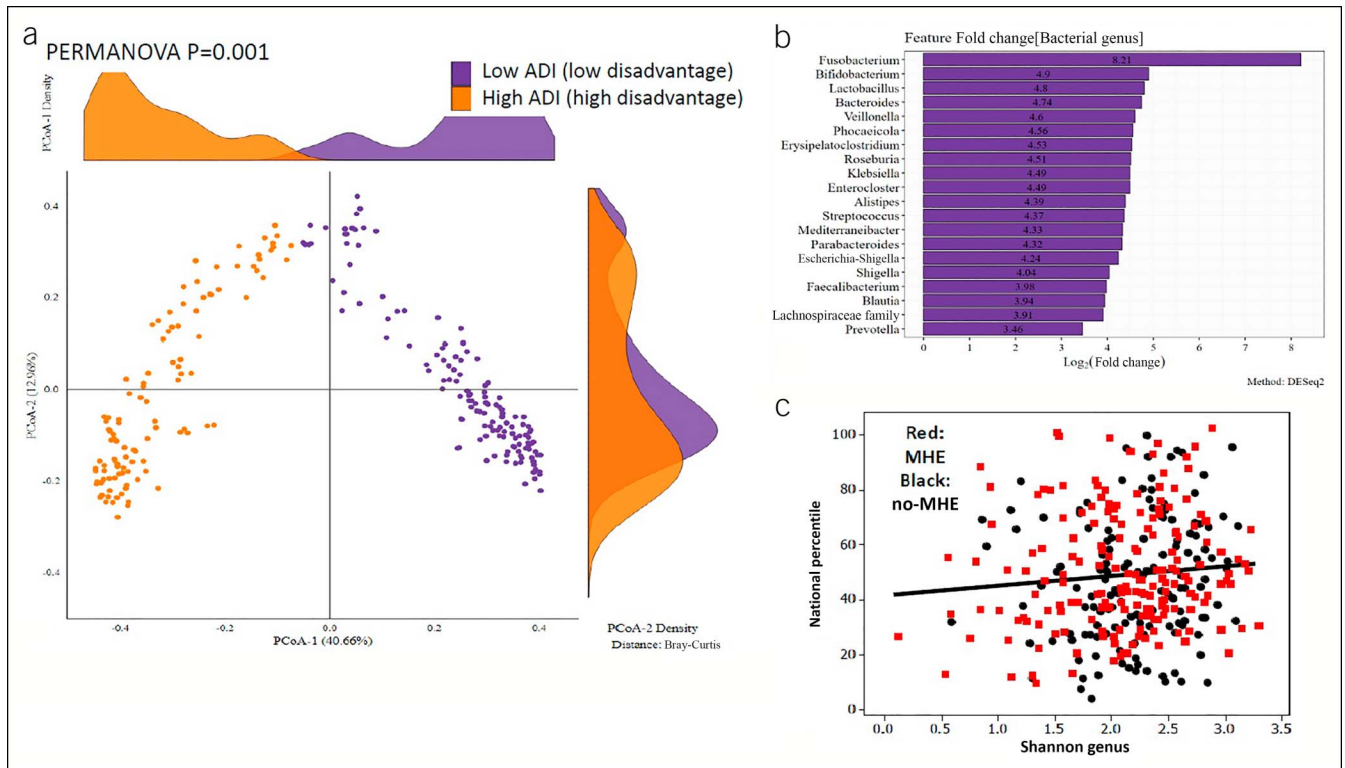
cirrhosis and chronic liver disease are a sum of associated factors such as obesity, alcohol, and drug use that are strongly rooted in neighborhood disadvantage (15,29,30). These factors could impair access to health care, affect dietary habits, affect acceptance and response to medications or therapy, and therefore affect important clinical and psychosocial outcomes (4,15,17,31–33). Cognitive impairment in cirrhosis due to HE is related to gut bacterial changes, and this complication also has the highest negative impact on daily function and economic status (22).

We found that neither severity of disease, prior HE, or MHE status, nor specific demographics such as age were linked with ADI either as a continuous variable or when dichotomized into high vs low at a state or national level. However, self-identification as non-Hispanic African American and Hispanic ethnicity was associated with greater neighborhood disadvantage, indicating the need to account for these constructs. The lack of linkage with liver-related variables is striking because we included patients with an extensive spread of ADI deciles and national percentiles.

Neighborhood disadvantage was associated with changes in microbial beta-diversity and specific microbial composition focused on lower SCFA-producing taxa. These findings from univariate analyses mirror prior findings in nondiseased cohorts around the world (8,9,34) and give credence to our underlying hypothesis that area deprivation relates to microbial alterations. However, when clinical variables related to cirrhosis were included, these microbial distinctions disappeared on multivariable analyses. Cognitive

impairment, as expected, was associated with worse liver disease, prior HE, along with contributions for microbial genera (higher *Lactobacillus* members and lower SCFA-producing taxa) indicating the validity of the overall results (35–37). A higher relative abundance of *Lactobacillus* genera could be because of lactulose use but has been associated with poor cognition even without lactulose in advanced liver disease (37,38). Moreover, Shannon diversity was associated with liver disease and cognitive performance, but not with national or state ADI rankings, again reiterating the impact of cirrhosis rather than the ADI on microbial composition (37). Fitting these multiple influences into the model proposed by Findley et al. (39) in cirrhosis, we included biological processes (MELD score, complications, and cirrhosis etiology), microbial composition (both diversity and individual taxa), and social and physical environmental factors using the surrogate ADI. The current results favor the relationship between microbiome and biological processes in this cross-sectional study as the main determinant of cognitive impairment in cirrhosis. The caveat of course is that ADI is only a surrogate of income, education, employment, and housing quality, and it is possible that alternative and direct methods of gauging social determinants of health may result in different results.

It is possible that the progression to cirrhosis rather than the postcirrhosis course that was included in this study may be more dependent on microbiota-ADI interactions. For instance, patients with lower SES may be more likely to be obese, have lower access to healthier foods such as yogurt and high-fiber diets, and



**Figure 4.** Microbial comparisons of area deprivation index (ADI) rankings at the national level. **(a)** Principal coordinate analysis of low ADI (purple) vs high ADI (orange) on PERMANOVA using Bray-Curtis distance; higher ranking indicates higher disadvantage. **(b)** Log<sub>2</sub> fold change differences between low ADI (purple) vs high ADI (orange); higher ranking indicates higher disadvantage. **(c)** Correlation between national percentile and Shannon diversity (red: minimal hepatic encephalopathy [MHE], black: no-MHE).

have lesser access to services that reduce alcohol and drug dependence (4,19,20,32,40). These may in turn affect the microbiota, brain function, and increase progression of patients with lower ADI toward cirrhosis (41–44). However, we found that once cirrhosis has set in, despite analyzing these factors from a univariate and multivariable approach, ADI was not significantly associated with cognitive testing results or microbiota composition in this cohort of people with cirrhosis.

Our study, although novel in its approach to understanding social determinants in cirrhosis and microbiome, has several limitations. This was a cross-sectional study only focused on patients who had already developed cirrhosis. It is possible that other, unexamined social determinants are implicated in the pathway toward interaction of environment, microbiota, and cirrhosis and HE development. ADI is distinct from individual SES and is a construct designed to capture allostatic load of living

**Table 3.** Significant variables on MAAsLin2 using minimal HE as the dependent variable

	Direction higher in minimal HE	P value	q value
MELD score	Yes	2.74E-05	0.006212
<i>Lactobacillus</i>	Yes	2.20E-05	0.006212
<i>Blautia</i>	No	4.33E-05	0.006559
Rifaximin use	Yes	6.57E-05	0.007459
Prior HE	Yes	2.12E-04	0.013763
Lactulose use	Yes	2.45E-04	0.013763
<i>Lachnoclostridium</i>	No	2.73E-04	0.013763
<i>Anaerobutyricum</i>	No	2.53E-04	0.013763
<i>Lactocaseibacillus</i>	Yes	1.63E-04	0.013763
<i>Mediterraneibacter</i>	No	3.80E-04	0.017244

Neither national percentile nor state decile was significantly related with minimal HE when added to the multivariable model above. HE, hepatic encephalopathy; MELD, model for end-stage liver disease.



in an area and is not intended to capture the economic situation of an individual or family (3). Accordingly, we found that ADI was associated with education in this population. However, we did not inquire regarding personal and family income in our patients to evaluate how ADI links with SES in this population. That said, ADI generally has been found to contribute to health outcomes, independent of SES (5,6,18). In addition, we included self-identified race and ethnicity not as a biological construct but rather a measure of diversity in our cohort (45).

In conclusion, neighborhood disadvantage, which is a surrogate measure of income, education, employment, and housing quality, was associated with gut microbiota composition in cirrhosis on univariable analysis. However, when cirrhosis-related variables were included, the influence of area deprivation index on cognitive impairment and microbial composition did not remain significant. Microbiota related to short-chain fatty acid and lactic acid production was linked with cognitive impairment independent of area deprivation index rankings. Further exploration of aspects of socioeconomic status other than area deprivation rankings and focusing on patients before cirrhosis has developed are needed to determine the contribution of social determinants of health on microbiota and cognitive impairment.

#### CONFLICTS OF INTEREST

**Guarantor of the article:** Jasmohan S. Bajaj, MD.

**Specific author contributions:** J.S.B. was involved in all aspects. A.F., S.M., and R.K.S. were involved in research conduct and data/sample collection. M.S. and P.M.G. were involved in microbiota analysis. S.R. was involved in critical revision.

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**Potential competing interests:** None to report.

**IRB approval:** This protocol was approved by the Richmond VA and VCU IRBs.

## Study Highlights

#### WHAT IS KNOWN

- ✓ Neighborhood disadvantage is associated with poor access to healthier diet and social and medical services and can associate with altered gut microbiota.
- ✓ Cirrhosis is also associated with altered gut microbiota that work through the gut-brain axis to promote encephalopathy.
- ✓ The impacts of neighborhood disadvantage and altered microbiota on cognitive dysfunction in patients with cirrhosis are unknown.

#### WHAT IS NEW HERE

- ✓ In this cohort of outpatients with cirrhosis, the area deprivation index was not significantly associated with cognitive performance or hepatic encephalopathy.
- ✓ Although the area deprivation index was associated with lower gut microbes that produce short-chain fatty acids and higher lactate producers and there were differences in beta-diversity, this association did not remain significant on multivariable analysis.
- ✓ The impact of cirrhosis on gut microbiota may be so profound that associations between area deprivation index and microbiota are less important.

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