Gut Microbiota Composition and Blood Pressure
The CARDIA Study

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See Editorial Commentary, pp 977–979

Abstract—Animal models support a role for the gut microbiota in the development of hypertension. There has been a lack of epidemiological cohort studies to confirm these findings in human populations. We examined cross-sectional associations between measures of gut microbial diversity and taxonomic composition and blood pressure (BP) in 529 participants of the biracial (black and white) CARDIA study (Coronary Artery Risk Development in Young Adults). We sequenced V3-V4 regions of the 16S ribosomal RNA marker gene using DNA extracted from stool samples collected at CARDIA's Year 30 follow-up examination (2015–2016; aged 48–60 years). We quantified associations between BP (hypertension [defined as systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg or antihypertension medication use] and systolic BP) and within and between-person diversity measures. We conducted genera-specific multivariable-adjusted regression analysis, accounting for multiple comparisons using the false discovery rate. Hypertension and systolic BP were inversely associated with measures of α-diversity, including richness and the Shannon Diversity Index, and were distinguished with respect to principal coordinates based on a similarity matrix of genera abundance. Several specific genera were significantly associated with hypertension and systolic BP, though results were attenuated with adjustment for body mass index. Our findings support associations between within-person and between-person gut microbial community diversity and taxonomic composition and BP in a diverse population-based cohort of middle-aged adults. Future study is needed to define functional pathways that underlie observed associations and identify specific microbial targets for intervention. **(*Hypertension*. 2019;73:998-1006. DOI: 10.1161/HYPERTENSIONAHA.118.12109.)** • **Online Data Supplement**

Key Words: blood pressure ■ epidemiology ■ gastrointestinal microbiome ■ hypertension ■ population

There is growing evidence that the gut microbiota may influence cardiovascular disease (CVD).[1–5] Proposed mechanisms include gut microbial effects on systemic inflammation[6,7] and the production of CVD-related metabolites, such as trimethylamine N-oxide[1,2] and short-chain fatty acids (SCFAs). Findings from animal and human studies are consistent with a role for the gut microbiota in obesity,[3,8] type 2 diabetes mellitus,[9–12] dyslipidemia,[3] metabolic syndrome,[5,13] and lifetime CVD risk.[4] Animal models have demonstrated gut microbial effects on blood pressure (BP).[14–17] Decreased microbial diversity has been observed in both animal models of hypertension and human samples.[16] Population-based human studies have revealed significant associations between microbial metabolites and BP.[18,19] However, there has been a lack of data on the gut microbiome and BP in population-based and sociodemographically diverse samples.

In the current study, we examined cross-sectional associations between gut microbial diversity and taxonomic composition and BP in 529 middle-aged adults recruited from 4 US urban field centers in the CARDIA Study (Coronary Artery Risk Development in Young Adults). CARDIA is a population-based and sociodemographically diverse sample of black and white participants, with clinic-based measurement of BP and extensive data on relevant covariates, including diet, antihypertensive medication use, and body mass index (BMI). At CARDIA's Year 30 follow-up examination in 2015–2016, we collected stool samples and sequenced the 16S ribosomal RNA (rRNA) prokaryotic marker gene. We hypothesized that

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(1) the gut microbial community differs significantly according to BP, (2) within-person diversity of the gut microbiota is inversely associated with hypertension and systolic BP (SBP), and (3) hypertension and SBP are associated with specific taxa, such as those involved in the production of the SCFA butyrate.

Methods

Data and Code Availability

All data used in the present analysis are available from the CARDIA Study Data Coordinating Center at the University of Alabama at Birmingham. The process for obtaining data through CARDIA is outlined at https://www.cardia.dopm.uab.edu/publications-2/publications-documents. Computer code/scripts used in the generation of data and statistical analysis are available from the authors upon request.

Study Participants

The CARDIA Study is a prospective multicenter cohort study designed to study the evolution of CVD over adulthood. CARDIA began in 1985–1986 and enrolled 5115 participants aged 18 to 30 years from 4 US urban centers (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA).[20] Since baseline, there have been 8 follow-up examination (years 2, 5, 7, 10, 15, 20, 25, and 30) with retention among survivors of 91%, 86%, 81%, 79%, 74%, 72%, 72%, and 71%, respectively.

A microbiome study was initiated at the Year 30 follow-up examination (2015–2016). Participants were recruited sequentially until the target sample size of 600 was reached (n=300 from the Chicago, IL, field center and n=100 from each of the other 3 field centers). Exclusions were based on a screening questionnaire administered at the time of CARDIA contact, including if participants were pregnant at the time of the clinic exam; used antibiotics in the past month; had ever been diagnosed with inflammatory bowel disease; and reported having had a gastrointestinal illness, vomiting, diarrhea, or atypical constipation in the past week. The present analysis includes data from CARDIA participants with complete sequencing data (n=538). Participants were excluded from analysis if they were missing data on BP medication (n=2), diet (n=2), or physical activity (n=5), for an analytic sample of n=529 participants. CARDIA was approved by institutional review boards of each field center; each study participant provided informed written consent for both the CARDIA core examination and the microbiome study.

Measurement of Sociodemographic, Behavioral, and Clinical Characteristics

Standard questionnaires were used to obtain demographic and health behavioral data at the CARDIA field centers during the core examination. The interviewer-administered CARDIA Physical Activity Questionnaire queried past year engagement in activities, from which a total activity score was calculated.[21] Participants reported their use of medication for hypertension, lipid-lowering, and diabetes mellitus; and their current and historic use of tobacco products. A brief 23-item frequency-based diet assessment was completed by participants in the microbiome study.[22] A summary measure of diet quality (a priori diet quality score) was derived as previously in CARDIA[23] and other studies.[24] Based on hypothesized impact on health, foods were classified into beneficial, adverse, or neutral quality and quartiles were created: beneficial foods were scored positively (0 to 3 for the first to fourth quartile, respectively), adverse foods were scored inversely (3 to 0 for the first to fourth quartile, respectively), and neutral foods were not scored. Scores were summed over all foods; higher scores reflect higher diet quality.

Standardized protocols were used by trained staff for all clinic measures. Resting SBP and diastolic BP measures were taken in the seated position with elbow and forearm resting on the chair armrest. BP values were calculated as the mean of the second and third of 3 measurements taken with oscillometer (*OmROn* HEM907XL automated/oscillometric BP monitor) calibrated to a random-zero sphygmomanometer. Arm cuff bladder size was based on arm circumference as follows (9 cm cuff for 17.0–22.5 cm arm; 12.0 cm for 22.6–32.5 cm arm; 15.0 cm for 32.6–42.5 cm arm; and 17.5 cm cuff for 42.6–50.0 cm arm). For individuals with an arm circumference >50 cm, a thigh cuff was used with an *OmROn* 108ML aneroid/manual BP monitor. Hypertension was defined as current use of antihypertensive medication, an SBP ≥140 mm Hg, or a diastolic BP ≥90 mm Hg. Height and weight were measured to the nearest 0.5 cm and 0.2 kg, respectively for BMI (kg/m^2). Fasting serum glucose was measured using hexokinase coupled to glucose-6-phosphate dehydrogenase. Diabetes mellitus was defined as having fasting glucose ≥126 mg/dL (7 mmol/L), 2-hour oral glucose tolerance test ≥200 mg/dL (11.1 mmol/L), HbA1c ≥6.5% (48 mmol/mol), or the use of hypoglycemic medications.

Microbiome Data Collection, Sequencing, and Data Processing

We followed standard protocols for stool collection and processing.[25,26] Briefly, stool samples were collected by participants in their home, shipped overnight to the study lab at UNC-Chapel Hill, where they were stored at −80°C until processing. Collection tubes were prefilled with RNA*later* to stabilize microbial DNA during transport to the lab. At the time of their stool collection, participants completed a short survey, including the time and date of their collection, past year antibiotic use, use of fiber supplements or probiotics, and their average weekly stool frequency.

DNA was extracted from 0.20 grams of stool using the MoBio PowerSoil kit. The V3-V4 hypervariable regions were amplified (primers: 341F/785R) and sequenced using the Illumina MiSeq platform (2×300). Processing of sequence data was completed with BioLockJ, a Java-based pipeline for metagenomics analysis.[27] Paired-end sequences were merged with Paired-End reAd mergeR (PEAR, v 0.9.8)[28] using default arguments; sequences for which primers did not match or for which 10 base pairs did not overlap were excluded. Taxonomic assignment was with the Ribosomal Database Project Classifier v2.12 (confidence threshold=80%).[29]

The R package vegan was used to generate measures of microbial diversity.[30] Within-person diversity (α-diversity) measures included the Shannon Diversity Index and richness, both derived at the genus level.[31] Richness was calculated as the number of distinct genera per participant, with total per-participant abundance rarified through random sampling to the minimum genera count across all participants. We used principal coordinates analysis (PCoA) to assess between-participant diversity (β-diversity) in microbial community composition. PCoA was used to generate orthogonal summary measures of microbial composition based on a distance matrix of microbial abundance (Bray-Curtis).[32] We report on PCoA axes that explain at least 5% of the variability in the taxonomic similarity measure. To assess sensitivity of findings to distance matrix, we additionally generated factors with principal components analysis based on a Euclidean distance matrix.

Statistical Analysis

We compared the analytic sample (n=529) to CARDIA participants who attended the Year 30 follow-up examination but did not participate in the microbiome study (n=2752). We assessed differences in categorical variables with χ^2 and continuous variables with a nonparametric test for comparing means, or medians if the variable was not normally distributed.

Primary outcomes were hypertension and SBP. We controlled for antihypertensive medication use in analysis of SBP, as medications may alter the gut microbiota.[33,34] We conducted multivariable-adjusted regression models for α- and β-diversity measures of microbial community composition, as well as for analysis of individual taxa. We tested for differences in β-diversity, represented using PCoA, with permutational multivariate ANOVA using distance matrices, through which pseudo-F ratios are generated and *P* values obtained through permutations[35] (here, 1000 permutations were used). In an

effort to evaluate the connection between specific taxa and PCoA ordination, we overlaid biplots with vectors for the 10 most abundant genera that significantly differentiate the PCoA axes. Vectors point in the direction of taxa-specific associations with respect to the PCoA axes, with vector length proportional to the correlation between the specific taxa and PCoA axes.

We conducted separate regression models for each taxonomic group with respect to (1) hypertension and (2) SBP. We focused our primary analysis on genera, the lowest level of classification from our 16S rRNA sequences. In addition, we conducted secondary analysis at the family level, which allowed us to test associations between BP and families that have been shown to carry genes for butyrate production pathways.[36] To account for spurious findings due to rare taxa, we restricted analysis to taxa that were present in at least 25% of participants; after this restriction, 149 genera and 42 families remained from among 379 genera and 100 families originally identified in the data.[37] Raw taxonomic counts were transformed for analysis as $\log_{10}[(RC/n)(x/N)+1]$, where RC is the total raw taxon count for a participant and n is the total count across all taxa for a participant, x is the total across all taxa and participants, and N is the total number of participants.[38] We controlled taxonomic analysis for multiple comparisons using the Benjamini-Hochberg method for false discovery rate (FDR).[39]

We conducted several multivariable-adjusted regression models. A minimal model (model 1) adjusted for sequencing run. Model 2 included additional covariate adjustment for field center (4 categories), sex (male/female), race (black/white), age (continuous), and educational attainment (continuous). In a more fully adjusted model (model 3), we adjusted for physical activity (continuous), smoking status (current, former, never), and diet quality score (continuous). We additionally adjusted for antihypertensive medication use in model 3 analysis of SBP. Models 4 and 5 adjusted for BMI (continuous) and waist circumference (continuous), respectively, potential intermediates of microbiome effects on BP. Data analysis was conducted in R 3.4.2 (http://www.r-project.org) and SAS version 9.4 (SAS Institute Inc, Cary, NC).

Results

Study participants differed slightly from the full CARDIA cohort examined at the Year 30 follow-up examination. Microbiome study participants were generally similar to nonparticipants (except for study center, by design of the microbiome study), though participants had statistically significantly lower mean BMI and waist circumference, and a smaller proportion had hypertension (Table 1). The relative abundance (percentage) of the 149 genera included in analysis (after removing rare taxa) ranged from a mean of 0.00044% for *Parascardovia* to 31.38% for *Bacteroides* (Table S1 in the online-only Data Supplement).

Several measures of gut microbial composition varied significantly with respect to sociodemographic and anthropometric variables in univariate analysis (Tables S2 through S7). There were significant differences (permutational multivariate ANOVA P value=0.001) in between-person diversity (β-diversity) for all variables: age, gender, race, BMI, and waist circumference. Within-person diversity (α-diversity) was inversely associated with BMI and waist circumference, but was not associated with age, gender, or race (Table S2). Specific genera were significantly associated with sociodemographic and anthropometric variables in FDR-adjusted univariate analysis of 149 genera. At an FDR-adjusted P-value threshold of 0.05, 5 genera were associated with age, 44 were associated with gender, 89 were associated with race, 63 were associated with BMI, and 58 were associated with waist circumference (Tables S3 through S7, respectively).

Table 1. Characteristics* of CARDIA (Coronary Artery Risk Development in Young Adults) Microbiome Study Participants and Nonparticipants† (2015–2016)

Participant Characteristic	Participants	Nonparticipants	*P* Value‡
N	529	2752	
Age, y	55.3 (3.4)	55 (3.6)	0.068
Female, %	53.9	57.9	0.09
Black, %	44.4	48.4	0.09
Field center, %			<0.0001
Birmingham	13.4	24.6	
Chicago	53.4	14.9	
Minneapolis	19.5	27.4	
Oakland	13.8	33.1	
Educational attainment, y	15.9 (2.6)	15.8 (3.1)	0.17
Smoking status, %			0.30
Current	12.3	14.5	
Former	22.2	23.3	
Physical activity, intensity units, med (IQR)	277 (127–510)	252 (116–456)	0.14
BMI, kg/m^2	29.4 (6.3)	30.8 (7.4)	0.0003
Waist circumference, cm	94.4 (15.6)	96.6 (16.6)	0.024
Diabetes mellitus, %	12.4	14.8	0.15
Systolic blood pressure, mm Hg	119.4 (15.8)	119.8 (16.1)	0.92
Diastolic blood pressure, mm Hg	72.9	73.2	0.91
Antihypertensive medication use, %	29.2	34.1	0.09
Hypertension, %	35.1	40.3	0.03

BMI indicates body mass index; and IQR, interquartile range.
*Mean (SD) unless noted.
†Nonparticipants who attended the CARDIA Year 30 examination.
‡Differences in categorical variables assessed with χ^2 and continuous variables with a nonparametric test for comparing means (or medians for physical activity).

Regression results were consistent with an inverse association between BP measures and microbial diversity, in particular, microbial richness (Table 2). In multivariable-adjusted regression models, hypertension was statistically significantly inversely associated with genera richness (model 3; odds ratio=0.75 [95% CI, 0.60–0.94] for an SD-unit increase in richness), but was not significantly associated with the Shannon diversity index. An SD-unit increase in richness was associated with −1.52 (−2.92 to −0.12) mm Hg lower SBP, and an SD-unit increase in Shannon diversity index was associated with −1.44 (−2.72 to −0.16) mm Hg lower SBP. Inverse relations were attenuated after further adjustment for BMI, or waist circumference potential intermediates (models 4 and 5, respectively). β-diversity was significantly associated with both hypertension and SBP in all multivariable-adjusted models (all permutational multivariate ANOVA P values=0.001).

Figures 1 and 2 present biplots for each pairwise comparison of the first 3 PCoA axes with respect to hypertension and

Table 2. Multivariable-Adjusted* Associations Between Gut Microbial α-Diversity† and Blood Pressure Measures‡ in CARDIA§

	Hypertension		Systolic Blood Pressure	
Model Specification	Odds Ratio (95% CI)	*P* Value	β Coefficient (95% CI)	*P* Value
Shannon index				
Model 1	0.83 (0.69 to 1.00)	0.053	−1.69 (−2.99 to −0.28)	0.018
Model 2	0.82 (0.67 to 1.00)	0.052	−1.50 (−2.78 to −0.22)	0.022
Model 3	0.86 (0.70 to 1.06)	0.10	−1.44 (−2.72 to −0.16)	0.028
Model 4	0.88 (0.71 to 1.10)	0.26	−1.33 (−2.60 to −0.052)	0.042
Model 5	0.90 (0.72 to 1.11)	0.32	−1.29 (−2.57 to −0.0087)	0.049
Richness				
Model 1	0.72 (0.59 to 0.88)	0.0014	−1.75 (−3.19 to −0.31)	0.018
Model 2	0.70 (0.56 to 0.87)	0.0013	−1.71 (−3.09 to −0.33)	0.016
Model 3	0.75 (0.60 to 0.94)	0.012	−1.52 (−2.92 to −0.12)	0.033
Model 4	0.78 (0.61 to 0.99)	0.037	−1.37 (−2.76 to 0.031)	0.056
Model 5	0.79 (0.62 to 1.00)	0.048	−1.32 (−2.73 to 0.083)	0.065

CARDIA indicates Coronary Artery Risk Development in Young Adults.

*Multivariable-adjusted regression models from—glm—command in R: family=binomial for odds ratios; family=Gaussian for β-coefficients. Model 1 adjusted for sequencing run. Model 2 additionally adjusted for age, gender, race, clinical field center, and education. Model 3 additionally adjusted for diet quality score, physical activity, and smoking status. Model 3 was also adjusted for antihypertensive medication use in models for systolic blood pressure. Model 4 included model 3 covariates, additionally adjusted for body mass index. Model 5 included model 3 covariates, additionally adjusted for waist circumference.

†Associations are per SD unit of genus-level diversity measures: Shannon index mean (SD)=2.46 (0.35); and richness (SD)=90.2 (11.3).

‡Hypertensive was defined as taking antihypertensive medication, having systolic blood pressure ≥140, or having diastolic blood pressure ≥90.

§Participants (n=529) at the CARDIA's Year 30 exam (2015–2016).

SBP, respectively. Each of the first 3 PCoA axes explained at least 5% of the variability in the microbial similarity measure (11.2%, 8.6%, and 5.4% for the first, second, and third PCoA axes, respectively). Vectors indicate the 10 most abundant genera that were significantly differentiated between PCoA axes. We note that significant vectors do not necessarily indicate that specific taxa are significantly associated with BP. Still, the vectors are generally consistent with what we observed in taxa-specific analysis. Vectors *Akkermansia*, *Ruminococcus*, *Anaerovorax*, *Sporobacter,* and *Asaccharobacter* tended to align in direction with individuals who were normotensive (Figure 1) or had lower SBP (Figure 2), whereas *Veillonella* aligned with individuals who were hypertensive (Figure 1) or had higher SBP (Figure 2). Furthermore, Spearman correlation coefficients for genera and PCoA axes were consistent with the displays of genera vectors and PCoA axes (Table

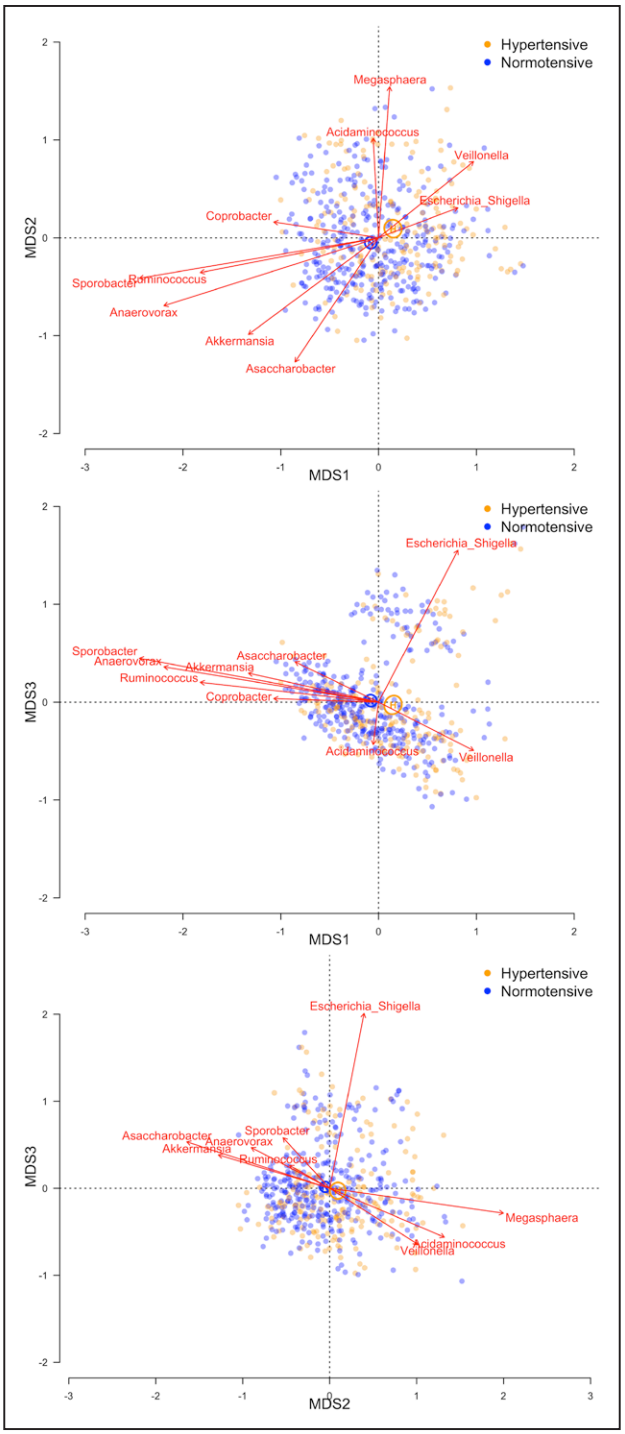

Figure 1. Microbial similarity biplots (joint principal coordinates analysis [PCoA] axes) for study participants with hypertension (orange) or normal blood pressure (blue). Biplots shown for PCoA axes that explain at least 5% of variability in microbial similarity. Centroids illustrate the 95% CI for the mean location of each population group. The 10 most abundant genera are shown with respect to their directional association along PCoA axes, with vector length indicating the strength of association. Permutational multivariate ANOVA *P* values were 0.001 for hypertension in each of the 5 multivariable-adjusted models. Model 1 adjusted for sequencing run; model 2 additionally adjusted for age, race, gender, study center, and educational attainment; model 3 additionally adjusted for smoking, physical activity, and diet quality score; model 4 additionally adjusted for body mass index; and model 5 adjusted for model 3 covariates, with the addition of waist circumference. MDS indicates multidimensional scaling.

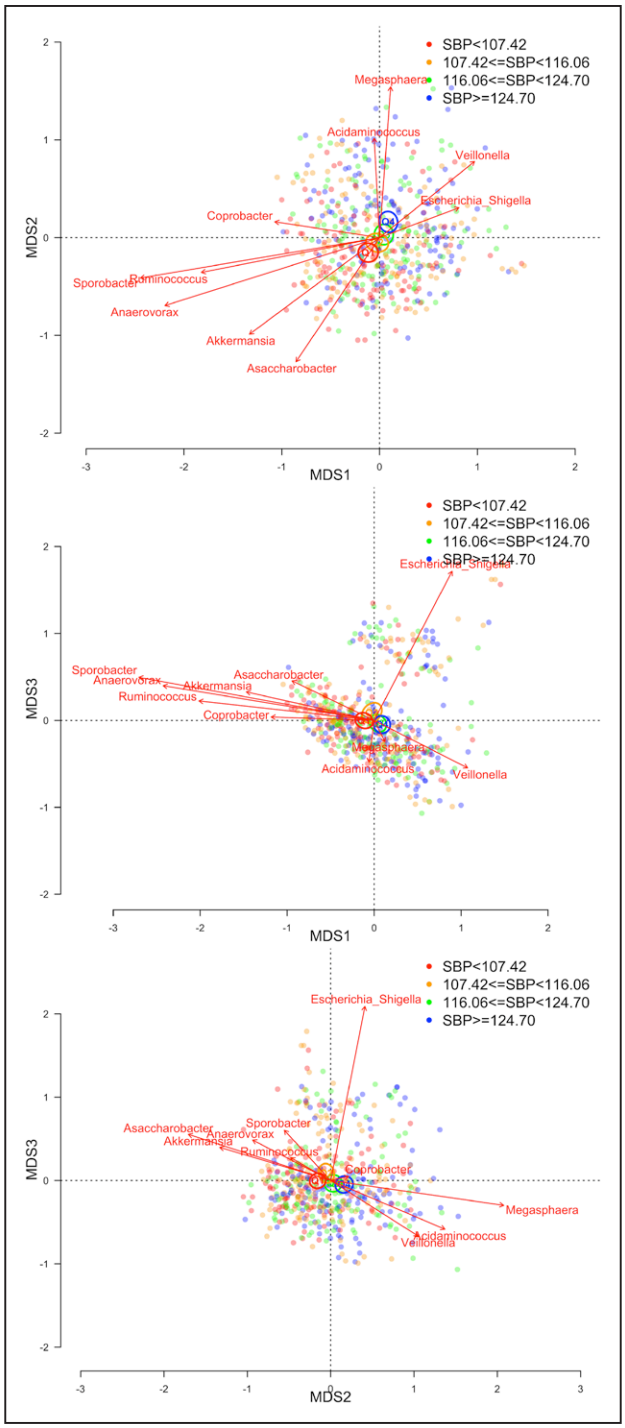

Figure 2. Microbial similarity biplots (joint principal coordinates analysis [PCoA] axes) for study participants with respect to quartiles (Q1–Q4) of systolic blood pressure (SBP; Q1: red; Q2: brown; Q3: green; and Q4: blue). Biplots shown for PCoA axes that explain at least 5% of variability in microbial similarity. Centroids illustrate the 95% CI for the mean location of each population group. The 10 most abundant genera are shown with respect to their directional association along PCoA axes, with vector length indicating the strength of association. Permutational multivariate ANOVA *P* values were 0.001 for SBP in each of the 5 multivariable-adjusted models. Model 1 adjusted for sequencing run; model 2 additionally adjusted for age, race, gender, study center, and educational attainment; model 3 additionally adjusted for smoking, physical activity, diet quality score, and antihypertensive medication; model 4 additionally adjusted for body mass index; and model 5 adjusted for model 3 covariates, with the addition of waist circumference. MDS indicates multidimensional scaling.

S1). For example, *Akkermansia* was negatively correlated with PCoA axes 1 and 3, which were positively associated with hypertension and SBP; whereas *Akkermansia* was positively associated with PCoA 2, which was negatively associated with BP.

We conducted multivariable-adjusted regression analysis of individual genera with respect to BP (Figures 3 and 4; Tables S8 and S9). In unadjusted analysis, a large number of genera were associated with hypertension (65 genera with FDR-adjusted *P* value <0.05 and 74 with FDR-adjusted *P* value <0.10) and SBP (34 genera with FDR-adjusted *P* value <0.05 and 51 with FDR-adjusted *P* value <0.10; Figure 3; Table S8). Findings attenuated with multivariable adjustment. Upon adjustment for sociodemographic variables age, race, sex, field center, and educational attainment (model 2), hypertension remained significantly associated with 21 genera at FDR-adjusted *P* value <0.05 and with 5 genera at FDR-adjusted *P* value <0.10 (Figure 2). Several genera were significantly associated with hypertension in directions consistent with PCoA findings (Table S1), such as positive associations between hypertension and genera *Anaerovorax*, *Clostridium IV*, *Oscillibacter*, and *Sporobacter*. With further adjustment for health behaviors (diet, physical activity, and smoking), 18 genera remained associated with hypertension with FDR-adjusted *P* values <0.10, including positive associations with *Anaerovorax*, *Clostridium IV*, *Oscillibacter*, and *Sporobacter*. Following control for BMI, a potential mediator, no genus was associated with hypertension with an FDR-adjusted *P* value <0.25. Results were not meaningfully different with adjustment for waist circumference instead of BMI (Table S8).

Findings between specific genera and SBP were appreciably weaker (Figure 4; Table S9). SBP was positively associated with *Catabacter* and *Robinsoniella* at FDR-adjusted *P* value <0.05 and with *Parasporobacterium* at FDR-adjusted *P* value <0.10 in models 2 and 3; SBP remained positively associated with *Catabacter* (FDR-adjusted *P* value <0.10) and *Robinsoniella* (FDR-adjusted *P* value <0.05) with additional adjustment for BMI (model 4). Similarly, both *Catabacter* and *Robinsoniella* remained significant at FDR-adjusted *P* value <0.05 when the model adjusted for waist circumference instead of BMI (Table S9). *Catabacter* and *Robinsoniella* were positively associated with hypertension in model 2 (FDR-adjusted *P* value <0.05), but these findings were attenuated with additional adjustment (FDR-adjusted *P* values 0.11 and 0.40 in models 3 and 4, respectively, for *Catabacter* and FDR-adjusted *P* values 0.11 and 0.40 in models 3 and 4, respectively, for *Robinsoniella*). We noted the possibility that results of hypertension may reflect use of antihypertensive medication and considered stratified analysis to distinguish hypertension and medication use. However, there was an insufficient sample size to examine subgroups robustly. Among the 183 participants with hypertension in the analysis, 153 reported taking antihypertensive medication, of whom 128 were controlled (SBP <140 mm Hg and diastolic BP <90 mm Hg). Therefore, analysis of medication use in participants with normal hypertension would have been limited

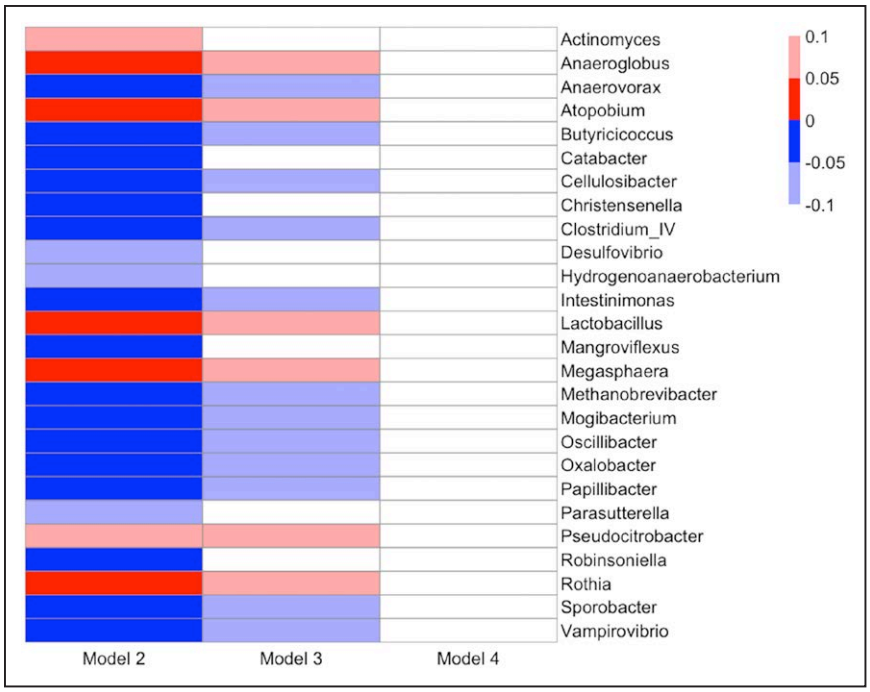

Figure 3. Heatmap of associations between genera and hypertension from multivariable-adjusted models. Direction of association is indicated by color (blue: negative; and red: positive) and false discovery rate-adjusted *P* values (*Q* values) are indicated by shading (bold: *Q* value<0.05; and light: 0.05≤*Q* value<1.0). Multivariable-adjusted regression models adjusted for: model 2: sequencing run, age, race, gender, study center, and educational attainment; model 3: additionally adjusted for smoking, physical activity, and diet quality score; and model 4: additionally adjusted for body mass index. Results are not shown for model 5, which adjusted for model 3 covariates plus waist circumference, as model 5 results were not meaningfully different from model 4 results.

to 128 individuals, and analysis of hypertension in participants not taking antihypertensive medication would have been limited to 30 individuals.

Given observed differences in the microbial community by race and sex (Tables S4 and S5),[40] we assessed the possibility of effect modification by race and sex by including a cross-product term for race or sex in regression models. These tests were not statistically significant, and we therefore present results adjusted for race and sex.

Secondary analysis of family-level data did not in general support a hypothesis of inverse associations between BP and families that we considered relevant for butyrate production, based on published literature.[36] We focused on 6 families that include numerous species shown to carry genes for enzymes in the acetyl-CoA butyrate production pathway: Lachnospiraceae, Peptostreptococcaceae, Clostridiales incertae sedis XI, Clostridiaceae, Ruminococcaceae, and Veillonellaceae.[36] Two families were significantly associated with hypertension in univariate and semi-adjusted models: Ruminococcaceae was inversely associated through model 2 (sociodemographics-adjusted); Veillonellaceae was positively associated through model 3 (sociodemographics and health behaviors; Table S10). No family was significantly associated with SBP in univariate or multivariable-adjusted models (Table S11).

Discussion

In the CARDIA microbiome study, several measures of the gut microbiota were significantly associated with BP in cross-sectional analysis. Measures of within-person microbial diversity were inversely associated with hypertension and SBP, and there was significant separation of BP according to microbial dissimilarity in PCoA. These differences remained significant after adjustment for a range of demographic and health behavior covariates. Several specific taxonomic groups appeared associated with hypertension and SBP, though these findings were sensitive to covariate adjustment, in particular BMI, and generally were not statistically significant after adjustment for multiple comparisons.

A growing body of literature supports a role of the gut microbiota in CVD risk, but there have been relatively few population-based studies of gut microbiota and CVD risk factors and we know of no study that has focused on BP. In a case-control analysis of 112 participants from the Bogalusa Heart Study, Kelly et al[4] found that microbial richness and several distinct taxonomic groups were associated with a

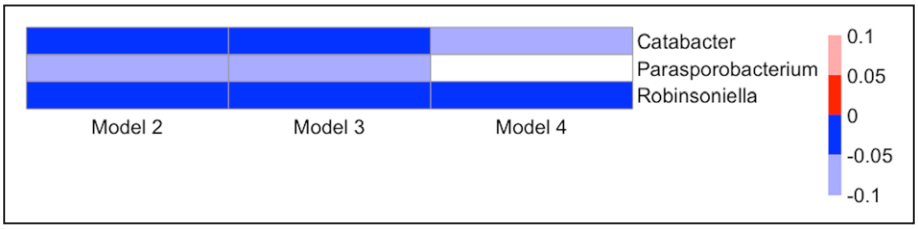

Figure 4. Heatmap of associations between genera and systolic blood pressure from multivariable-adjusted models. Direction of association is indicated by color (blue: negative; and red: positive) and false discovery rate-adjusted *P* values (*Q* values) are indicated by shading (bold: *Q* value<0.05; and light: 0.05≤*Q* value<1.0). Multivariable-adjusted regression models adjusted for: model 2: sequencing run, age, race, gender, study center, and educational attainment; model 3: additionally adjusted for smoking, physical activity, diet quality score, and antihypertensive medication use; and model 4: additionally adjusted for body mass index. Results are not shown for model 5, which adjusted for model 3 covariates plus waist circumference, as model 5 results were not meaningfully different from model 4 results.

measure of lifetime CVD risk score comprising fasting glucose, LDL-C (low-density lipoprotein cholesterol), and SBP. Similar to Kelly et al,[4] and other studies of CVD risk factors,[10] our findings for microbial community richness were more robust than findings for diversity measures that incorporate both richness and evenness such as the Shannon Diversity Index.

There has been a lack of analysis on microbiome and BP in population-based adult cohorts. Hypertension has been induced in normotensive rats through transplantation of cecal contents from hypertensive rats.[15,41] Data support microbiota-dependent production of SCFAs, such as butyrate, acetate, and propionate, as one mechanism through which gut microbiota may influence BP.[42–45] In a study of 205 overweight and obese pregnant women, BP was associated with gut microbiota composition and, specifically, inversely associated with butyrate-producing bacteria in the gut microbiota.[45] Microbiota-generated SCFAs have been shown to influence BP through olfactory receptors expressed in the vasculature and kidneys.[42,43] Additional microbial metabolites of dietary components may also play a role. In a population-based metabolomics analysis, urinary hippurate was inversely associated with BP in the International Population Study on Macronutrients and BP[18]; serum hydroxyhippurate was positively associated with incident hypertension in Atherosclerosis Risk in Communities study.[19]

Results were more robust for microbial diversity (α- and β-diversity) measures, as compared to analysis of specific taxa. These findings are consistent with previous support for community-level measures.[3–5] Analyses of microbial diversity will be more powerful than multiple comparisons adjusted analyses of individual taxa. In addition, these results may reflect aspects of the gut microbial community not captured in analysis of specific genera. Diversity measures remained significant after adjustment for potential confounders, but many individual genera lost statistical significance after adjustment for demographic, health behavior, and clinical covariates. In particular, BMI, a potential intermediate, appeared to account for much observed attenuation, especially in analysis of hypertension. At this stage of microbiome research, the relevance of various covariates has not been firmly established, and studies have varied with respect to adjustments included in analysis. For example, adjustment for diet had a modest impact in our analysis, but was an important covariate in Bogalusa[4]; diet was not included as a covariate in analyses of Lifelines-DEEP or the METabolic Syndrome In Men study.[3,5] Future work and a growing number of studies with microbiome data will contribute to our understanding.[46,47]

The larger number of significant associations of genera with hypertension, as compared to SBP, may reflect the greater severity of the phenotype. We also considered the possibility that the use of antihypertensive treatment may influence the gut microbiome, but were unable to disentangle associations between hypertension and medication use in our analysis, given the very small number of individuals who were discordant on hypertension status and antihypertensive medication use. Data from animal models are supportive of a causal effect of the gut microbiome on BP,[15,41–43] but longitudinal data and larger samples are needed to confirm the relevance of the gut microbiome in human populations and robustly identify specific bacteria that may serve as targets for intervention.

Our analysis provides 2 approaches to assessing specific taxa with respect to BP. Several of the most abundant genera that differentiated PCoA axes have been previously associated with pathways that may influence BP. Notably, *Akkermansia*—aligned with axes associated with normotension in analysis—may signal improved gut epithelial integrity and has been associated with obesity, diabetes mellitus, and inflammation.[48–50] *Sporobacter* and *Ruminococcus*—both aligned with axes associated with normotension—are members of the Ruminococcaceae family within the phylum Firmicutes. Several genera were associated with BP in both PCoA and taxa-specific analysis; for example, *Sporobacter* and *Anaerovorax* were inversely associated with hypertension in both analyses. Taxa-specific analyses revealed additional genera-BP associations, with *Robinsoniella* and *Catabacter* positively associated with both hypertension and SBP.

Based on our 16S rRNA sequence data, results did not support our hypothesis that taxa, at the family level, related to the production of SCFAs, particularly butyrate, are inversely associated with BP. For this analysis, we focused on taxa at the family level, given the availability of published data for genes in butyrate-producing pathways at family and species, but not genus, levels.[36] One challenge with this approach is that our data may not be sufficiently precise, as we would expect appreciable variability in function within taxonomic levels available from 16S rRNA data. Analysis at the gene level, using whole-metagenomic sequencing, would allow improved pathway assignment based on the presence of relevant genes. Furthermore, SCFAs are a diverse class of molecules, with reported inverse associations between BP and acetate,[51] propionate,[44] and formate.[18] Vital et al[36] provide a catalog of families and species relevant for butyrate production, but there is a paucity of literature defining the full set of pathways for comprehensive analysis of SCFAs.

Our article addresses a lack of population-based studies of the gut microbiota with respect to BP. The CARDIA cohort allowed analysis of a sociodemographically diverse group of adults at a critical life period for increasing CVD risk. BP was measured by trained field center clinic staff using a standardized protocol. We used validated protocols for the collection and processing of samples and 16S rRNA sequencing. CARDIA collects extensive covariate information using standardized and validated instruments, and we were able to control for major potential confounders, including health behaviors, antihypertensive medication use, and clinic-based assessment of anthropometry.

Our study also has limitations. This was the first collection of microbiome data in CARDIA, which prevents the establishment of temporality in these cross-sectional analyses. In particular, we cannot distinguish the role of the gut microbiota in the development or progression of hypertension from the possibility that BP itself, or associated covariates, may alter the microbiota. The gut microbiome has been associated with several CVD risk factors that correlate with BP[3–5]; aside from BMI and health behaviors; we did not include other risk factors in regression modeling, and it is possible that some of the microbial variability associated with BP reflects other clinical measures. Our sample size was along the lines of other epidemiological studies of gut microbiota, but it is possible that

we lacked power in our multiple comparisons analysis of individual genera. In addition, there are few population-based studies with microbiome data, particularly with representation similar to CARDIA, and we lacked data for replication of results. Future analysis of BP and microbiome in independent samples is needed to confirm our findings. Our analysis was limited to 16S rRNA sequence data, which yields only compositional measures and taxonomic analysis to the genus level.

Perspectives

Our findings support an association between the gut microbiota and BP in a biracial middle-aged population-based cohort. Microbial diversity was inversely associated with hypertension and SBP. Several specific genera were significantly associated with BP after adjustment for potential confounders and for multiple comparisons, but findings were attenuated upon adjustment for BMI. Further studies are needed to quantify prospective associations in larger samples and with functional measures and refined compositional information to assess subgenus taxonomies and functional differences that underlie observed associations.

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Disclosures

None.

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Novelty and Significance

What Is New?

- To our knowledge, this is the first population-based cohort study focused on investigating associations between gut microbial community composition and blood pressure (BP).

What Is Relevant?

- Animal models have demonstrated mechanistic pathways through which the gut microbiota may influence BP.
- Our results demonstrate significant associations between gut microbial composition and BP.

Summary

In this population-based cohort of middle-aged US whites and blacks, there were significant differences in the composition of the gut microbiota with respect to BP. Gut microbial diversity was inversely associated with both hypertension and systolic BP. These results support additional research to understand the role of the gut microbiome in BP.