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Original Research Article

Healthy dietary patterns are associated with the gut microbiome in the Hispanic Community Health Study/Study of Latinos

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A B S T R A C T

Background: Dietary patterns high in healthy minimally processed plant foods play an important role in modulating the gut microbiome and promoting cardiometabolic health. Little is known on the diet–gut microbiome relationship in US Hispanics/Latinos, who have a high burden of obesity and diabetes.
Objective: In a cross-sectional analysis, we sought to examine the relationships of 3 healthy dietary patterns—the alternate Mediterranean diet (aMED), the Healthy Eating Index (HEI)-2015, and the healthful plant-based diet index (hPDI)—with the gut microbiome in US Hispanic/Latino adults, and to study the association of diet-related species with cardiometabolic traits.
Methods: The Hispanic Community Health Study/Study of Latinos is a multi-site community-based cohort. At baseline (2008-2011), diet was assessed by using 2, 24-hour recalls. Shotgun sequencing was performed on stool samples collected in 2014-17 (n = 2444). Analysis of Compositions of Microbiomes 2 (ANCOM2) was used to identify the associations of dietary pattern scores with gut microbiome species and functions, adjusting for sociodemographic, behavioral, and clinical covariates.
Results: Better diet quality according to multiple healthy dietary patterns was associated with a higher abundance of species from class Clostridia, including *[Eubacterium] eligens*, *Butyrivibrio crossotus*, and *Lachnospiraceae bacterium TF01-11*, but functions related to better diet quality differed for the dietary patterns (e.g., aMED with pyruvate:ferredoxin oxidoreductase, hPDI with L-arabinose/lactose transport). Poorer diet quality was associated with a higher abundance of *Acidaminococcus intestini* and with functions of manganese/iron transport, adhesin protein transport, and nitrate reduction. Some healthy diet pattern-enriched Clostridia species were related to more favorable cardiometabolic traits such as lower triglycerides and waist-to-hip ratio.
Conclusions: Healthy dietary patterns in this population are associated with a higher abundance of fiber-fermenting Clostridia species in the gut microbiome, consistent with previous studies in other racial/ethnic groups. Gut microbiota may be involved in the beneficial effect of higher diet quality on cardiometabolic disease risk.

Keywords: gut microbiome, diet, Hispanic, Latino, cardiometabolic health, dietary pattern, Mediterranean diet, healthy eating index

Abbreviations used: aMED, alternate Mediterranean diet; ANCOM, Analysis of Composition of Microbiomes; CLR, centered log ratio; CVD, cardiovascular disease; DGA, Dietary Guidelines for Americans; HCHS/SOL, Hispanic Community Health Study/Study of Latinos; HDL, high-density lipoprotein; HEI-2015, Healthy Eating Index 2015; HOMA-IR, homeostatic model assessment of insulin resistance; hPDI, healthful plant-based diet index; JSD, Jensen-Shannon Divergence.

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Introduction

Poor diet quality is the leading risk factor for death globally, primarily from cardiovascular disease (CVD) [1]. Diets high in sodium and low in whole grains, fruit, and nuts and seeds are associated with the highest risk of mortality [1], consistent with many observational studies and clinical trials showing the significance of these dietary factors in cardiometabolic disease risk [2–7]. Recognizing this evidence, the Dietary Guidelines for Americans (DGA) issued by the US Departments of Agriculture and Health and Human Services recommends dietary patterns that are high in fruit, vegetables, and whole grains and low in sodium, as well as other criteria [8]. Starting in 2015, the DGA identified several healthful dietary patterns that should promote optimal health—the Healthy US-Style, Mediterranean style, and vegetarian dietary patterns. Indeed, adherence to healthy dietary patterns is associated with reduced CVD risk in large observational prospective studies [9–11] and some randomized clinical trials [12, 13].

Biological mechanisms by which healthful dietary patterns exert protective effects are complex and multifactorial, involving synergistic actions of the individual foods and nutrients present in the dietary pattern [14–17]. Importantly, the influence of diet is mediated not only through effects on human cells but also through effects on human-resident gut microbes [18]. Since the early landmark studies in mice implicating the gut microbiome in dietary energy harvest and diet-induced obesity [19–23] and proof-of-principle studies demonstrating the impact of short-term extreme diet changes on the human gut microbiome [24–26], population-level human studies have revealed that long-term habitual food intakes are small but significant determinants of gut microbiome composition [27–30]. Studies focusing on healthy dietary patterns have found significant associations with the gut microbiome [31–34], with higher diet quality (particularly healthy plant food intake) associated with a higher abundance of fiber-fermenting Firmicutes members (e.g., *Roseburia*, *Feacalibacterium*). In addition, healthy diet-linked microbial species tend to associate with favorable cardiometabolic profiles [31–33], supporting the role of gut microbiota in diet-related disease risk [18]. However, microbial species related to healthy dietary patterns in diverse populations remain elusive because most of the large extensively phenotyped gut microbiome studies have been conducted in the populations of European ancestry [31, 32]. Variation in the human gut microbiome has been widely observed across populations of different race/ethnicity [35–37].

Here, we identify gut microbial species related to multiple healthy dietary patterns in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). US Hispanics hail from diverse genetic backgrounds and countries of origin and harbor distinct gut microbiota shaped by geographic relocation [38], providing an opportunity to identify potentially novel gut microbiota related to healthy dietary patterns. We additionally explore whether healthy diet-related gut microbiota are associated with favorable cardiometabolic traits, of particular importance in US Hispanics/Latinos with a high burden of type 2 diabetes and other cardiometabolic risk factors [39–41].

Methods

Study cohort

The HCHS/SOL is a prospective, population-based cohort study of 16,415 Hispanic/Latino adults (aged 18-74 years at the time of recruitment during 2008-2011) who were selected by using a multistage probability sampling design from randomly sampled census block areas within 4 US communities (Chicago, IL; Miami, FL; Bronx, NY; and San Diego, CA) [42, 43]. The first (2008-2011) and second (2014-2017) clinic visits entailed a comprehensive battery of interviews and a clinical assessment with fasting blood draw, conducted in-person by trained, certified, and bilingual staff. The first visit also included collection of 2 24-hour dietary recalls, discussed in further detail below. The current analysis used data from the HCHS/SOL Gut Origins of Latino Diabetes ancillary study [38], which was conducted to examine the role of gut microbiome composition on diabetes and other outcomes, enrolling participants from the HCHS/SOL approximately concurrent with the second in-person HCHS/SOL visit cycle. Starting with $n = 3035$ participants with a microbiome sample, we then excluded participants with missing dietary data ($n = 50$), prevalent cancer ($n = 161$), or with <500 K sequence reads in their microbiome sample ($n = 380$), thus retaining $n = 2444$ participants for this analysis (Figure 1A). There were no participants with implausible energy intake (>6000 or <600 kcal/day in men or >4000 or <400 kcal/day in women). The study was conducted with the approval of the Institutional Review Boards of all HCHS/SOL study centers. Written informed consent was provided by all study participants.

Diet assessment and calculation of dietary scores

Information on dietary intake was collected using 2 24-hour dietary recalls [44, 45]. The first recall was administered through in-person interviews conducted at the time of the first HCHS/SOL clinic visit, whereas the second was performed primarily via telephone approximately 30 days after the first interview. Participants estimated portion sizes with the use of food models (in-person) or a food-amount booklet (for telephone interviews). Data on foods and nutrients were collected and analyzed using the multiple-pass methods of Nutrition Data System for Research software (version 11) from the Nutrition Coordinating Center at the University of Minnesota. Dietary data from both recalls were then averaged for use in deriving dietary pattern scores. We focused on 3 dietary patterns closely reflecting the 3 healthful patterns in the DGA—the alternate Mediterranean diet (aMED), the Healthy Eating Index (HEI)-2015, and the healthful plant-based diet index (hPDI), with scoring criteria presented in Supplemental Figure 1. Briefly, the aMED score was adapted by Fung et al. [46] to reflect adherence to the Mediterranean diet, and each of its 9 components was assigned 0 or 1 point according to intake median or moderate drinking, with the total score ranging from 0 to 9. The Healthy Eating Index 2015 (HEI-2015) assesses the extent to which an individual's diet aligns with the 2015 to 2020 DGA, and it includes 13 components and ranges from 0 to 100 [47]. Although the aMED and HEI-2015 include both food and nutrient components, the hPDI comprises solely food groups that were coded based on intake quintiles [48, 49]. Higher intakes of 6 "healthy plant foods" (e.g., whole grains) were awarded points, whereas intakes of 5 animal foods and 4 "less healthy plant foods" (e.g., sugar-sweetened beverages and fruit juices) both were reverse-coded, leading to a range of 15 to 75 for the total score of hPDI. For all dietary patterns, a higher score indicates a healthier diet quality.

Microbiome measurement

Stool samples were collected by participants at their homes by using stool collection kits provided at or around the time of the second HCHS/SOL clinic visit [38]. Samples received in the laboratory were immediately frozen at −80°C. The median time between sample receipt in the laboratory and shipment for sequencing was 392 days (range: 23-601). Shotgun sequencing was conducted in the Knight laboratory at the University of California, San Diego by using a

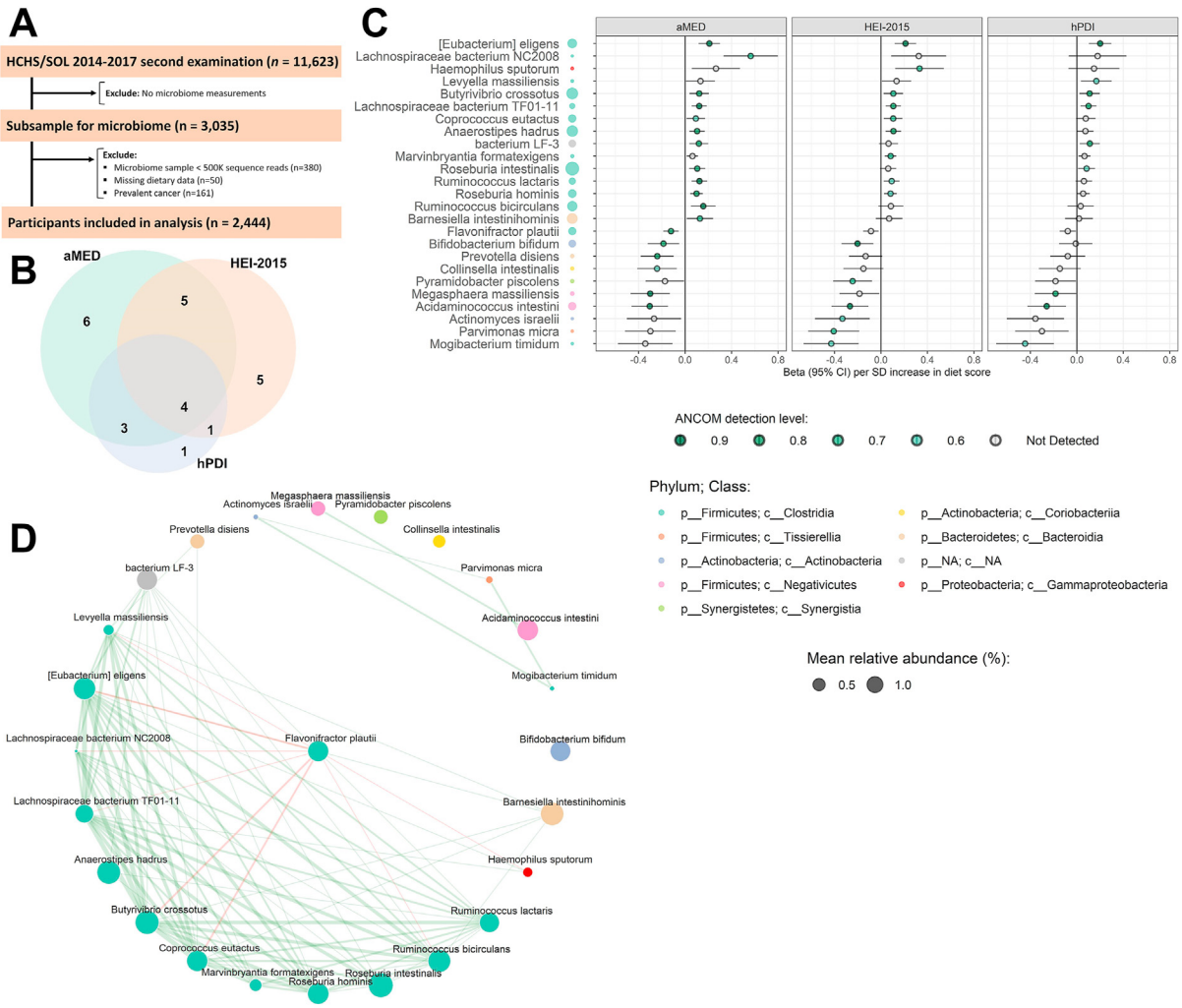

FIGURE 1. Gut microbiome species associated with 3 healthy dietary patterns in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) ($N = 2444$). (A) Flow diagram of the exclusion criteria for the current analyses. (B) We used ANCOM2 to identify species for which species abundance was associated with the alternate Mediterranean diet (aMED), the Healthy Eating Index (HEI)-2015, or the healthful plant-based diet index (hPDI) scores. ANCOM2 models were adjusted for age, sex, field center, Hispanic/Latino background, US nativity, antibiotics use, probiotics use, Bristol stool score, and total energy intake. The number of species detected for each dietary score, and overlapping species, is shown in the Venn diagram. (C) For each species associated with at least one dietary score in ANCOM2 (detection level $\geq$0.60), we show the mean relative abundance and the estimated effect size (Beta) per SD increase in dietary score from multivariable linear regression models, with CLR-transformed species abundance as outcomes, adjusting for same covariates listed in (A). (D) A network graph representing Spearman correlations among species associated with at least one dietary score. CLR-transformed species abundance was used for correlations. Correlations greater than 0.20 with $q < 0.05$ are shown with lines, with line thickness corresponding to the magnitude of correlation. Green and red lines represent positive and negative correlations, respectively. Sizes of the dots are based on relative abundance of the species. CLR, centered log ratio.

shallow approach [50, 51]. Briefly, DNA is extracted from fecal samples following the Earth Microbiome Project protocol [52]. Input DNA is quantified by using a PicoGreen fluorescence assay (ThermoFisher, Inc.) and is normalized to 1 ng by using an Echo 550 acoustic liquid-handling robot (Labcyte, Inc.). Enzyme mixes for fragmentation, end repair and A-tailing, ligation, and PCR are added by using a Mosquito HV micropipetting robot (TTP Labtech). Fragmentation is performed at 37°C for 20 minutes, followed by end repair and A-tailing at 65°C for 30 minutes. Sequencing adapters and barcode indices are added in 2 steps, following the iTru adapter protocol [53]. Universal "stub" adapter molecules and ligase mix are first added to the end-repaired DNA by using the Mosquito HV robot, and ligation was performed at 20°C for 1 hour. Unligated adapters and adapter dimers are removed by using AMPure XP magnetic beads and a BlueCat purification robot (BlueCat Bio). Next, individual i7 and i5 are added to the adapter-ligated samples by using the Echo 550 robot. Then, eluted bead-washed ligated samples are added to the PCR master mix and are PCR-amplified for 15 cycles. The amplified and indexed libraries are purified again by using magnetic beads and the BlueCat robot, resuspended in water, and transferred to a 384-well plate by using the Mosquito HTS liquid-handling robot for library quantitation, sequencing, and storage. Samples are then normalized based on a PicoGreen fluorescence assay, for sequencing on Illumina NovaSeq.

Microbiome bioinformatics processing

FASTQ sequence reads were demultiplexed, sequence adapters were trimmed, and reads mapping to the human genome identified by using Bowtie2 [54] were removed. The quality-controlled paired-end sequences were then aligned against the NCBI RefSeq representative prokaryotic genome collection (release 82) [55] by using Bowtie2 [54],

and per strain coverage was calculated by using the default SHOGUN [50, 56] settings. Reads mapping to a single reference genome are labeled with NCBI taxonomy at the species level, whereas reads mapping to multiple genomes are labeled with the lowest common ancestor [50]. Species tables were subset to bacterial species only (making up >99.5% of reads), and indices of α-diversity (Shannon diversity index) and β-diversity Jensen-Shannon Divergence (JSD) were calculated by using "vegan" and "phyloseq" packages in R [57, 58]. Functional profiles were obtained by using SHOGUN through sequence alignment to a nucleotide gene database derived from NCBI RefSeq (release 82) and annotated with the Kyoto Encyclopedia of Genes and Genomes (KEGG) orthology [56, 59].

Assessment of cardiometabolic traits

Cardiometabolic traits were based on the data collected at HCHS/SOL visit 2. By using an automatic sphygmomanometer, 3 seated blood pressure measures were obtained for each participant after a 5-minute rest period, and means of the second and third measurements were used to derive systolic blood pressure and diastolic blood pressure [60]. Centralized laboratory tests included blood glucose, insulin, hemoglobin A1c, triglycerides, and total high-density lipoprotein (HDL) and low-density lipoprotein cholesterol, all measured after overnight fast [61]. Homeostatic model assessment of insulin resistance (HOMA-IR) was derived by using a common equation based on fasting glucose and insulin [62].

Other covariates

Participant characteristics were included for statistical adjustment in our analysis, based on known or suspected relationships with diet and/or the gut microbiome. These included age (years), sex (male, female), field center (Bronx, Chicago, San Diego, and Miami), Hispanic/Latino background (Central or South American, Cuban, Dominican, Mexican, Puerto Rican, and more than one heritage), US nativity (born in 50 US states/DC or not born in the 50 US states/DC), use of antibiotics in past 6 months (yes or no), use of probiotics in past 6 months (yes or no), Bristol stool score (8 categories), total dietary energy intake (kcal/day), educational attainment (<9th grade, at least some high school, high school diploma, and more than high school), income (≤20K, 20-40 K, and >40 K), smoking history (never, former, and current), alcohol use (none, low, and high), physical activity based on the Global Physical Activity Questionnaire (MET-min/day), BMI (kg/m^2), prevalent diabetes (yes or no), prevalent CVD (yes or no), use of lipid-lowering medication (yes or no), and use of blood pressure medication (yes or no). With the exception of total energy intake, all other covariates are based on the data collected at HCHS/SOL visit 2. Missing covariate data were imputed at the median and mode for continuous and categorical variables, respectively, except for categorical variables with >1% missing, for which a missing category was created (Supplemental Tables 1-3).

Statistical analysis

General principles

Primary data analysis goals were to relate dietary patterns with gut microbiome features and then to examine the relationship of diet-related gut microbiome features with cardiometabolic traits. For examining the associations of diet with gut microbiome features, continuous dietary pattern scores were Z-score standardized, and nested models were developed to serially adjust for the sets of potentially confounding variables: Model 1 (demographic factors, microbiome-related factors, and total energy intake)—age, sex, field center, Hispanic/Latino background, US nativity, antibiotics use, probiotics use, Bristol stool score, and total energy intake—Model 2 (socioeconomic and behavioral factors)—additionally adjusted for educational attainment, income, smoking history, alcohol use, and physical activity—and Model 3 (cardiometabolic factors)—additionally adjusted for BMI, prevalent diabetes, prevalent CVD, use of lipid-lowering medication, and use of blood pressure medication. All statistical analyses were conducted in R version 3.6.3.

Within-subject (α-) and between-subject (β-) diversity

Multivariable linear regression was used to examine the associations of dietary patterns with the Shannon diversity index, adjusting for covariates as described above. Permutational multivariate analysis of variance was used to assess the association of dietary patterns with overall microbiome composition, as measured by the JSD, adjusting for aforementioned covariates. In a sensitivity analysis, we excluded participants with prevalent diabetes and CVD.

Species, functional modules, and orthologs

Microbial species, KEGG functional modules, and KEGG orthologs were analyzed in the following 2 stages: first by using the Analysis of Composition of Microbiomes (ANCOM2) method (implemented with the "ancom" function in the "ANCOMBC" Bioconductor package) [63], followed by confirmatory multivariable linear regression, described below. ANCOM2 was used to detect species, functional modules, and orthologs associated with dietary patterns, adjusting for Model 1 covariates described above. We controlled the false discovery rate at 10% and excluded species, modules, or orthologs from testing if they were present in <20% of the study population. We also excluded modules for which the average coverage was <50% and orthologs that were not annotated with enzyme information. An ANCOM detection level ≥0.6 was considered significant–this level indicates that the ratios of the species, module, or ortholog to at least 60% of other taxa, modules, or orthologs were detected to be significantly associated with a dietary pattern (false discovery rate $q < 0.10$). These thresholds were chosen to minimize false negatives because diet is well known to broadly affect the gut microbiome and to facilitate comparison across the dietary patterns. For the ANCOM-selected species, modules, and orthologs, we constructed multivariable linear regression models, with the centered log ratio (CLR)-transformed species/module/ortholog abundance as outcomes and dietary pattern as the main predictor, adjusting for covariates in Models 1, 2, and 3 described above. Partial Spearman's correlations (adjusting for Model 1 covariates) were used to assess the relationships of ANCOM-selected microbiome features (species, modules, and orthologs) with individual diet score components (e.g., fruit and whole grains).

Association with cardiometabolic traits

This analysis was performed in a subset of participants not taking antidiabetic, antihypertensive, or lipid-lowering medications to avoid bias of reverse causation (i.e., disease-related medication use influencing the gut microbiome). Multivariable linear regression was used to examine the association of CLR-transformed gut microbial species, modules, and orthologs (predictors) with continuous Z-score standardized cardiometabolic traits (outcomes), adjusting for Model 1 covariates. All species/modules/orthologs related to at least one dietary pattern were included. We also checked the association of the diet scores with the cardiometabolic traits in multivariable linear regression models adjusting for age, sex, field center, Hispanic/Latino background, US nativity, and total energy intake. We developed a healthy

diet-related microbiome score to relate with cardiometabolic traits. First, the CLR-transformed abundance of species associated with at least 2 dietary patterns was Z-score standardized to give equal weight to each species; then, those species related to a better diet were summed, whereas species related to a poorer diet were substracted within each participant to derive the score.

Results

Participant characteristics

Data from 2444 participants (65% women) were included in the current analysis, with a median age of 58 years (interquartile range 52-64). Participants with healthier dietary patterns according to the aMED, HEI-2015, and hPDI were more likely to be older, to have been born outside the United States, to be of Mexican background, to be never smokers, and to have less educational attainment (Table 1; Supplemental Tables 1-3). In addition, a higher aMED score was associated with lower BMI, higher income, higher physical activity, and higher probiotics usage; a higher HEI-2015 score was associated with female sex and higher prevalence of diabetes; and a higher hPDI score was associated with female sex, lower alcohol use, lower physical activity, and higher prevalence of diabetes (Table 1; Supplemental Tables 1-3).

Dietary patterns and overall microbiome diversity and composition

The 3 dietary patterns were not associated with gut microbiome α-diversity, as measured by the Shannon diversity index, in nested multivariable linear regression models adjusting for demographic

TABLE 1
Characteristics of participants according to healthy dietary patterns in the Hispanic Community Health Study/Study of Latinos (n = 2444)[1]

	aMED quintile		HEI-2015 quintile		hPDI quintile	
	1 (score 0-2)	5 (score 6-9)	1 (score<47.1)	5 (score≥71.1)	1 (score<42)	5 (score≥53)
n	642	250	487	485	445	470
Age, y; median (IQR)	57 (50-63)	58 (53-64)	56 (51-63)	58 (52-65)	54 (47-61)	60 (54-66)
BMI, kg; median (IQR)	29.7 (26.6-33.9)	28.84 (25.6-32.2)	29.8 (26.5-33.6)	29.3 (26.0-32.8)	29.4 (26.1-33.7)	29.4 (26.1-32.4)
Women, %	64.5	66.0	61.2	71.8	48.8	78.3
Center, %						
Bronx	38.6	9.6	37.4	12.8	31.0	24.3
Chicago	23.1	31.2	22.2	37.7	24.0	32.3
Miami	26.3	10.0	29.8	7.2	27.2	11.9
San Diego	12.0	49.2	10.7	42.3	17.8	31.5
Hispanic/Latino background, %						
Dominican	10.9	7.6	9.7	6.6	7.6	15.3
Central/South American	7.5	10.0	8.6	8.0	7.0	10.4
Cuban	20.7	6.0	22.2	5.0	20.2	5.1
Mexican	20.9	66.4	18.1	67.8	27.4	53.6
Puerto Rican	31.8	4.4	33.1	7.2	29.4	8.7
More than 1 heritage	6.7	4.4	7.4	4.1	6.3	5.7
Education, %						
<9th grade	18.2	27.6	18.5	32.8	12.8	37.7
Some HS	13.1	10.8	10.1	9.5	11.0	10.0
HS diploma	25.6	21.6	25.1	21.9	26.5	17.9
More than HS	42.2	38.4	45.4	34.9	48.5	33.2
Income, %						
≤20K	45.3	36.4	42.9	35.9	39.6	40.0
>20-40K	28.0	27.2	30.4	32.6	31.0	28.9
>40K	19.5	32.8	20.9	25.8	24.7	23.2
Cigarette use, %						
Never smoker	56.4	66.0	56.5	71.8	53.5	67.0
Former smoker	24.9	28.0	24.2	21.7	25.8	23.2
Current smoker	18.7	6.0	19.3	6.6	20.7	9.8
Alcohol use, %						
No current use	45.8	48.0	43.5	52.0	36.9	51.1
Low level use	51.3	48.8	52.0	45.0	59.3	45.7
High level use	3.0	3.2	4.5	3.1	3.8	3.2
GPAQ total physical activity MET-min/d, median (IQR)	120.0 (0-530.0)	171.4 (28.6-677.1)	137.14 (0-587.1)	171.4 (25.7-600)	180.0 (11.4-874.3)	132.9 (17.1-426.4)
Probiotics in the past 6 months, %	6.4	12.4	7.4	10.5	7.4	11.7
Antibiotics in the past 6 months, %	28.2	27.2	26.9	27.0	26.1	33.6
US born, %	21.0	9.2	21.2	8.0	28.8	6.0
Prevalent diabetes, %	27.7	28.4	25.9	35.1	23.4	35.5
Prevalent cardiovascular disease, %	8.7	5.2	8.4	8.0	7.2	7.9
Blood pressure medication use, %	38.5	30.8	36.1	34.2	31.2	37.9
Lipid-lowering medication use, %	21.7	19.6	18.1	25.6	19.1	26.8
Antidiabetic medication use, %	19.2	15.6	17.3	24.7	15.1	26.0

[1] Only 1st and 5th quintiles are included here because of space constraints. Full versions located in Supplemental Tables 1-3 include all quintiles, number missing for each characteristic, and P values for association of dietary pattern quintile with the characteristics. aMED, alternate Mediterranean diet; HEI-2015, Healthy Eating Index 2015; hPDI, healthful plant-based diet index.

factors, microbiome-related factors, and total energy intake (Model 1); socioeconomic and behavioral factors (Model 2); and cardiometabolic factors (Model 3) (Supplemental Table 4). The aMED and hPDI scores were marginally related to the overall gut microbiome composition assessed by the JSD in Permutational multivariate analysis of variance models with full covariate adjustment ($P = 0.07$ for both), whereas the HEI-2015 score was not ($P = 0.22$) (Supplemental Table 5). These results were consistent in a sensitivity analysis excluding participants with prevalent diabetes and CVD ($n = 1615$; Supplemental Tables 4 and 5).

Dietary patterns and gut microbiome species abundance

Of the 494 gut microbiome species tested, a total of 18, 15, and 9 species met the ANCOM2 criteria for association with the aMED, HEI-2015, and hPDI dietary patterns, respectively, adjusting for demographic factors, microbiome-related factors, and total energy intake. Among these species, all of which had the same direction of association with the 3 dietary patterns, 9 overlapped in ANCOM2 detection for 2 dietary patterns, and 4 overlapped for all 3 patterns (Figure 1B; Supplemental Table 6). A higher score for all 3 dietary patterns was associated with a higher abundance of *[Eubacterium] eligens*, *Butyrivibrio crossotus*, and *Lachnospiraceae bacterium TF01-11* and a lower abundance of *Acidaminococcus intestini* (Figure 1C). Higher aMED and HEI-2015 scores were both additionally associated with a higher abundance of *Coprococcus eutactus*, *Anaerostipes hadrus*, *Ruminococcus lactaris*, and *Roseburia hominis* and a lower abundance of *Bifidobacterium bifidum*. Higher aMED and hPDI scores were both

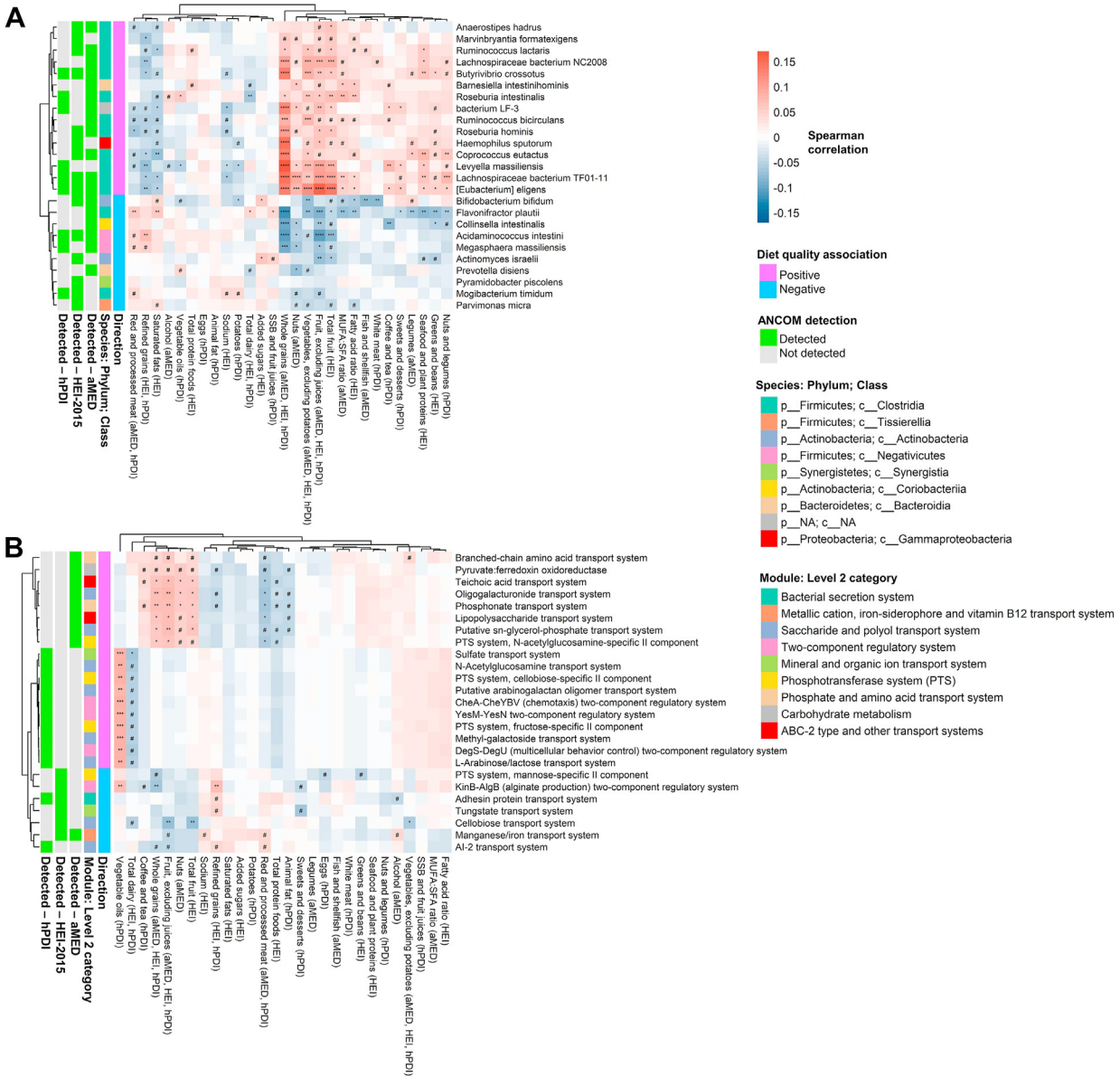

FIGURE 2. Correlations of diet score food components with diet score-related species and modules in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) ($N = 2444$). The heatmap displays partial Spearman correlations of food components with CLR-transformed (A) species or (B) module abundance, adjusted for age, sex, field center, Hispanic/Latino background, US nativity, antibiotics use, probiotics use, Bristol stool score, and total energy intake. The dietary score (aMED, HEI-2015, or hPDI) relevant to each food component is shown in parentheses next to the food component (note: some foods were components of multiple dietary scores). Side annotation for species/modules indicates direction of association with overall dietary scores, taxonomic class or module category, and whether the species/module was detected with ANCOM2 for the aMED, HEI-2015, or hPDI scores. *P* values (per species) were adjusted for the false discovery rate. #$P < 0.05$, *$q < 0.05$, **$q < 0.01$, ***$q < 0.001$, ****$q < 0.0001$. CLR, centered log ratio.

additionally related to a higher abundance of *Bacterium LF-3* and *Roseburia intestinalis* and a lower abundance of *Megasphaera massiliensis*. Finally, higher HEI-2015 and hPDI scores were both additionally associated with the reduced abundance of *Mogibacterium timidum*. These associations remained consistent on further adjustment for socioeconomic/behavioral factors and cardiometabolic factors in multivariable linear regression models (Supplemental Table 6). Most species associated with better diet quality were from the class Clostridia, whereas the species associated with poorer diet quality were from a more diverse taxonomic range (Figure 1C). Most healthy diet pattern-enriched Clostridia species formed a positive correlation network with each other (Figure 1D). *Flavonifractor plautii*, a species from Clostridia associated with a lower aMED dietary score, negatively correlated with many of the other Clostridia species (Figure 1D).

Gut microbiome species that were enriched with better diet quality tended to be positively correlated with dietary intake of whole grains, nuts, vegetables, and fruit and negatively correlated with a dietary intake of red and processed meat, refined grains, and saturated fat (Figure 2A). Dietary intake of whole grains, in particular, was most strongly correlated with diet pattern-related species.

Dietary patterns and gut microbiome functional capacity

Of the 281 KEGG functional modules tested, a total of 9, 6, and 12 modules met the ANCOM2 criteria for association with the aMED, HEI-2015, and hPDI dietary patterns, respectively, adjusting for demographic factors, microbiome-related factors, and total energy intake (Figure 3A; Supplemental Table 7). Most diet pattern-related modules belonged to the overarching "environmental information processing" KEGG pathway (Supplemental Table 7). Although no modules were associated with all 3 dietary scores, higher aMED and HEI-2015 scores were both associated with a lower abundance of the "manganese/iron transport system," and higher HEI-2015 and hPDI scores were both associated with a lower abundance of the "adhesin protein transport system" (Figure 3A). The direction of association for dietary pattern scores with functional modules was usually consistent for all 3 scores, although some functional modules were uniquely associated with a

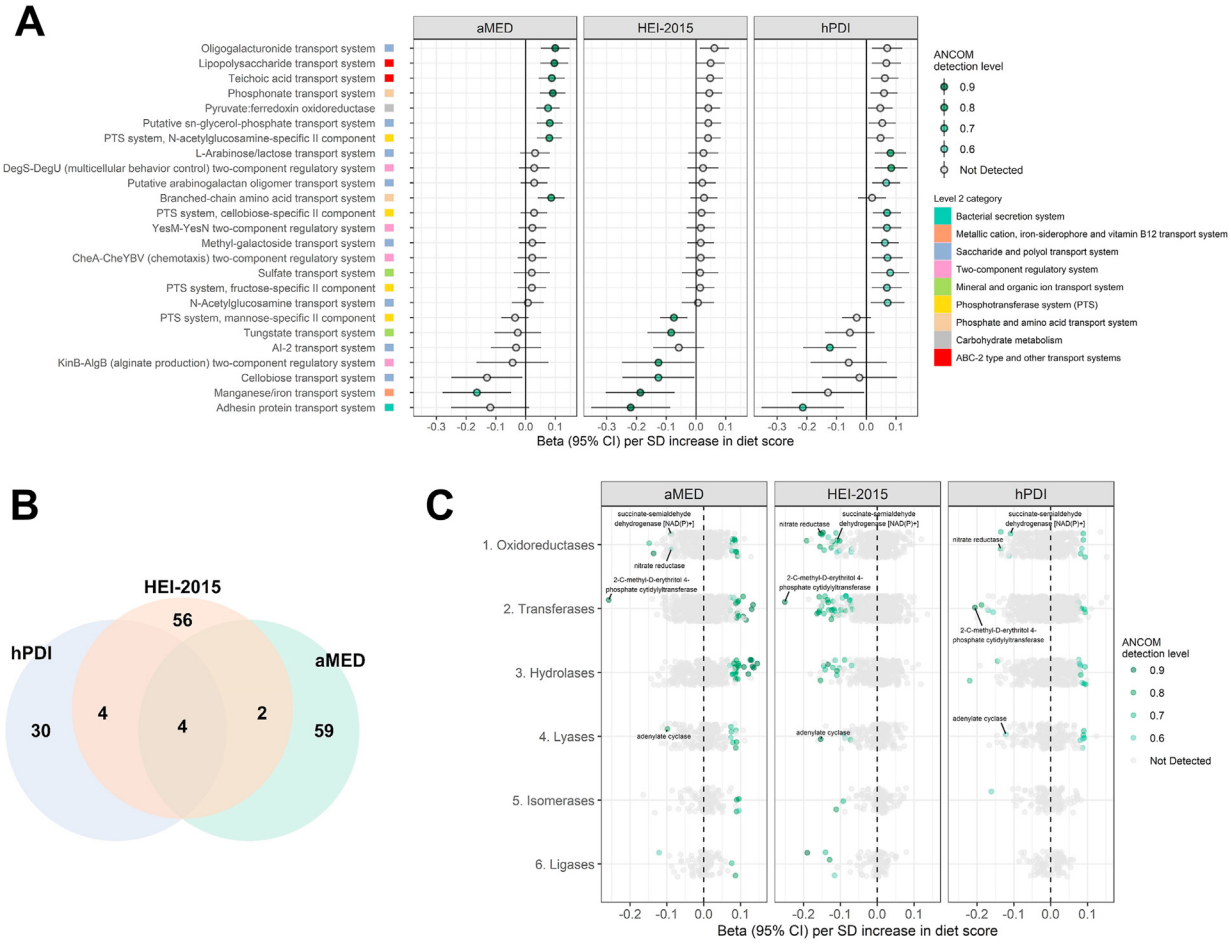

FIGURE 3. Gut microbiome functions associated with healthy dietary patterns in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) ($N = 2444$). (A) We used ANCOM2 to identify KEGG modules for which abundance was associated with the alternate Mediterranean diet (aMED), the Healthy Eating Index (HEI)-2015, or the healthful plant-based diet index (hPDI) scores. ANCOM2 models were adjusted for age, sex, field center, Hispanic/Latino background, US nativity, antibiotics use, probiotics use, Bristol stool score, and total energy intake. For each module associated with at least one dietary score in ANCOM2 (detection level $\geq$0.60), we show the estimated effect size (Beta) per SD increase in dietary score from multivariable linear regression models, with CLR-transformed module abundance as outcomes, adjusting for same covariates as used in ANCOM2. (B) We used ANCOM2, as described in (A), to detect KEGG orthologs associated with dietary pattern scores. The number of orthologs detected for each dietary score, and overlapping orthologs, is shown in the Venn diagram. (C) For all tested KEGG orthologs, we show the estimated effect size (Beta) per SD increase in dietary score from multivariable linear regression models, with CLR-transformed ortholog abundance as outcomes, adjusting for same covariates as above. Orthologs are grouped by level 1 enzyme classification and colored by the ANCOM2 detection level. Orthologs named on the plot are those that overlapped for all 3 dietary patterns. CLR, centered log ratio.

specific dietary pattern, such as the "branched-chain amino acid transport system" with the aMED score, and the "L-arabinose/lactose transport system" with the hPDI score (Figure 3A). Associations of dietary patterns with modules remained consistent on additional adjustment for socioeconomic/behavioral and cardiometabolic factors (Supplemental Table 7). Functional modules uniquely associated with the aMED score, such as the "branched-chain amino acid transport system," "pyruvate:ferredoxin oxidoreductase," and "oligogalacturonide transport system," were positively correlated with a dietary intake of whole grains, fruit, and nuts and negatively correlated with red and processed meat intake, whereas modules uniquely associated with the hPDI score were positively correlated with vegetable oil intake and negatively correlated with dairy intake (Figure 2B).

Finally, of the 1991 KEGG orthologs tested, a total of 65, 67, and 38 orthologs met the ANCOM2 criteria for association with the aMED, HEI-2015, and hPDI dietary patterns, respectively (Figure 3B; Supplemental Table 8). The ANCOM2-detected orthologs differed greatly for the 3 dietary patterns (Figure 3B, C). However, all 3 dietary patterns were associated with a lower abundance of adenylate cyclase, nitrate reductase (K00371), succinate-semialdehyde dehydrogenase [NAD(P)+], and 2-C-methyl-D-erythritol 4-phosphate cytidylyltransferase (Figure 3C). In addition, higher aMED and HEI-2015 scores were associated with a lower abundance of NAD(P)+ transhydrogenase (AB-specific) and glutamate dehydrogenase, whereas higher HEI-2015 and hPDI scores were associated with a lower abundance of nitrate reductase (K00370), nitrate reductase (K00374), RNA helicase, and sulfur carrier protein ThiS adenylyltransferase (Supplemental Table 8). These orthologs that were inversely associated with multiple dietary patterns tended to be positively correlated with a dietary intake of refined grains and negatively correlated with an intake of vegetables, fruit, nuts, and whole grains (Supplemental Figure 2).

Healthy diet pattern-enriched gut microbiome species tended to be positively correlated with diet pattern-enriched KEGG modules (Supplemental Figure 3A). In particular, the abundance of *Roseburia hominis* was strongly positively correlated with the abundance of aMED-enriched modules, including pyruvate:ferredoxin oxidoreductase and transport systems for branched-chain amino acids, sn-glycerol phosphate, oligogalacturonide, lipopolysaccharide, phosphonate, and techoic acid. In addition, positive correlations were observed between species and KEGG orthologs related to poorer diet quality (Supplemental Figure 3B). Particularly strong positive correlations were observed for *Acidaminococcus intestini* and 2-C-methyl-D-erythritol 4-phosphate cytidylytransferase, and *Bifidobacterium bifidum* and NAD(P)+ transhydrogenase (AB-specific). A search of the *Acidaminococcus intestini* and *Bifidobacterium bifidum* genomes in the KEGG database revealed that these species do contain the respective gene orthologs (https://www.genome.jp/kegg/catalog/org_list.html) [59].

Diet pattern-related gut microbiota and cardiometabolic traits

When exploring the associations of dietary pattern scores with continuous markers of dyslipidemia, glycemic control, adiposity, and hypertension in multivariable linear regression models adjusting for demographic factors and total energy intake, we observed that higher aMED scores were significantly related to lower fasting insulin, HOMA-IR, and waist-to-hip ratio; higher HEI-2015 scores were related to lower fasting insulin; and the hPDI scores were not related to any cardiometabolic traits (Supplemental Table 9). We next examined associations of diet pattern-related gut microbiome species, modules, and orthologs with the cardiometabolic traits in multivariable linear regression models adjusting for demographic factors, microbiome-related factors, and total energy intake (Figure 4; Supplemental Figures 4 and 5). Healthy diet pattern-enriched Clostridia species tended to be associated with more favorable cardiometabolic profiles, although not always. For example, healthy diet pattern-enriched *Ruminococcus lactaris*, *Lachnospiraceae bacterium TF01-11*, *Butyrivibrio crossotus*, and *[Eubacterium] eligens* were associated with lower triglycerides; *Ruminococcus lactaris* and *Marvinbryantia formatexigens* were associated with lower fasting insulin and HOMA-IR; and *Anaerostipes hadrus* and *Marvinbryantia formatexigens* were related to lower waist circumference and waist-to-hip ratio (Figure 4). Unexpectedly, healthy diet pattern-enriched *Ruminococcus bicirculans*, *Roseburia hominis*, *Roseburia intestinalis*, and *Coprococcus eutactus* were associated with lower HDL cholesterol and *Flavonifractor plautii*, the only Clostridia species related to poorer diet quality, was associated with a more favorable cardiometabolic profile, including lower waist circumference, waist-to-hip ratio, BMI, fasting glucose, and hemoglobin A1c (Figure 4). Some species related to poorer diet quality were associated with unfavorable cardiometabolic profiles, such as *Collinsella intestinalis* with higher blood pressure and *Bifidobacterium bifidum* with higher waist circumference, waist-to-hip ratio, fasting insulin, and HOMA-IR. To form a clearer picture of the healthy diet-related microbiome and cardiometabolic health, we developed a microbiome score that included all species associated with at least 2 dietary patterns. The healthy diet-related microbiome score was related to lower fasting insulin, HOMA-IR, and waist-to-hip ratio (Figure 4).

Similarly, some functional modules and orthologs positively related to the aMED score (e.g., pyruvate:ferredoxin oxidoreductase) were associated with more favorable cardiometabolic traits (i.e., lower BMI and waist circumference), whereas others were unexpectedly related to lower HDL cholesterol (Supplemental Figures 4 and 5). In addition, unexpectedly, modules and orthologs related uniquely to the hPDI score were associated with higher BMI, waist circumference, fasting insulin, and HOMA-IR (Supplemental Figures 4 and 5).

Discussion

In this large study of diet quality and the gut microbiome in US Hispanic/Latino adults, better diet quality according to multiple diet patterns was associated with enrichment of a Clostridia species network and lower functional capacity for microbial manganese/iron transport and nitrate reduction, among others. Intakes of whole grains, fruit, and vegetables—common components of the aMED, HEI-2015, and hPDI patterns—were the strongest drivers of dietary pattern-related gut microbe composition. By contrast, components specific to a dietary pattern, such as nuts (aMED) and vegetable oils (hPDI), may have driven different associations of the dietary patterns with gut microbiome functions. Some healthy diet-enriched Clostridia species were related to more favorable cardiometabolic traits, suggesting that gut microbiota may be involved in the protective effect of diet quality on cardiometabolic disease.

Previous large epidemiological studies have examined the associations of dietary patterns with the gut microbiome, focused mostly in the populations of European ancestry. We replicated several of their findings, indicating some universal gut microbiome signatures of diet quality. For example, studies with deep shotgun sequencing such as the U.K./US PREDICT1 ($n = 1098$) and the Dutch Lifelines ($n = 8208$) reported that better diet quality related to enrichment of *Eubacterium eligens*, *Roseburia hominis*, *Ruminococcus lactaris*, *Haemophilus parainfluenzae*, *Anaerostipes hadrus*, and *Butyrivibrio crossotus* and

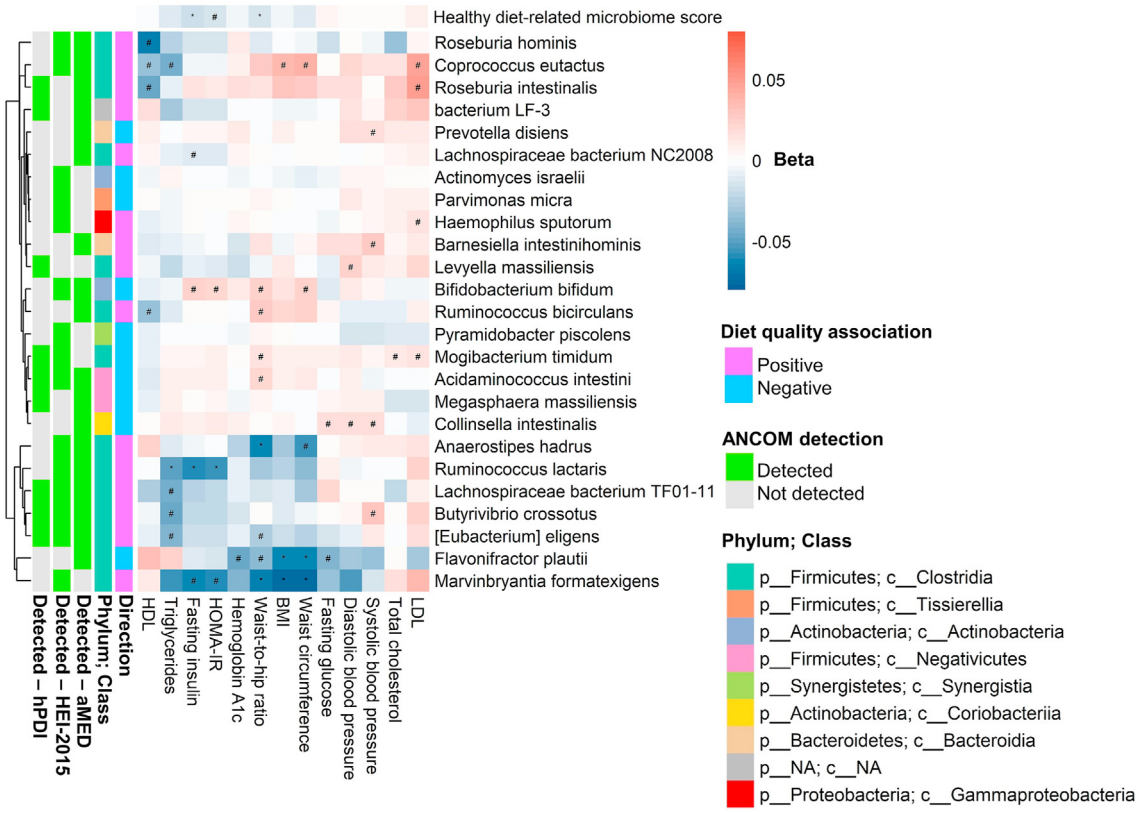

FIGURE 4. Associations of diet score-related gut microbiome species with cardiometabolic traits in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) ($N = 1084$). Continuous cardiometabolic trait outcomes were Z-score standardized and used as outcomes in multivariable linear regression models, with CLR-transformed species (or healthy diet-related microbiome score) as the main predictor and adjusting for age, sex, field center, Hispanic/Latino background, US nativity, antibiotics use, probiotics use, Bristol stool score, and total energy intake. $N = 1084$ after excluding participants taking lipid-lowering, antidiabetic, or antihypertensive medications for this analysis. Side annotation for species indicates direction of association with overall dietary scores, taxonomic class, and whether the species was detected with ANCOM2 for the aMED, HEI-2015, or hPDI scores. *P* values (per species) were adjusted for the false discovery rate. #$P < 0.05$, *$q < 0.05$, **$q < 0.01$, ***$q < 0.001$, ****$q < 0.0001$. CLR, centered log ratio.

depletion of *Bifidobacterium bifidum* and *Flavonifractor plautii* (31, 32), similar to our findings. Studies with 16S rRNA gene sequencing in Germany ($n = 1992$), the United States ($n = 1735$), and China ($n = 1920$) found associations of better diet quality with enrichment of Lachnospiraceae, *Roseburia*, *Coprococcus*, *Ruminococcus*, and *Anaerostipes* and depletion of *Collinsella* and *Acidaminococcus* [33, 34, 64]. Moreover, a randomized trial in Europe ($n = 612$) found that 1-year Mediterranean diet intervention enriched operational taxonomic units (OTUs) from *Eubacterium eligens*, *Roseburia hominis*, and *Anaerostipes hadrus* and decreased OTUs from *Flavonifractor plautii* and *Mogibacterium* [65]. Despite these similarities, the relationship of diet quality with the gut microbiome may differ in US Hispanic/Latinos. For example, previous studies identified a strong association of better diet quality with an increased abundance of *Faecalibacterium prausnitzii* and a decreased abundance of *Clostridium* species, which we did not observe here. Although carriage of *Faecalibacterium prausnitzii* in our study was 100%, the average relative abundance was low (1.84%) compared with other populations [66]. Unique components of US Hispanic/Latino diets [44, 67] or gut microbiomes [38], genetic background, and high prevalence of metabolic disease could contribute to inconsistencies with other studies. Previous research has shown that although food and nutrient intakes differ between US Hispanic/Latino subgroups [44], US Hispanics/Latinos, on average, have higher diet quality according to the aMED, HEI-2015, and hPDI, compared with US non-Hispanic Whites and non-Hispanic Blacks [10, 67, 68]. However, higher acculturation and being born in the United States are associated with poorer diet quality among US Hispanics/Latinos [67,69,70]. Interestingly, we found that *Acidaminococcus intestini* and *Megasphaera massiliensis* were related to poorer diet quality, and these genera were related to longer exposure to the United States in our previous HCHS/SOL analysis [38], suggesting that the history of relocation could underlie some diet–gut microbiome relationships in US Hispanics/Latinos.

Diet broadly influences the functional capacity of the gut microbiome, driven largely by microbial metabolism of complex plant polysaccharides [22, 24, 71]. The prominent role of healthy plant food intake in shaping the gut microbiome may explain the many similar species associations for the 3 dietary patterns because each pattern places great emphasis on minimally processed plant foods including whole grains, fruit, and vegetables. Enrichment of *Eubacterium eligens*, *Roseburia hominis*, and other Clostridia species with healthier diet patterns is likely related to their ability to ferment complex dietary fibers in plant-based foods [24]. Similarly, enrichment of the pyruvate:ferredoxin oxidoreductase pathway [72, 73] and the transport system for oligogalacturonide [74] with the aMED score may also reflect higher plant food intake and fiber fermentation. On the other hand, microbial functions associated with poorer diets may reflect a higher intake of red and processed meat (aMED, hPDI), refined grains (HEI-2015, hPDI), or sodium (HEI-2015). For example, the transport system for manganese/iron was inversely related to the aMED score

and positively correlated with red and processed meat intake, which could relate to the high concentrations of iron in meat foods. Functional pathways associated uniquely with the hPDI pattern, such as transport systems for L-arabinose/lactose and sulfate, were driven by a higher dietary intake of vegetable oils and a lower intake of dairy products. Because the hPDI was the only dietary pattern to positively rate all vegetables oils and negatively rate all animal foods, microbiome functions related uniquely to the hPDI score may be compensatory for reduced dietary availability of certain nutrients (e.g., lactose). The multitude and complexity of dietary interactions with gut microbiota [71] clearly result in shifts in gut microbiome functionality, with some consistency but also with some specificity across dietary patterns.

Our results suggest that some healthy diet enriched gut species and functions may favorably influence cardiometabolic health. The idea of a "healthy microbiome signature," related to both a healthy diet and physical health, has been purported by several studies [31, 32, 75]. Consistently, we observed a group of healthy diet-enriched species (*Anaerostipes hadrus*, *Ruminococcus lactaris*, *Lachnospiraceae bacterium TF01-11*, *Butyrivibrio crossotus*, *[Eubacterium] eligens*, and *Marvinbryantia formatexigens*) and functions (pyruvate:ferredoxin oxidoreductase) associated with favorable cardiometabolic traits. Previous studies also related *Butyrivibrio crossotus* and *[Eubacterium] eligens* with a better diet and favorable cardiometabolic health [31, 32, 76]. Some of our poorer diet-related microbial functions suggest increased susceptibility to infection, such as the adhesin protein transport system [77], KinB-AlgB regulatory system [78], adenylate cyclase [79], and succinate-semialdehyde dehydrogenase [80]. Unexpectedly, poorer diet-related *Flavonifractor plautii* was associated with favorable glycemic and body weight traits, whereas some healthy diet-enriched species (e.g., *Roseburia hominis*) were associated with lower HDL cholesterol. Microbial functional pathways related uniquely to the hPDI score were associated with higher BMI and HOMA-IR, possibly suggesting that the hPDI pattern does not promote an optimal gut microbiome for cardiometabolic health.

This study was strengthened by large sample size, comprehensive participant data allowing for the control of confounders, and the diverse US Hispanic/Latino population, complementing studies in other racial/ethnic groups. Our study was limited by its cross-sectional design, precluding the temporal analysis of diet, gut microbiome, and disease risk, and possibly limited in generalizability to other racial/ethnic groups. Our analysis was exploratory, by using lenient significance thresholds to minimize false negatives and facilitate comparison across dietary patterns. Dietary assessment was performed ≈6 years before stool sample collection; hence, the changes over time in diet may have diluted or obscured associations. The 24-hour dietary recall method may not capture the long-term diet or rarer foods. However, dietary patterns, at least those measured by the food frequency questionnaire [81], and the gut microbiome [82] exhibit a level of stability over years. Our replication of multiple diet pattern-associated species from other large studies supports that the diet measures used here captured sufficient long-term dietary patterns, at least to the extent that we could observe expected relationships with the gut microbiome.

In conclusion, healthy dietary patterns in US Hispanics/Latinos are associated with enrichment of fiber-fermenting gut Clostridia species, replicating findings from other large study populations. Interestingly, *Faecalibacterium prausnitzii*, associated with good diet quality in numerous studies across different populations [31–34, 64, 76], was not associated with diet quality here—underlining the importance of replication in diverse populations when searching for common signatures. Our study contributes to a large body of evidence indicating that healthy diets, consisting of whole grains, fruit, and vegetables, modulate the gut microbiome to promote optimal host health. Gut species such as *[Eubacterium] eligens* and *Butyrivibrio crossotus*, repeatedly associated with healthy diets and better overall health status in large studies from different geographic and racial/ethnic contexts, should be further probed for universal mechanisms and utility in potential health-promoting interventions. Although a healthy diet is inarguably important for the prevention of cardiometabolic diseases, therapeutic modulation of the gut microbiome in concert with dietary changes may further improve cardiometabolic health.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2022.11.020.

Conflict of Interest Statement

The authors declare no conflicts of interest.

Author Contributions

Designed research: QQ, FBH; collected the samples and data: RCK, RDB; performed microbiome sequencing: RK; performed microbiome bioinformatics: MU; conducted the data analysis: JX; wrote the manuscript: BAP; revised the manuscript critically for intellectual

content: ZW, GC, BT, ACC, MLD, and DS. All authors read and approved the final manuscript.

Data Availability

HCHS/SOL data are archived at the National Institutes of Health repositories dbGap and BIOLINCC. Sequence data from the samples described in this study is deposited in QIITA (study ID 11666). HCHS/SOL has established a process for the scientific community to apply for access to participant data and materials, with such requests reviewed by the project's Steering Committee. These policies are described at https://sites.cscc.unc.edu/hchs/.

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