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Association between Residential Greenness and Human Microbiota: Evidence from Multiple Countries

Yi-Dan Zhang,[1] Shu-Jun Fan,[2,3*] Zheng Zhang,[4] Jia-Xin Li,[1] Xiao-Xuan Liu,[1] Li-Xin Hu,[5] Luke D. Knibbs,[6] Payam Dadvand,[7,8,9] Bin Jalaludin,[10] Matthew H.E.M. Browning,[11] Tianyu Zhao,[12,13,14,15] Joachim Heinrich,[16,17] Zhini He,[18] Cheng-Zhi Chen,[19] Yuanzhong Zhou,[20] Guang-Hui Dong,[1] and Bo-Yi Yang[1]*

[1]Guangdong Provincial Engineering Technology Research Center of Environmental Pollution and Health Risk Assessment, Department of Occupational and Environmental Health, School of Public Health, Sun Yat-sen University, Guangzhou, China
[2]Department of Environmental Health, Guangzhou Center for Disease Control and Prevention, Guangzhou, China
[3]Institute of Public Health, Guangzhou Medical University and Guangzhou Center for Disease Control and Prevention, Guangzhou, China
[4]Department of Central Laboratory, Beijing Obstetrics and Gynecology Hospital, Capital Medical University, Beijing Maternal and Child Health Care Hospital, Beijing, China
[5]Department of Maternal and Child Health, School of Public Health, Sun Yat-sen University, Guangzhou, China
[6]School of Public Health, University of Sydney, Camperdown, New South Wales, Australia
[7]ISGlobal, Barcelona, Spain
[8]Universitat Pompeu Fabra, Barcelona, Spain
[9]CIBER Epidemiología y Salud Pública, Madrid, Spain
[10]School of Population Health, University of New South Wales, Kensington, New South Wales, Australia
[11]Department of Park, Recreation, and Tourism Management, Clemson University, Clemson, South Carolina, USA
[12]Institute and Clinic for Occupational, Social and Environmental Medicine, Hospital of the Ludwig-Maximilians-Universität München (LMU Munich), Munich, Germany
[13]Comprehensive Pneumology Center Munich, LMU Munich, Munich, Germany
[14]German Center for Lung Research, Justus Liebig University Giessen, Giessen, Germany
[15]Institute of Epidemiology, Helmholtz Zentrum München–German Research Center for Environmental Health, Neuherberg, Germany
[16]Institute and Clinic for Occupational, Social and Environmental Medicine, LMU Munich, Munich, Germany
[17]Allergy and Lung Health Unit, Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Victoria, Australia
[18]Food Safety and Health Research Center, Guangdong Provincial Key Laboratory of Tropical Disease Research, School of Public Health, Southern Medical University, Guangzhou, China
[19]School of Public Health and Management, Research Center for Medicine and Social Development, Innovation Center for Social Risk Governance in Health, Chongqing Medical University, Chongqing, China
[20]Department of Epidemiology, School of Public Health, Zunyi Medical University, Zunyi, China

Background: Greenness, referring to a measurement of the density of vegetated land (e.g., gardens, parks, grasslands), has been linked with many human health outcomes. However, the evidence on greenness exposure and human microbiota remains limited, inconclusive, drawn from specific regions, and based on only modest sample size.

Objectives: We aimed to study the association between greenness exposure and human microbial diversity and composition in a large sample across 34 countries and regions.

Methods: We explored associations between residential greenness and human microbial alpha-diversity, composition, and genus abundance using data from 34 countries. Greenness exposure was assessed using the normalized difference vegetation index and the enhanced vegetation index mean values in the month before sampling. We used linear regression models to estimate the association between greenness and microbial alpha-diversity and tested the effect modification of age, sex, climate zone, and pet ownership of participants. Differences in microbial composition were tested by permutational multivariate analysis of variance based on Bray–Curtis distance and differential taxa were detected using the DESeq2 R package between two greenness exposure groups split by median values of greenness.

Results: We found that higher greenness was significantly associated with greater richness levels in the palm and gut microbiota but decreased evenness in the gut microbiota. Pet ownership and climate zone modified some associations between greenness and alpha-diversity. Palm and gut microbial composition at the genus level also varied by greenness. Higher abundances of the genera *Lactobacillus* and *Bifidobacterium*, and lower abundances of the genera *Anaerotruncus* and *Streptococcus*, were observed in people with higher greenness levels.

Discussion: These findings suggest that residential greenness was associated with microbial richness and composition in the human skin and gut samples, collected across different geographic contexts. Future studies may validate the observed associations and determine whether they correspond to improvements in human health. https://doi.org/10.1289/EHP12186

Introduction

Greenspaces—such as parks, forests, and gardens—are critical components of the human living environment. As stated in the biophilia hypothesis, human beings have an innate tendency to commune with nature.[1] Rapid urbanization has greatly disrupted natural vegetation cover and poses challenges to provide people with sufficient access to the natural environment.[2] Consequently, potential associations between greenspace and human health have

*These authors contributed equally to this work.
Address Correspondence to Bo-Yi Yang, Guangdong Provincial Engineering Technology Research Center of Environmental Pollution and Health Risk Assessment, Department of Occupational and Environmental Health, School of Public Health, Sun Yat-sen University, 74 Zhongshan 2nd Rd., Yuexiu District, Guangzhou 510080, China. Email: yangby23@mail.sysu.edu.cn. And, Guang-Hui Dong, Guangdong Provincial Engineering Technology Research Center of Environmental Pollution and Health Risk Assessment, Department of Occupational and Environmental Health, School of Public Health, Sun Yat-sen University, 74 Zhongshan 2nd Rd., Yuexiu District, Guangzhou 510080, China. Email: donggh5@mail.sysu.edu.cn.

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attracted increasing scientific attention. Hundreds of studies have examined greenspaces' health effects, and the evidence generally supports beneficial associations between exposure and health outcomes (e.g., lower risk of metabolic syndrome, mental disease).[3] The mechanisms underlying the greenspace–health relationship are somewhat unclear, but several hypotheses exist. These include reducing exposure to environmental hazards (e.g., air pollution, noise, heat, artificial light at night), encouraging physical activity, reducing mental stress, and enhancing social cohesion.[4] The biodiversity hypothesis postulates that contact with organisms in the natural environment can enrich the human microbiota, promote immune regulation, and protect from inflammatory disorders and immune disease.[5] Thus, microbiodiversity, may be a novel pathway by which greenspace exposure benefits human health.

The human microbiota, including the gut, oral, and skin bacteria, play a critical role in human health through their roles in digestive, metabolic, and immune processes. The diversity of skin and gut microbiota is essential for "training" the immune system.[6] Meanwhile, the by-products of the gut microbiota, such as butyrate, are important for regulating glucose tolerance and preventing gut inflammation.[7,8] Microbial dysbiosis (loss of diversity and imbalance in the composition) is associated with various diseases, including metabolic disorders, neurological diseases, digestive symptoms, and cancers.[9] The human microbiota is affected by numerous factors, such as age, ethnicity, and environmental exposures, including greenspaces.[5,10,11] Plants can modulate the microbiome in the rhizosphere[12] and phyllosphere.[13,14] These environmental modifications may directly affect the environmental microbiota that humans inhale or ingest. In addition, greenspaces may indirectly influence microbial communities by modifying air pollution and air temperature levels, frequency and intensity of physical activity, and mental health—each of which is closely related to the human microbiota.[4]

An increasing number of epidemiological studies have examined associations between greenspace exposure and human microbial diversity and composition.[15–31] Among these, skin and gut microbiotas are the most frequently investigated. The results of the studies are mixed, especially for the gut microbiota. For example, although two cross-sectional studies in infants and adults observed that higher residential greenness levels were associated with lower diversities of gut microbiota,[15,26] a randomized controlled trial reported adding biodiverse forest floor vegetation and sod to kindergartens increased children's gut microbial diversity.[24] Further limiting the understanding of the greenspace–microbiota relationship is the relative lack of studies on the oral microbiota, which has been implicated in the development of many diseases (e.g., esophageal cancer, cardiovascular diseases) and can theoretically be affected by environmental microbes.[32] Prior studies on greenspace and the human microbiota have been limited to specific regions (e.g., Finland,[17] Canada,[26] United States[15]) and modest sample sizes (ranging from 2 to 2,443), which limit their generalizability.

To fill in these knowledge gaps, we aimed to determine whether residential greenness was associated with microbial diversity and composition in the gut, skin, and oral microbiota. Furthermore, we evaluated whether greenness exposure was associated with the abundances of specific genera. We performed these analyses using data from multiple countries in Europe, North and South America, Oceania, and Asia.[33]

Methods

Sample Collection and Processing

This analysis was based on the data from the Qiita platform, which gathers microbiome data from projects/studies conducted globally.[33] The platform has collected data from 652 projects/studies, including >460,000 samples. We selected projects or studies according to the following criteria: *a*) were observational; *b*) contained human samples; *c*) provided skin, oral, or gut microbiota data and covariates; *d*) provided participants' residential coordinates; and *e*) amplicon sequence variants (ASVs) data were 90 nt in length and processed with Deblur[34] from the 16S-V4 gene amplicon data of samples.

Based on these criteria, we included three independent projects/studies. First, the America Gut Project—a citizen scientist cohort mainly from North America, Europe, and Oceania—contained 32,196 samples from 20,625 participants.[35] Second, a repeated measures study of skin, oral, and gut microbiota contained 456 samples from 115 participants.[36] Third, a microbial survey mainly in South America contained 2,227 samples from 217 participants.[37] These three projects provided a total of 35,408 microbial samples from 20,957 participants across 66 countries (Figure 1; Table S1). We excluded 3,320 environmental or animal samples; 9,389 samples without coordinate information and collection dates; 2,538 samples without valid greenness data; 3,397 samples with sequence reads ≤10,000; 2,071 samples without valid age, sex, body mass index (BMI), and ethnicity; and 2,839 duplicated samples. Finally, a total of 9,581 participants with 610 skin samples (included 360 palm samples and 250 forehead samples), 9,219 gut samples, and 899 oral samples from 34 countries were included in our analysis. The geographic distributions of participants are shown in Figure 2.

All participants gave written informed consent before participation. Ethnical committee approval for the collection of the America Gut Project were obtained at the University of Colorado Boulder (protocol no. 12-0582; December 2012–March 2015) and the University of California, San Diego (protocol no. 141853; February 2015 to present).[35] The study protocol of the American college student study was approved by the institutional review board of the University of Colorado, Boulder (no. 409.13), Northern Arizona University (no. 12.0169), and North Carolina State University (no. 2443).[36] The microbial survey mainly in South America was approved by the institutional review board of the University of Puerto Rico (no. 112-172), Ministry of Health of Peru (no. 001-2013-CIEI/INS), and Federal University of Amazonas in Manaus, Brazil (no. 46532).[37]

Microbial Diversity and Taxonomic Composition

We obtained the preprocessed data of these three projects directly from the Qiita database. The amplicon sequences of all three projects were uniformly preprocessed following the same procedures.[35–37] Briefly, the V4 hypervariable region of the 16S rRNA gene was sequenced with the Illumina platform. The sequencing data were trimmed to 90 nt and clustered to distinct ASVs using the Deblur pipeline.[34] We performed quality control by filtering out the ASVs that appeared less than three times in the data set to remove possible outliers.

To assess microbial diversity and composition, we calculated alpha-diversity, beta-diversity, and genus abundance. The ASV data of the samples were rarified to 10,000 reads. We assessed alpha-diversity using three indexes: *a*) observed ASVs, *b*) Pielou's evenness, and *c*) Shannon index, which represent microbial richness, evenness, and a combination of them, respectively. Beta-diversity, representing the extent of change in microbial composition between individuals or populations with different characteristics, was measured using the Bray–Curtis dissimilarity and visualized with principal coordinate analysis (PCoA) plots. Samples with similar microbial composition are closer on the PCoA plots. Taxonomic assignments were based on the GREENGENES reference database (version 13.8), and abundances of taxa were

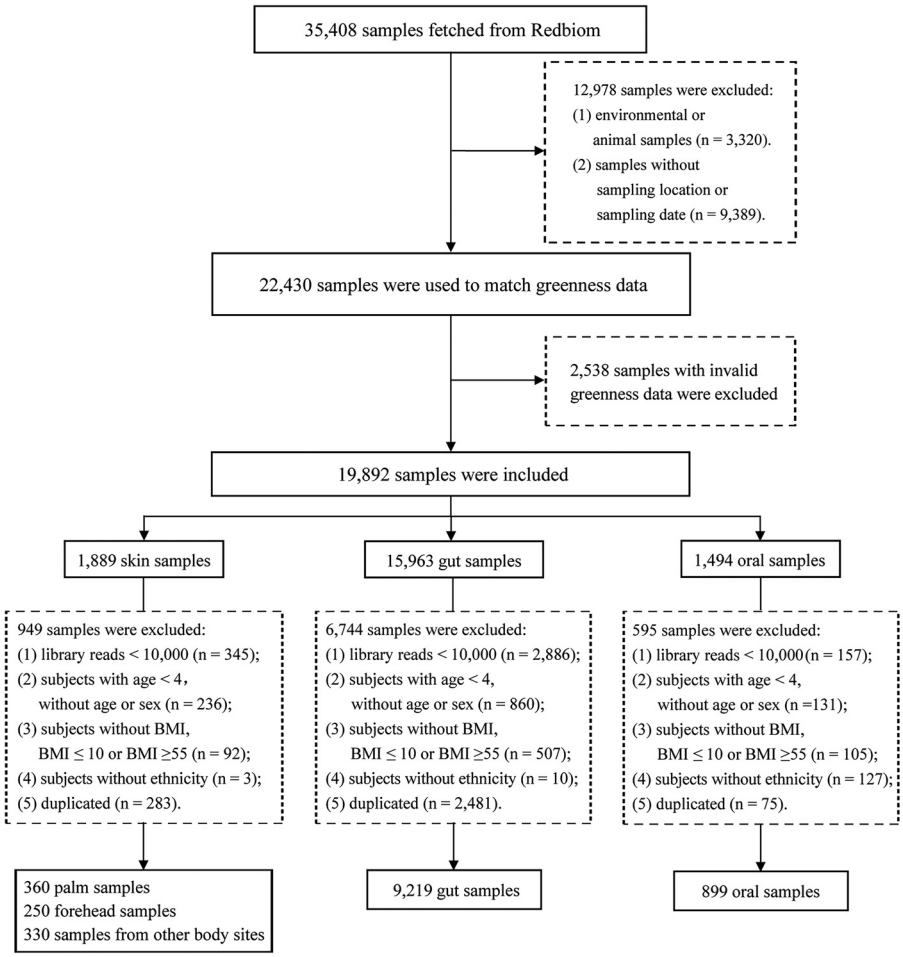


Figure 1. Flow chart of sample selection of participants from 34 countries between 2012 and 2020. The 330 samples from other body sites included 152 arm or leg samples, 148 foot samples, and 18 torso or hair samples and were not included in our analysis because the sample size of each sample type was limited and both sites of samples were mixed and unclear. Note: BMI, body mass index.

calculated from the kingdom to the genus levels. All calculations were performed in the Quantitative Insights Into Microbial Ecology 2 (QIIME2) software (2021.11 release)[38] and the vegan R package.[39]

Greenness Assessment

We estimated greenness levels using two satellite-based vegetation indices: the normalized difference vegetation index (NDVI)[40] and the enhanced vegetation index (EVI).[41] Both were derived from the Moderate Resolution Imaging Spectroradiometer (MODIS) satellite instrument, which provides precalculated NDVI and EVI products (https://modis.ornl.gov/data/modis_webservice.html). The spatial resolution is 250 m^2, and the temporal unit is every 16 d. The NDVI and the EVI are calculated based on the land surface reflectance of the electromagnetic spectrum's visible (red) and near-infrared bands. The EVI corrects for the difference in atmospheric conditions and solar incidence angles. Both indices range from −1 to 1, with higher values indicating higher vegetation levels: values close to 0 representing barren areas, and values close to −1 corresponding to water, ice, or snow. We converted all negative NDVI and EVI values to 0 (which indicates subsets of non-greenspace) so that negative values would not offset positive values in calculating areal averages.[42]

Residential greenness was estimated as the mean NDVI and EVI values within circular buffers with radii of 250, 500, and 1,000 m around the coordinates of each participant's home for the month prior to the sampling date. The 250-m radius represents greenness directly accessible outside each individual residence, whereas the 500- and 1,000-m radii represent greenness within 5- to 10- and 10- to 15-min walking distances, respectively.[43]

Covariates

The identification of confounders was determined by the following criteria: *a*) predictor of human microbiota, *b*) related to greenness exposure, and *c*) not the effect of greenness exposure nor a mediator in the pathway between greenness exposure and human microbiota.[44] We constructed a directed acyclic graph (DAG; Figure S1) to determine a minimally sufficient set of adjustment variables to include in the regression models. The following covariates were retained in the final models: age (in years), sex (male vs. female), ethnicity (Caucasian vs. others; others included Achuar, African American, Afro, Asian or Pacific Islander, Caucasian Asian, Caucasian Hispanic, Hispanic, Hispanic Armenian, Japanese American, Japanese, and Mestizo), season of sample collection (spring vs. summer vs. fall vs. winter) and population density within a 2,500-m radius of each participant's home (≤median vs. >median). Notably, the identification of ethnicity was self-reported by participants, and we used the ethnic terms they reported in our study. Because the number of Asian or Pacific Islander, Hispanic, African American, and other ethnicities were limited, we dichotomized ethnicity into Caucasian vs. others and then used this variable in our models. Regarding population

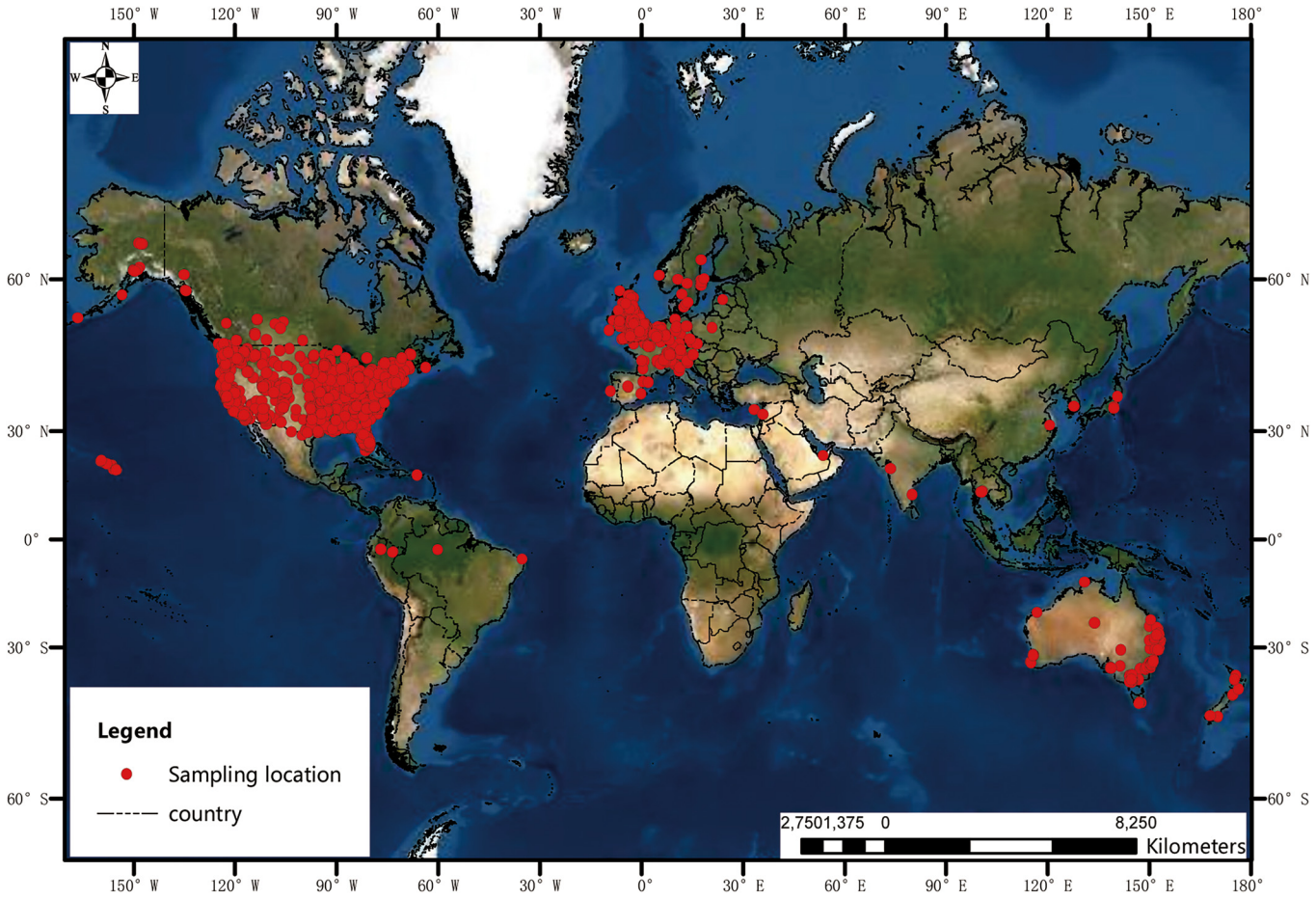


Figure 2. World map showing sampling locations (including 34 countries between 2012–2020). Base map data were obtained from ArcMap (version 10.4; Esri), Esri, Maxar, GeoEye, Earthstar Geographics, CNES/Airbus DS, USDA, USGS, AeroGRID, IGN, and the GIS User Community.

density, we obtained annual average population data from between 2012 and 2020 from the LandScan website (https://landscan.ornl.gov/). We calculated the mean population density in a 2,500-m radius around each residential location (approximately equal to the median size of a U.S. Census tract) in the sampling year. The population density was split by its median value and incorporated into the models as a dichotomous variable.

Statistical Analysis

Descriptive characteristics were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR) for continuous variables and as frequencies with percentages for categorical variables. Pair-wise correlations between the NDVI and the EVI were examined with Pearson coefficients.

We employed linear regression models to evaluate the associations between greenness and alpha-diversity indices (i.e., observed ASVs, Pielou's evenness, and Shannon index). We fitted crude models and models adjusted for covariates selected from the DAG. Main models used the NDVI and the EVI in 500-m buffers, representing distances reachable in 5–10 min of walking. Effect estimates were expressed as β and the corresponding 95% confidence interval (CI) per 0.1-unit increase in NDVI and EVI.

We also evaluated the associations between greenness exposure and human microbial composition with permutational multivariate analysis of variance (PERMANOVA) based on PCoA analysis and Bray–Curtis dissimilarity. Given that beta-diversity represent the extent of change in microbial composition between two samples, we divided the samples from each body site into two groups based on whether they were above or below the NDVI and EVI median values of samples from each body site (i.e., high vs. low greenness). We compared microbial composition between these groups at the genus level (representing the maximum resolution achieved by 16S rRNA gene amplicon sequencing technique) and the ASV level (representing the overall microbial composition), using the adonis function in the vegan R package.[39] Adonis R^2 of PERMANOVA was calculated to assess how much of the difference in microbiota composition between the groups could be attributed to differences in greenness levels. The results generated by PERMANOVA tests determined the dissimilarity of the centroids and difference of samples' dispersion in each group. Therefore, to see whether the difference between groups was caused only by the dissimilarity of centroids, we also tested the homogeneity of dispersion between groups using the beta.dispers function in the vegan R package.[39]

We further assessed differences in the abundance of bacterial genera between high- and low-level greenness groups using the DESeq2 R package.[45] Genera with a mean relative abundance of <0.01% or prevalence of <10% were filtered out owing to the limited performance of the DESeq2 package with low-abundant taxon with relatively high variance. The "log2FoldChange" values were computed for each genus and represented the $\log_2$ of the ratio between the means of the abundances in each group. *p*-Values for differences in abundance were calculated with Wald's tests and corrected with the Benjamini–Hochberg[46] procedure to account for multiple testing. These results were visualized with the circlize R package.[47]

In addition, we explored the potential modification of the associations between $NDVI_{500m}$ and EVI_{500m} with microbial alpha-diversity by age (≤median vs. >median), sex, climate zone (north temperate zone, tropic, vs. south temperate zone; classified by the Tropic of Cancer and the Tropic of Capricorn; Table S2), and pet ownership (having dogs or cats vs. having neither a dog nor a cat at the time of sample collection in all three projects; participants missing this information were excluded). To differentiate the effect of different kinds of pets, we performed additional subgroup analyses by dividing pet ownership into three groups (i.e., dogs vs. cats vs. without a dog or a cat; participants having both dogs and cats were excluded). We fitted separate regression models for each subgroup and obtained subgroup-specific effect estimates. *p*-Values for differences of the associations between subgroups were calculated using two-sample *z*-tests (two subgroup comparisons) and analyses of variance (three subgroup comparisons), based on the point estimates and standard errors of the effect estimate in each subgroup.

To assess the robustness of our results, we performed a series of sensitivity analyses. First, we repeated the main models with 250- and 1,000-m buffers to explore whether the results were sensitive to averaging greenness in different aerial units. Second, we categorized greenness of samples from each body site into tertiles and repeated analyses (only for the alpha-diversity index), considering the possible nonlinear trend of greenness and microbial diversity. Third, we evaluated the associations between greenness and human microbial composition using the PERMANOVA test based on weighted unifrac dissimilarity. Fourth, we repeated the analyses excluding participants who used antibiotics within a month of sampling or were diagnosed with an inflammatory bowel disease or diabetes by medical professionals (i.e., doctor or physician assistant) to exclude potential antibiotic effects on microbiota. Further, we additionally and individually adjusted the main models for other predictors of microbial variations, including pet ownership (defined by "dogs" and "cats" items; modeled as a multicategorical variable: dogs vs. cats vs. both vs. no dog or cat) and BMI, given that these factors could be associated with human microbiota. Missing values of the above variables (i.e., antibiotics history, inflammatory bowel disease, diabetes, pet ownership, and BMI) were excluded from analyses. Finally, we fitted mixed models for greenness and microbial alpha-diversity by incorporating the projects from which the participant's data were collected as a random effect term to account for the potential effects of sampling sources.

All statistical analyses were completed using R (version 4.1.0; R Development Core Team). A two-tailed $p < 0.05$ was considered statistically significant.

Results

Participants' Characteristics

We included 9,581 participants from 34 countries (360 in palm samples, 250 in forehead samples, 9,219 in gut samples, and 899 in oral samples) (Figure 1). The mean ± SD age was 30.5 ± 17.7, 37.7 ± 18.2, 46.4 ± 17.3, and 41.56 ± 19.3 y in the palm, forehead, gut, and oral samples, respectively (Table 1). Across these four samples, 43%–51% were males, 52%–88% were Caucasian, 37%–71% had a college degree or higher level of education, and 54%–88% were from North America. Other regions with larger samples included western Europe and southwestern Australia (Figure 2). In addition, we observed that the distribution of the basic characteristics was similar between the participants included in our analysis and those in the total sample of the three projects, with the exception that our analysis included more participants from North America (Table S1).

The median (IQR) for $NDVI_{500m}$ was ∼0.4 (0.2) and the median (IQR) for EVI_{500m} was ∼0.3 (0.2) (Table 2). However, the ranges for $NDVI_{500m}$ and EVI_{500m} across samples were 0.0–0.9 and 0.0–0.8, respectively. The NDVI and the EVI in different buffers were highly correlated with r_s ranging from 0.83 to 0.97 (Table S3).

Greenness and Microbial Alpha-Diversity

Significant associations were observed between greenness and microbial alpha-diversity, but the direction and magnitude of the associations differed between samples and indices (Table 3; Table S4). $NDVI_{500m}$ and EVI_{500m} were associated with increased observed ASVs in palm and gut samples [e.g., for $NDVI_{500m}$ in palm samples: $\beta = 262.5$ (95% CI: 85.99, 438.99), $p = 0.0037$] but not in forehead and oral samples. $NDVI_{500m}$ and EVI_{500m} levels were also associated with decreased Pielou's evenness levels in gut samples [for EVI_{500m}: $\beta = -0.02$ (95% CI: −0.04, 0.00), $p = 0.024$] but not in other samples. Greenness was not associated with the Shannon index in any sample.

Greenness and Microbial Composition

Significant differences at the genus and ASV levels were observed between the two greenness groups (low vs. high) in the palm ($NDVI_{500m}$: $F = 4.0$, $p = 0.002$, $R^2 = 0.001$) and gut microbiota ($NDVI_{500m}$: $F = 4.0$, $p = 0.001$, $R^2 = 0.0004$) (Figure 3; Excel Table S1 and Figure S2). These associations were generally confirmed by further heterogeneity tests for variance at the genus level, but not at the ASV level. Oral microbiota beta-diversity also differed between the two greenness groups ($NDVI_{500m}$: $F = 6.3$, $p = 0.001$, $R^2 = 0.006$), but the heterogeneity tests did not confirm the variance in oral microbial composition between the greenness groups. We did not detect differences in microbial composition between the two greenness groups in the forehead sample.

Greenness and Microbiota Taxonomy

There were significant differences in genus abundance of palm, forehead, gut, and oral microbiota between greenness groups (Figure 4; Excel Table S2). Greater abundances of several genera, including potential beneficial members, were observed in the high-greenness groups, such as *Lactobacillus* [$\log_2$-fold change (LFC) = 2.29, $p = 0.001$] and *Oscillospira* (LFC = 2.06, $p = 0.035$) in the palm samples, as well as *Bifidobacterium* (LFC = 0.33, $p < 0.0001$) in the gut samples. Smaller abundances of some genera that might contain pathogenic species were also observed in the high-greenness groups, such as *Holdemania*[20] (LFC = −0.17, $p = 0.004$), *Anaerotruncus*[48] (LFC = −0.37, $p = 0.0006$), and *Streptococcus*[49] (LFC = −0.24, $p = 0.0002$) in the gut samples. In the palm samples, the abundance of several genera that are commonly found in the natural environment [i.e., *Actinomycetospora*[50] (LFC = 2.41, $p < 0.0001$), *Brachybacterium*[51] (LFC = 2.72, $p < 0.0001$), and *Dietzia*[52] (LFC = 2.60, $p = 0.0002$)] were observed in the high-greenness group.

Stratified Analyses

Associations between greenness and alpha-diversity varied by pet ownership and climate zone (Table 4; Tables S5 and S6). For example, in the palm sample, regressing observed ASVs on $NDVI_{500m}$ showed that associations between greenness and observed ASVs was not significant for participants with dogs or cats, whereas for participants with no dog or cat, the association was significant ($p_{Difference} < 0.001$). Similar effect modifications by pet ownership were observed with the Shannon index. When we further divided the participants into three new groups (dogs

Table 1. Characteristics of the participants from 34 countries between 2012 and 2020 (palm samples, $n = 360$; forehead samples, $n = 250$; gut samples, $n = 9{,}219$; and oral samples, $n = 899$).

	Participants			
Characteristics	Palm samples	Forehead samples	Gut samples	Oral samples
Age [y (mean ± SD)]	30.49 ± 17.70	37.74 ± 18.22	46.35 ± 17.30	41.56 ± 19.30
Sex [*n* (%)]				
Male	160 (44.4)	127 (50.8)	4,250 (46.1)	386 (42.9)
Female	200 (55.6)	123 (49.2)	4,969 (53.9)	513 (57.1)
Country [*n* (%)]				
United States	192 (53.3)	218 (87.2)	6,720 (72.9)	604 (67.2)
United Kingdom	4 (1.1)	17 (6.8)	1,758 (19.1)	85 (9.5)
Other[a]	164 (45.6)	15 (6.0)	741 (8.0)	210 (23.4)
Continent [*n* (%)]				
North America	196 (54.4)	220 (88.0)	6,810 (73.9)	614 (68.3)
Europe	7 (1.9)	27 (10.8)	2,007 (21.8)	107 (11.9)
South America	157 (43.6)	0 (0.0)	132 (1.4)	155 (17.2)
Oceania	0 (0.0)	3 (1.2)	259 (2.8)	23 (2.6)
Asia	0 (0.0)	0 (0.0)	11 (0.1)	0 (0.0)
Ethnicity [*n* (%)]				
Caucasian	188 (52.2)	215 (86.0)	8,083 (87.7)	664 (73.9)
Other[b]	172 (47.8)	35 (14.0)	1,136 (12.3)	235 (26.1)
BMI [kg/m^2 (mean ± SD)]	23.35 ± 5.11	24.03 ± 5.02	24.08 ± 4.93	24.06 ± 5.22
Collection season [*n* (%)]				
Spring	59 (16.4)	64 (25.6)	2,535 (27.5)	216 (24.0)
Summer	64 (17.8)	43 (17.2)	2,348 (25.5)	207 (23.0)
Fall	18 (5.0)	24 (9.6)	1,885 (20.4)	122 (13.6)
Winter	219 (60.8)	119 (47.6)	2,451 (26.6)	354 (39.4)
Population density ($persons/km^2$) [median (IQR)][c]	2,059.6 (3,791.6)	1,448.3 (2,867.1)	843.5 (2,157.0)	1,090.0 (3,695.0)
Education level [*n* (%)]				
≥College	132 (100.0)	170 (98.9)	6,558 (92.8)	480 (93.9)
≤High school	0 (0.0)	4 (1.1)	508 (7.2)	31 (6.1)
Missing	228	76	2,153	388
Pet ownership [*n* (%)]				
Only have dogs	76 (21.1)	53 (21.2)	2,075 (22.5)	201 (22.4)
Only have cats	28 (7.8)	37 (14.8)	1,641 (17.8)	127 (14.2)
Both have dogs and cats	44 (12.3)	21 (8.4)	871 (9.5)	86 (9.6)
Have neither a dog nor a cat	211 (58.8)	139 (55.6)	4,622 (50.2)	483 (53.8)
Missing	1	0	10	2
Antibiotic history [*n* (%)]				
<1 month	24 (6.8)	17 (7.0)	506 (6.0)	67 (8.4)
>1 month	332 (93.2)	227 (93.0)	8,624 (94.0)	825 (91.6)
Missing	4	6	89	7
IBD [*n* (%)]				
Yes	5 (2.5)	7 (2.9)	387 (4.4)	29 (3.2)
No	196 (97.5)	231 (97.1)	8,352 (95.6)	687 (95.9)
Missing	159	12	480	183
Diabetes [*n* (%)]				
Yes	3 (1.5)	8 (3.3)	211 (2.4)	11 (1.5)
No	197 (98.5)	233 (96.7)	8,736 (97.6)	721 (98.5)
Missing	160	9	272	167
Shannon index (mean ± SD)	5.24 ± 1.26	4.09 ± 1.25	3.17 ± 0.92	3.17 ± 0.92
Pielou's evenness (mean ± SD)	0.62 ± 0.11	0.52 ± 0.13	0.53 ± 0.13	0.52 ± 0.13
Observed ASVs (mean ± SD)	398.21 ± 281.64	247.33 ± 152.49	70.07 ± 34.69	70.09 ± 34.77

Note: ASV, amplicon sequence variant; BMI, body mass index; IBD, inflammatory bowel disease; IQR, interquartile range; SD, standard deviation.
[a]Detailed information on "other" countries is provided in Table S17.
[b]Detailed information on "other" ethnicities is provided in Table S18.
[c]Population density within a 2,500-m radius around each participant's home.

vs. cats vs. without a dog or a cat), the results were similar in that significant associations of $NDVI_{500m}$ and EVI_{500m} with observed ASVs in palm samples were observed in participants without a dog or a cat but not in those owning dogs or cats ($p_{Difference}$ was 0.004 and 0.014, respectively; Tables S7–S10). In addition, the association between greenness and microbiota were not significantly different between participants owning dogs and those owning cats (Tables S7–S10). The associations of greenness with observed ASVs were also stronger for the gut microbiota of participants in tropical than in temperate zones ($p < 0.001$ for both). We did not observe significant effect modifications by age and sex.

Sensitivity Analyses

We found similar results when repeating analyses of greenness and alpha-diversity (Table S11), beta-diversity (Figures S3–S6, Excel Table S1), and genus abundance (Figures S7 and S8, Excel Tables S3 and S4) using NDVI and EVI within 250- and 1,000-m greenness buffers. When greenness indices were categorized as tertiles, we found trends similar to those of the main models. Participants in the third tertile of greenness level had significantly higher observed ASVs than those in the first tertial (Tables S12 and S13). When we repeated the beta-diversity analyses using weighted unifrac dissimilarity, we found results similar to those using the Bray–Curtis dissimilarity, with the

Table 2. Descriptive statistics of greenness levels among participants from 34 countries between 2012 and 2020 (palm samples, $n = 360$; forehead samples, $n = 250$; gut samples, $n = 9{,}219$; and oral samples, $n = 899$).

Greenness index	mean ± SD	Median (IQR)	P_{25}	P_{75}	Minimum	Maximum
Palm samples						
$NDVI_{250m}$	0.42 ± 0.23	0.35 (0.44)	0.21	0.65	0.00	0.88
$NDVI_{500m}$	0.47 ± 0.24	0.41 (0.35)	0.28	0.63	0.00	0.90
$NDVI_{1,000m}$	0.43 ± 0.24	0.28 (0.35)	0.26	0.61	0.08	0.85
EVI_{250m}	0.24 ± 0.15	0.19 (0.29)	0.12	0.41	0.00	0.65
EVI_{500m}	0.31 ± 0.18	0.27 (0.24)	0.16	0.40	0.00	0.67
$EVI_{1,000m}$	0.26 ± 0.16	0.18 (0.25)	0.14	0.39	0.03	0.63
Forehead samples						
$NDVI_{250m}$	0.41 ± 0.20	0.43 (0.26)	0.25	0.51	0.00	0.90
$NDVI_{500m}$	0.44 ± 0.21	0.44 (0.28)	0.28	0.56	0.00	0.91
$NDVI_{1,000m}$	0.39 ± 0.20	0.32 (0.25)	0.26	0.51	0.01	0.91
EVI_{250m}	0.23 ± 0.15	0.19 (0.18)	0.11	0.29	0.00	0.73
EVI_{500m}	0.27 ± 0.14	0.27 (0.17)	0.16	0.33	0.00	0.76
$EVI_{1,000m}$	0.22 ± 0.14	0.17 (0.18)	0.12	0.30	0.01	0.76
Gut samples						
$NDVI_{250m}$	0.46 ± 0.22	0.46 (0.34)	0.29	0.63	0.00	0.97
$NDVI_{500m}$	0.48 ± 0.22	0.48 (0.33)	0.32	0.65	0.00	0.94
$NDVI_{1,000m}$	0.46 ± 0.20	0.45 (0.30)	0.31	0.61	0.00	0.91
EVI_{250m}	0.27 ± 0.15	0.24 (0.22)	0.15	0.37	0.00	0.84
EVI_{500m}	0.30 ± 0.16	0.27 (0.22)	0.18	0.40	0.00	0.85
$EVI_{1,000m}$	0.27 ± 0.14	0.24 (0.19)	0.17	0.36	0.00	0.76
Oral samples						
$NDVI_{250m}$	0.44 ± 0.23	0.44 (0.40)	0.23	0.63	0.00	0.90
$NDVI_{500m}$	0.48 ± 0.23	0.47 (0.38)	0.28	0.66	0.00	0.94
$NDVI_{1,000m}$	0.44 ± 0.22	0.41 (0.35)	0.26	0.61	0.00	0.89
EVI_{250m}	0.26 ± 0.15	0.23 (0.24)	0.13	0.37	0.00	0.81
EVI_{500m}	0.30 ± 0.17	0.27 (0.23)	0.16	0.39	0.00	0.77
$EVI_{1,000m}$	0.26 ± 0.15	0.23 (0.21)	0.15	0.36	0.00	0.73

Note: EVI, enhanced vegetation index; IQR, interquartile range; NDVI, normalized difference vegetation index; P_{25}, 25th percentile; P_{75}, 75th percentile; SD, standard deviation.

only exception being that significant association between greenness and beta-diversity of palm microbiota disappeared (Figure S9, Excel Table S5). After excluding participants who used antibiotics in the previous month, were diagnosed with an inflammatory bowel disease or diabetes, or after adjusting models for other predictors of microbiota (i.e., BMI and pet ownership), results were generally consistent with those of the main analyses (Tables S14 and S15, Figures S10–S13, Excel Tables S6–S9). Including which project the data were retrieved from as a random effect term did not change the overall associations between greenness and microbial alpha-diversity (Table S14).

Discussion

We explored associations of residential greenness with the diversity and composition of the human microbiota in a 34-country sample. Residential greenness was associated with microbial alpha-diversity, although associations depended on body site and alpha-diversity indices. Pet ownership and climate zone modified some of the associations between greenness and alpha-diversity. Greenness was also associated with microbial composition on the palm and in the gut. Moreover, higher abundances of the genera *Lactobacillus*, *Bifidobacterium*, and *Actinomycetospora* and lower abundances of the genera *Anaerotruncus* and *Streptococcus* were observed in the groups of people with higher greenness exposure level.

Table 3. Adjusted associations between greenness indexes (NDVI and EVI within a 500-m buffer) and microbial alpha-diversity indexes (observed ASVs, Pielou's evenness, and Shannon index) among participants from 34 countries between 2012 and 2020 (palm samples, $n = 360$; forehead samples, $n = 250$; gut samples, $n = 9{,}219$; and oral samples, $n = 899$).

	Observed ASVs		Pielou's evenness		Shannon index	
Categories	β (95% CI)[a]	*p*-Value[b]	β (95% CI)[a]	*p*-Value[b]	β (95% CI)[a]	*p*-Value[b]
Palm samples[c]						
$NDVI_{500m}$	262.49 (85.99, 438.99)	0.0037	−0.04 (−0.12, 0.04)	0.36	0.20 (−0.68, 1.07)	0.66
EVI_{500m}	483.48 (261.81, 705.15)	<0.0001	−0.01 (−0.12, 0.09)	0.80	0.96 (−0.15, 2.07)	0.091
Forehead samples[c]						
$NDVI_{500m}$	8.31 (−91.60, 108.22)	0.87	0.02 (−0.07, 0.10)	0.71	−0.06 (−0.82, 0.69)	0.80
EVI_{500m}	−31.39 (−184.28, 121.50)	0.69	−0.01 (−0.14, 0.11)	0.86	−0.47 (−1.61, 0.68)	0.703
Gut samples[c]						
$NDVI_{500m}$	7.63 (1.65, 13.61)	0.012	−0.01 (−0.03, 0.00)	0.15	−0.06 (−0.19, 0.08)	0.42
EVI_{500m}	9.00 (1.23, 16.78)	0.023	−0.02 (−0.04, −0.00)	0.024	−0.14 (−0.31, 0.03)	0.12
Oral samples[c]						
$NDVI_{500m}$	8.26 (−6.61, 23.14)	0.28	0.01 (−0.04, 0.07)	0.63	0.12 (−0.27, 0.51)	0.56
EVI_{500m}	13.23 (−3.49, 29.95)	0.12	−0.01 (−0.07, 0.06)	0.83	0.03 (−0.41, 0.46)	0.91

Note: Effect estimates were scaled to 0.1-unit increments and were calculated using linear regression models. ASV, amplicon sequence variant; β, regression coefficient; CI, confidence interval; EVI, enhanced vegetation index; NDVI, normalized difference vegetation index.

[a] $\beta > 0, = 0$, and < 0 suggests increasing, no, and decreasing effects of greenness on human microbial diversity, respectively.

[b] *p*-Values were derived from linear regression analyses.

[c] Models are adjusted for age, sex, ethnicity, season of sample collection, and population density within a 2,500-m radius around each participant's home.

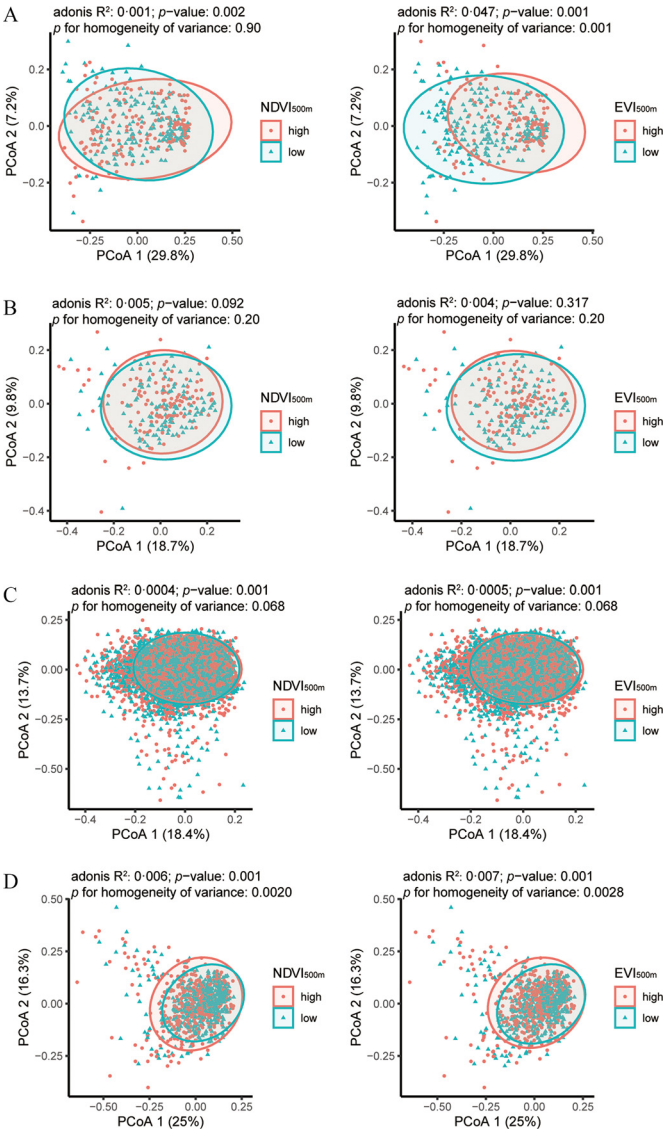


Figure 3. Differences of genus-level microbial composition between groups split by medians of $NDVI_{500m}$ and EVI_{500m}, testing by PERMANOVA with Bray–Curtis distance in (A) palm samples ($n = 360$), (B) forehead samples ($n = 250$), (C) gut samples ($n = 9{,}219$), and (D) oral samples ($n = 899$) among participants from 34 countries between 2012 and 2020. Models were adjusted for age, sex, ethnicity, season of sample collection, and population density within a 2,500-m radius of each participant's home. *p*-Values were derived from two-group PERMANOVA tests. Numeric data for this figure is available in Excel Table S1. Note: EVI, enhanced vegetation index; NDVI, normalized difference vegetation index; PCoA, principal coordinate analysis; PERMANOVA, permutational multivariate analysis of variance.

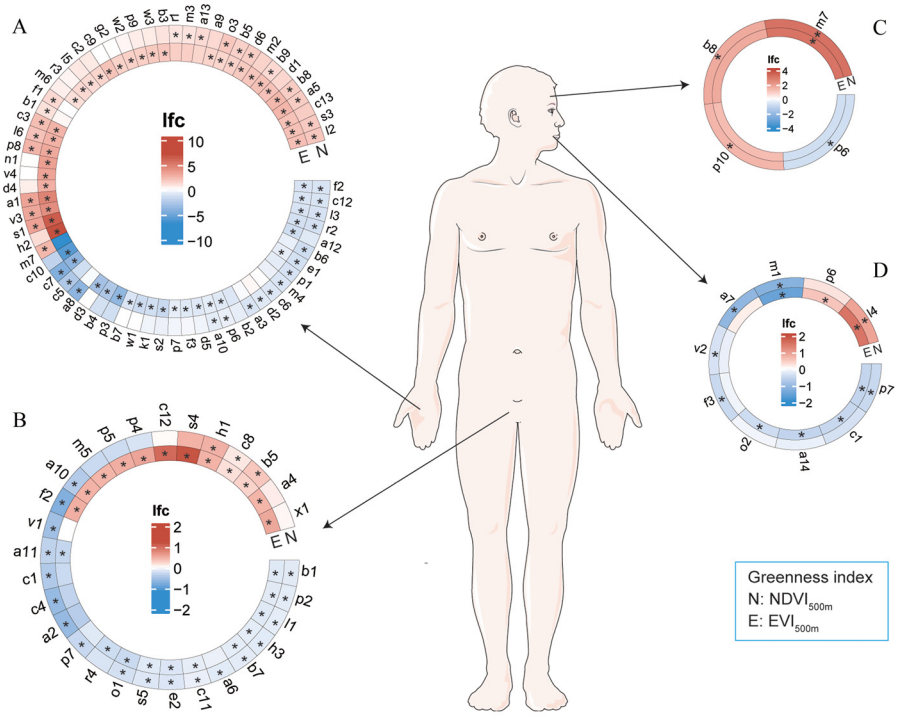
In analyses of alpha-diversity, higher greenness levels were associated with increased observed ASVs on the palm and gut samples but with decreased Pielou's evenness in the gut samples. A plausible explanation for this discrepancy is that contact with greenspace may be associated with increasing number of human microbial species and with the overgrowth of certain species,[53] which would lead to lower evenness values. Given that the Shannon index is the product of richness and evenness, the direction of its variation may be uncertain.

Three previous cross-sectional and seven experimental studies have explored associations of greenspace or greenness with human microbial alpha-diversity (Table S16). Cross-sectional studies focused on the gut ($n = 3$) or oral ($n = 1$) microbiota.[15,26,31] Among them, one study of Chinese adults found a positive association between greenness and gut microbial observed ASVs,[31] which was consistent with our findings. The other studies reported no such associations. One study of greenness and gut microbial evenness detected a significant and inverse association,[26] which was also consistent with our result, but the other study failed to find significant associations.[15] However, all three studies explored associations between greenness and Shannon index values.[15,26,31] In line with our findings, one study did not detect associations between greenness and the gut microbial Shannon index.[15] A study in Chinese adults found a positive association between residential surrounding greenness, measured by NDVI, and the Shannon index of gut microbiota.[31] In contrast, Nielsen et al. found that having greenspace around the home was associated with lower gut microbial Shannon diversities in 4-month-old infants.[26] However, it is noteworthy that infants in early life generally have less outdoor exposure and cannot choose to be indoors or out. These inconsistent findings with our results might be attributable to differences in participants' characteristics (i.e., age and lifestyle) and greenness characteristics (i.e., type of plants and ecosystems).

Regarding previous experimental studies, five were conducted on the gut, six on the skin, and two on the oral microbiota.[17,23,24,27–29] These studies had small sample sizes (2–89 participants) and explored diverse interventions, including walking/playing in greenspace, supplementing a kindergarten with forest vegetation, and providing physical contact with natural materials (i.e., soil and plants). Most studies ($n = 6$) detected positive effects of nature on microbial richness (measured by observed species) or the Shannon index. It is difficult to compare our results to these experimental studies owing to our study's design, but these prior findings support our correlation analyses being the result of cause-and-effect relationships between greenness exposure and microbial diversity.

With regard to microbial beta-diversity, we observed that greenness exposure was associated with microbial composition at the genus level in the palm and gut microbiota. The R^2 of greenness indexes ranged from 0.0004 to 0.047, suggesting that the variation in microbial composition explained by greenness exposure was relatively small, and hence the biological significance of these findings was not clear. Ten prior studies have evaluated greenness exposure and microbial beta-diversity, including 5 for skin, 7 for gut, and 3 for oral microbiota (Table S16). Most indicated that greenness exposure affected the microbial composition, especially in the skin and gut samples, corroborating our findings.[17,18,23–26,28,29] However, an experimental study of 89 Finnish children found the oral microbial composition changed after a nature-based intervention in kindergartens.[24] We posit that the participants' ages led to these contrasting findings. During greenspace exposure, children are more likely to play in close contact with soil, lick dirty hands, and generally ingest soil more than adults, as suggested by previous research on children's gut microbiota better mimicking soil microbiota than that of their parents.[54]

We further observed that greenness was associated with the higher relative abundance of genera whose members have potential benefits (e.g., *Lactobacillus*, *Bifidobacterium*) or are commonly found in soil (e.g., *Actinomycetospora*, *Brachybacterium*) and lower relative abundance of genera that might contain pathogenic species (e.g., *Holdemania*, *Streptococcus*). A prepost study also showed that ∼1 h of urban greenspace exposure resulted in adults' palm microbiota becoming more similar to soil microbiota, and abundances of *Corynebacterium* and *Finegoldia*, which correlate with opportunistic infections,[55] decreased.[29] Similarly, a Dutch study reported that greenness exposure was associated with decreased abundances of the pathogenic *Anaerotruncus*, which has been associated with metabolic disorder[48] in human guts.[20] A 28-d interventional study found that inserting nature-based experiences



Genus

a1	Acetobacter	c2	Candidatus.Nitrososphaera	h1	Haemophilus	p4	Peptoniphilus
a2	Acidaminococcus	c3	Candidatus.Solibacter	h2	Halococcus	p5	ph2
a3	Actinobacillus	c4	Catenibacterium	h3	Holdemania	p6	Porphyromonas
a4	Actinomyces	c5	Chroococcidiopsis	k1	Kingella	p7	Prevotella
a5	Actinomycetospora	c6	Chryseobacterium	l1	Lachnospira	p8	Pseudonocardia
a6	Adlercreutzia	c7	Chryseomicrobium	l2	Lactobacillus	p9	Pseudoxanthomonas
a7	Aggregatibacter	c8	Clostridium	l3	Lactococcus	p10	Paracoccus
a8	Alishewanella	c9	Comamonas	l4	Lautropia	r1	Rhodoplanes
a9	Alloiococcus	c10	Conchiformibius	l5	Leptolyngbya	r2	Rubellimicrobium
a10	Anaerococcus	c11	Coprococcus	l6	Leuconostoc	r3	Rubrobacter
a11	Anaerotruncus	c12	Corynebacterium	m1	Megasphaera	r4	Ruminococcus
a12	Ardenscatena	c13	Cystobacter	m2	Methylibium	s1	Salinisphaera
a13	Arthrobacter	d1	DA101	m3	Methylobacterium	s2	Skermanella
a14	Atopobium	d2	Deinococcus	m4	Micrococcus	s3	Staphylococcus
b1	Bacteroides	d3	Dermabacter	m5	Mogibacterium	s4	Stenotrophomonas
b2	Balneimonas	d4	Dermacoccus	m6	Mycobacterium	s5	Streptococcus
b3	Bdellovibrio	d5	Dialister	m7	Mycoplasma	v1	Varibaculum
b4	Bergeyella	d6	Dietzia	n1	Nesterenkonia	v2	Veillonella
b5	Bifidobacterium	e1	Enhydrobacter	o1	Odoribacter	v3	Vibrio
b6	Blastococcus	e2	Eubacterium	o2	Oribacterium	v4	Vogesella
b7	Blautia	f1	Faecalibacterium	o3	Oscillospira	w1	WAL_1855D
b8	Brachybacterium	f2	Finegoldia	p1	Paludibacter	w2	Wautersiella
b9	Brevibacterium	f3	Fusobacterium	p2	Parabacteroides	w3	Weissella
c1	Campylobacter	g1	Gordonia	p3	Pasteurella	x1	1.68

Figure 4. Difference of genus abundance between groups split by medians of $NDVI_{500m}$ and EVI_{500m} in (A) palm samples ($n = 360$), (B) gut samples ($n = 9{,}219$), (C) forehead samples ($n = 250$), and (D) oral samples ($n = 899$) among participants from 34 countries between 2012 and 2020. Heatmaps show $\log_2$-fold changes of the higher greenness indices group vs. the lower greenness indices group. Models are adjusted for age, sex, ethnicity, season of sample collection, and population density within a 2,500-m radius around each participant's home. *p*-Values were calculated with Wald's tests and corrected with the Benjamini–Hochberg procedure. All genera that had an adjusted $p < 0.05$ were selected. Red represents a higher relative abundance in the high-greenness group, and blue represents a lower relative abundance in the high-greenness group. *, Adjusted $p < 0.05$. Numeric data for this figure is available in Excel Table S2. Note: EVI, enhanced vegetation index; lfc, $\log_2$-fold change; NDVI, normalized difference vegetation index.

into kindergartens affected children's gut microbes, particularly the family *Ruminococcaceae*, which includes butyrate-producing bacteria and is associated with the maintenance of gut health.[17] Collectively, these findings reinforce the evidence for the positive associations between greenness exposure and beneficial microbial profiles.

In stratified analyses, pet ownership modified associations between greenness and palm microbial alpha-diversity. Stronger associations were observed in participants without a dog or a cat. We cannot compare our findings with other studies given that we are unaware of literature on this topic. One possible explanation might be that the pet owners' homes contain more diverse bacterial taxa and higher levels of bacterial products brought in by their pets.[56,57] Skin microbiota might have been influenced by these complex indoor microbes, masking the modest effects of greenness. We also observed that the gut microbiota of people living in tropic zones showed significant associations of greenness with observed ASVs. Differences in plant diversity may explain this phenomenon given that plant diversity decreases with increases in latitude.[58] Thus, even with similar EVI values, tropical inhabitants may be in contact with more diverse plant microbes than temperate inhabitants. In addition, this may be due to variation in architectural and social contexts across different geographic locations. For example, buildings may have greater natural ventilation capacity in tropical areas, and windows may be open year-round.[59] These features encourage microbiota to

Table 4. Modification effect of participants' characteristics on the association between greenness index and observed ASVs among participants from 34 countries between 2012 and 2020 (palm samples, $n = 360$; forehead samples, $n = 250$; gut samples, $n = 9{,}219$; and oral samples, $n = 899$).

	Palm samples			Forehead samples			Gut samples			Oral samples		
Subgroup	n	β (95% CI)	$p_{Difference}$ Value[a]	n	β (95% CI)	$p_{Difference}$ Value[a]	n	β (95% CI)	$p_{Difference}$ Value[a]	n	β (95% CI)	$p_{Difference}$ Value[a]
$NDVI_{500m}$[b]												
Age[c]	—	—	0.64	—	—	0.74	—	—	0.70	—	—	0.33
<Median	181	391.84 (73.79, 709.89)	—	128	−11.84 (−155.29, 131.61)	—	4,428	5.66 (−3.02, 14.34)	—	460	20.45 (−0.98, 41.88)	—
≥Median	179	203.54 (−7.96, 415.04)	—	122	12.99 (−133.48, 159.46)	—	4,791	8.43 (0.08, 16.77)	—	439	−2.31 (−23.55, 18.94)	—
Sex	—	—	0.84	—	—	0.95	—	—	0.36	—	—	0.031
Male	160	285.69 (37.49, 533.88)	—	127	21.07 (−98.91, 141.05)	—	4,250	4.69 (−4.27, 13.65)	—	386	−3.46 (−26.87, 19.95)	—
Female	200	223.41 (−22.65, 469.48)	—	123	15.80 (−155.27, 186.87)	—	4,969	10.39 (2.35, 18.42)	—	513	18.77 (−0.36, 37.89)	—
Climate zone	—	—	0.16	—	—	/	—	—	<0.001	—	—	0.93
North temperate	198	15.66 (−165.99, 197.32)	—	241	1.78 (−102.45, 106.01)	—	8,789	2.55 (−3.21, 8.32)	—	716	−5.62 (−21.70, 10.45)	—
Tropic	162	432.86 (−152.74, 1,018.46)	—	3	/	—	180	172.44 (6.33, 338.56)	—	160	1.62 (−128.32, 131.56)	—
South temperate	0	/	—	6	/	—	250	37.07 (−5.86, 80.00)	—	23	−36.63 (−146.10, 72.84)	—
Dog/cat ownership	—	—	<0.001	—		0.72	—	—	0.86	—	—	0.98
No	211	431.60 (289.97, 573.23)	—	139	3.43 (−112.94, 119.80)	—	4,622	7.14 (−1.61, 15.89)	—	483	6.93 (−16.00, 29.87)	—
Yes[d]	149	24.90 (−173.30, 223.10)	—	111	−27.81 (−202.71, 147.09)	—	4,597	8.61 (0.45, 16.77)	—	416	6.67 (−12.11, 25.45)	—
EVI_{500m}[b]												
Age[c]	—	—	0.64	—	—	0.79	—	—	0.54	—	—	0.30
<Median	181	684.98 (308.27, 1,061.68)	—	128	−64.57 (−329.30, 200.16)	—	4,428	172.44 (6.33, 338.56)	—	460	35.53 (10.98, 60.08)	—
≥Median	179	354.93 (82.66, 627.21)	—	122	−31.95 (−238.55, 174.65)	—	4,791	172.44 (6.33, 338.56)	—	439	−3.36 (−26.92, 20.21)	—
Sex	—	—	0.96	—	—	0.69	—	—	0.37	—	—	0.080
Male	160	477.53 (144.38, 810.68)	—	127	6.30 (−174.08, 186.69)	—	4,250	5.33 (−6.45, 17.11)	—	386	−2.75 (−28.85, 23.34)	—
Female	200	454.06 (165.06, 743.07)	—	123	−48.92 (−319.41, 221.56)	—	4,969	12.13 (1.79, 22.47)	—	513	27.15 (5.50, 48.80)	—
Climate zone	—	—	0.17	—	—	/	—	—	<0.001	—	—	0.75
North temperate	198	149.02 (−110.85, 408.88)	—	241	−40.76 (−199.84, 118.32)	—	8,789	0.33 (−7.31, 7.96)	—	716	−7.60 (−25.30, 10.10)	—
Tropic	162	822.67 (−99.14, 1,744.48)	—	3	/	—	180	260.22 (42.70, 477.75)	—	160	−4.36 (−143.59, 134.86)	—
South temperate	0	/	—	6	/	—	250	14.46 (−23.12, 52.03)	—	23	20.32 (−166.00, 206.64)	—
Dog/cat ownership	—	—	0.47	—	—	0.70	—	—	0.88	—	—	0.77
No	211	691.42 (494.81, 888.02)	—	139	−30.08 (−215.07, 154.90)	—	4,622	10.19 (−1.29, 21.66)	—	483	14.50 (−11.40, 40.41)	—
Yes[d]	149	189.51 (−89.00, 468.01)	—	111	−81.07 (−331.22, 169.09)	—	4,597	8.38 (−2.13, 18.89)	—	416	9.27 (−11.76, 30.30)	—

Note: Effect estimates were scaled to 0.1-unit increment and were calculated using linear regression models. —, not applicable; /, not available (the sample size was too small for calculating the regression coefficient and confidence interval); ASV, amplicon sequence variant; β, regression coefficient; CI, confidence interval; EVI, enhanced vegetation index; NDVI, normalized difference vegetation index.

[a]p-Values for difference were calculated by two-sample z-tests for two subgroup comparisons and analysis of variances for three subgroup comparisons.

[b]Models are adjusted for age, sex, ethnicity, season of sample collection, and population density within a 2,500-m radius around each participant's home, except where the variable was stratified.

[c]Median value of age were 26, 32, 48, and 41 for palm, forehead, gut, and oral samples, respectively.

[d]The sum of participants who have only dogs, have only cats, and have both dogs and cats.

enter indoor environments from the surrounding greenspace more frequently,[60,61] where they can be transferred to humans. In addition, different dietary patterns between urban and rural populations in tropical zones[62] may also contribute to this association.

The exact mechanisms by which greenness affects the human microbiome is unclear, but there are a few hypotheses. First, greenspaces are likely to shape the microbiota of the surrounding environment. For example, vegetation can regulate the microbiome of the rhizosphere and phyllosphere, thereby increasing soil microbial diversity.[63] Trees and grasses may shape the air microbiome by releasing plant particles carrying microbes, secreting volatile organic compounds, and changing the microclimate that then influences airborne microbial activities.[15,64] Evidence also suggests that residential greenspace may alter the indoor dust microbiota.[65] Exposure to greenspaces thus may increase the likelihood of transferring environment-source microbes to humans via inhalation, contact, or ingestion. Second, greener areas are associated with lower levels of air pollution,[66] which can change the diversity and abundance of the human microbiota, especially in the gut.[67] It is plausible that lower ambient air pollution levels are associated with higher levels of greenness—which may explain our observed associations. Moreover, many studies have confirmed that regular physical activity can influence intestinal microbial composition and benefit gut metabolism and health.[68] Greenspaces near the home can encourage physical activity and benefit the gut. Third, greenness is associated with alleviating psychological stress,[4] which can alter gut microbiota through activating the hypothalamic–pituitary–adrenal axis.[69]

The strengths of our study include a large and population-based sample from 34 countries and diverse regions of the world. This extensive coverage improved the representativeness of our results and provided sufficient statistical power. Further, we documented that the association between greenness exposure and human microbiota exists across populations with divergent geographies, climates, vegetation types, urban contexts, sociodemographic characteristics, and lifestyles. In addition, we evaluated associations of greenspace with microbiota in different sites of the human body, providing comprehensive evidence for the hypothesized link between greenness and human microbiota.

Several limitations of our study should be noted. First, our cross-sectional data prevented us from determining causal relationships between greenness exposure and human microbiota. Second, regarding exposure assessment, although the satellite-derived vegetation indexes can quantify all greenness types in a standardized and objective way and have been reported to be a reasonable surrogate for surrounding greenness,[70] their shortcomings cannot be neglected. The NDVI has less accuracy in highly vegetated areas.[71] The EVI has been considered a modified NDVI metric with improved sensitivity to high biomass regions but, rather, the EVI is more susceptible to topographic conditions.[72] In addition, both the NDVI and the EVI are sensitive to seasons and cannot differentiate between the quality and type of vegetation, preventing us from identifying the associations between types of greenspaces and the human microbiota. Further, we assessed residential greenness within only 250- and 1,000-m radii of the home, thus, associations of residential greenspace in smaller (e.g., family gardens) and larger zones (e.g., city parks >1,000 m from the home) with human microbiota remain unclear. In addition, we considered greenness levels only around participants' homes, whereas people may also be exposed to greenspace during commuting or during recreational activities, which were not captured. Third, the method of sampling and data collection, as well as DNA extraction, differed between the three project data sources, which may have introduced variability in our analysis. Fourth, we could not control for socioeconomic status because 20%–50% of our samples were missing these data. Fifth, we included population from 34 countries, most of which were in North America and Europe and represented Western populations. This coverage could limit the generalizability of our results to other populations and geographies, such as Asian and African. A final limitation is that, we excluded participants with missing data on greenness indices and confounding factors, which may have introduced some selection bias (for the distribution of participants' characteristics before and after excluding those missing values; see Table S1).

In summary, our study suggests that residential greenness was associated with increased microbial richness and that this association varied by pet ownership and climate zone. The microbial composition and the relative abundance of several genera in humans may vary under different levels of greenness exposure. Longitudinal studies and randomized control trials across diverse regions and populations are needed to replicate and better interpret these results, as well as to uncover their downstream health effects.

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