

Association between dietary fiber intake and perioperative neurocognitive disorders in elderly arthroplasty patients: a mediation analysis of short-chain fatty acids

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Abstract

Background Perioperative neurocognitive disorders (PND) are common complications in elderly surgical patients, associated with adverse outcomes and increased healthcare burden. Dietary fiber intake has been linked to improved cognitive function and reduced risk of neurodegenerative diseases, but its relationship with PND remains underexplored. Short-chain fatty acids (SCFAs), metabolites of dietary fiber fermentation, may mediate this association through gut-brain axis interactions.

Methods This single-center prospective cohort study enrolled 442 elderly patients undergoing total knee or hip arthroplasty. Dietary fiber intake was assessed via a Food Frequency Questionnaire and participants were categorized into high (HDF) and low (LDF) intake groups. PND was diagnosed based on Z-scores derived from the Montreal Cognitive Assessment test (MoCA). Serum SCFAs levels were measured using LC-MS/MS. Propensity score matching and multiple logistic regression models were used to control for confounders. Mediation analysis was performed to evaluate the role of SCFAs.

Results The incidence of PND was significantly lower in the HDF group (13.4%) compared to the LDF group (25.9%) (RR=0.519, $P=0.002$). High dietary fiber intake was associated with reduced PND risk (OR=0.445, 95% CI: 0.266 to 0.743). SCFAs levels were significantly higher in the HDF group and were negatively correlated with PND risk. Mediation analysis indicated that dietary fiber had a significant negative direct, indirect (via SCFAs), and total effect on the risk of PND.

Conclusions Higher preoperative dietary fiber intake was significantly associated with a reduced risk of PND in elderly patients undergoing joint arthroplasty, and SCFAs may exert a complete mediating effect in this protective association. These findings support the potential of dietary fiber as a preventive strategy against PND, thereby highlighting the role of gut-derived metabolites in cognitive health.

Introduction

PND refers to cognitive dysfunction that arises in patients preoperatively, intraoperatively, or in the postoperative period. It encompasses a spectrum of manifestations ranging from mild cognitive decline to severe cognitive impairment. As one of the common postoperative complications in patients receiving anesthesia and surgery, it has a markedly higher incidence in the elderly[1]. The resulting cognitive decline exerts multidimensional impacts on patients, healthcare systems, and social families: for patients, it increases short-term risks such as infections and falls[2, 3], may lead to long-term cognitive impairment and raises the 1-year post-operative mortality rate[4, 5]; for healthcare systems, it prolongs hospital stays, increases costs and readmission rates, and necessitates long-term rehabilitation[6]; for social families, it exacerbates care burdens, adds extra expenses, and consumes social resources[7].

Currently, there is no specific therapeutic drug for PND, and nonpharmacological measures mainly target modifiable risk factors[8–10]. Additionally, prevention can proactively intervene in risk factors, thereby reducing the occurrence of diseases or mitigating their harms at the source[11]. Therefore, efforts should be focused on "prevention and mitigation" to address the clinical bottleneck. Dietary fiber is a type of carbohydrate that cannot be digested and absorbed in the human small intestine. Primarily derived from grains, fruits, and vegetables, it plays a crucial role in maintaining human health[12]. Several cohort studies have linked dietary fiber intake to enhanced cognitive function in US older adults and reduced risk of neurodegenerative diseases[13–15]. Prospective studies have also demonstrated that fiber-rich, plant-based dietary patterns and fruit/vegetable consumption are significantly associated with decreased risk of memory decline in older adults[16]. In a cohort study, higher habitual dietary fiber intake before surgery was associated with a lower risk of postoperative complications among patients[17]. Whereas, direct evidence linking dietary fiber intake to PND risk is scarce.

Bacterial fermentation of dietary fiber occurs predominantly in the colon, yielding metabolites, primarily SCFAs, which are then absorbed and utilized by the host. Notably, SCFAs have been found to mediate the crosstalk between the gut microbiota and the central nervous system, and they are being actively investigated as potential therapeutic agents for treating neurodegenerative diseases[18]. In patients with Parkinson's Disease (PD), fecal SCFAs levels were significantly reduced[19].

A similar manifestation occurs in another neurodegenerative disease, multiple sclerosis (MS). In the feces and blood of MS patients, significant decrease of acetate, propionate, and butyrate has been found[20].

To date, dietary fiber intake has been identified as an effective strategy for preventing both cognitive decline and neurodegenerative diseases, as evidenced by findings from animal models[21–23]. The results of these studies underscore the value of developing dietary strategies centered on fiber—interventions that not only enhance SCFAs production but also hold promise for slowing the advancement of neurodegenerative disorders among older adults. Herein, the aim of this study was to investigate the association between dietary fiber intake and the risk of PND in elderly patients undergoing joint replacement surgery, while accounting for potential mediating factors, and to provide a novel strategy for PND prevention in clinical practice.

Methods

Study design and population

This study is a single-center prospective cohort study approved by the Ethics Committee of the Hebei Medical University Third Hospital (NO.2024-093-1; Medicalresearch.org.cn:MR-13-25-036943; ChiCTR2300070834), to assess the risk factors for PND in the elderly orthopedic surgical patients. A total of 852 patients were enrolled from July 2024 to June 2025. In phase 1, patients were excluded if they were under 65 years of age, were not scheduled for total knee arthroplasty (TKA) or total hip arthroplasty (THA), or refused to sign the informed consent form. In phase 2, we excluded participants with cognitive impairment, hearing or visual impairment, psychiatric disorders, hepatic or renal failure, gastrointestinal dysfunction, or those who were lost to follow-up (Fig. 1). The characteristics of the analytic sample (n = 442) in our study are summarized in Table 1.

Dietary Fiber Intake assessment

The Food Frequency Questionnaire (FFQ) is employed to assess the average intake frequency and per-serving consumption of foods over a defined period in the past, as well as to estimate the long-term average dietary fiber intake of respondents [24]. The Spearman correlation coefficient between the FFQ and the Weighed Food Record (WFR) ranges from 0.36 to 0.77 [25]. Dietary fiber is typically obtained through the consumption of vegetables, fruits, whole grains, nuts, and other analogous foods. Based on the frequency selections provided by study participants, these values were converted into average daily intake frequencies (supplementary Fig. 1), which are then multiplied by the weight per serving to calculate the average daily intake of each food item [16]. Referring to the Chinese Food Composition Table, the dietary fiber content of the consumed foods is computed. Based on Reference[26] and the pilot study, participants' dietary fiber intake was sorted in ascending order and divided into four equal quantiles (Q1, Q2, Q3, Q4). To investigate the effect of different levels of dietary fiber intake on cognitive function, participants were classified into two groups based on intake quantiles: those with intake above the fourth quartile (Q4, top 25%) were designated as the exposed group, also referred to as the high dietary fiber intake group (HDF, 18.24 g/d), while those with intake below the first quartile (Q1, bottom 25%) were classified as the unexposed group, termed the low dietary fiber intake group (LDF, 8.32 g/d).

Neurocognitive assessment

To streamline the diagnostic process, the Montreal Cognitive Assessment (MoCA) is widely utilized for detecting mild cognitive impairment[27, 28]. To quantify the learning or practice effect, baseline scores were contrasted with scores from the 1-week test. This analysis generated the average practice effect ($\Delta X_{\text{control}}$) and its standard deviation [$SD(\Delta X_{\text{control}})$] for the control group. In this study, the control group was comprised 70 relatives of patients without surgical intervention, and the inclusion criteria matched those of the patient group. For each patient in the surgical group, the difference (ΔX) between their baseline score and the score obtained one week postoperatively was first calculated. Subsequently, this difference (ΔX)

was subtracted by the average practice effect of the control group ($\Delta X_{\text{control}}$), and the result was divided by the standard deviation of the control group [$SD(\Delta X_{\text{control}})$] to yield the Z-score for the individual test. A patient was defined as having PND when the Z-scores in individual tests were < -1.96 [29].

$$Z = (\Delta X - \Delta X_{\text{control}}) / SD(\Delta X_{\text{control}}) \text{ [30]}$$

Serum SCFAs concentrations

On the day prior to surgery and at 7 days postoperatively, 2 ml of fasting venous blood was collected from each patient following the standard operating procedure. After serum preparation, the samples were stored in a -80°C freezer for subsequent analysis. 100 μl of plasma sample was first placed into a 1.5 ml centrifuge tube. 10 μl of stable isotope-labeled internal standard working solution ($^{13}\text{C}_2$ -acetate, $^{13}\text{C}_3$ -propionate, $^{13}\text{C}_4$ -butyrate) was added, and the mixture was vortexed for 30 s. Subsequently, 400 μl of acetonitrile containing 0.1% formic acid was added, followed by vortexing for 1 min and ice bath incubation for 10 min. The sample was then centrifuged at 12,000 rpm (4°C) for 10 min, and 300 μl of the supernatant was passed through a 0.22 μm organic phase filter membrane. Gradient elution was performed with 0.1% formic acid aqueous solution (Phase A) and acetonitrile (Phase B): 90% B (0 ~ 2 min), a linear gradient from 90% B to 50% B (2 ~ 8 min), then return to 90% B (8 ~ 10 min). The column temperature was maintained at $30 \sim 35^{\circ}\text{C}$, the injection volume was 5 ~ 10 μl , and the flow rate was 0.3 ~ 0.4 ml/min. Detection of samples was performed using an LC-MS/MS system (AB Sciex 4000Q TRAP) in multiple reaction monitoring (MRM) mode. Set ion source parameters: spray voltage – 4500 V, ion source temperature $350 \sim 400^{\circ}\text{C}$. MRM ion pairs (precursor ion, product ions): acetate (m/z59, m/z43/29), propionate (m/z73, m/z57/43), butyrate (m/z87, m/z71/57). The coefficients of variation for acetate, propionate, and butyrate were 4.4%, 10.5%, and 10.8%.

Covariates

Potential confounders were selected based on DAGs (supplementary Fig. 2) and prior knowledge, which depicted the best known relations between the variables in this study[31–33]. Sociodemographic data collected at baseline included sex, age, weigh, height, educational level (illiteracy, primary school, middle school, senior high school, college). Health-related covariates assessed at baseline comprised ASA classification, comorbidities (hypertension, diabetes, coronary heart disease, chronic obstructive pulmonary disease and stroke), type of surgery, anesthesia time, anesthesia method, postoperative analgesia, surgical history and Chinese revised Mini-Mental State Examination (CMMS) score.

Statistical Analysis

Baseline characteristics of the analytical sample in the present study were described across two groups categorized by dietary fiber intake: categorical variables were presented as numbers (%), and continuous variables were presented as mean $\pm$ standard deviation (SD). Multiple imputation with chain equations was employed to handle missing data in this study, with the assumption that data were missing at random. For missing continuous variables, multiple linear regression was used for imputation, while binary variables were imputed via a logistic regression model. Six imputed datasets were generated, and the same statistical model was applied to each imputed dataset. These six sets of independent results were then integrated into one final comprehensive result in accordance with Rubin's pooling rules. With reference to [34] and the DAG to control confounding factors and reduce selection bias, we chose to adopt the Propensity Score Matching (PSM) method for analysis (Fig. 1).

- All statistical assumptions underwent testing prior to result interpretation, and the data met the required distributional criteria in all scenarios. Continuous variables were analyzed using independent samples t-tests; A McNemar was used to analyze the incidence of PND between the two patient groups. Univariate logistic regression was used to analyze the relationships between dietary fiber intake and PND, dietary fiber intake and SCFAs, as well as SCFAs and PND. Different logistic regression models were constructed by incorporating age, ASA classification, educational level, hypertension, CHD, and stroke[35]. Within the logistic regression model, the odds ratio (OR) and 95% confidence interval (95% CI) were

employed to quantify the association strength between the exposure and the outcome, with OR reflecting the effect size and 95% CI assessing statistical reliability.

- The receiver operating characteristic (ROC) curve and area under the curve (AUC) were employed to assess the predictive efficacy of the logistic regression model, offering critical support for both model optimization and real-world implementation. To clarify the mediating mechanism of SCFAs in the association between Dietary Fiber Intake and PND, this study utilized a structural equation model integrated with the Bootstrap sampling method (5000 repetitions) for validation, with the primary focus on testing the chain pathway of "Dietary Fiber Intake→SCFAs→PND". Specifically, the Bootstrap method was applied to calculate the 95% CI of the indirect effect, and the presence or absence of 0 within the CI served as the criterion for determining the statistical significance of the mediating effect. Additionally, based on the significance of the "direct effect of Dietary Fiber Intake on PND" derived from the model output, two mediation patterns were differentiated: partial mediation (characterized by a significant direct effect) and complete mediation (characterized by a non-significant direct effect). Furthermore, age, gender, and educational level were incorporated as control variables in the analysis to ensure the robustness of the results.

Sample size calculation

Studies have demonstrated that the mediterranean diet, characterized by high dietary fiber intake, confers a protective effect on cognitive function. Specifically, it reduces the risk of developing Mild Cognitive Impairment by 17%~27% and the risk of Alzheimer's Disease (AD) by 36%~40%[36–37]. Additionally, research data indicates that the incidence of PND among patients who have undergone joint replacement surgery ranges from 23.68% to 27.1%[10, 38, 39]. Drawing on proportional extrapolation of the aforementioned analogous effects and inferences from pilot study findings, we deduce that dietary fiber intervention may reduce the incidence of PND in post-joint replacement patients from 27% to 14%. To validate the efficacy of this intervention, sample size estimation was performed in the present study, with parameters set as follows: significance level ($\alpha = 0.05$) and statistical power ($1 - \beta = 0.9$). In the calculation process, assumptions included a PND incidence of 27% in the exposed group and 14% in the unexposed group. Additionally, a potential loss-to-follow-up rate of 10% was accounted for. The final analysis concluded that 221 participants are required per group, resulting in a total sample size of approximately 442 cases.

Sensitivity analyses

We conducted several additional sensitivity analyses to evaluate the robustness of our findings. First, the diagnostic criteria established by the study[30] were adopted to assess and diagnose PND based on Z-scores. Secondly, data regarding the total dietary fiber intake of study participants were collected using an FFQ. The participants were then grouped according to the quartiles of total dietary fiber intake within the cohort. Third, PSM was employed to control for potential confounding factors, where a 1:1 matching ratio was applied, and key variables including age, ASA classification, presence of hypertension, CMMS score, and educational level as matching variables, with only successfully matched samples included in the subsequent statistical analysis. Finally, we performed sequential sensitivity analyses to assess potential confounding by age and education: (1) excluding people aged 80 and above; (2) excluding illiterate individuals; (3) excluding people aged 80 and above, and excluding illiterate individuals.

All statistical analyses were performed in IBM SPSS Statistics 27.0 and R (R version 4.4.0). We used the following packages: mice, for imputation method; MatchIt, for PSM; mediation and dplyr, for single mediation effect analysis; lavaan, semTools and tidyverse, for total mediation effect analysis. A two-tailed significance level was set at $P < 0.05$.

Results

Baseline characteristics

This cohort study initially enrolled 852 patients. In the first phase, 63 patients were excluded due to age under 65 years, refusal to participate, or not being TKA or THA patients. During the second phase, an additional 347 patients were excluded based on criteria such as participants with a daily dietary fiber intake of 8.32 ~ 18.24g, psychiatric disorders, and visual or auditory abnormalities. Ultimately, 442 eligible patients were included in the study. After PSM, 201 patients were allocated to each of the LDF and HDF groups for final analysis (Fig. 1).

Table 1 displays the baseline patient data and MoCA Z-scores before and after PSM, stratified by the two dietary fiber intake groups. The mean age of participants in both groups was 73 years, with a male-to-female ratio of 150:51. No statistically significant differences were found in ASA classification, anesthesia, surgical details, or education level. Nevertheless, a significant difference was observed in the incidence of coronary heart disease (CHD) ($P = 0.001$). Additionally, the LDF group demonstrated significantly lower postoperative MoCA Z-scores compared to the HDF group. Figure 2 demonstrates the incidence of PND in the two groups: 52 cases (25.9%) in the LDF group and 27 cases (13.4%) in the HDF group. The risk ratio (RR) was 0.519, indicating a significantly lower incidence in the HDF group ($P = 0.002$)(Fig. 2).

Table 1
Comparison of demographic characteristics before and after PSM at baseline (mean $\pm$ SD/n [%])

	UnPSM		PSM					
	LDF (221)	HDF (221)	SMD	P value	LDF (201)	HDF (201)	SMD	P value
Age (year)	72.9 $\pm$ 4.6	74.2 $\pm$ 5.9	0.23	0.016	73.11. $\pm$ 4.72	73.48 $\pm$ 5.55	0.072	0.468
Sex				0.278				1
Female	158 (71.5)	169 (76.5)			150 (74.6)	150 (74.6)		
Male	63 (28.5)	52 (23.5)			51 (25.4)	51 (25.4)		
Weigh (kg)	67.1 $\pm$ 11.1	68.4 $\pm$ 10.1		0.172	67.2 $\pm$ 11.2	68.8 $\pm$ 10.1		0.153
Height (cm)	161.5 $\pm$ 7.6	161.1 $\pm$ 7.5		0.549	161.4 $\pm$ 7.6	161.3 $\pm$ 7.6		0.902
ASA			0.027	0.848			0.092	0.422
Ⅰ	98 (44.3)	95 (43.0)			84 (41.8)	93 (46.3)		
Ⅱ	123 (55.7)	126 (57.0)			117 (58.2)	108 (53.7)		
Hypertension	116 (52.5)	125 (56.6)	0.073	0.504	108 (53.7)	112 (55.7)	0.041	0.764
Diabetes	35 (15.8)	32 (14.5)		0.691	30 (14.9)	29 (14.4)		1
CHD	67 (30.3)	31 (14.0)		0.001	61 (30.3)	29 (14.4)		0.001
COPD	19 (8.6)	21 (8.5)			16 (8.0)	19 (9.5)		0.723
Stroke	69 (31.2)	52 (23.5)		0.07	52 (25.9)	49 (24.3)		0.818
Type of surgery								
TKA	137 (62.0)	138 (62.4)		0.922	126 (62.7)	125 (62.2)		0.918
THA	84 (38.0)	83 (37.6)			75 (37.3)	76 (37.8)		
Anesthesia time (min)	150.2 $\pm$ 39.3	149.3 $\pm$ 31.4		0.627	151.4 $\pm$ 40.2	148.3 $\pm$ 30.5		0.379
Anesthesia method								0.461
General anesthesia + nerve block	136 (61.5)	149 (67.4)		0.196	129 (64.2)	137 (68.2)		
Lumbar anesthesia	85 (38.5)	72 (32.6)			72 (35.8)	64 (31.8)		
Postoperative analgesia	207 (93.7)	209 (94.6)		0.686	125 (62.2)	128 (63.7)		0.595
Surgical history	20 (9.0)	36 (16.3)		0.022	20 (10.0)	32 (15.9)		0.461
Educational level			0.144	0.687			0.063	0.983
Illiteracy	20 (9.0)	18 (8.1)		0.734	14 (7.0)	12 (6.0)		

	UnPSM				PSM			
	LDF (221)	HDF (221)	SMD	P value	LDF (201)	HDF (201)	SMD	P value
Primary school	88 (39.8)	104 (47.1)		0.125	103 (51.2)	104 (51.7)		
Middle school	63 (28.5)	55 (24.9)		0.391	47 (23.4)	50 (24.9)		
Senior high school	28 (12.7)	26 (11.8)		0.39	22 (10.1)	22 (10.9)		
College	22 (10.0)	16 (8.2)		0.309	15 (7.5)	13 (6.5)		
CMMS score	27.7 ± 2.3	28.6 ± 4.2	0.066	0.576	28.4 ± 3.3	28.1 ± 4.2	0.043	0.396
MoCA z-score	-1.6 ± 1.3	-1.3 ± 1.0		0.001	-1.6 ± 1.2	-1.3 ± 0.9		0.005

UnPSM: Without propensity score matching. PSM: Propensity score matching. SMD: Standardized mean difference

CHD: Coronary heart disease. COPD: Chronic obstructive pulmonary disease. TKA: Total knee arthroplasty. THA: Total hip arthroplasty. CMMS score: Chinese revised Mini-Mental State Examination. MoCA z-score: Montreal Cognitive Assessment z-score

25.9%

Figure 2 Comparison of pnd incidence between exposed and unexposed groups

RR: relative risk

Association between different dietary fiber intake and PND

A binary logistic regression model was employed to analyze the relationship between dietary fiber intake and PND. The results indicated that a high dietary fiber intake acted as a protective factor, which was associated with a reduced incidence of PND (OR = 0.445, 95% CI: 0.266 to 0.743, $P = 0.002$). A similar result was observed after adjusting for the following covariates: age, ASA classification and educational level (OR = 0.434, 0.259 to 0.729, $P = 0.002$); comorbidities (OR = 0.406, 0.238 to 0.692, $P < 0.001$); anesthetic details (OR = 0.409, 0.239 to 0.698, $P < 0.001$); and surgical details (OR = 0.423, 0.248 to 0.723, $P = 0.002$)(Table 2).

Table 2

Association between different dietary fiber intake and PND using the Logistic regression method and sensitivity analysis

	unadjusted	Model 1	Model 2	Model 3	Model 4	Model 1'	Model 2'
	OR/95% CI	95% CI	95% CI	OR/95% CI	OR/95% CI	95% CI	95% CI
LDF	Reference	Reference	Reference	Reference	Reference	Reference	Reference
HDF	0.445 (0.266,0.743)	0.434 (0.259,0.729)	0.406 (0.238,0.692)	0.409 (0.239,0.698)	0.423 (0.248,0.723)	0.384 (0.217,0.680)	0.352 (0.192,0.638)
Note: OR: Odds Ratio.							
95% CI: Confidence interval							

unadjusted : Analyzed using the Logistic regression method, in which the variables were not adjusted.

Model 1: Analyzed using the Logistic regression method considering age, ASA and illiteracy.

Model 2: Analyzed using the Logistic regression method considering covariates age, ASA classification, illiteracy, hypertension, CHD and stroke.

Model 3: Analyzed using the Logistic regression method considering covariates age, ASA classification, illiteracy, hypertension, CHD, stroke, type of surgery and anesthesia time.

Model 4: Analyzed using the Logistic regression method considering covariates age, ASA classification, illiteracy, hypertension, CHD, stroke, type of surgery, anesthesia time and postoperative analgesia.

Sensitivity analysis:

Model 1': Analyzed using the Logistic regression method considering age (excluding people aged 80 and above), ASA classification and educational level.

Model 2': Analyzed using the Logistic regression method considering year (excluding individuals aged 80 and above), ASA classification and educational level (excluding illiterate individuals).

The ROC curve for Model 4 showed that the area under the curve (AUC) for predicting PND based on preoperative dietary fiber intake was 0.830 (95% CI:0.591 to 0.895 $P < 0.001$), indicating that preoperative dietary fiber intake has good predictive power for PND (supplementary Fig. 3). To ensure the robustness of our findings, a sensitivity analysis, which excluded patients aged over 80 and those with illiteracy, yielded consistent results (Table 2).

Association between different dietary fiber intake and SCFAs

We measured the plasma concentrations of SCFAs, including acetic acid, propionic acid, and butyric acid, in two patient groups before and after surgery. The results illustrated that the SCFAs levels were significantly higher in the HDF group than in the LDF group ($P < 0.001$)(Table 3). We further evaluated the relationship between dietary fiber intake and SCFAs (acetic acid, propionic acid, and butyric acid) levels. Using linear regression models, we found that dietary fiber intake had a significant positive effect on SCFAs concentrations (preoperative acetic acid: $\beta = 12.421$, 95% CI: 11.002 to 16.992, $P < 0.001$; propionic acid: $\beta = 0.341$, 95% CI: 0.214 to 0.819, $P < 0.001$; butyric acid: $\beta = 0.273$, 95% CI: 0.133 to 0.295, $P < 0.001$. Postoperative acetic acid: $\beta = 11.391$, 95% CI: 9.818 to 15.719, $P < 0.001$; propionic acid: $\beta = 0.304$, 95% CI: 0.265 to 0.657, $P < 0.001$; butyric acid: $\beta = 0.294$, 95% CI: 0.140 to 0.372, $P < 0.001$) both before and after surgery (supplementary table 1, 2).

Table 3
Comparative analysis of short-chain fatty acid concentrations in two patient groups before and after surgery($\mu\text{mol/L}$, mean $\pm$ SD)

Preoperative	LDF	HDF	P
Acetic acid	73.6 $\pm$ 13.43	87.5 $\pm$ 16.62	< 0.001
Propionic acid	5.7 $\pm$ 1.32	6.8 $\pm$ 1.71	< 0.001
Butyric acid	0.91 $\pm$ 0.33	1.11 $\pm$ 0.38	< 0.001
Postoperative			
Acetic acid	69.8 $\pm$ 13.6	82.6 $\pm$ 16.3	< 0.001
Propionic acid	5.4 $\pm$ 1.44	6.4 $\pm$ 1.52	< 0.001
Butyric acid	0.71 $\pm$ 0.31	0.92 $\pm$ 0.36	< 0.001

This association remained significant after adjusting for age, sex, and diabetes, indicating robust results (preoperative acetic acid: $\beta = 11.922$, 95% CI: 10.988 to 15.625, $P < 0.001$; propionic acid: $\beta = 0.339$, 95% CI: 0.208 to 0.614, $P < 0.001$; butyric acid:

$\beta = 0.244$, 95% CI: 0.134 to 0.256, $P < 0.001$. Postoperative acetic acid: $\beta = 10.891$, 95% CI: 9.787 to 13.509, $P < 0.001$; propionic acid: $\beta = 0.303$, 95% CI: 0.262 to 0.556, $P < 0.001$; butyric acid: $\beta = 0.285$, 95% CI: 0.141 to 0.373, $P < 0.001$) (supplementary table 1, 2).

Association between SCFAs and PND

We used a binary logistic regression model to analyze the relationship between SCFAs and PND. The results indicated a significant negative correlation between preoperative acetic (OR = 0.897, 95%CI:0.867 to 0.929, $P < 0.001$), propionic (OR = 0.373, 0.272 to 0.511, $P < 0.001$), and butyric acid levels (OR = 0.046, 0.014 to 0.154, $P < 0.001$) and the risk of PND, suggesting that SCFAs may be a protective factor against PND. This association remained significant after adjusting for confounding factors including age, sex, educational level, and anesthetic details. Of note, postoperative SCFAs also demonstrated a protective effect. Furthermore, sensitivity analyses, which excluded patients over 80 years of age and male patients, yielded results consistent with the above findings, confirming the robustness of the study's conclusions (Table 4).

Table 4
Association between SCFAs and PND using the Logistic regression method and sensitivity analysis

	unadjusted	Model 1	Model 2	Model 1'	Model 2'
	OR	OR	OR	OR	OR
	95% CI	95% CI	95% CI	95% CI	95% CI
Preoperative					
Acetic acid	0.897 (0.867, 0.929)	0.897 (0.865, 0.929)	0.895 (0.864, 0.928)	0.877 (0.840, 0.917)	0.868 (0.828, 0.910)
Propionic acid	0.373 (0.272, 0.511)	0.346 (0.245, 0.489)	0.347 (0.245, 0.490)	0.287 (0.187, 0.440)	0.282 (0.183, 0.436)
Butyric acid	0.046 (0.014, 0.154)	0.039 (0.101, 0.147)	0.041 (0.011, 0.152)	0.035 (0.008, 0.153)	0.027 (0.006, 0.132)
Postoperative					
Acetic acid	0.911 (0.881, 0.942)	0.900 (0.868, 0.990)	0.900 (0.868, 0.933)	0.900 (0.865, 0.936)	0.898 (0.859, 0.939)
Propionic acid	0.352 (0.253, 0.490)	0.307 (0.210, 0.443)	0.308 (0.211, 0.450)	0.276 (0.179, 0.425)	0.280 (0.170, 0.459)
Butyric acid	0.029 (0.007, 0.123)	0.025 (0.005, 0.113)	0.026 (0.006, 0.120)	0.031 (0.006, 0.160)	0.012 (0.001, 0.109)
Note: OR: Odds Ratio.					
95% CI: Confidence interval					

unadjusted

Analyzed using the Logistic regression method, in which the variables were not adjusted.

Model 1: Analyzed using the Logistic regression method considering age, sex, illiteracy, hypertension, CHD and stroke.

Model 2: Analyzed using the Logistic regression method considering age, sex, illiteracy, hypertension, CHD, stroke, anesthesia method and postoperative analgesia.

Sensitivity analysis

Model 1': Analyzed using the Logistic regression method considering age (excluding people aged 80 and above), sex, illiteracy, hypertension, CHD and stroke.

Model 2': Analyzed using the Logistic regression method considering age (excluding people aged 80 and above), sex (excluding male), illiteracy, hypertension, CHD, stroke, anesthesia method and postoperative analgesia.

The mediating role of SCFAs

- In the multiple mediation analysis with short-chain fatty acids (SCFAs) included as the mediator, the effect decomposition yielded the following results. For preoperative indicators, dietary fiber exerted a significant negative direct effect on the risk of postoperative neurocognitive dysfunction (PND) (Estimate = -0.601, 95% CI: -1.404 to -0.239, $P = 0.01$). Meanwhile, dietary fiber had a significant negative indirect effect on PND risk mediated by SCFAs (Estimate = -1.135, 95% CI: -3.918 to -0.601, $P = 0.007$). The total effect of dietary fiber intake on PND risk was also significantly negative (Estimate = -1.736, 95% CI: -2.746 to -0.771, $P = 0.002$). Collectively, these findings indicate that SCFAs play a partial mediating role in the association between dietary fiber and PND (Fig. 3A) .
- After adjusting for age, gender and diabetes status, the results of multiple mediation analysis were as follows. Preoperatively, dietary fiber showed a non-significant negative direct effect on the risk of PND (Estimate = -0.383, 95% CI: -1.244 to 1.552, $P = 0.067$). The indirect effect of dietary fiber on PND risk mediated by SCFAs was significantly negative (Estimate = -1.458, 95% CI: -4.060 to -1.656, $P = 0.006$). The total effect of dietary fiber intake on PND risk remained significantly negative (Estimate = -1.841, 95% CI: -3.768 to -0.883, $P = 0.005$) (Fig. 3B). These findings suggest that after adjustment for the above covariates, SCFAs exert a full mediating effect in the association between dietary fiber and PND.

In the simple mediation analysis, the direct effect of dietary fiber on PND was not statistically significant ($P > 0.05$). The indirect effects of dietary fiber on PND mediated by acetate, propionate and butyrate were significantly negative ($P < 0.001$). The total effect exerted a significant negative predictive effect on PND ($P < 0.002$) (Supplementary Fig. 4). After adjusting for age, sex and diabetes status, the simple mediation analysis revealed that the direct effect of dietary fiber on PND was not statistically significant ($P > 0.05$). The indirect effects of dietary fiber on PND mediated by acetate, propionate and butyrate were significantly negative ($P < 0.001$), and the total effect showed a significant negative predictive effect ($P < 0.002$) (Supplementary Fig. 5).

Discussion

- To our knowledge, this is the first cohort study to investigate the association between dietary fiber intake and PND, while also evaluating the mediating role of SCFAs. Our results indicate that higher dietary fiber intake before surgery is significantly associated with a lower incidence of PND in elderly patients undergoing joint replacement, with SCFAs acting as a mediating variable and playing a substantial protective role in this relationship.
- PND remains a globally recognized health concern. Effective preventive strategies can reduce the incidence of PND, thereby benefiting elderly patients. Previous studies have identified several interventions such as preoperative psychological interventions[33], active housework [8] and exogenous melatonin supplementation[40], which may help sustainably maintain cognitive reserve in individuals susceptible to POCD. Dietary fiber, defined as edible carbohydrates and related substances that are fully or partially fermented in the large intestine, plays a significant role in human metabolism and contributes to the prevention and management of various diseases[13, 17]. Few studies have investigated the association between dietary fiber intake and PND.
- In this study, we found that the incidence of PND was significantly lower in the high dietary fiber intake group compared to the low intake group, indicating a strong inverse association between dietary fiber consumption and PND. Consistent results were obtained after adjusting for potential confounding factors and in sensitivity analyses[3]. "Food is Medicine"

is an important concept increasingly emphasized in the fields of public health and clinical nutrition[41]. It refers to the use of scientifically designed dietary interventions such as tailored meal plans for managing diabetes and neurodegenerative diseases, to prevent and treat diseases, rather than relying solely on medication. This approach highlights the essential role of nutrition in health maintenance and therapeutic care. This information may help individuals make informed choices and take effective measures to prevent memory decline. Our findings further demonstrate that postoperative memory impairment is potentially modifiable. Although this study has not yet identified the precise mechanisms underlying these effects, they may include reducing the risk of cerebrovascular events, suppressing oxidative stress and inflammatory responses, and regulation of neurotransmitters[21, 42–44].

- SCFAs are produced through the fermentation of dietary fiber by colonic microbiota and play a crucial role in the regulation of neurodegenerative diseases. Our preliminary studies demonstrated that SCFAs can ameliorate PND by modulating the C1q complement system and the BDNF/PI3K/Akt signaling pathway[21, 22]. Analogously, previous research investigating the correlation between gut microbiota and stroke risk found that an increased risk of stroke is associated with the enrichment of opportunistic pathogens and reduced fecal butyrate levels[45]. First, the results of this study revealed a positive correlation between dietary fiber intake and plasma SCFA levels. Pre- and postoperative SCFAs levels were higher in the high dietary fiber intake group than in the low intake group. Secondly, the further analysis indicated that high plasma SCFAs levels were significantly associated with a lower incidence of PND. To verify whether SCFAs mediate the relationship between dietary fiber intake and PND, a mediation analysis was conducted. The results demonstrated that high dietary fiber intake significantly reduced the occurrence of PND. In the total effect model, dietary fiber intake had a significant negative predictive effect on the risk of PND. After controlling for SCFAs levels, the direct effect of dietary fiber on PND was positive but not statistically significant. These findings testify that SCFAs act as a suppressing variable in the relationship between dietary fiber and PND, exerting a strong protective effect.

Although numerous studies have explored the association between dietary fiber intake and diseases, few have focused on PND, which is a condition that can affect older adults undergoing surgery and differs from general cognitive dysfunction. The present study offered an opportunity to observe cognitive function in older adults with varying levels of dietary fiber intake. Furthermore, a comprehensive set of variables were incorporated into the analysis, including age, educational attainment, and clinically relevant factors. Additionally, preoperative and postoperative plasma SCFAs levels were included as mediating variables to conduct a mediation effect analysis. However, our study also has some limitations. First, as this was a single-center study with a relatively small sample size, the generalizability of our findings may be limited. Future multi-center studies are warranted for validation. Second, dietary fiber intake was assessed using an FFQ, which relies on subjective recall and is susceptible to measurement error. Third, cognitive function was assessed using only one neuropsychological test, which may not comprehensively reflect overall cognitive ability. Nevertheless, it is important to note that the MoCA is a well-established core tool for cognitive assessment, and we applied Z-score standardization to address large individual differences in cognitive outcomes, thereby enhancing comparability. Additionally, repeated testing within a short period might lead to practice effects, potentially inflating scores and undermining the accuracy of true cognitive performance. Fourth, in the mediation analysis, unmeasured factors (such as specific inflammatory markers) that influence both SCFAs and PND could introduce bias into the estimated mediation effect. Future studies should incorporate multi-center designs, more frequent biomarker measurements (e.g., inflammatory factors), standardized diagnostic criteria for PND, and more precise dietary assessment methods to further validate our findings.

Conclusions

In this cohort study, our findings demonstrate that higher preoperative dietary fiber intake is associated with a reduced risk of PND in older patients undergoing TKA or THA. Moreover, our analysis indicates that SCFAs mediate this association, serving as a significant mediating factor. This study offers valuable insights that may help inform strategies to protect older adults from postoperative cognitive impairment.

Declarations

Conflict of interest disclosure

The authors have no relevant financial or non-financial interests to disclose.

Availability of Data and Materials

The raw data supporting the findings of this study are not publicly available due to restrictions related to participant privacy. Relevant datasets can be obtained from the corresponding author upon reasonable formal request via email: wangqiujunxl@163.com.

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Figures

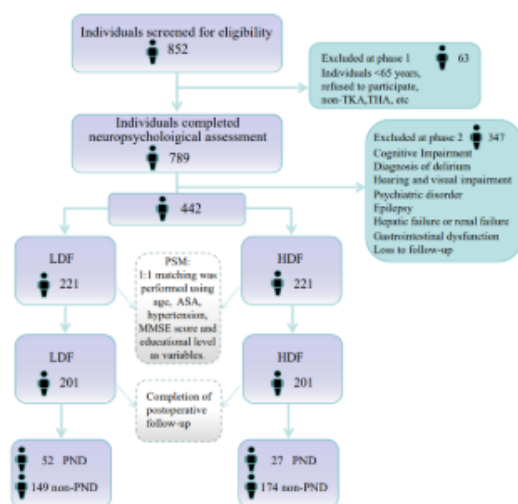


Figure 1

Flow diagram of participant selection and exclusion with PSM.

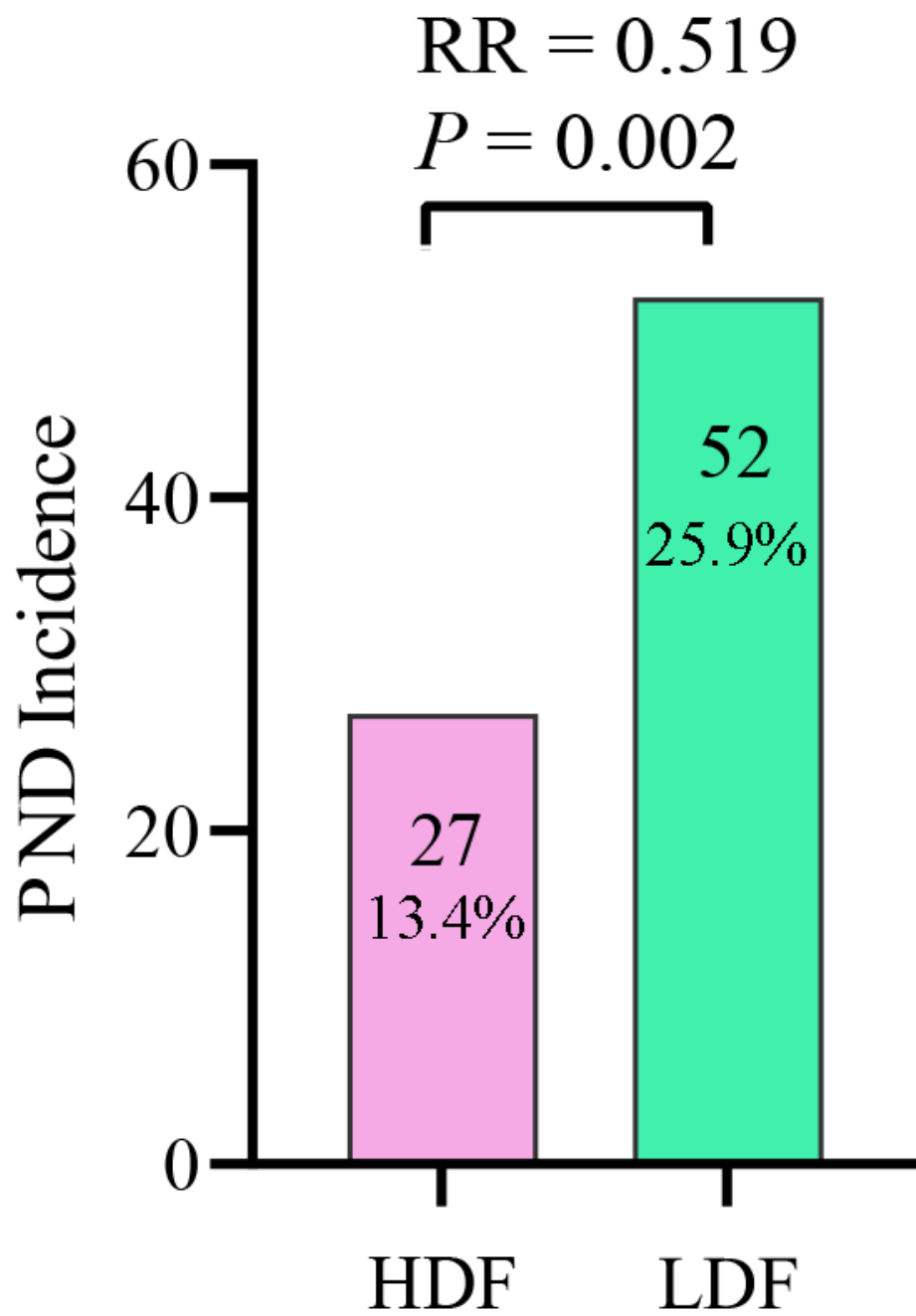


Figure 2

Comparison of pnd incidence between exposed and unexposed groups

RR: relative risk

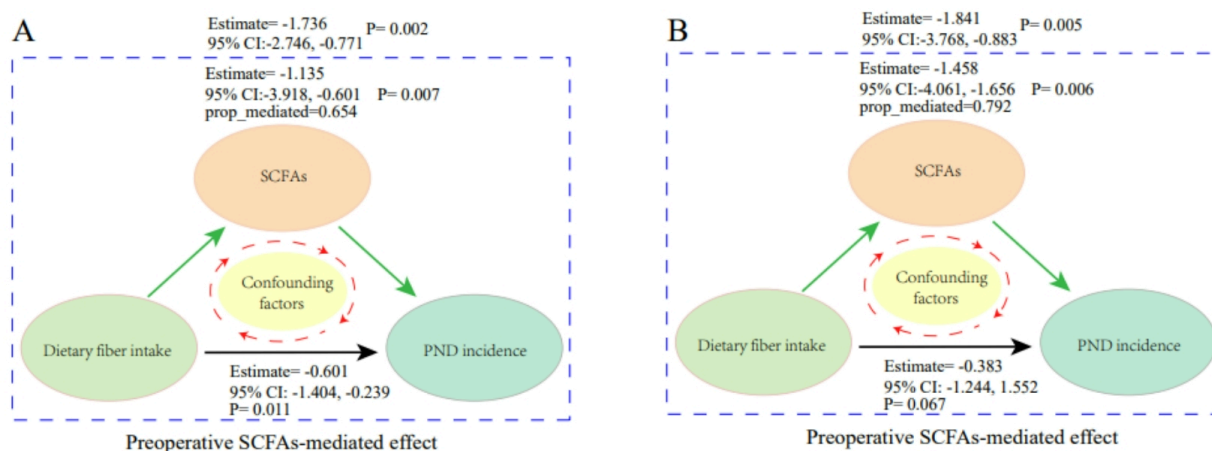


Figure 3

Mediation analysis focusing on SCFAs.

A. Multiple mediation analysis focusing on SCFAs in preoperation.

B. Multiple mediation analysis of preoperative SCFAs, adjusted for age, sex, and diabetes status.

Supplementary Files

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