BRIEF REPORT

Gut Microbial Metabolites and Future Risk of Parkinson's Disease: A Metabolome-Wide Association Study

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ABSTRACT: Background: Alterations in gut microbiota are observed in Parkinson's disease (PD). Previous studies on microbiota-derived metabolites in PD were small-scale and post-diagnosis, raising concerns about reverse causality.

Objectives: Our goal was to prospectively investigate the association between plasma microbial metabolites and PD risk within a metabolomics framework.

Methods: A nested case–control study within the prospective EPIC4PD cohort, measured pre-diagnostic plasma microbial metabolites using untargeted metabolomics.

Results: Thirteen microbial metabolites were identified nominally associated with PD risk (P-value < 0.05), including amino acids, bile acid, indoles, and hydroxy acid, although none remained significant after multiple testing correction. Three pathways were implicated in PD risk: valine, leucine, and isoleucine degradation, butanoate metabolism, and propanoate metabolism. PD-associated microbial pathways were more pronounced in men, smokers, and overweight/obese individuals.

Conclusion: Changes in microbial metabolites may represent a pre-diagnostic feature of PD. We observed biologically plausible associations between microbial pathways and PD, potentially influenced by individual characteristics.

Key Words: gut-brain axis; microbial metabolites; Parkinson's disease; pre-diagnostic biosamples; untargeted metabolomics

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The gut-brain hypothesis has gained interest for Parkinson's disease (PD) pathogenesis, with evidence indicating altered gut microbiota composition in PD cases.[1] Microbiota-derived metabolites, released into the bloodstream, have emerged as promising biomarkers reflecting gut microbiota functionality.[2] These microbial metabolites fall into three categories: (1) metabolites directly produced by gut microbiota from diets, like short-chain fatty acids and indole derivatives; (2) metabolites initially produced by the host and subsequently modified by microbiota, such as secondary bile acids; and (3) metabolites synthesized de novo by microbiota, like polysaccharide A.[3]

Previous studies have reported changes in short-chain fatty acids and secondary bile acids in PD patients compared to controls.[4,5] However, the issue of reverse causality persists, as biosamples were collected post-diagnosis. Dietary changes because of pre-clinical PD symptoms like dysphagia, hyposmia, and constipation, as well as anti-PD medications like levodopa and catechol-*O*-methyltransferase inhibitors, could also influence gut microbiota and their metabolites.[5,6]

This study used the EPIC4PD cohort, a population-based prospective cohort where plasma samples were collected before PD diagnosis.[7] A prior study within this cohort showed that plasma lipopolysaccharide-binding protein (LBP), a biomarker of bacterial invasion and intestinal permeability, is associated with an elevated risk of PD, indicating the potential involvement of gut microbiota in early disease development.[8] We aim to conduct a metabolome-wide association study (MWAS) within this cohort, focusing on plasma microbial metabolites, to further explore the gut-brain interplay in PD.

Methods

Study Design

We conducted a nested case–control study within the EPIC4PD cohort (total subject number: 220,494) across seven European countries. Cohort and PD case ascertainment details have been reported previously.[7,8] Of the 734 confirmed incident PD cases, 351 were eligible for inclusion based on the availability of baseline plasma samples. Controls were selected from the same cohort using incidence density sampling, matching by age at recruitment, sex, and study center with cases (1:1 ratio). Diet intake and lifestyle factors were collected at enrollment.[9]

Untargeted Metabolomics and Microbial Metabolite Annotation

Plasma samples were retrieved from the EPIC centralized biobank and analyzed at Columbia University, United States. The untargeted metabolome was measured by liquid chromatography-high resolution mass spectrometry (LC-HRMS) in two complementary modes, namely hydrophilic interaction liquid chromatography-electrospray ionization (ESI^+) and reverse-phase chromatography-ESI^-, referred to as "HILIC-ESI^+" and "C18-ESI^-", respectively. After quality control procedures, batch effect corrections, and missing imputation, 7487 features for HILIC-ESI^+ and 6968 for C18-ESI^- were retained for analysis.

Microbial metabolites within the metabolome were annotated using an internal spectral library and the Exposome-Explorer database.[3] In total, 167 features (78 HILIC-ESI^+ and 89 C18-ESI^- features) were identified as microbial metabolites, mainly categorized into amino acids and peptides (n = 42), fatty acyls (n = 20), carbohydrates and conjugates (n = 10), indoles and derivatives (n = 10), and phenylpropanoids and polyketides (n = 10) (Supplementary Table S1). Details on analytical methods and annotation are provided in Supplementary Data S1, Text S1.

Statistical Analysis

Conditional logistic regression was applied for the matched case–control sets, estimating odds ratios (ORs), and 95% confidence intervals (CIs) for each metabolite (log2-transformed and scaled by standard deviation). Models included smoking status and body mass index (BMI) as covariates. The Benjamini-Hochberg procedure was applied to account for false positives from multiple testing, and metabolites were considered significant at a false discovery rate (FDR) threshold of 20%.

Stratified analyses were performed by sex, smoking status (smokers or non-smokers at baseline), BMI (normal weight <25 kg/m^2, overweight/obese ≥25 kg/m^2), and plasma LBP concentrations (lower or higher than median, 25.6 μg/mL) to assess potential effect modification. Sensitivity analyses included: (1) limiting PD cases to those diagnosed after 8 years since recruitment (n = 170) to address possible reverse causality; (2) restricting to PD cases with higher diagnostic validity (n = 188, labeled as "definite" and "very likely"[7]); and (3) adjusting for individual food categories (fruit, vegetables, meat, cereal, dairy, and fish/seafood) at baseline to account for dietary impact on gut microbiota.

An MWAS was performed on the entire metabolome (7487 HILIC-ESI^+ and 6968 C18-ESI^- features) to enable pathway enrichment analysis. Metabolites with a raw *P*-value <0.05 were chosen for pathway enrichment analysis using MetaboAnalystR 5.0 (Xia lab, Canada).[10] The mass tolerance, analytical mode, and permutation number were set as ±5 ppm, mixed ("positive" for HILIC-ESI^+ and "negative" for C18-ESI^-), and 1000, respectively. Enriched metabolic pathways were identified using a γ threshold (*P*-value derived from the permutation tests for the pathway) of 0.05 and required the presence of at least three metabolites associated with PD risk. This study presents enriched

pathways related to gut microbiota. The selection criteria for determining pathways associated with the microbiota were knowledge-driven, based on extensive literature searches, particularly using the Exposome-Explorer database. For instance, the butanoate metabolism pathway is chosen because of the database's documented evidence of butyric acid.

Results

PD patients had a median period of 8 years (ranging from 0.2–18 years) between recruitment and diagnosis (Supplementary Table S2). In the MWAS of annotated microbial metabolites, 13 metabolites were nominally associated with PD risk (raw *P*-value <0.05), but none met the FDR 20% threshold (Table 1). Most metabolites, including arginylglutamate, creatinine, leucylproline, phenylalanine, Δ-aminovaleric acid, xylose, indole-3-propionic acid, purine, gallic acid, L-2-hydroxyglutarate, and 4-hydroxyphenylpyruvic acid, were found in higher abundance in PD cases compared with controls. In contrast, dihydroresveratrol and taurocholic acid were lower in PD cases.

Short-chain fatty acids and bile acids are well-studied microbial metabolites. Butyric acid exhibited a lower, albeit non-significant, abundance in PD cases (OR: 0.91, 95% CI: 0.76–1.08). Chenodeoxycholic and taurocholic acid, primary bile acids, exhibited altered abundance with ORs of 1.13 (95% CI: 0.97–1.31) and 0.81 (95% CI: 0.67–0.96), respectively. Secondary bile acids, like lithocholic acid, glycodeoxycholic acid, and 3-oxodeoxycholic acid, did not show significant differences between cases and controls (Supplementary Table S1).

In the whole metabolome MWAS, 1000 metabolic features (547 HILIC-ESI$^+$ and 453 C18-ESI$^-$ features) showed nominal associations with PD risk (raw *P*-value <0.05), but none met the FDR 20% threshold (Supplementary Fig. S1). Three pathways related to microbiota activity were enriched: valine, leucine and isoleucine degradation; butanoate metabolism; and propanoate metabolism (Fig. 1). Interestingly, these microbial pathways were heterogeneous across subgroups. More pathways were seen for individuals who were male, overweight/obese, and smokers. Only amino acid pathways were associated with PD among individuals with lower LBP levels, whereas short-chain fatty acids pathways were further enriched among those with higher LBP levels.

Sensitivity analyses, which limited PD cases to those with higher diagnostic certainty and those diagnosed more than 8 years because recruitment, showed consistent effect estimates with the main analyses (Supplementary Fig. S2). Additional adjustments for food intake also yielded similar results (Supplementary Fig. S3).

TABLE 1 *Microbial metabolites associated with Parkinson's disease risk (raw* P*-value <0.05)*

Metabolite	Evidence on microbial origin[a]	Analytical method	*m/z*	Retention time (s)	OR (95% CI)[b]	*P*-value
Arginylglutamate	In vivo	C18-ESI$^-$	302.1553	32.2	1.22 (1.03–1.45)	0.020
Creatinine	In vivo	HILIC-ESI$^+$	114.0662	33.6	1.22 (1.01–1.48)	0.035
Leucylproline	In vivo	HILIC-ESI$^+$	229.1548	50.0	1.27 (1.03–1.55)	0.022
Phenylalanine	Both	C18-ESI$^-$	164.0716	34.3	1.19 (1.01–1.41)	0.037
Δ-Aminovaleric acid	Both	C18-ESI$^-$	116.0718	30.4	1.18 (1.00–1.40)	0.049
Xylose	In vivo	C18-ESI$^-$	149.0456	37.3	1.25 (1.05–1.49)	0.011
Indolepropionic acid	Both	HILIC-ESI$^+$	190.0864	34.2	1.22 (1.05–1.43)	0.011
Dihydroresveratrol	In vitro	C18-ESI$^-$	229.0808	73.6	0.84 (0.70–1.00)	0.047
Purine	In vitro	C18-ESI$^-$	119.0351	34.7	1.24 (1.03–1.48)	0.020
Gallic acid	Both	C18-ESI$^-$	169.0134	38.8	1.22 (1.03–1.46)	0.024
Taurocholic acid	In vivo	HILIC-ESI$^+$	516.3055	35.5	0.81 (0.67–0.96)	0.016
L-2-hydroxyglutarate	In vitro	C18-ESI$^-$	147.0299	29.2	1.40 (1.05–1.85)	0.020
4-Hydroxyphenylpyruvic acid	In vivo	HILIC-ESI$^+$	181.0530	41.0	1.30 (1.11–1.52)	0.001

[a]Defined in the Exposome-Explorer database. "Both" indicated that the specific metabolite simultaneously met in vitro (production by gut bacteria) and in vivo (reduction of concentrations by antibiotics or in germ-free animals) evidence supporting a microbial origin. "in vivo/in vitro" represented that evidence was limited to either in vivo or in vitro studies.
[b]Conditional logistic regression for the matched case–control sets, adjusted by smoking status and BMI. OR was calculated per SD increase of log2 ion intensity.
Abbreviations: *m/z*, mass-to-charge ratio; OR, odds ratio; CI, confidence interval; BMI, body mass index; SD, standard deviation.

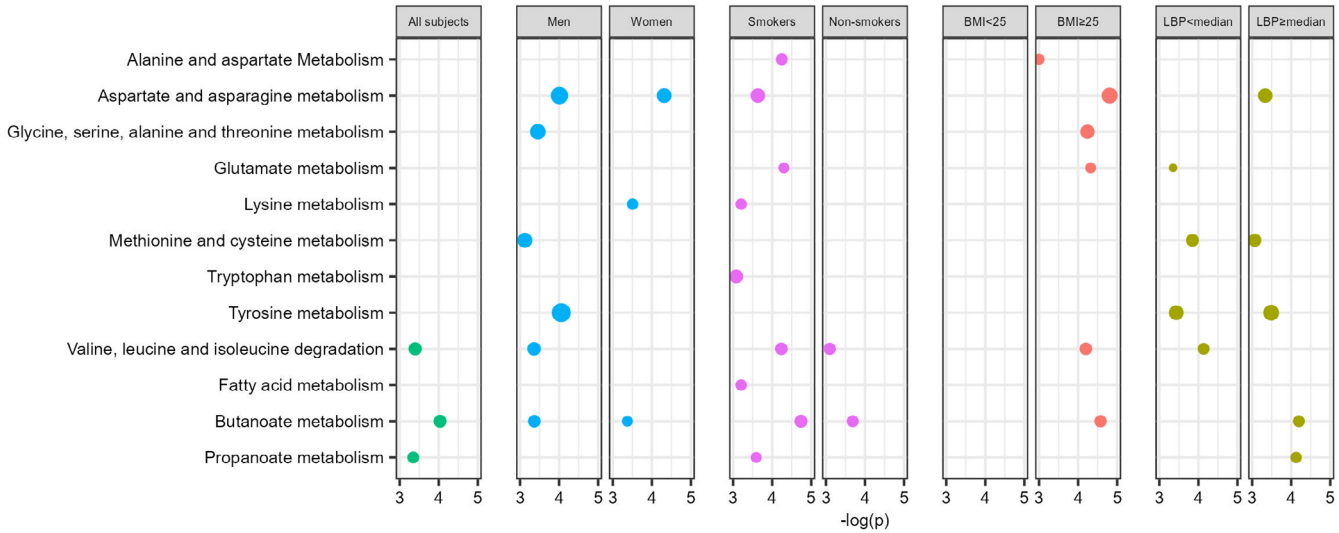

FIG. 1. Microbiota-relevant pathways associated with Parkinson's disease (PD) in the main analyses and stratified analyses. Pathways enriched with PD-associated metabolic features were identified using MetaboAnalyst 5.0. The position of the dot on the *x*-axis corresponds to the −log10 *P*-value calculated for the pathway, and the size of the dot corresponds to the number of features meeting *P*-value <0.05 in the pathway. [Color figure can be viewed at wileyonlinelibrary.com]

Discussion

Our study is the first prospective investigation into the role of pre-diagnostic microbial metabolites in PD risk. We identified 13 metabolites and three microbial pathways nominally associated with PD. Notably, individual characteristics might influence the variability in the involvement of gut microbiota in PD.

Previous studies have indicated increased blood levels of both short-chain fatty acids and secondary bile acids in PD patients compared with healthy controls (Supplementary Table S3).[4-11] However, our study found minimal changes in these metabolites. These discrepancies may stem from differences in the timing of metabolite assessment, with previous studies examining post-diagnostic samples versus our pre-diagnostic samples. Despite this, we observed alterations at the pathway level in short-chain fatty acid metabolism associated with PD, highlighting the need for further exploration of short-chain fatty acids and secondary bile acids within the gut-brain axis.

Our study provides novel evidence that certain microbial metabolites may contribute to PD development. For example, phenylalanine and L-2-hydroxyglutarate, recognized for their neurotoxic effects,[12,13] were associated with increased PD risk, whereas dihydroresveratrol, known for its neuroprotective properties,[14] showed an inverse association with PD. Interestingly, indole-3-propionic acid, despite its anti-inflammatory and antioxidant properties,[15] displayed a positive relationship with PD risk.

We noted differences in metabolite profiles and pathway enrichment related to sex, smoking status, and BMI. Similarly, our previous study on another microbiota-related marker, LBP, revealed sex- and BMI-specific effects.[8] These findings suggest personal characteristics may modify the relationship between microbial dysbiosis and PD. Previous research suggests smoking and obesity can induce gut microbiota dysbiosis, increase intestinal permeability, and contribute to gut inflammation.[16,17] Sex-related differences may be attributed to sex hormones affecting microbiota composition.[18] Additionally, individuals with higher LBP levels exhibited more microbiota-relevant pathways than those with lower LBP levels. Elevated LBP levels have been proposed as a biomarker for intestinal permeability,[19] suggesting intestinal leakage and increased microbial metabolites in the blood.

We acknowledged some limitations in this study. First, the extended prodromal phases of PD could introduce residual reverse causality. Early prodromal symptoms of PD, such as chronic constipation and loss of taste and smell, may occur up to 10 years before the onset of motor symptoms[20] and could influence gut microbiota. Sensitivity analyses using an 8-year pre-diagnosis cutoff were consistent with our main findings. Additionally, extended analysis regressing time-to-diagnosis (ranging from <1–18 years) to the 13 metabolites associated with PD showed no effect of time-to-diagnosis on metabolites abundance (Supplementary Fig. S4), suggesting a limited influence of the prodromal stage. Second, many microbial metabolites are co-metabolized by the host and microbiota, making it difficult to distinguish the contributions from microbiota without a more direct measurement of gut microbiota. Third, a one-time measurement may not fully capture the dynamic changes of microbial metabolism. High heterogeneity of microbiota among individuals might limit the power to detect significant changes, even with a large sample size. Fourth, our findings of the nominally

associated 13 metabolites and three microbial pathways need further external validation. The effect estimates varied across the four national sub-cohorts involved, but were generally directionally consistent (Supplementary Table S4). Replication in external PD groups is necessary for full validation.

In summary, our study identified several metabolites nominally associated pre-diagnostically with PD incidence. These metabolites were linked to biological pathways, including valine, leucine and isoleucine degradation, butanoate metabolism, and propanoate metabolism. This is the first large-scale prospective study examining gut microbial metabolites in pre-clinical PD. Our results warrant further investigation into the role of gut microbiota in PD development.

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Data Availability Statement

Research data are not shared.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.