Association of Fecal and Plasma Levels of Short-Chain Fatty Acids With Gut Microbiota and Clinical Severity in Patients With Parkinson Disease

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Abstract

Background and Objectives

Short-chain fatty acids (SCFAs) are gut microbial metabolites that promote the disease process in a rodent model of Parkinson disease (PD), but fecal levels of SCFAs in patients with PD are reduced. Simultaneous assessments of fecal and plasma SCFA levels, and their interrelationships with the PD disease process, are scarce. We aimed to compare fecal and plasma levels of different SCFA subtypes in patients with PD and healthy controls to delineate their interrelations and link to gut microbiota changes and clinical severity of PD.

Methods

A cohort of 96 patients with PD and 85 controls were recruited from National Taiwan University Hospital. Fecal and plasma concentrations of SCFAs were measured using chromatography and mass spectrometry. Gut microbiota was analyzed using metagenomic shotgun sequencing. Body mass index and medical comorbidities were evaluated and dietary information was obtained using a food frequency questionnaire. To assess motor and cognitive impairment, we used the Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and the Mini-Mental Status Examination (MMSE).

Results

Compared with controls, patients with PD had lower fecal but higher plasma concentrations of acetate, propionate, and butyrate. After adjustment for age, sex, disease duration, and anti-PD medication dosage, MDS-UPDRS part III motor scores correlated with reduced fecal levels of acetate ($\rho = -0.37$, $p = 0.012$), propionate ($\rho = -0.32$, $p = 0.036$), and butyrate ($\rho = -0.40$, $p = 0.004$) and with increased plasma propionate concentrations ($\rho = 0.26$, $p = 0.042$) in patients with PD. MMSE scores negatively correlated with plasma levels of butyrate ($\rho = -0.09$, $p = 0.027$) and valerate ($\rho = -0.032$, $p = 0.033$) after adjustment for confounders. SCFAs-producing gut bacteria correlated positively with fecal levels of SCFAs in healthy controls but revealed no association in patients with PD. In the PD patient group, the abundance of proinflammatory microbes, such as *Clostridiales bacterium NK3B98* and *Ruminococcus sp AM07-15*, significantly correlated with decreased fecal levels and increased plasma levels of SCFAs, especially propionic acid.

Discussion

Reductions in fecal SCFAs but increased plasma SCFAs were observed in patients with PD and corelated to specific gut microbiota changes and the clinical severity of PD.

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Glossary

AUC = area under the receiver operating characteristic curve; **BBB** = blood–brain barrier; **CI** = confidence interval; **FFQ** = Food Frequency Questionnaire; **IFN-γ** = interferon-γ; **LEDD** = levodopa equivalent daily dose; **MDS-UPDRS** = Movement Disorder Society–Unified Parkinson's Disease Rating Scale; **MMSE** = Mini-Mental State Examination; **OR** = odds ratio; **PD** = Parkinson disease; **PDD** = Parkinson disease with dementia; **ROC** = receiver operating characteristic; **SCFA** = short chain fatty acid; **TNF-α** = tumor necrosis factor–α.

Classification of Evidence

This study provides Class III evidence that gut metabolite SCFAs distinguish between patients with PD and controls and are associated with disease severity in patients with PD.

Emerging evidence suggests that the pathologic hallmarks of Parkinson disease (PD), Lewy bodies, originate in the gut enteric nervous system before the onset of motor dysfunction in patients with PD.[1] Studies in rodent PD models have shown that α-synuclein aggregations could propagate from the enteric nervous system to the brainstem through the vagus nerve.[1,2] Gastrointestinal symptoms may precede motor symptoms by decades.[3] This gut–brain hypothesis has led to numerous studies showing that patients with PD have a distinct gut microbiota structure compared with controls and that changes in gut microbiota correlate with disease severity and progression.[4-6]

Short-chain fatty acids (SCFAs) are the main metabolites produced by gut bacterial fermentation of dietary fiber and are speculated to be pivotal in gut–brain crosstalk.[7,8] SCFAs are absorbed in the colonocytes and transported to the liver via the portal venous system, and some SCFAs enter the systemic circulation. Acetic acid (C2), propionic acid (C3), and butyric acid (C4) are the most abundant SCFAs in the colon.[9] SCFAs have local effects in maintaining intestinal barrier integrity and shaping gut mucosal innate immunity.[10] They also have remote effects in the blood–brain barrier (BBB) by promoting tight junction proteins and crossing BBB to activate neurons through stimulation of G protein–coupled receptors.[11,12] An in vivo study using a transgenic α-synuclein–expressing mouse model demonstrated that a germ-free environment eliminates disease phenotypes but that oral feeding with SCFAs resurfaced PD-related neuropathology by augmenting neuroinflammation.[7] These findings suggest that SCFAs are required for the development of the PD process. However, results for SCFAs in patients with PD conflict with these findings. Compared with healthy controls, patients with PD have reduced fecal SCFAs and their producing bacteria compared to healthy controls.[8,13-15] Only a few studies have reported on circulating levels of SCFAs in patients with PD.[16,17] An integrated study examining both fecal and plasma levels of SCFAs is lacking. Hence, we aimed to analyze and compare fecal and plasma levels of SCFAs in patients with PD and unaffected controls to delineate the interrelations of these levels and link to changes in gut microbiota and clinical severity of PD.

Primary Research Questions

Our primary research question was to determine whether fecal and plasma levels of SCFAs could distinguish patients with PD from controls and correlate with disease severity in patients with PD.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

The investigation conformed to the principles outlined in the Declaration of Helsinki. The study protocol was approved by the institutional review board of National Taiwan University Hospital. All participants signed written informed consent.

Participants and Clinical Evaluation

A total of 96 patients with PD and 85 control participants were recruited from National Taiwan University Hospital. PD was diagnosed according to the United Kingdom PD Society Brain Bank Clinical Diagnostic Criteria.[18] Controls were neurologically unaffected participants who were spouses or accompanying friends of the patients with PD. Participants were excluded if they had previously used neuroleptic agents; had a history of inflammatory bowel disease, irritable bowel syndrome, colitis, colon cancer, or use of antibiotics or probiotic supplements within 3 months of enrollment; or were vegetarians. Of the enrolled participants, 30 patients with PD and 24 controls had also received 16S ribosomal RNA sequencing, which was previously published.[19]

A comprehensive dietary history was collected using the Food Frequency Questionnaire (FFQ).[20,21] We evaluated motor symptom severity with the Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III score[22] and Hoehn & Yahr staging during the "on" and "off" phase of PD.[23] During "off" phase, patients with Hoehn & Yahr stage <3 were classified as having early-stage PD and those with stage ≥3 as having advanced-stage PD. Cognition was assessed with the Mini-Mental State Examination (MMSE) during the "on" phase of PD.[24] PD with dementia (PDD) was diagnosed according to the criteria proposed by the Movement Disorder Society.[25] An MMSE score ≤25 was

applied as the cut-off value for significant cognitive impairment combined with any impairment in the 8 instrumental activities for the diagnosis of PDD.[26] The dosage of anti-PD medications during the study period was converted into a levodopa equivalent daily dosage (LEDD).

Measurement of Fecal and Plasma Levels of SCFAs

We collected 10 mL of venous blood and fresh feces from each participant. Blood was sampled in the morning after participants had fasted for at least 10 hours. Total fecal DNA was extracted using a QIAamp DNA Stool Mini Kit (Qiagen). Fecal SCFA analysis was performed using the fresh fecal sample collected in a plastic tube within 24 hours after collection. Dietary information was obtained on the same day as blood collection using a self-administered FFQ.[20,21] Fecal and plasma analyses for individual SCFAs were performed with gas chromatography–mass spectrometry and liquid chromatography–tandem mass spectrometry as described in eAppendix 1 (links.lww.com/WNL/B718).[27,28]

Measurement of Plasma Cytokine Levels

The plasma levels of proinflammatory cytokines, including interleukin-2, tumor necrosis factor–α, and interferon-γ (IFN-γ), were measured using the ProcartaPlex Human Th1/Th2 Cytokine Panel (Thermo Fisher Scientific) according to the manufacturer's instructions.

Gut Microbiota Analyses With Shotgun Metagenomic Sequencing

Fecal samples were collected into stool specimen collection tubes containing DNA stabilizer (Sarstedt), which were immediately flash-frozen on dry ice and stored at −80°C before analyses. Total fecal DNA was extracted using a QIAamp DNA Stool Mini Kit, as previously described and detailed in eAppendix 1 (links.lww.com/WNL/B718).[19]

Statistical Analysis

Continuous variables are expressed as mean ± SD and categorical variables as numbers and percentages. We tested the homogeneity of variances using the Levene test. Variables were compared with 2-tailed t tests or analysis of variance if normally distributed and with the nonparametric Mann-Whitney U test if assumptions of normality or homoscedasticity were violated. The concentrations of SCFAs in feces or plasma were log-transformed to achieve normal distribution before further analysis. A logistic regression model was applied to examine the relationship between SCFA levels and the occurrence of PD, with adjustment for age and sex. We used the area under the receiver operating characteristic (ROC) curve (AUC) to quantify the model's diagnostic performance for exploring the ability of SCFAs to distinguish between patients with PD and controls. To examine the associations between SCFAs and motor or cognitive symptom severity, we used multivariable linear regression models with MDS-UPDRS part III during "off" phase and MMSE scores as dependent factors. Independent variables included the log-transformed SCFA levels, age, sex, disease duration, LEDD,

and usage of entacapone. For shotgun sequencing and bioinformatic analysis,[29,30,31] details are addressed in eAppendix 1 (links.lww.com/WNL/B718).

Data Availability

The raw anonymized microbiome sequencing data were uploaded to the NCBI BioSample database (ncbi.nlm.nih.gov/biosample/) with the submission ID SUB10308106. Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

A total of 181 participants including 96 patients with PD (67.5 ± 11.5 years of age, 60.4% male) and 85 normal controls (64.8 ± 8.2 years of age, 48.2% male) were enrolled in this study. Of the enrolled patients with PD, 10 were drug-naive (10.4%), 12 had motor fluctuation (12.5%), and 9 experienced peak-dose dyskinesia (9.4%) (Table 1). Among the control participants, 73 (85.9%) were spouse controls. The dietary intake patterns in all participants in the past year using the FFQ are summarized in eTable 1 (links.lww.com/WNL/B718). Patients and controls did not differ significantly in demographics or dietary intake patterns, including fiber intake, which is the main dietary source of SCFAs.

Fecal and Plasma Levels of Different Types of SCFAs in Patients With PD and Controls

Patients with PD had significantly lower fecal concentrations of acetic acid ($p = 0.004$), propionic acid ($p = 0.006$), and butyric acid ($p = 0.003$) than controls (Table 1 and Figure 1, A–D). In contrast, plasma concentrations of circulating propionic acid ($p = 0.009$), butyric acid ($p = 0.004$), and valeric acid ($p = 0.047$) were increased in patients with PD compared to controls (Table 1 and Figure 2, A–D).

We first examined the possible influence of age on fecal and plasma SCFA levels. We found that age did not correlate with either measure for the individual SCFA types, except for plasma levels of isovaleric acid modestly correlating with age in controls ($\rho = −0.37$, $p = 0.016$). There were no significant correlations between fecal and plasma levels of the individual types of SCFAs (eFigure 1; links.lww.com/WNL/B718). We further observed that plasma levels of acetic acids correlated with IFN-γ ($\rho = 0.301$, $p = 0.003$) and showed a trend with TNF-α ($\rho = 0.197$, $p = 0.051$); plasma levels of butyric acids tended to correlate with IFN-γ ($\rho = 0.194$, $p = 0.06$) (eFigure 2).

We next examined whether fecal or plasma levels of individual SCFA types distinguished between patients with PD and controls. With adjustment for age and sex in multivariate logistic regression analysis, higher fecal levels of acetic acid (odds ratio [OR] 0.16, 95% confidence interval [CI] 0.04–0.57; $p = 0.006$), propionic acid (OR 0.20, 95% CI 0.06–0.60; $p = 0.006$), and butyric acid (OR 0.27, 95% CI 0.10–0.67; $p = 0.007$) were associated with a lower chance to be present in patients with

**Table 1** Clinical Characteristics and SCFA Levels in All Participants

	Healthy controls (n = 85)	Patients with PD (n = 96)	p Value
Age, y	64.8 ± 8.2	67.5 ± 11.5	0.075
Sex, male	41 (48.2)	58 (60.4)	0.100
Height, cm	163.3 ± 8.2	162.8 ± 8.0	0.653
Weight, Kg	64.6 ± 7.5	62.0 ± 10.4	0.155
BMI	24.2 ± 2.4	23.4 ± 3.4	0.182
Education, y	13.1 ± 2.2	12.8 ± 2.6	0.463
Diabetes mellitus	4 (4.7)	8 (8.3)	0.328
Hypertension	18 (21.2)	26 (27.1)	0.355
Hyperlipidemia	12 (14.1)	12 (12.5)	0.749
Disease duration, y	NA	6.1 ± 5.1	
Hoehn & Yahr stage ("off")	NA	2.3 ± 1.2	
Early stage	NA	59 (61.5)	
Advanced stage	NA	37 (38.5)	
Hoehn & Yahr stage ("on")	NA	1.8 ± 0.9	
MDS-UPDRS part III score ("off")	NA	27.5 ± 20.1	
MDS-UPDRS part III score ("on")	NA	17.3 ± 12.5	
Motor fluctuations	NA	12 (12.5)	
Peak-dose dyskinesia	NA	9 (9.4)	
MMSE score	NA	25.7 ± 6.5	
LEDD	NA	550 ± 474	
Use of entacapone	NA	12 (12.5)	
Fecal levels of SCFAs, μmol/g			
Acetic acid (C2)	386 ± 204	283 ± 210	0.004**
Propionic acid (C3)	145 ± 101	102 ± 85	0.006**
Butyric acid (C4)	69 ± 44	51 ± 55	0.003**
Isobutyric acid (iC4)	7.6 ± 4.8	7.8 ± 5.5	0.978
Valeric acid (C5)	9.2 ± 12.1	9.0 ± 9.6	0.839
Isovaleric acid (iC5)	4.7 ± 3.3	5.3 ± 3.9	0.479
Plasma levels of SCFAs, μM			
Acetic acid (C2)	48 ± 35	45 ± 39	0.359
Propionic acid (C3)	1.4 ± 0.7	1.8 ± 1.0	0.009*
Butyric acid (C4)	3.4 ± 2.3	4.0 ± 1.4	0.004**
Isobutyric acid (iC4)	0.25 ± 0.08	0.29 ± 0.12	0.091
Valeric acid (C5)	0.06 ± 0.05	0.10 ± 0.13	0.047*
Isovaleric acid (iC5)	0.29 ± 0.24	0.32 ± 0.25	0.248

Abbreviations: BMI = body mass index; LEDD = levodopa equivalent daily dose; MDS-UPDRS = Movement Disorder Society–Unified Parkinson's Disease Rating Scale; MMSE = Mini-Mental State Examination; NA = not available; PD = Parkinson disease; SCFA = short chain fatty acid.
Variables are expressed as mean ± SD or n (%).
*p < 0.05; **p < 0.01.

Figure 1 Comparison of Fecal Levels of Short Chain Fatty Acids in Patients With PD and Healthy Controls
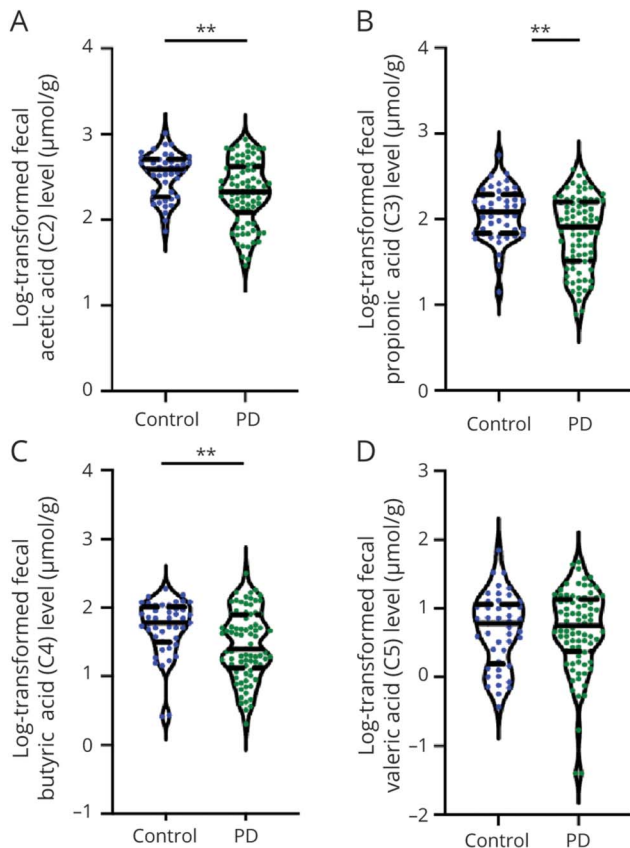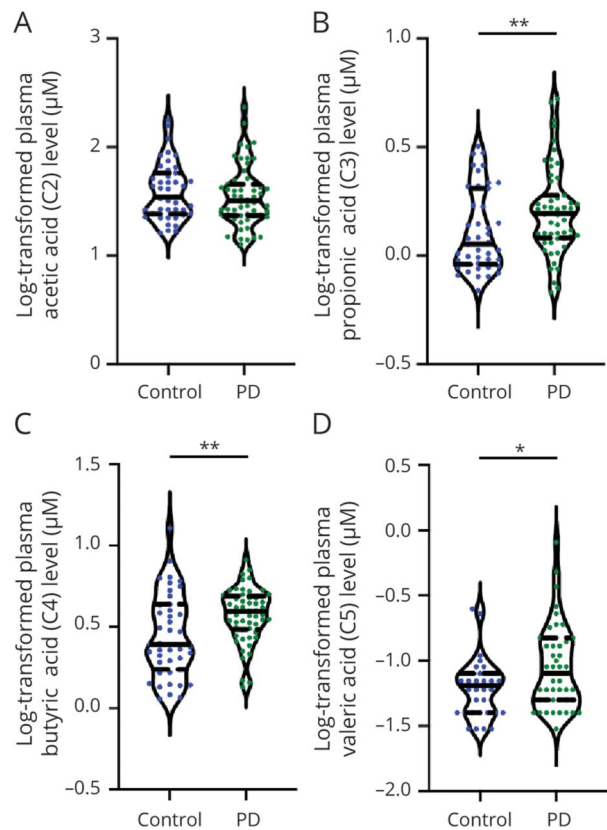

Violin plot shows data density and median with interquartile range (solid and dashed horizontal lines) for fecal levels of acetic acid (A), propionic acid (B), butyric acid (C), and valeric acid (D) in patients with Parkinson disease (PD) and unaffected controls. Mean ± SD (solid horizontal line, dashed horizontal line) is shown. *$p < 0.05$, **$p < 0.01$.

Figure 2 Comparison of Plasma Concentrations of Short Chain Fatty Acids in Patients With PD and Healthy Controls


Violin plot shows data density and median with interquartile range (solid and dashed horizontal lines) for plasma concentrations of acetic acid (A), propionic acid (B), butyric acid (C), and valeric acid (D) in patients with Parkinson disease (PD) and unaffected controls. Mean ± SD (solid horizontal line, dashed horizontal line) is shown. *$p < 0.05$, **$p < 0.01$.

PD. In contrast, the occurrence of PD was associated with higher plasma levels of propionic acid (OR 14.4, 95% CI 1.63–159; $p = 0.021$), butyric acid (OR 17.8, 95% CI 2.50–152; $p = 0.006$), and valeric acid (OR 8.70, 95% CI 1.49–67.3; $p = 0.025$) (eTable2, links.lww.com/WNL/B718).

Based on the results of the logistic regression analyses, we next performed ROC curve analysis to predict PD occurrence. The prediction accuracy, expressed as the AUC, improved from 0.55 in the basic model (age and sex; $p = 0.357$) to 0.65 with the addition of fecal levels of acetic acid, propionic acid, and butyric acid, which differed significantly between the PD and control groups in the multivariate logistic regression analysis ($p = 0.004$). The AUC was 0.67 with the addition of plasma levels of propionic acid, butyric acid, and valeric acid ($p = 0.003$), which differed significantly between patients with PD and controls in the multivariate logistic regression analysis. The AUC further improved to 0.72 ($p < 0.001$) in the full model, which included age, sex, and the fecal and plasma levels of the targeted SCFAs (Figure 3A and Table 2).

Fecal and Plasma SCFA Levels and Motor Symptom Severity

Fecal levels of acetic acid, propionic acid, butyric acid, and valeric acid were all significantly reduced in patients with advanced-stage PD compared to those with early-stage disease (all $p < 0.01$; eFigure 3A, links.lww.com/WNL/B718). In contrast, plasma levels of valeric acid were significantly increased in patients with advanced-stage disease compared to those with early-stage PD (advanced-stage vs early-stage: 0.18 ± 0.19 vs 0.06 ± 0.06 μM; $p = 0.003$; eFigure 3B). Furthermore, fecal levels of acetic acid ($\rho = -0.37$, $p = 0.005$), propionic acid ($\rho = -0.32$, $p = 0.015$), and butyric acid ($\rho = -0.40$, $p = 0.002$) negatively correlated with MDS-UPDRS part III motor scores (Figure 3, B–D). However, plasma levels of propionic acid trended to correlate with MDS-UPDRS part III scores ($\rho = 0.26$, $p = 0.086$; eFigure 3C).

After adjustment for age, sex, disease duration, LEDD, and entacapone use, multivariate linear regression analysis revealed negative correlations of MDS-UPDRS part III scores with fecal levels of acetic acid, propionic acid, butyric acid, and isobutyric

Figure 3 ROC Curves for Distinguishing Patients With PD From Controls and Correlations Between SCFA Levels and Clinical Motor Symptom Severity in Patients With PD
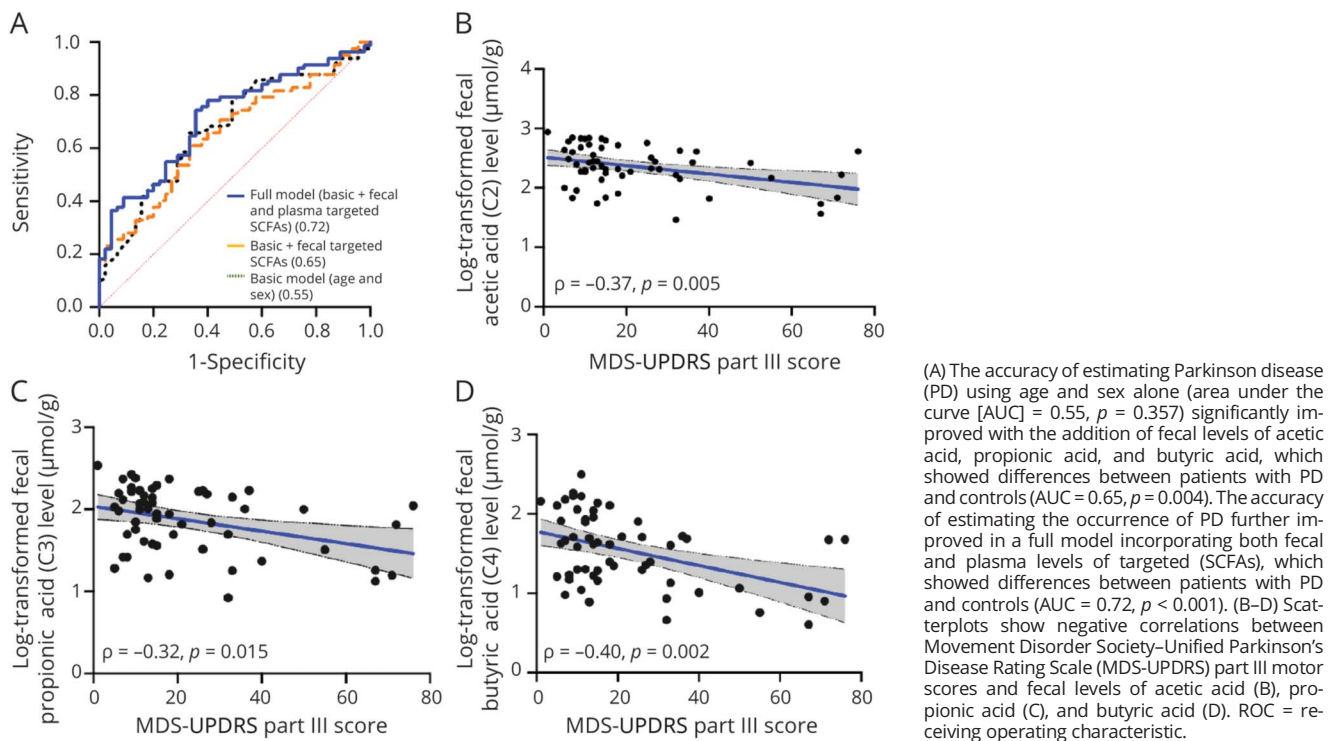
(A) The accuracy of estimating Parkinson disease (PD) using age and sex alone (area under the curve [AUC] = 0.55, p = 0.357) significantly improved with the addition of fecal levels of acetic acid, propionic acid, and butyric acid, which showed differences between patients with PD and controls (AUC = 0.65, p = 0.004). The accuracy of estimating the occurrence of PD further improved in a full model incorporating both fecal and plasma levels of targeted (SCFAs), which showed differences between patients with PD and controls (AUC = 0.72, p < 0.001). (B–D) Scatterplots show negative correlations between Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III motor scores and fecal levels of acetic acid (B), propionic acid (C), and butyric acid (D). ROC = receiving operating characteristic.

acid (Table 3). We included adjustment for LEDD and entacapone use in the multivariate analyses because of a recent study reporting that circulating propionic acid level is negatively correlated with entacapone use.[15] Plasma propionic acid levels positively correlated with MDS-UPDRS part III scores after adjustment for the covariates (coefficient = 24.4, 95% CI 1.00–47.7, p = 0.042; Table 3). These findings suggested that lower fecal levels of most SCFAs and increased plasma levels of propionic acid were associated with worse motor performance in patients with PD.

Fecal and Plasma SCFAs Levels and Cognitive Symptom Severity

Fecal levels of different types of SCFAs were comparable between patients with PD with normal cognition and those with PDD (eFigure 4A, links.lww.com/WNL/B718). However, plasma levels of isobutyric acid (0.37 ± 0.17 vs 0.26 ± 0.08 μM; p = 0.023) and valeric acid (0.19 ± 0.21 vs 0.07 ± 0.06 μM; p = 0.005) were significantly higher in patients with PDD than in patients with PD with normal cognition (eFigure 4B). Consistent with this pattern, plasma levels of isobutyric acid (ρ = −0.41, p = 0.014) correlated negatively with MMSE scores, and valeric acid levels showed a trend to negatively correlate with MMSE scores in patients with PD (ρ = −0.32, p = 0.070; eFigure 4C).

With adjustment for age, sex, disease duration, LEDD, and entacapone use in the multivariate linear regression model, plasma levels of butyric acid (coefficient = −11.7, 95% CI −21.9 to −1.44; p = 0.027) and valeric acid (coefficient = −6.58, 95% CI −12.6 to −0.60; p = 0.033) were persistently found to negatively correlate with MMSE scores (Table 3), whereas fecal levels of butyric acid positively correlated with MMSE scores (coefficient = 2.95, 95% CI 0.60–5.31; p = 0.015; Table 3). These findings suggested that lower fecal but higher plasma butyric acid and increased plasma valeric acid were associated with worse cognition in patients with PD.

Table 2 Receiver Operating Characteristic Association Statistics for Predicting Development of Parkinson Disease

	AUC (95% CI)	p Value
Basic (age, sex)	0.55 (0.44–0.67)	0.357
Basic + fecal acetic acid, propionic acid, and butyric acid	0.65 (0.56–0.75)	0.004**
Basic + plasma propionic acid, butyric acid, and valeric acid	0.67 (0.57–0.78)	0.003**
Full model[a]	0.72 (0.63–0.81)	<0.001**

Abbreviations: AUC = area under the receiver operating characteristic curve; CI = confidence interval.
The independent variables used in the models included continuous variables of age, fecal and plasma levels of log-transformed short chain fatty acid levels, and the categorical variable of sex.
[a] Full model indicated basic variables in addition to corresponding fecal and plasma targeted biomarkers.
**p < 0.01.

Table 3 Correlations Between Fecal and Plasma Levels of Individual Type of SCFAs and Symptom Severity in PD

	MDS-UPDRS part III score			MMSE score		
	ρ	Coefficient (95% CI)	*p* Value	ρ	Coefficient (95% CI)	*p* Value
Fecal level of SCFAs						
Acetic acid (C2)	−0.37	−17.6 (−31.0 to −4.14)	0.012*	0.08	2.07 (−1.33 to 5.46)	0.226
Propionic acid (C3)	−0.32	−13.2 (−25.4 to −0.93)	0.036*	0.09	1.44 (−1.44 to 4.32)	0.319
Butyric acid (C4)	−0.40	−16.1 (−26.9 to −5.28)	0.004**	0.17	2.95 (0.60 to 5.31)	0.015*
Isobutyric acid (iC4)	−0.17	−21.7 (−36.2 to −7.25)	0.004**	0.08	−0.22 (−4.01 to 3.57)	0.909
Isovaleric acid (iC5)	−0.14	−14.2 (−28.6 to 0.08)	0.051	0.03	−1.10 (−4.76 to 2.56)	0.548
Valeric acid (C5)	−0.24	−6.94 (−16.1 to 2.22)	0.134	−0.05	0.40 (−1.78 to 2.57)	0.714
Plasma level of SCFAs						
Acetic acid (C2)	−0.18	−0.05 (−19.1 to 18.9)	0.996	0.05	4.50 (−1.18 to 10.2)	0.115
Propionic acid (C3)	0.26	24.4 (1.00 to 47.7)	0.042*	−0.11	−0.57 (−8.85 to 7.71)	0.887
Butyric acid (C4)	−0.01	16.9 (−15.5 to 49.2)	0.297	−0.09	−11.7 (−21.9 to −1.44)	0.027*
Isobutyric acid (iC4)	0.11	26.0 (−5.27 to 57.3)	0.100	−0.41	−6.75 (−17.7 to 4.22)	0.216
Isovaleric acid (iC5)	−0.09	−6.33 (−25.9 to 13.2)	0.515	−0.29	−3.54 (−11.5 to 4.39)	0.364
Valeric acid (C5)	0.11	7.46 (−12.1 to 27.0)	0.440	−0.32	−6.58 (−12.6 to −0.60)	0.033*

Abbreviations: CI = confidence interval; MDS-UPDRS = Movement Disorder Society–Unified Parkinson's Disease Rating Scale; MMSE = Mini-Mental State Examination; SCFA = short chain fatty acid.
Spearman rank sum tests and multivariate linear regression models were applied to evaluate the correlations between SCFAs and disease severity and duration. In the regression models of disease severity, the severity of motor function (MDS-UPDRS part III motor score) or cognitive performance (MMSE) was the dependent factor. The independent variables included log-transformed SCFAs, age, sex, disease duration, levodopa equivalent daily dose, and use of entacapone. As for analyses of SCFAs and disease duration, disease duration was the dependent factor in the regression model and independent factors included log-transformed SCFAs, age, and sex.
*$p < 0.05$; **$p < 0.01$.

## Gut Microbiome Species Correlate With Plasma and Fecal Levels of SCFAs

Metagenomic analysis of gut microbiome species showed that the bacterial richness within each sample (α-diversity) tended to be higher in patients with PD than in healthy controls (eFigure 5A, links.lww.com/WNL/B718), which are consistent with previous studies.[19] The principal coordinates analysis revealed that patients with PD had different gut microbiota composition from healthy controls (β-diversity, analysis of similarities, $p = 0.05$; eFigure 5B).

We further explored the correlations between the relative abundance of gut microbiota and fecal or plasma levels of SCFAs. Heat maps representing Spearman correlations for the relative abundance of differential bacteria and SCFA concentrations in feces or plasma revealed that fecal levels of acetic acid, propionic acid, and butyric acid all correlated with the abundance of *Bacteroides sp AM16-15* and *Bacteroides sp AM25-34* in control participants (eFigure 6A, links.lww.com/WNL/B718). However, we did not find these positive correlations in patients with PD (eFigure 6B). Among patients with PD, the abundance of proinflammatory microbes, such as *Clostridiales bacterium NK3B98* and *Ruminococcus sp AM07-15*, significantly correlated with decreased fecal levels and increased plasma levels of SCFAs, especially propionic acid

(eFigure 6, B and C). Of note, plasma propionic acid levels were associated with PD occurrence and with motor symptom severity (Tables 2 and 3). Furthermore, the abundance of *Ruminococcus sp AM28-29LB* consistently correlated with reduced fecal levels of all SCFAs and increased plasma butyric acid (eFigure 6, B and C), which was associated with cognitive decline in PD (Table 3).

While combing the fecal and plasma SCFAs data as plasma-to-fecal ratios of the individual types of SCFAs, the abundance of *Clostridiaceae bacterium AF31-3BH* correlated with an elevated plasma-to-fecal ratio of propionic acid (Figure 4), a species closely related to *Clostridium bacterium*. The abundance of *Roseburia sp Am16-25* correlated with the plasma-to-fecal ratio of acetic acid, and the abundance of *Bifidobacterium bifidum* and *Eisenbergiella massiliensis* correlated with an increased plasma-to-fecal ratio of butyric acid, which also was increased in patients with PDD. Of note, the abundance of *Prevotella sp P3-122* was negatively associated with the plasma-to-fecal ratios of all measured SCFAs (Figure 4). Furthermore, as shotgun metagenomics analysis could provide extensive metabolic prediction capabilities, we observed that plasma levels of SCFAs, especially propionic acid, positively correlated with pathways of peptidoglycan maturation, guanosine nucleotides biosynthesis, L-aspartate and L-asparagine biosynthesis, and glycolysis IV
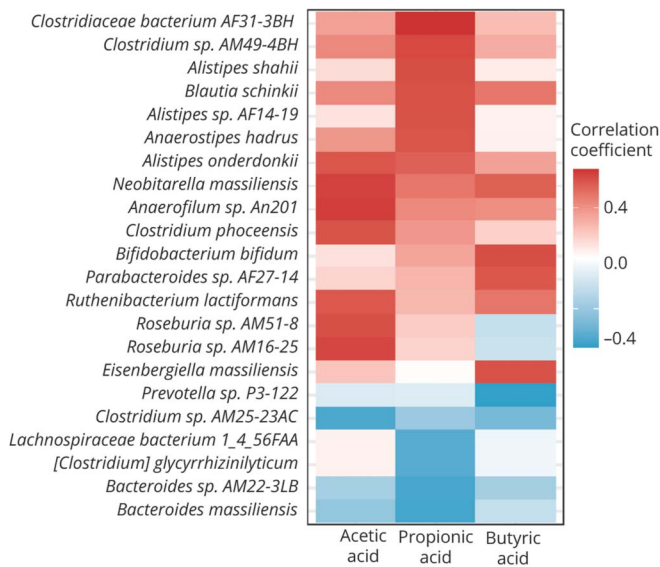
Correlations between plasma-to-fecal ratios of different types of short-chain fatty acids (SCFAs) in patients with Parkinson disease. The *r* values are represented by gradient colors, where red and blue cells indicate positive and negative correlations, respectively.

(eFigure 7, links.lww.com/WNL/B718). Taken together, these findings indicate that alterations in the abundance of specific gut microbiota species with related metabolic pathways in patients with PD relative to unaffected controls are associated with plasma and fecal levels of different SCFAs, which correlate with either motor or cognitive severity in PD.

Classification of Evidence

This study provides Class III evidence that gut metabolite SCFAs distinguish between patients with PD and controls and are associated with disease severity in patients with PD.

Discussion

To our knowledge, this is the first integrated study concomitantly examining both plasma and fecal levels of individual SCFA types and linking to changes in gut microbiota and symptom severity in patients with PD compared with unaffected controls. We found that patients with PD had lower fecal but higher plasma concentrations of SCFAs compared to controls. We further demonstrated that after adjustment for confounders, the reduced fecal levels but increased plasma levels of SCFAs associated with gut microbiota changes and the clinical severity of PD.

In stool, we observed lower levels of SCFAs in patients with PD than controls, in line with several studies that previously found reduced fecal SCFAs levels in patients with PD.[8,13-15] Similar to the findings of the current study, Tan et al.[14] also found an association between reduced fecal SCFAs and worse cognitive and motor outcomes, whereas Aho et al.[15] did not find correlations between fecal SCFAs and nonmotor symptom burden in PD. Consistently, recent evidence indicates that SCFAs-producing microbiota are also less abundant in association with PD disease severity, which predicts rapid motor and cognitive deterioration.[4,32] In addition, we found that reduced fecal levels of SCFAs could distinguish patients with PD from controls and extend the current knowledge that levels of these SCFAs negatively correlated with motor severity after adjustment for potential confounders. Moreover, cognitive decline is one of the most disturbing nonmotor symptoms of PD. We observed that reduced fecal levels of butyric acid also correlated with cognitive decline in patients with PD. Gut luminal SCFAs are absorbed in colonocytes and are beneficial for maintaining the intestinal barrier and homeostasis.[33] Reduced fecal SCFAs, especially butyric acid, are linked to the loss of intestinal tight junctions leading to leaky gut and increased intestinal inflammation, which is associated with aggravating the PD disease process.[33] In healthy controls of this study, we found a positive correlation of fecal acetic acid, propionic acid, and butyric acid levels with abundance of *Bacteroides sp AM16-15* and *Bacteroides sp AM25-34*, which are SCFA-producing microbiota.[34,35] Notably, this correlation was not present in patients with PD. In line with these findings, in a recent study in a European population, a positive correlation between SCFAs and relative abundance of *Bacteroides* genera was reported in controls but not in patients with PD. Our results support a previous study that found SCFAs-producing bacteria to be reduced in PD but not REM sleep behavior disorder, suggesting that SCFAs may play a role in the development of PD.[36]

In plasma, we identified contradictory results that patients with PD had higher plasma concentrations of SCFAs than controls, except acetic acid. Plasma levels of propionic acid correlated with motor symptom severity, whereas butyrate and valerate concentrations associated with cognitive decline. One recent study similarly found plasma propionate level to be higher in patients with PD than controls, while the plasma levels of acetic acid and propionic acid decreased in patients with multiple system atrophy compared to those with PD.[17] A case–control study in a Korean population also showed that plasma acetic acid was increased in patients with PD even though the level did not correlate with motor symptom severity.[16] Recent evidence also revealed that concentrations of SCFAs are elevated in saliva and urine in patients with PD compared to the general population.[15,37] Most of the SCFAs produced in the colon are absorbed and utilized by colonocytes, leaving only a minority entering the peripheral circulation.[12] The current findings demonstrate that systemic levels of SCFAs were increased even as fecal levels of SCFAs were consistently reduced in patients with PD. One possible explanation for this divergence may come from increased intestinal permeability that allows SCFAs to enter the systemic circulation, implying an intestinal barrier malfunction. In support of this hypothesis, increased fecal zonulin level, a

marker of gut permeability, and increased fecal calprotectin, a marker of gut inflammation, were recently reported in patients with PD compared to controls.[15] In vivo rodent model studies also have shown that one of the earliest pathologic changes in PD is intestinal inflammation with impaired intestinal tight junctions that allow for increased infiltration of gut microbial metabolites into the systemic circulation.[38] The "leaky gut phenomenon" in patients with PD may lead to a higher penetration of SCFAs from gut to the systemic circulation. However, among the subtypes of SCFAs, plasma level of acetic acid was not significantly increased in patients with PD. In addition to the possible leaky gut phenomenon effect, several conditions may contribute to the plasma levels of acetic acid. Acetic acid can be produced endogenously and the plasma level is influenced by metabolic stress, such as prolonged fasting, lipolysis, and glucagon-like peptide-1concentrations.[39] These factors may influence the observed comparable plasma levels of acetic acid between patients with PD and controls in this study. The elevated SCFAs in systemic circulation may cross the BBB and affect the neuron–microglia microenvironment in the CNS. Although accumulating evidence supports the beneficial effects of SCFAs, including maintaining BBB integrity and affecting neurogenesis through epigenetic mechanisms, SCFAs may also exert pathologic effects if the level is over a concentration range that was shown to promote neuroinflammation in a transgenic α-synuclein rodent model.[7] Further studies on the molecular mechanisms of different SCFAs at various concentration range in the CNS are warranted. Furthermore, while motor symptom severity positively correlated with plasma propionic acid levels, cognitive dysfunction correlated with circulating butyric acid and valeric acid concentrations. These associations may reflect the diverse pathophysiologic processes of motor and cognitive decline in PD.[37] Links between systemic levels of valeric acid and brain pathology also have been reported in patients with Alzheimer disease,[40] with higher plasma valeric acid associated with a greater degree of amyloid deposition and circulating inflammatory marker expression. In addition, levels of propionic acid in the systemic circulation correlated with motor symptom severity in the current work. In earlier studies, increased levels of this SCFA were reported to trigger mitochondrial dysfunction, activate T-cell immunity, and increase oxidative stress, especially in the striatum, leading to motor dysfunction in patients with autism spectrum disorder.[41] The positive correlations between plasma levels of SCFAs and inflammatory markers in this study could be interpreted as supporting a relevant association between SCFAs and systemic inflammation. Further experimental studies exploring the molecular mechanisms of individual types of SCFAs in promoting neuroinflammation and neurodegeneration are warranted.

The plasma-to-fecal ratio of individual types of SCFAs could provide a better landscape of individual SCFAs in the leaky gut condition of PD process. We observed that the plasma-to-fecal ratios of separated SCFAs types were linked to the respective abundance of specific gut microbiota. For example,

Bifidobacteria and *Bacteroides spp* produce acetate, whereas microbes from the Firmicutes phylum (*Roseburia*, *Eubacterium*, and *Lachnospira*) actively produce butyrate.[42] The *Bacteroides spp* are Gram-negative *Bacteroidetes* and predominate in the human gut. Acetic acid is the most abundant SCFA and acts in maintenance of the normal structure, integrity, and function of the intestines.[34] The absence of positive correlations between *Bacteroides spp* abundance and fecal levels of all types of SCFAs in patients with PD may suggest a dysbiosis state that leads to impaired intestinal barrier function in the disease process of PD.[34] In addition, among patients with PD, we found that abundance of the proinflammatory *Clostridiales bacterium* correlated with the plasma-to-fecal ratio of propionic acid, whereas the abundance of another proinflammatory microbe, *Ruminococcus sp AM28-29B*, correlated with an increased plasma level of butyric acid. *Clostridiales bacterium* and *Clostridiaceae* taxa, such as *Clostridium spp*, are also associated with inflammatory bowel disease.[43] The abundance of members of the *Clostridiales* order correlates positively with the regulatory T-cell transcription factor Foxp3, as does abundance of members of the phylum *Verrucomicrobia*.[44] We therefore speculate that *Clostridiales bacterium* and *Ruminococcus sp AM28-29B* may be able to induce intestinal regulatory immune responses leading to intestinal inflammation and possibly explain the increased plasma-to-fecal ratios of propionic acid and butyric acid. Of note, the abundance of *Prevotella spp P3-122* correlated with reduced plasma-to-fecal ratios of all SCFAs. Several studies, including our previous work, have shown a decreased abundance of *Prevotellaceae* and *Prevotella* genera in patients with PD.[6,19] As commensals, *Prevotellaceae* bacteria are involved in mucin synthesis in the gut mucosal layer and in production of neuroactive SCFAs through fiber fermentation.[45] The *Prevotella sp P3-122* may partially explain the decreased plasma-to-fecal ratio of all SCFAs in patients with PD. Finally, although numerous studies have shown that propionic acid and butyric acid have anti-inflammatory effects, results conflict.[7,13] Both pro- and anti-inflammatory activities of SCFAs have been documented, and dietary supplementation with SCFAs produces variable effects on inflammation that appear to be strongly influenced by SCFA concentration. Our further analysis showed plasma levels of SCFAs, especially propionic acids, positively correlated with peptidoglycan maturation pathway and glycolysis IV. Peptidoglycan is one of the pathogen-associated molecular patterns and has been shown to enhance proinflammatory cytokine secretion from activated microglia.[46] Glycolysis is the conversion of glucose to pyruvate or lactate, which results in the generation of ATP and has been shown to be abnormally regulated in neurons in patients with PD.[47] An in vivo model of zebrafish deficient in the familial PD–associated protein PTEN-induced kinase 1 observed an upregulation of TigarB, the ortholog of human TP53 induced glycolysis regulatory phosphatase (TIGAR).[48] Further investigation is needed into how different concentrations of individual SCFA types affect immune responses in the context of PD pathology.

Our study has several limitations. First, we did not directly measure colonic SCFA concentrations but used fecal SCFA

levels as a surrogate for colonic SCFA production and absorption. Second, we did not examine intestinal barrier function using a gut permeability assay in our participants, although one recent study has demonstrated gut hyperpermeability in patients with PD compared to controls.[15] Third, cognitive function was assessed using MMSE. Further detailed neuropsychological tests are needed for assessing the correlation between SCFA levels and individual cognitive domain decline in patients with PD. Fourth, dietary intake pattern assessed by FFQ was comparable between patients with PD and controls, while some other studies reported between-group differences.[49,50] As some controls enrolled in this study were spouses of the patients with PD, we speculate the common environment shared between spouse controls and patients with PD may contribute to the comparable dietary intake pattern between patients with PD and controls in this study. In addition, constipation and use of laxatives and anticholinergic agents or cholinesterase inhibitors may influence the results of gut microbiota and gut metabolites. Studies enrolling healthy controls from general populations and considering these potential confounders should be taken into account in the future. Furthermore, the diagnosis of PD was based on clinical diagnostic criteria in this study and lacks neuropathology confirmation. Finally, the cross-sectional study design precludes any inferences of a causal relationship between SCFAs and the disease process in PD. Further longitudinal follow-up studies with serial measurements of both fecal and plasma SCFAs are warranted.

Our findings suggest that gut metabolite SCFAs may serve as surrogate gut-oriented markers for distinguishing patients with PD from controls and reflecting disease severity. Further studies of the exact mechanisms of different SCFAs at neurons and microglia in experimental models should help to elucidate the complex gut–brain interactions in PD.

Disclosure
The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Appendix Authors

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Ya-Ting Lin, MSc	School of Pharmacy, College of Medicine, National Taiwan University, Taipei	Analysis or interpretation of data
Yu-Wei Wu, PhD	Graduate Institute of Biomedical Informatics, College of Medical Science and Technology, Taipei Medical University, Taiwan	Analysis or interpretation of data
Jyh-Ming Liou, MD, PhD	Division of Gastroenterology and Hepatology, Department of Internal Medicine, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei	Analysis or interpretation of data
Ming-Shiang Wu, MD, PhD	Division of Gastroenterology and Hepatology, Department of Internal Medicine, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei	Analysis or interpretation of data
Ching-Hua Kuo, PhD	School of Pharmacy, College of Medicine, and The Metabolomics Core Laboratory, NTU Centers of Genomic and Precision Medicine, National Taiwan University; and Department of Pharmacy, National Taiwan University Hospital, Taipei	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Chin-Hsien Lin, MD, PhD	Department of Neurology, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

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