

Original Paper

Cutaneous Bacteria in the Gut Microbiome as Biomarkers of Systemic Malodor and People Are Allergic to Me (PATM) Conditions: Insights From a Virtually Conducted Clinical Trial

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Abstract

Background: The skin is a dynamic ecosystem of microbes and the source of many chemical compounds that affect human health. Skin-microbiome interactions can cause persistent, psychosocially devastating body smell despite good hygiene. Since odor production is often transient, malodors may not be perceptible during medical examinations. Therefore, having odor complaints can be diagnosed as body dysmorphic disorder and referred for psychological evaluations. Development of simple at-home tests and virtual care programs could improve the diagnosis and management of socially debilitating malodor conditions.

Objective: The aim of this study was to assess potential effectiveness of at-home gut microbiome testing in the diagnosis and management of idiopathic body and breath odor and in people are allergic to me (PATM) syndrome.

Methods: We contacted participants of prior metabolic body odor (MEBO) and PATM studies and online support groups by email or social media. Individuals who consented to participate were mailed test kits for at-home collection of gut microbiome samples. Participants completed an online survey (specially developed for this study) addressing their symptoms and other quality-of-life indicators at baseline and after sampling. Participants collected stool samples after flare-ups or symptom improvements and mailed them to the laboratory to be processed and analyzed. We evaluated between-group differences in symptom severity, as well as symptom improvement observations for the same individuals. For differential abundance testing of microbial taxa, we performed nonparametric statistical analyses using Mann-Whitney *U* tests for unpaired samples and Wilcoxon signed rank test for paired samples.

Results: A total of 112 individuals from 21 countries consented to participate. About half the participants had been tested for the metabolic disorder trimethylaminuria, and about half of those tested were diagnosed with the disorder. The levels of bacteria previously associated with cutaneous body odor were significantly elevated in gut samples. For the combination of species from *Anaerococcus*, *Corynebacterium*, *Campylobacter*, and *Propionibacterium* genera, the differences were $P=.002$ for active (73 participants, 182 samples) versus regression or remission groups (30 participants, 51 samples); $P=.01$ for those experiencing symptoms most or all of the time (46 participants, 88 samples) versus those who had symptoms sometimes, rarely, or never (25 participants, 74 samples); and $P<.001$ for improvement of symptoms in the same individuals (22 participants, 43 sets of matched samples). Changes in microbial diversity were significant for between- but not within-participant comparisons.

Conclusions: Changes in the gut microbiome composition affect MEBO and PATM severity. In particular, an increase in intestinal bacteria producing odor when in skin flexures was associated with increased intensity of self-reported symptoms. The changes were consistent in the within-group and between-group analyses. Our findings support the feasibility of remote and decentralized clinical studies of malodor conditions. Supplementary sample collection procedures may help to meet established research quality standards.

Trial Registration: ClinicalTrials.gov NCT03582826; <http://clinicaltrials.gov/ct2/show/NCT03582826>

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KEYWORDS

microbiome; idiopathic body odor; systemic malodor; PATM; TMAU; MEBO; bromhidrosis; halitosis; body dysmorphic disorder; virtual care; decentralized clinical trials; diagnosis; management; patient-reported outcome; PRO; at-home test

Introduction

Background

The term people are allergic to me (PATM) was coined by a person who believed they were the cause of allergy-like symptoms in surrounding people (see this 2006 post reposted in the PATM support group [1] that received over 8800 responses; [Multimedia Appendix 1](#) shows a screenshot of the webpage). The condition was defined as itchy nose, throat, and eyes in people exposed to the person with PATM, manifesting as sniffing, sneezing, coughing, nose-covering, and throat-clearing behavior. PATM was picked as the name for several online support groups with hundreds of members sharing similar stories (eg, this private Facebook group with over 2100 members [2]). Our molecular diagnostic study conducted in 2009-2012 [3] concluded that PATM may be a subtype of metabolic body odor (MEBO) syndrome. MEBO is another term coined by an affected person to describe idiopathic malodor due to conditions such as trimethylaminuria (TMAU) and other as-yet uncharacterized metabolic disorders. A recent study [4] identified volatile chemicals, eye and nose irritants, toluene, and xylene emitted from the skin of a person with PATM at higher concentrations. Bacterial species recently linked to underarm malodor with sour characteristics in children and teens, *Staphylococcus epidermidis* [5], was found to be overabundant in the nasal cavity of a person with PATM [4]. With the exception of these studies, however, PATM and some cases of self-reported idiopathic malodor are viewed as a dermatological nondisease [6].

The human body can shed a variety of substances that are invisible to the naked eye and are capable of creating discomfort to people in the shedder's vicinity, depending on their olfactory and immune responses. These substances include odorant molecules stemming from an altered metabolism [7], such as high levels of ketones in diabetic ketoacidosis or buildup of urea in kidney failure. Human body odor is also produced by the microbial degradation of metabolic waste excreted from the body [8,9]. Infections caused by all types of pathogenic organisms—viruses, prokaryotes, and eukaryotes—can produce volatile compounds because of infection-fighting physiological processes in the human body, as well as shifts in the intestinal microflora [9-12]. The odor can linger long after the infection is gone. Microscopic flecks of skin and hair can also become airborne and irritate the respiratory system [13]. Skin flaking can be influenced by the composition of the skin microbiome [14]. Microorganisms are informative indicators of genetic diseases linked to malodor, as well as nongenetic malabsorption and metabolic inefficiencies [15,16].

Objective

In recent years, cutaneous microbial networks responsible for localized malodors (eg, foot [17], axilla [5,18], neck and head [5]) have been mapped by using next-generation sequencing approaches. These studies used professional assessors to rate

odor intensity, and were limited geographically and by numbers of study participants (30 or fewer). This patient-centric study was, to our knowledge, the largest fully virtual microbiome investigation of idiopathic body odor that was open to all of those affected who were interested in participating. Our objective was to assess the potential effectiveness of at-home gut microbiome testing in the diagnosis and management of idiopathic body and breath odor and in PATM syndrome.

Methods

Design

The experimental design of this study and the format of the paper follow the Consolidated Standards of Reporting Trials statement for reporting randomized controlled trials and the Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth (CONSORT-EHEALTH) checklist [19]. See [Multimedia Appendix 2](#) for CONSORT-EHEALTH checklist (V 1.6.1). The trial was registered at ClinicalTrials.gov (no. NCT03582826).

Recruitment

We recruited participants from previous studies (eg, [3,20]), via social media and clinicaltrials.gov (#NCT03582826). Study participants provided electronic informed consent after they were given a complete description of the study, as described in the protocol [21], approved by MEBO Research (Miami, FL, USA) Institutional Review Board on May 11, 2018. Study information and questionnaires were provided in English and Spanish. This research was conducted according to the guidelines established by the Declaration of Helsinki and the International Ethical Guidelines for Biomedical Research Involving Human Subjects. Participants did not receive any incentives.

Data Collection

Individuals who consented to participate were mailed 3 gut microbiome sampling kits to the address they provided when enrolling. Sampling kits contained 2 sterile polyester swabs, sterile water to prewet the swabs, 2 tubes containing zirconia beads and a lysis and stabilization buffer [22], and sampling instructions (see [Multimedia Appendix 1](#)).

Participants completed an online survey (specially developed for this study) addressing their symptoms and other quality-of-life (QoL) indicators at baseline and after sampling. The QoL questionnaire was an open voluntary survey that did not collect personally identifiable information. The survey asked for unique identifiers so the study coordinator could link the data to a prior medical history protected from unauthorized access. The survey also asked for the sample kit ID associated with answers to the survey. Kits were distributed in such a way that researchers from sequence processing facilities did not have access to medical histories and identities of participants. The study coordinator had access to the identifiable information and

linked medical histories with test results and answers to the QoL questionnaire.

We assessed MEBO and PATM symptoms in several ways: whether the person thought their condition was in an active state versus regression or remission (asked at the time of enrollment and when collecting a sample), by frequency of symptoms (answering the question “Have you [or your trust buddy] detected any MEBO/PATM symptoms in the past 24 hours or past few days?” on 5-point Likert scale), symptom detection distance (10-point scale), and symptom duration. We added questions assessing the severity of symptoms via related behavior, psychological symptoms (anxiety, stress, depression), social (negative) interactions, physical health, and medical comorbidities to measure internal consistency. We developed the QoL survey in January 2018 and made a few minor iterations incorporating community feedback. We administered the System Usability Scale to a few selected volunteers and found the questionnaire to be acceptable for fielding. Qualitative feedback from participants was continuously obtained through emails and private support groups. A professional health psychologist offered participants personalized behavioral intervention solutions for a wide variety of their mental health needs.

The study’s primary outcome was relative abundance of bacterial classes as measured by operational taxonomic units (OTUs). We categorized these data as active versus regression and remission disease states. Secondary outcomes focused on changes in fecal gut microbiota with symptom improvement.

We used the Strengthening the Reporting of Observational Studies in Epidemiology guidelines and Checklist for Reporting Results of Internet E-Surveys [23] to ensure proper reporting of results (see [Multimedia Appendix 3](#)).

Microbiome Sequencing and Annotation

Participants collected gut microbiome samples after flare-ups or symptom improvements using the kit instructions and mailed the samples in the provided return envelope. Microbial particles were disintegrated, nucleic acid purified, amplified, sequenced in multiplex, demultiplexed, quantified, and assigned to taxonomic membership using previously described methods [24]. In the first step, cells were mechanically disrupted by grinding with glass beads. In the second step, DNA was purified from lysed samples using a liquid-handling robot by a guanidine thiocyanate silica column-based purification method. DNA was amplified with barcoded primers (515F: GTGCCAGCMGCCGCGGTAA; and 806R: GGACTACHVGGGTWTCTAAT) targeting the V4 region of the bacterial 16S ribosomal RNA (rRNA) gene. Indexed polymerase chain reaction products were pooled by taking the same volume from each reaction, column purified, and size selected through microfluidic DNA fractionation. Consolidated libraries were quantified by quantitative polymerase chain reaction using the Kapa iCycler kit on a MyiQ (Bio-Rad Laboratories, Inc) and sequenced on the NextSeq 500 platform (Illumina, Inc), rendering 2×150 base pair paired-end sequences. After sequencing, demultiplexing of reads according to sample-specific barcodes was performed using Illumina’s BCL2FASTQ algorithm. Reads were filtered using an average Q score greater than 30. After removal of primers and any

leading bases, forward and reverse 16S rRNA gene reads were appended together and clustered using version 2.1.5 of the Swarm algorithm, with a distance of 1 nucleotide and the “fastidious” and “usearch-abundance” flags. Depending on the percentage identity, the most abundant forward-reverse read pair per Swarm cluster was assigned taxonomic annotation to the same species, family, order, class, or phylum as in the SILVA V.132 rRNA database [25]. Best hits for the forward and reverse reads with greater than 97% identity to the same sequence in SILVA were annotated to the same species of the hit in SILVA.

Statistical Analysis

Sequencing data were linked to QoL survey responses using unique identifiers.

We addressed the large variability of the total counts per sample through normalization of raw counts before the analysis, starting from dividing the raw abundances by the total number of counts per sample (number of reads mapped to the taxon divided by the total number of reads mapped to any 16S sequence in the SILVA database). We evaluated several normalization approaches including log ratio. Finally, we applied a centered log-ratio (CLR) transformation to account for the compositional nature of the data. Abundance-weighted phylogenetic diversity was calculated according to McCoy and Matsen [26], by weighting phylogenetic entropy contributed by each lineage by its relative abundance distribution along the rooted phylogenetic tree built for the microbial community. We also estimated other alpha diversity measures, including classical phylogenetic diversity and its partial abundance-weighted extensions.

We identified significant associations between microbial taxa and malodor through a combination of statistical tests, mainly unpaired and paired Mann-Whitney-Wilcoxon tests, herein referred to as Mann-Whitney *U* if used to compare 2 independent groups and Wilcoxon if used for paired dependent samples. OTUs with consistently significant *P* values were adjusted using the Benjamini-Hochberg procedure to avoid type I errors (false positives) and decrease the false discovery rate. All statistical analyses and visualizations were performed using Python v3.7 with the NumPy (v1.16.4), pandas (v0.25.1), scipy (v1.3.1), scikit-learn (v0.22.2), and matplotlib (v3.1.1) toolkits.

Results

Participants

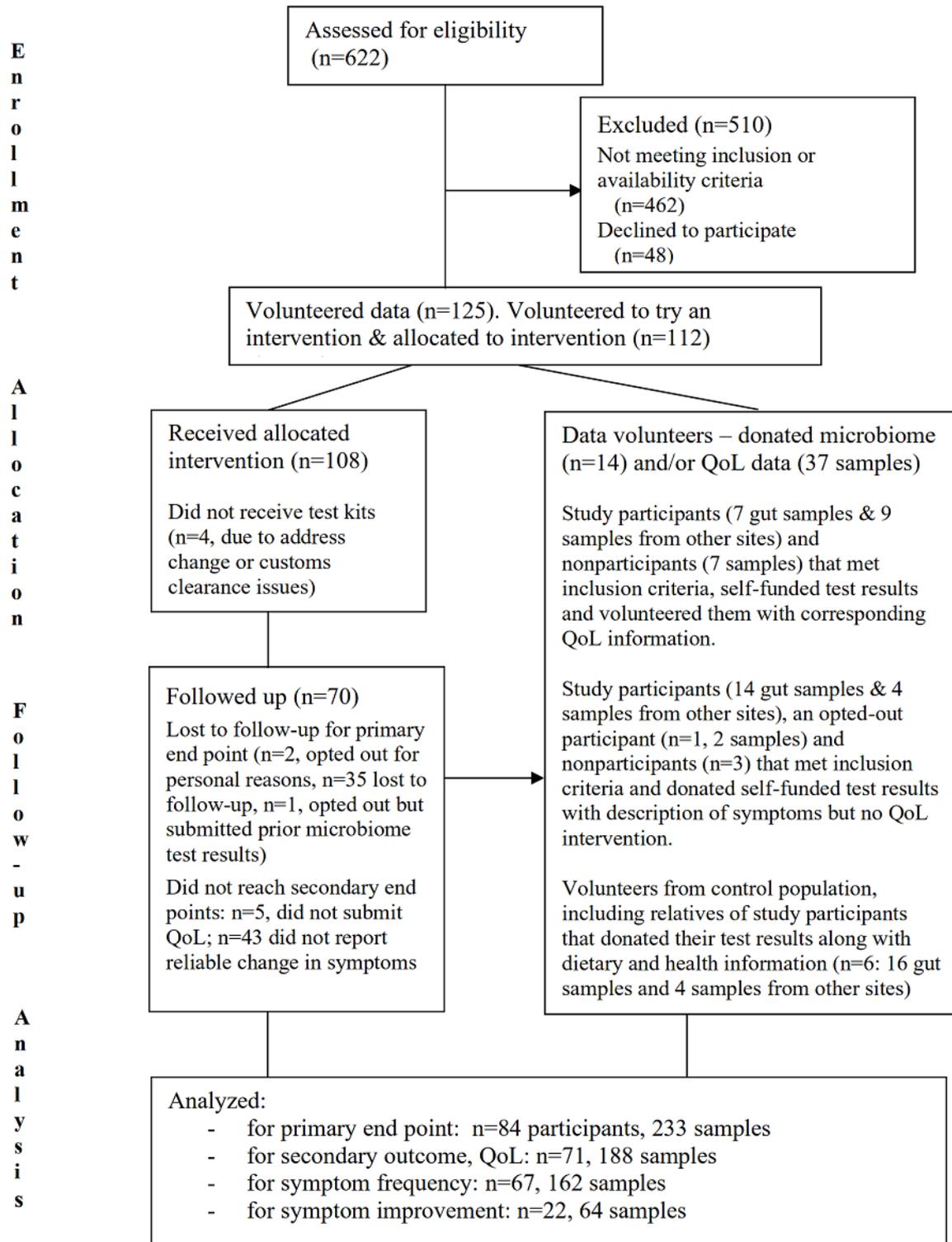
Individuals who provided consent received their kits between June and December 2018, answered the QoL questionnaire [21], and sent stool samples for processing between June 2018 and July 2019.

Figure 1 shows the participant flow diagram of the study. A total of 112 individuals consented to participate and were mailed 3 gut microbiome sampling kits to the address they provided when enrolling. Volunteers represented 21 countries: the United States, United Kingdom, Argentina, Brazil, Burkina Faso, Canada, Colombia, France, Hong Kong, Italy, Kenya, Mexico, Morocco, the Netherlands, Nigeria, Pakistan, Peru, Philippines, South Africa, Spain, and Sweden. Of these, 4 participants were not able to receive the kits because of unexpected customs fees

or change in address. A total of 38 did not follow up, but 1 of them submitted results of prior microbiome tests, joining 13 others who did not participate in the study but volunteered the data (from the United States, United Kingdom, and Portugal). Of these, 6 did not identify themselves with MEBO or PATM. As a result, we collected 233 samples from 84 participants,

including 13 who did not enroll to participate in the study but volunteered the data and 112 who consented to participate, minus the 4 participants who did not receive the kits, 2 who opted out, and 35 who neither followed up on survey responses nor sent their samples.

Figure 1. Participant flow through the metabolic body odor/people are allergic to me (MEBO/PATM) Microbiome trial. QoL: quality of life.



We analyzed the resulting data by first grouping them into disease states: active versus remission, regression, or healthy controls (never experienced MEBO or PATM). Of the

noncontrol participants, 71 submitted answers to the QoL questionnaire [21] for 188 samples. A total of 49 participants could not comment on their symptoms because of their inability

to smell, unavailability of a “trust buddy” to objectively evaluate their condition, or no change in their symptoms. The remaining 22 participants reported both flare-ups and improvements in their symptoms that we could use in a paired comparison analysis.

Baseline Characteristics

Of 336 test kits distributed to 112 consenting individuals, 189 samples were mailed for analysis by 73 participants (73/112, 65.2%; 189/336 distributed kits, 56.3%). Unfortunately, 4 of these samples (3 participants) were not processable, and 8 participants who submitted valid samples did not answer the QoL questionnaire.

Intervention dropout rates were similar to previously reported rates, and more of those who discontinued the study were women [27]. All nonrespondents received several personalized email reminders, but this did not significantly improve survey response and sample submission rates. On the other hand, 15 compliant participants from the intervention group submitted 21 additional samples using kits they purchased on their own. One participant opted out of the intervention but submitted 2 samples using previously purchased kits. In addition, 6 non-MEBO and 8 MEBO volunteers who did not participate in the intervention contributed 27 gut samples to this study. As a result, we collected 233 samples from 84 participants (Figure 1). Table 1 shows the characteristics of these individuals.

Table 1. Baseline demographic and clinical characteristics of study participants who submitted valid samples (N=84, unless otherwise stated).

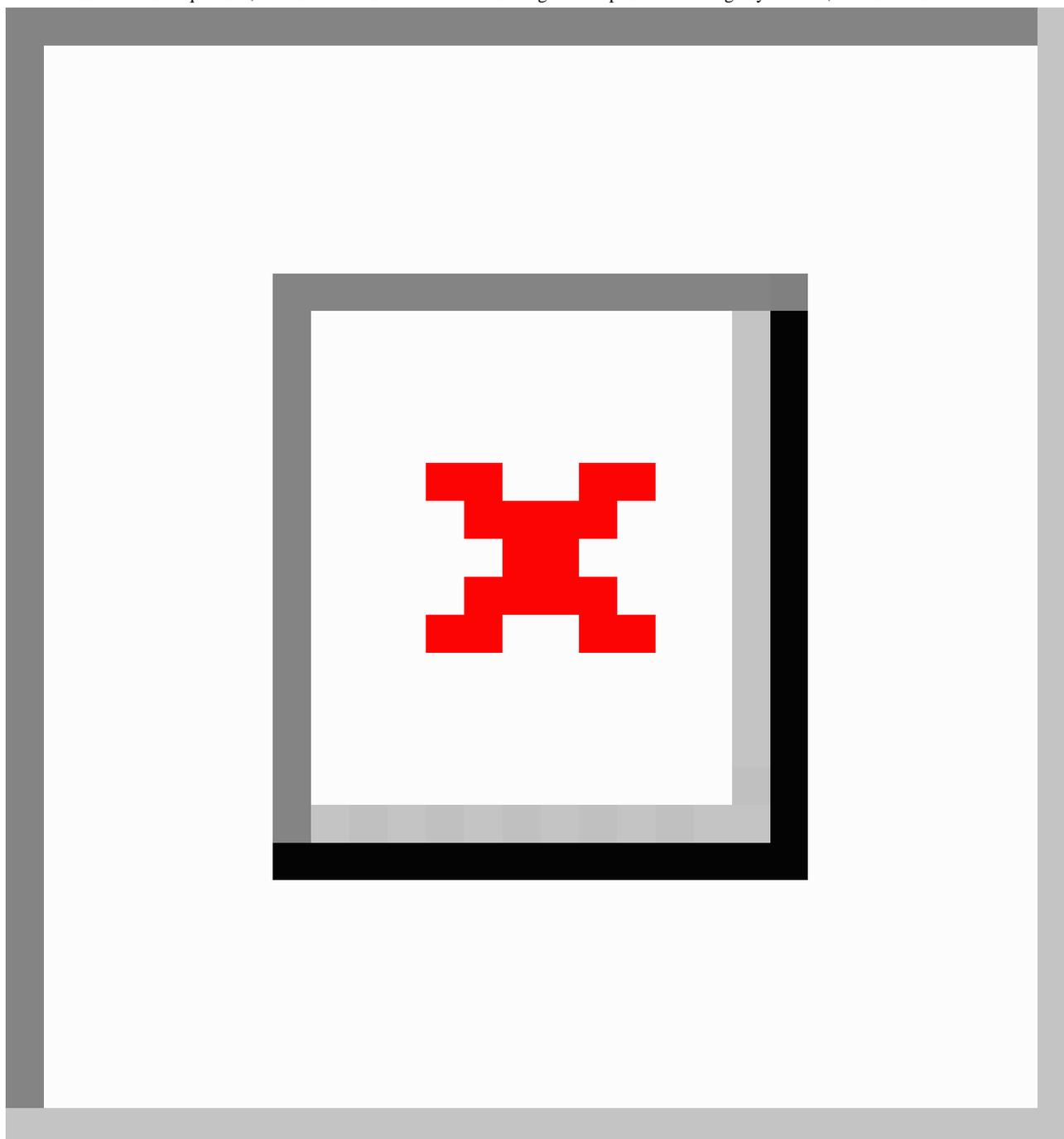
Characteristics	Values
Age (years), mean (SD)	
All	40 (12)
Female	42 (11)
Male	37 (12)
Sex, n (%)	
Male	34 (40)
Female	50 (60)
Trimethylaminuria, n (%) (n=41)	
Positive	21 (51)
Negative	20 (49)
Self-diagnosis of PATM, n (%) (n=77)	34 (44)

Of the 84 study volunteers, 41 (49%; 41/78, 53% of MEBO/PATM cohort) tested for the odor-producing disorder TMAU, with 13 positives for primary TMAU and 8 for secondary TMAU, a nongenetic form arising from dysbiosis in the gut bacteria [15]. Of 78 MEBO/PATM participants, only 10 were confident about the primary source of their malodor: in 9 (12%) cases it was nose or mouth, or both, and in 1 (1%) it was the genital area. Of these individuals, 6 thought they also had body odor in other areas. A total of 43 (55%) participants described malodor or PATM toxins emanating from their entire body, not just selected areas. Many participants commented that odor has to build up to be noticed (eg, after spending more than 15 minutes in a closed room with bad air circulation). The remaining 25 (32%) study participants named body sites they thought could be contributing to their malodor: underarm, feet, genitals, scalp, and face (mostly the oily T-zone), in all possible combinations thereof. Several participants were officially diagnosed with hyperhidrosis and bromhidrosis, while in 2 cases bromhidrosis was ruled out by dermatologists. In 2 other cases, patients were treated with botulinum toxin A (Botox) injected into the underarm but they continued to experience body odor after this procedure. In all these instances, patients thought that underarm odor was not their only odor.

Evaluation of Outcomes

We performed Mann-Whitney *U* tests to identify OTUs that showed significantly different frequencies between distinct groups in our study. Remarkably, microbes known to cause malodor when present on skin were consistently significantly overabundant in active versus regression or remission states of the condition and on acute flare-up versus nonflare-up days. In particular, these included *Corynebacterium* species thought to be the primary causal agents of axillary odor dependent on secretions of the apocrine gland [18,28,29], *Anaerococcus* species also found to correlate with cutaneous odor formation [29], commensal skin bacteria *Cutibacterium* and *Propionibacterium* contributing to foot odor [30], and *Campylobacter* contributing to axillary, in addition to oral, odor in some individuals [18,31]. Figure 2 shows boxplots for microbial diversity, Corynebacteriales, and a combination of selected species from the abovementioned bacterial genera (selected cutaneous species), namely *Anaerococcus* species S9 PR-5, *Anaerococcus hydrogenalis*, *Anaerococcus lactolyticus*, *Anaerococcus octavius*, *Anaerococcus prevotii*, *Anaerococcus provencensis*, *Campylobacter hominis*, *Corynebacterium atypicum*, *Corynebacterium durum*, *Corynebacterium freiburgense*, and *Propionibacterium freudenreichii* species.

Figure 2. Changes in centered log-ratio–transformed abundances of selected bacterial species, Corynebacteriales, and microbial diversity with changes in long-term disease state (regression/remission vs active state), short-term flare-ups (24-hour symptoms observed never/rarely or sometimes vs all/most of the time), and improvement of symptoms for the same individuals. The central line in each box is the median, the upper and lower boundaries of the box mark the first and third quartiles, the thin lines show the lowest and largest data points excluding any outliers, and the diamonds show the outliers.



In short-term flare-ups, symptoms were grouped into 3 categories to reduce the noise of subjective self-reporting (all or most of the time vs never, rarely, or sometimes vs those who could not objectively evaluate if they experienced episodes of malodor in the past few days). It is possible to see differences among all answers on a 5-point scale (“all the time,” “most of the time,” “sometimes,” “rarely,” and “never”) as [Multimedia Appendix 1](#) shows.

[Table 2](#) shows the results of paired and unpaired tests for different groups of participants. The difference in the selected cutaneous species defined above is statistically significant

independently of analytical approaches used for data preprocessing and normalization and after the false discovery rate correction (adjusted $P < .001$). For pairwise comparison of samples before versus after improvement for the same individuals, the 95% CI is 26-163 for normalized raw counts, 0.14-1.6 for logarithm to base 10 of relative abundance in participants’ stool, and 1.4-56.2 for CLR-transformed counts. For the Corynebacteriales order, the adjusted $P < .02$. Microbial diversity did not significantly change with improvement of symptoms. We note that these 22 participants submitted 73 samples, donating additional kits they purchased on their own. A total of 64 samples out of 73 were accompanied by QoL

questionnaires. As a result, 6 participants submitted only 2 samples corresponding to “better” and “worse” states (6 pairs); 12 participants submitted 3 samples and 4 submitted 4 samples that could be paired in 37 different ways, since some individuals were able to recognize their symptoms at a fine-grained level. Hence, we report data for the 43 pairs of samples, although we computed Wilcoxon signed rank tests for several different pairings. *P* values were significant in all scenarios, including the smallest 22-pair set representing the largest improvement observed for each individual ($P=.001$ for normalized counts and $P=.004$ for CLR-transformed counts of cutaneous bacteria). We investigated long-term disease activity by comparing participants with different overall MEBO/PATM status, self-reported in the QoL survey. We evaluated short-term effects by comparing 24-hour recalls. The selected cutaneous species index is higher for participants in the active state versus remission or regression and in those who were experiencing symptoms all or most of the time versus never or rarely or sometimes. Adjusted *P* values are higher in these cases, which could be because nonmatched

individuals self-assessing their symptoms are more problematic to compare, but the difference is still significant or marginally significant ($P<.01$ for long term and $P=.06$ for short term activity). The 95% CI for CLR-transformed counts is 0.6-3.45 for long-term effects and 0-2.7 for short-term effects. For 24-hour recall, between-group comparisons of changes in Corynebacteriales and microbial diversity are significant even after false discovery rate adjustment. Table 2 also lists results for potential confounding factors, such as females versus males, younger versus older individuals, and those who mentioned underarm odor as one of their problem odors versus those who ruled the axilla out of their odor sources. Differences between these groups were not significant after false discovery rate adjustment and only marginally significant otherwise. We note that individuals who self-diagnosed PATM had significantly higher levels of cutaneous species than those who self-reported malodor only (95% CI 0.5-3.36 for CLR cutaneous species). Yet we see the same patterns for disease severity within each of the groups as within the entire population (Figure 3).

Table 2. *P* values for Mann-Whitney *U* tests for unpaired samples and Wilcoxon signed rank test for paired samples.

Test, groups, and preprocessing	Selected species	Corynebacteriales	Microbial diversity
Before and after improvement (Wilcoxon test for 43 pairs of matched samples of 22 participants)			
Normalized counts	<.001	<.001	.6
CLR ^a -transformed	<.001	.02	
Active vs regression/remission/no disease status (Mann-Whitney <i>U</i> test for 182 samples of 73 participants vs 51 samples of 30 participants)^b			
Normalized counts	.004	.05	.3
CLR-transformed	.002	.008	
Experienced MEBO^c/PATM^d episodes all/most of the time vs never/rarely/sometimes (Mann-Whitney <i>U</i> test for 88 samples of 46 participants vs 74 samples of 25 participants)^b			
Normalized counts	.01	.005	.02
CLR-transformed	.04	.002	
Females vs males: 138 vs 95 samples, 84 participants			
Normalized counts	.3	.2	.3
CLR-transformed	.09	.2	
Individuals with underarm odor vs those who ruled it out: 36 samples/13 participants vs 54 samples/15 participants			
Normalized counts	.02	.07	.08
CLR-transformed	.07	.04	
Participants with MEBO (121 samples/44 participants) vs those with self-diagnosed PATM (96 samples/34 participants)			
Normalized counts	.09	.1	.2
CLR-transformed	.008	.2	
Those who tested negative for trimethylaminuria (58 samples/20 participants) vs positive (56 samples/21 participants)			
Normalized counts	.2	.4	.3
CLR-transformed	.4	.5	
Age <40 years (115 samples/39 participants) vs ≥40 years (118 samples/45 participants)			
Normalized counts	.05	.4	.1
CLR-transformed	.05	.4	

^aCLR: centered log-ratio.

^bThe sum of participants in active disease versus remission (73+30>84) and “most of the time” versus “sometimes” groups (46+25>67) is greater than the total number of participants because some individuals changed their answers to surveys associated with follow-up samples.

^cMEBO: metabolic body odor.

^dPATM: people are allergic to me.

Figure 3. Change in abundance of selected cutaneous species (log scale) with long- and short-term improvement of symptoms in metabolic body odor (MEBO) vs people are allergic to me (PATM) groups of study volunteers. Red boxes represent active state of disease or symptoms observed all or most of the time. Blue boxes show remission or regression and symptoms reported as never, rarely, or sometimes.

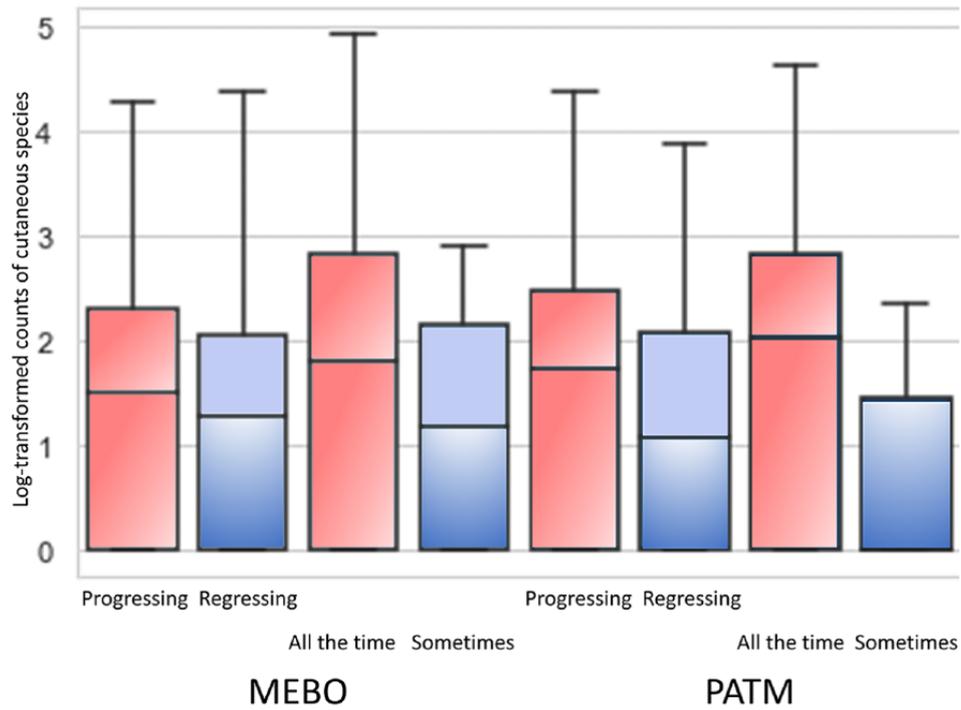


Figure 4 shows similar trends in all other groups, except cases when underarm odor was ruled out as a potential problem. Changes in abundances of cutaneous bacteria are not significant in remission only in the latter case.

Figure 5 shows how the selected cutaneous species index changed with symptom improvements in the 22 participants (12 female and 10 male) who reported flare-ups and improvements. Figure 6 shows changes in genera for 1 of the volunteers, F7, who reported fine-grained symptoms for multiple observations (refer to Multimedia Appendix 1 for more details).

Figure 4. Change in selected species of bacteria (centered log-ratio [CLR]-transformed cutaneous species) with long-term improvement of symptoms analyzed separately for different subgroups of study participants: males and females, those including or excluding underarm odor in self-reported symptoms, and participants grouped into 2 age brackets: 20-39 and 40-66 years. Red boxes represent active state of disease. Blue boxes show remission or regression.

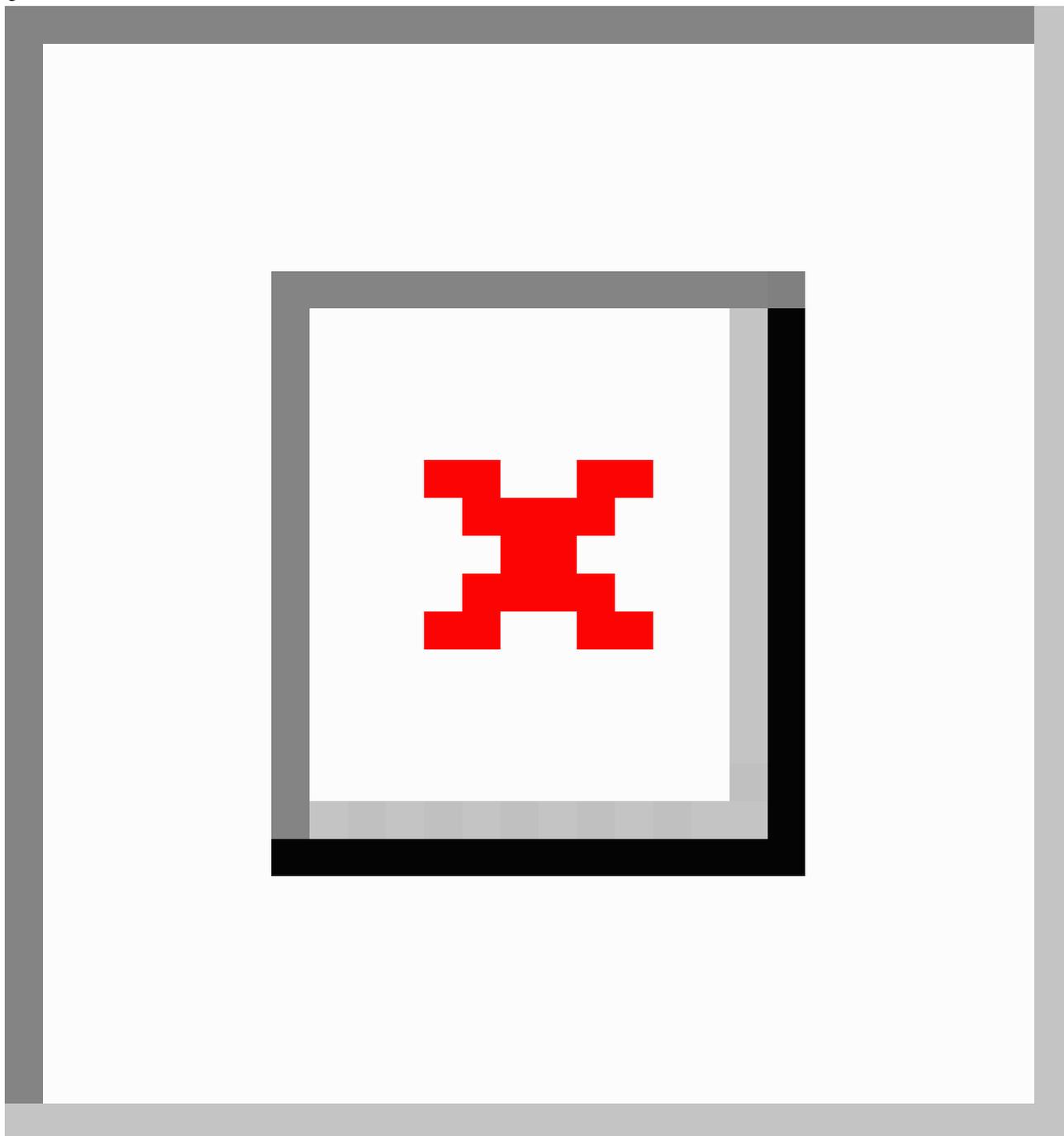


Figure 5. Changes in microbial diversity vs abundances of selected bacterial species (CSS) for 12 female (F) and 10 male (M) participants who self-reported both flare-ups (beginning of the arrow) and improvements (end of the arrow).

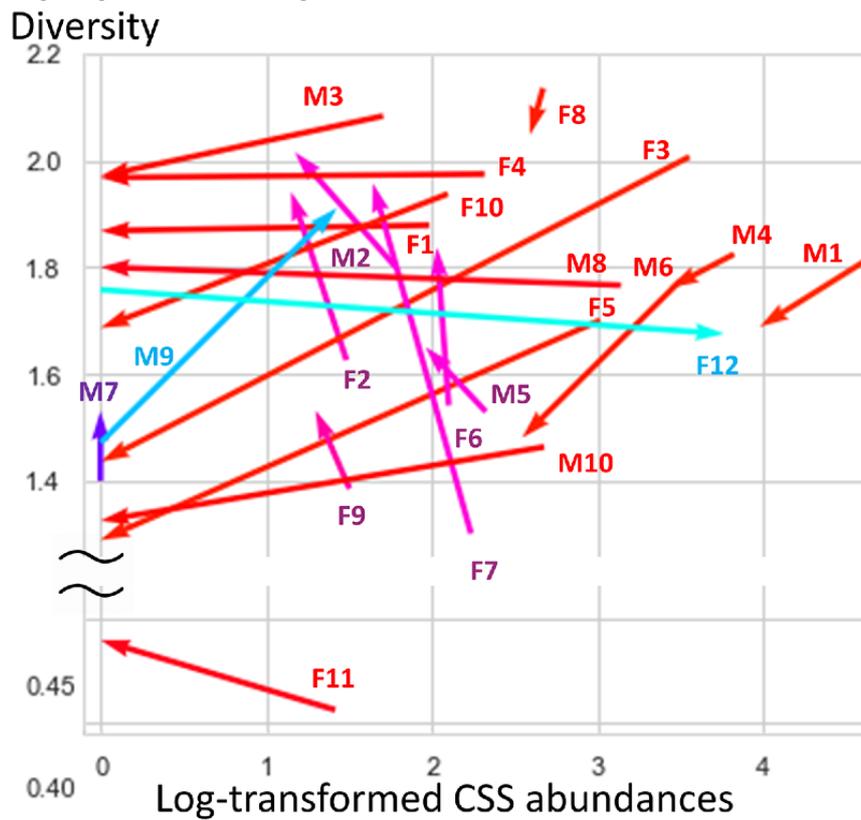
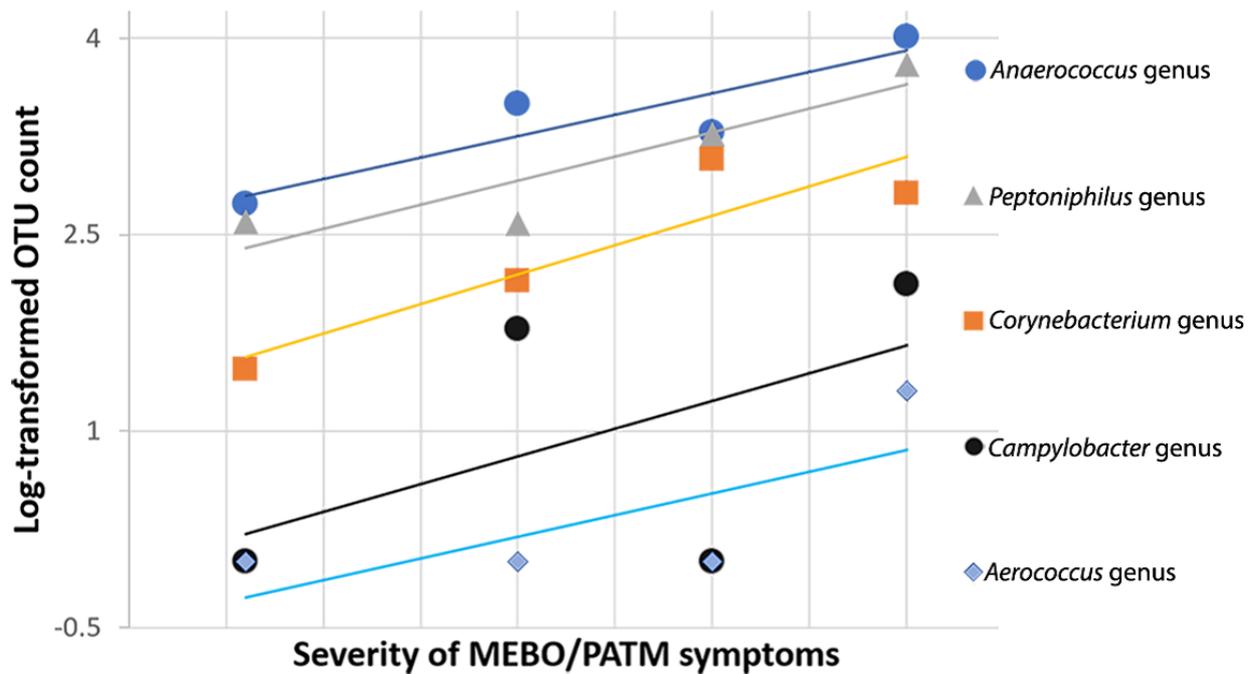


Figure 6. Changes in abundances of common dermal bacteria in the gut microbiome of participant F7. Each genus represents the total number of reads mapped to species identified in the gut sample. MEBO: metabolic body odor; OTU: operational taxonomic unit; PATM: people are allergic to me.



Discussion

Principal Findings and Prior Work

Previous studies have demonstrated differences in the skin and oral microbiomes of individuals experiencing body odor or halitosis [5,8,17,18,28-31]. The gut microbiota is linked to skin disorders such as psoriasis, rosacea, and atopic dermatitis [32-34] and is a target for the treatment of MEBO [35]. Yet prior studies of malodor had limited sample sizes and were lacking insights into the gut microbial community [36], focusing on skin (including vulvar) and oral microbial compositions. In this study, we observed significant differences in cutaneous gut microbes (able to colonize skin and cause skin malodor) between various groups of MEBO and PATM conditions. Levels of these bacteria were always significantly lower with improvement of symptoms, whether long- or short-term or when observed for the same individuals. There was a moderately positive relationship between answers to the QoL survey about the progression of the MEBO or PATM condition and the intensity of recent symptoms. However, since all individuals answered the question about the state of their condition (84 participants), whereas only 80% (67 participants) reported daily observations and many were not sure about some aspects of their condition, we analyzed multiple illness severity grouping systems. Remarkably, cutaneous malodor bacteria were reproducibly associated with increasing intensity of MEBO and PATM. Based on survey responses, we noticed differences in coping mechanisms between males and females and associations between answers such as “My appearance was affected because of MEBO/PATM” and “I had problems concentrating.” In our future research, we plan to investigate the QoL outcomes and data sets from our past diagnostic studies at a more granular level.

Results of case-by-case studies aligned with overall statistics. As Figure 5 shows, the only exceptions to the conclusion that the fewer cutaneous bacteria in the gut, the fewer skin emanations were M7, M9, and F12. All of them observed very minor if not negligible (and easy to misinterpret) improvement of their condition (flare-ups happening from “all the time” to “most of the time”). M7 was seen by a professional dermatologist, who concluded that a diagnosis of bromhidrosis didn't seem warranted. F12 had undergone a Botox procedure to treat her hyperhidrosis about 15 years previously. M9 did not report any skin odors and noted only halitosis. It is interesting to note that, whereas those with higher abundances of cutaneous bacteria in the gut benefited from reducing their microbial diversity and bacterial counts in general, those with lower abundances benefited from increasing their microbial diversity. As in a recent study investigating differences in diversity with respect to human personality and other parameters of daily living [37], we, too, found sociability associated with higher diversity, and anxiety, depression, and stress with reduced diversity. We also analyzed differences in fiber, calcium, fat, vegetable, and heterocyclic amine intake, as well as of fermented foods and probiotic supplements. However, the impact of these factors was more profound on microbial diversity than on counts of cutaneous species in the gut microbiome. In some of these cases, such as probiotic supplements, abundances of cutaneous

species were significantly lower in both flare-ups and remissions, but the impact of these bacteria remained the same: higher levels with more severe symptoms, similar to the data shown in Figures 3 and 4.

As observed earlier, abundances of common skin bacteria seemed to correlate with each other. Figure 6 shows similar effects on self-reported severity of symptoms observed for genera responsible for axillary and foot odor: *Corynebacterium*, *Anaerococcus*, *Peptoniphilus*, *Campylobacter*, and *Aerococcus*.

Limitations

The challenges of relying solely on perception of odors by nonprofessionals were previously discussed [5]. In this study [5], “malodor” and “no malodor” groups of children defined by their parents were not statistically significantly different when evaluated by professional odor assessors (Wilcoxon test $P>.1$). The self-reported nature of this study is a limitation, but medical examination may also be prone to errors and the consistency of our findings for different groups and with data from other studies demonstrates that fully remote studies of malodor are feasible.

Measuring the microbiome is not like measuring a single isolated variable pertaining to physiology. Since the data are complex and compositional, daily fluctuations get amplified, requiring multiple longitudinal sampling for patients. Multiomic measurements can improve statistical inferences, avoid false positives, and increase the overall efficiency of clinical trials.

Another limitation of this study was that we did not have data on the time period from sample collection to sequencing for all kits processed. The storage condition of gut samples introduced some biases in microbial diversity and the relative abundance of functional bacteria, even when using the best commercial stabilizers for preserving fecal samples at room temperatures [38]. However, most storage conditions and storage time had minor and acceptable impacts on nucleic acid yields or quality.

An additional limitation of this study was that we did not use incentives for participation.

Conclusions

The hypothesis of this study was that in spite of genetic heterogeneity, MEBO and PATM conditions display common patterns in the gut microbiome [21]. The collective intestinal microbiome in the study population stratified by disease severity exhibited a relative increase in bacterial species from genera associated with dermal odor. The finding was consistent in active versus remission states, and short-term flare-ups versus relative improvements.

Skin conditions often lead to difficulties in emotional, psychological, and social functioning. Our study showed that web-based research has the potential to not only offer much-needed psychosocial support [39], but also help to develop virtual care solutions for conditions resembling dermatological nondisease [40].

Our work paves the way for the development of cost-effective diagnostics of MEBO and PATM conditions based on an at-home stool test. Current methods (such as trimethylamine N-oxide urine or small intestinal bacterial overgrowth breath

diagnostics) rely on tolerance tests that take many hours of preparation, testing, and recovery. External microbiome sampling may require multiple swabs, such as from the oral cavity, forearm, axilla, scalp, and feet. Simple at-home microbiome stool sampling could simplify testing.

Another implication of this work is that individuals with a high abundance of cutaneous malodor bacteria in the gut might benefit from reducing levels of these bacteria. We note that one of the common causes of both halitosis and axillar odor is a zinc deficiency. Zinc oxide is known to decrease populations of bacteria discussed in this work when applied externally [41],

attenuating self-perceived malodor. Zinc also contributes to the reduction of halitosis [42]. However, not all people with MEBO and PATM are zinc deficient, and it is important to retain certain levels of cutaneous odor-producing bacteria in the body, as they prevent some skin, ear, and respiratory infections [43].

Future work will focus on incorporating more background knowledge and test results for higher precision data mining. Additional studies are needed to uncover the root causes of socially debilitating malodor and PATM conditions and, most importantly, to connect patient experiences to the development of personalized therapies.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Supplementary materials.

[\[DOCX File , 1274 KB-Multimedia Appendix 1\]](#)

Multimedia Appendix 2

CONSORT-EHEALTH checklist V1.6.1.

[\[PDF File \(Adobe PDF File\), 3553 KB-Multimedia Appendix 2\]](#)

Multimedia Appendix 3

Checklist for Reporting Results of Internet E-Surveys (CHERRIES).

[\[DOCX File , 28 KB-Multimedia Appendix 3\]](#)

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Abbreviations

CLR: centered log-ratio

CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth

MEBO: metabolic body odor

OTU: operational taxonomic unit

PATM: people are allergic to me

QoL: quality of life

rRNA: ribosomal RNA

TMAU: trimethylaminuria

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