The American Journal of Clinical Nutrition 122 (2025) 1579–1590

The American Journal of CLINICAL NUTRITION

journal homepage: https://ajcn.nutrition.org/

Original Research Article

Preoperative plasma short- and branched-chain fatty acids in relation to risk of complications after colorectal cancer surgery: a prospective cohort study

Niels Klaassen-Dekker [1,*], Erwin G Zoetendal [2], Edoardo Capuano [3], Renate M Winkels [1], Fränzel JB van Duijnhoven [1], N Tjarda van Heek [4], Flip M Kruyt [4], Arve Ulvik [5], Adrian McCann [5], Per Magne Ueland [5], Johannes HW de Wilt [6], Ellen Kampman [1], Dieuwertje E Kok [1]

[1] *Division of Human Nutrition and Health, Wageningen University & Research, Wageningen, The Netherlands;* [2] *Laboratory of Microbiology, Wageningen University & Research, Wageningen, The Netherlands;* [3] *Food Quality and Design Group, Wageningen University & Research, Wageningen, The Netherlands;* [4] *Department of Surgery, Gelderse Vallei Hospital, Ede, The Netherlands;* [5] *BEVITAL AS, Bergen, Norway;* [6] *Department of Surgery, Radboud University Medical Centre, Nijmegen, The Netherlands*

A B S T R A C T

Background: Emerging evidence suggests that nutritional prehabilitation reduces risk of complications after colorectal cancer (CRC) surgery. The gut microbiota and its metabolic activity potentially link preoperative diet to postoperative outcomes.

Objective: To investigate associations between preoperative plasma levels of microbial-derived metabolites and postoperative complications in patients with CRC.

Methods: We used data from a prospective cohort study among 1220 patients with nonmetastatic CRC. The short-chain fatty acids (SCFAs) acetate, propionate, butyrate, and valerate, as well as the branched-chain fatty acids (BCFAs) isovalerate, isobutyrate, and α-methylbutyrate, were measured in plasma collected at diagnosis. Prevalence ratios (PR) were calculated using regression models adjusted for age, sex, tumor location, smoking status, and physical health status.

Results: Acetate levels of 40.0 μmol/L were associated with a lower risk of any postoperative complications compared with the reference of 20.0 μmol/L [PR: 0.76; 95% confidence interval (CI): 0.62, 0.93]. Higher levels of propionate (per 1 μmol/L) were associated with a lower risk of any complications (PR: 0.84; 95% CI: 0.73, 0.96). Similar associations were found for acetate (per 20 μmol/L) and propionate (per 1 μmol/L) in relation to surgical complications (PR: 0.75; 95% CI: 0.60, 0.93; and PR: 0.83; 95% CI: 0.69, 1.00; respectively). No associations were found for BCFAs in relation to complications. Low (below median) total SCFA levels combined with high (above median) total BCFA levels were least favorable in terms of complication risk (PR: 1.35; 95% CI: 1.02, 1.80) when compared with a low SCFA/low BCFA profile.

Conclusions: Our findings suggest that microbial fermentation processes, mainly those resulting in higher SCFA levels, may be linked to postoperative recovery. These findings provide leads for future studies investigating the role of preoperative diet, especially the balance between fiber and protein intake, and microbial metabolism in relation to postoperative recovery of patients with CRC.

This study was registered at clinicaltrials.gov with registration number NCT03191110.

Keywords: microbial metabolites, short-chain fatty acids, colorectal surgery, postoperative complications, dietary fiber, protein, nutritional prehabilitation, colorectal cancer

Introduction

Colorectal cancer (CRC) is one of the most common cancers worldwide, with 1.9 million estimated new diagnoses in 2020 [1]. In Western countries, most patients with CRC undergo surgical resection of the primary tumor [2]. Up to one third of these patients experience postoperative complications [3], such as anastomotic leakage, surgical site infection, and ileus, which are associated with impaired quality of life, prolonged hospital stay, and higher mortality rates [3–5].

Abbreviations: ASA, American Society of Anesthesiologists; BCFA, branched-chain fatty acid; CI, confidence interval; COLON, COlorectal cancer: Longitudinal, Observational study on Nutritional and lifestyle factors; CRC, colorectal cancer; DCRA, Dutch ColoRectal Audit; LOD, limit of detection; NCR, Netherlands Cancer Registry; PR, prevalence ratio; SCFA, short-chain fatty acid.

* Corresponding author.
E-mail address: niels.klaassen@wur.nl (N. Klaassen-Dekker).

https://doi.org/10.1016/j.ajcnut.2025.10.001
Received 21 October 2024; Received in revised form 30 September 2025; Accepted 6 October 2025; Available online 10 October 2025

Earlier work in the Colorectal cancer: Longitudinal, Observational study on Nutritional and lifestyle factors (COLON) study showed that higher habitual dietary fiber intake before surgery was associated with a lower risk of postoperative complications [6]. Preclinical studies also hint toward a protective role of preoperative nutritional interventions (i.e., low-fat/high-fiber) in the context of postoperative recovery, although biological mechanisms have not been fully elucidated [7–10]. Emerging evidence suggests that the gut microbiota is involved in the pathogenesis of complications of abdominal surgery [11–13]. The gut microbiota interacts with the host, among others, via the production of microbial metabolites derived from fermentation of undigested dietary components such as fiber or protein [14,15]. These microbial metabolites could be absorbed by colonocytes and may subsequently appear in the systemic circulation [14].

The main products of fiber fermentation are short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate [16,17]. SCFAs serve as energy source for colonocytes, support gut barrier function, and can have anti-inflammatory effects [16,18–20]. Animal studies have shown that SCFAs increased anastomotic strength as well as collagen synthesis and maturation, which are important for wound healing [20,21]. Hence, these findings may point toward a protective role for SCFAs regarding complications after abdominal surgery.

When dietary fiber intake is low, the gut microbiota may switch from fermentation of fiber, referred to as saccharolytic fermentation, to fermentation of protein, called proteolytic fermentation [15,22]. Proteolytic fermentation results in production of several metabolites, including branched-chain fatty acids (BCFAs) such as isovalerate, isobutyrate, and α-methylbutyrate [15,23]. Although little is known about the impact of BCFAs on host physiology [15,24], increased production of BCFAs is often accompanied by production of other proteolytic metabolites, including hydrogen sulfide, p-cresol, and biogenic amines that are known to induce intestinal inflammation or damage the colonic epithelium [23,25]. Therefore, we speculate that increased BCFA production may have implications for colonic healing after surgery.

So far, clinical studies on SCFAs and BCFAs in the context of CRC surgery are lacking. Here, we investigated whether preoperative plasma SCFA and BCFA levels are associated with risk of postoperative complications and with length of hospital stay in patients with nonmetastatic CRC. Furthermore, the potential combined impact of plasma SCFA and BCFA levels on postoperative complications was evaluated, as we hypothesized that the balance between microbial saccharolytic and proteolytic fermentation is important for recovery after CRC surgery.

Methods

Patients

We used data from the COLON study, which has been described in detail before [26]. Briefly, the COLON study is a prospective cohort study among 2107 patients with CRC, focusing on diet and other lifestyle factors that may influence tumor recurrence, survival, and quality of life. Patients newly diagnosed with CRC were recruited from 11 hospitals in the Netherlands between 2010 and 2020 and followed during and after treatment. Both men and women, aged ≥18 y, with any stage of disease were included. Non-Dutch-speaking patients, or patients with a history of CRC or (partial) bowel resection, inflammatory bowel disease, hereditary CRC syndromes, or a mental condition affecting abilities to complete questionnaires were not included in the study. All participants provided written informed consent. The COLON study was approved by the Committee on Research involving Human Subjects, region Arnhem-Nijmegen, the Netherlands (2009–349), and was registered at clinicaltrials.gov with identifier NCT03191110. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology guideline.

For this study, we used the data of patients with stage I–III CRC who provided preoperative blood samples (Figure 1). Patients with stage IV disease ($n = 141$) were excluded, as metastases in major organs (especially liver) may affect circulating SCFA and BCFA levels [27]. Patients who did not undergo surgery ($n = 17$), underwent nonelective surgery ($n = 6$), underwent transanal endoscopic surgery ($n = 16$), had hyperthermic intraperitoneal chemotherapy ($n = 2$), had a blood sample drawn after surgery ($n = 40$), or missing date of blood draw ($n = 10$) were also excluded from analyses. Additionally, patients with missing data on postoperative complications ($n = 109$) were excluded, resulting in a study population of 1220 patients (Figure 1).

Preoperative circulating SCFA and BCFA levels

Nonfasted venous blood samples were drawn in EDTA-tubes around the time of diagnosis. All blood samples were centrifuged and aliquoted according to standardized protocols and plasma was stored at –80°C until further analysis. Plasma levels of the SCFAs acetate, propionate, butyrate, and valerate, and the BCFAs isovalerate, isobutyrate, and α-methylbutyrate were measured at BEVITAL AS (www.bevital.no). The method, using stable isotope-labeled internal standards for all analytes, involved sample precipitation using acetonitrile and a benzyl alcohol/pyridine/methylchloroformate mix for derivatization, before extraction with hexane followed by quantification with GC-MS/MS (Agilent 6890A GC coupled to a Waters Quattro microTM MS in electron ionization mode using CP-Sil 24-CB capillary column – 15 × 250 × 0.25 μm). Automated sample processing for all samples, calibrators and quality controls was performed by a robotic workstation. Limit of detection (LOD) for the method ranged between 0.02 μmol/L for isovalerate and 5.0 μmol/L for acetate, and within- and between-day coefficient of variation ranged between 2.7% and 4.6% and 4.3% and 6.0%, respectively. The GSimp imputation procedure [28] was used to impute (left-censor) missing data due to measures that were below the LOD (butyrate: $n = 49$, LOD = 0.2 μmol/L; valerate: $n = 454$, LOD = 0.05 μmol/L; α-methylbutyrate: $n = 24$, LOD = 0.05 μmol/L).

Clinical outcomes

Hospital records and linkage with the Dutch ColoRectal Audit (DCRA) [29] and Netherlands Cancer Registry (NCR) were used to obtain clinical data. Traditionally, complications occurring within 30 d after surgery were reported in the DCRA. However, the DCRA prolonged postoperative follow-up to 90 d after surgery since 2018, which was the case for 132 patients (11%) in our study population. Occurrence of postoperative complications during these 30 or 90 d is recorded as yes/no and incidence dates are not available. Clinical outcomes considered for this study were *1*) any postoperative complications, *2*) surgical postoperative complications, and *3*) anastomotic leakage. Any complications included surgical and all other postoperative complications (e.g., pulmonary, neurological, infectious, or cardiac) occurring within 30 or 90 d after surgery. Surgical postoperative complications included among others anastomotic leakage, surgical site infection, and ileus. Data on anastomotic leakages were retrieved from the NCR. Anastomotic leakage was only considered in patients with an anastomosis ($n = 1100$) and was defined as an anastomotic leakage requiring a reintervention within 2 mo after surgery.

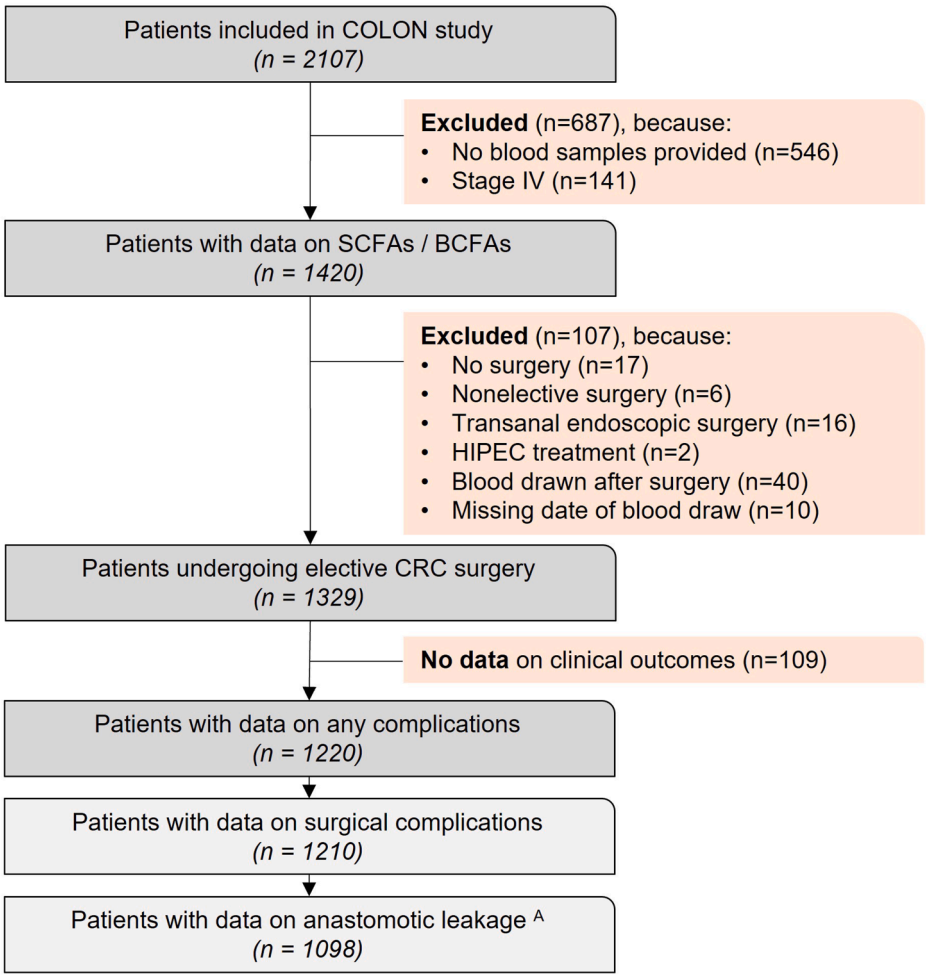


FIGURE 1. Flow diagram showing the number of patients included in the study. BCFA, branched-chain fatty acid; CRC, colorectal cancer, HIPEC, hyperthermic intraperitoneal chemotherapy; SCFA, short-chain fatty acid. [a]Of 1100 patients having an anastomosis.

Additionally, length of hospital stay was considered as clinical outcome because complications often result in prolonged hospital stay, and length of hospital stay is commonly used to examine effectiveness of prehabilitation programs before surgery [30,31]. On the basis of data of the DCRA, length of hospital stay was defined as the number of days between date of surgery and date of discharge from the hospital. When data on hospital stay were missing in the DCRA ($n = 4$), we used data on hospital stay from the NCR. Patients ($n = 6$) who died in the hospital (between 1 and 35 d after surgery) were excluded from the analyses regarding length of hospital stay.

Other relevant disease or treatment characteristics, including cancer stage (I, II, III), tumor location (colon, rectum), surgical approach (open, laparoscopic), temporary or permanent end stoma created during surgery (yes, no), physical health status of the patient before surgery based on classification of the American Society of Anesthesiologists (ASA-score I, II, III, and IV), and neoadjuvant radiotherapy or chemoradiotherapy (yes, no) were obtained from hospital records and linkage with the DCRA and NCR. Type of surgery was retrieved from the NCR and classified as *1*) hemicolectomy ($n = 445$), *2*) sigmoid resection ($n = 265$), *3*) low anterior resection ($n = 406$), *4*) abdominoperineal resection ($n = 80$), and other resections ($n = 24$). Other resections include transversectomy ($n = 11$), subtotal colectomy ($n = 10$), total colectomy ($n = 1$), and unspecified ($n = 2$).

Descriptive data and covariates

Relevant sociodemographic and lifestyle factors were obtained through questionnaires completed by the patients at time of diagnosis. BMI (in kg/m^2) was calculated based on self-reported weight and height. Smoking status was self-reported as current, former, or never smoker. The validated Short QUestionnaire to ASsess Health-enhancing physical activity was used to assess the level of moderate-to-vigorous physical activity in minutes per week [32]. Plasma levels of creatinine (μmol/L) were also analyzed at BEVITAL AS (www.bevital.no) by liquid chromatography-tandem mass spectrometry and considered as a potential confounder (log2-transformed) to adjust for potential differences in renal clearance of SCFAs and BCFAs.

Data analysis

Baseline characteristics of patients are presented as median and interquartile range (Q1–Q3) or numbers and percentages. Spearman correlations across plasma levels of SCFAs and BCFAs were calculated. Only correlations with a Bonferroni-adjusted P value ($P < 0.05/21$) are depicted in the correlation plot. Differences in plasma levels of SCFAs and BCFAs between patients with and without complications were tested using Mann-Whitney U tests.

All regression analyses were adjusted for age (continuous in years), sex (female, male), tumor location (colon, rectum), smoking status

(current, former, never), and ASA classification (I, II, III–IV). These variables are known to be associated with postoperative complications [5,33,34], or were used as covariates in earlier studies [35,36]. Other potential confounders, including BMI (continuous in kg/m^2), neoadjuvant radiotherapy or chemoradiotherapy (yes, no), cancer stage (I, II, III), type of resection (hemicolectomy, sigmoid resection, low anterior resection, other), surgical approach (open, laparoscopic), and creatinine levels (continuous in μmol/L) were added one by one to the models. Because none of these variables changed the risk or effect estimates by >10%, these variables were not included in the final models, except for analyses regarding length of hospital stay that were also adjusted for surgical approach (open, laparoscopic).

Restricted cubic splines, based on multivariable-adjusted Cox proportional hazards regression analyses with a constant time variable, were used to investigate linearity of the associations between SCFA and BCFA levels and any complications, surgical complications, and anastomotic leakage. Knots were placed at the 10th, 50th, and 90th percentiles, and the graphs were truncated at the first and 99th percentile. The median intake of the first tertile of each metabolite was used as the reference. The Wald chi-square test was used to test nonlinearity of the associations. If evidence of nonlinearity was found ($P_{\text{non-linearity}} < 0.05$), the data from the restricted cubic spline were used to calculate the prevalence ratio (PR) and 95% confidence intervals (95% CI). If no evidence of nonlinearity was found, the PRs

TABLE 1
Baseline characteristics of the study population by occurrence of any postoperative complications.

	Overall (n = 1220)	Any complications (n = 1220)	
		No 852 (70%)	Yes 368 (30%)
Age at diagnosis (y)	67 (61–72)	66 (61–72)	67 (62–73)
Sex			
Female	449 (37%)	342 (40%)	107 (29%)
Male	771 (63%)	510 (60%)	261 (71%)
BMI[1] (kg/m^2)	26.2 (24.0–29.0)	26.1 (23.9–28.9)	26.4 (24.0–29.1)
Smoking[2]			
Current	127 (11%)	65 (8%)	62 (18%)
Former	717 (60%)	521 (62%)	196 (56%)
Never	343 (29%)	250 (30%)	93 (26%)
Physical activity[3] (min/wk)	685 (330–1200)	720 (345–1200)	660 (330–1140)
Tumor location			
Colon	810 (66%)	608 (71%)	202 (55%)
Rectum	410 (34%)	244 (29%)	166 (45%)
Cancer stage			
Stage I	342 (28%)	250 (29%)	92 (25%)
Stage II	350 (29%)	248 (29%)	102 (28%)
Stage III	528 (43%)	354 (42%)	174 (47%)
Received neoadjuvant radio- or chemoradiotherapy	268 (22%)	150 (18%)	118 (32%)
ASA classification[4]			
Score I	379 (31%)	297 (35%)	82 (22%)
Score II	681 (56%)	463 (54%)	218 (59%)
Score III–IV	159 (13%)	92 (11%)	67 (18%)
Type of surgery			
Hemicolectomy	445 (36%)	328 (38%)	117 (32%)
Sigmoid resection	265 (22%)	212 (25%)	53 (14%)
Low anterior resection	406 (33%)	250 (29%)	156 (42%)
Abdominoperineal resection	80 (7%)	48 (6%)	32 (9%)
Other[5]	24 (2%)	14 (2%)	10 (3%)
Surgical approach[6]			
Open	254 (21%)	174 (21%)	80 (22%)
Laparoscopic	945 (79%)	668 (79%)	277 (77%)
Anastomosis[7]	1100 (91%)	780 (92%)	320 (88%)
Stoma after surgery[8]	338 (28%)	179 (21%)	159 (44%)
Length of hospital stay[9] (d)	5 (4–9)	5 (4–6)	11 (7–18)

Abbreviation: ASA, American Society of Anesthesiologists.
Median (interquartile range; Q1–Q3) are reported for continuous variables, and counts (%) for categorical variables.
[1] Data were missing for n = 5.
[2] Data were missing for n = 33.
[3] The level of moderate-to-vigorous physical activity. Data were missing for n = 36.
[4] Physical health status before surgery based on classification of the American Society of Anesthesiologists (ASA-score). Data were missing for n = 1.
[5] Other resections include transversectomy (n = 11), subtotal colectomy (n = 10), total colectomy (n = 1), unspecified (n = 2).
[6] Data were missing for n = 21.
[7] Data were missing for n = 5.
[8] Both temporary and permanent stomas created during surgery. Data were missing for n = 21.
[9] Data of patients (n = 6) who died in the hospital (between 1 and 35 d after surgery) were not considered in this table, and also excluded from the analyses regarding length of hospital stay.

and 95% CIs were calculated using multivariable-adjusted Cox proportional hazards regression analyses with a constant time variable and continuous increment in metabolite levels.

Associations between plasma metabolite levels and length of hospital stay were investigated using multivariable-adjusted linear regression analyses calculating betas and 95% CIs. Length of hospital stay, and metabolite levels were log2-transformed to meet the assumption on normality of the distribution, and therefore metabolites levels are modeled per doubling in metabolite level.

To investigate the potential combined impact of plasma SCFA and BCFA levels on postoperative complications, the patients were categorized in 4 groups based on the median split for total SCFA and total BCFA levels: low SCFA/low BCFA ($n = 358$, reference group); low SCFA/high BCFA ($n = 252$); high SCFA/low BCFA ($n = 252$); and high SCFA/high BCFA ($n = 358$). Associations for each of the SCFA/BCFA profiles (in comparison with the low SCFA/low BCFA group) and any complications, surgical complications, anastomotic leakage were investigated using multivariable-adjusted Cox proportional hazards regression analyses with a constant time variable. Associations for each of the SCFA/BCFA profiles and length of hospital stay were investigated using multivariable-adjusted linear regression analyses.

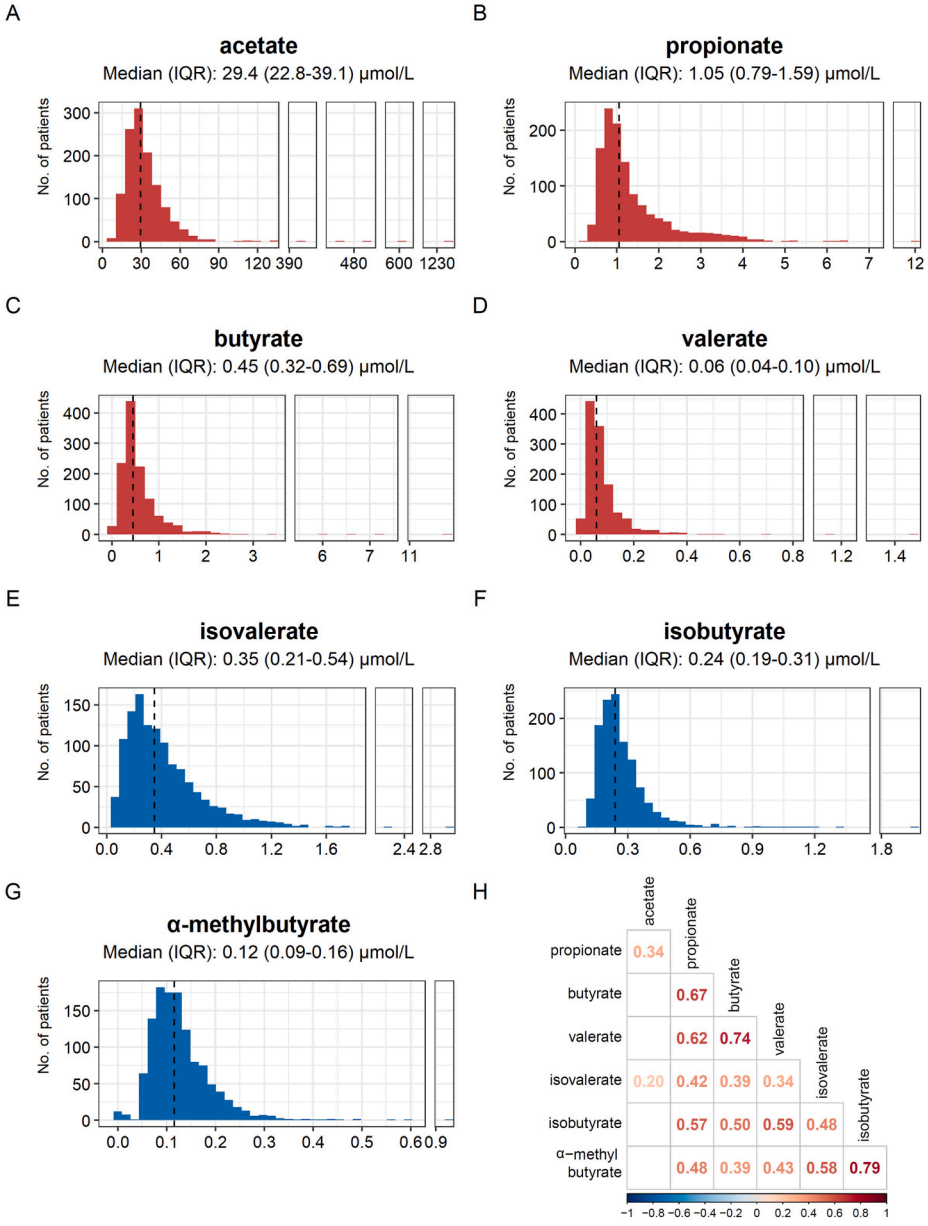


FIGURE 2. (A–G) Histograms of preoperative plasma levels of short-chain fatty acids (red) and branched-chain fatty acids (blue) of patients with colorectal cancer undergoing surgery. Dashed lines indicate median concentrations. All values are presented in µmol/L. (H) Heatmap showing the Spearman correlation coefficients. Only statistically significant (Bonferroni-corrected P value: $P < 0.0024$) correlations are depicted. Coloring indicates the strength of the correlations according to the legend at bottom of the heatmap. IQR, interquartile range = Q1–Q3.

All data analyses were performed using R Statistical Software (version 4.2.1). Analyses were not adjusted for multiple testing given the hypothesis-driven nature of the work and the relatively limited number of metabolites that were studied. A 2-sided P value <0.05 and 95% CIs not containing 1 for PRs or 0 for betas were considered statistically significant.

Results

Characteristics of the study population

Within the context of a prospective cohort study, we used data of 1220 patients with stage I–III CRC who underwent elective surgery. The median (quartiles 1–3, Q1–Q3) age at diagnosis was 67 (61–72) y, 63% were men, and 66% and 34% of the patients were diagnosed with colon and rectal cancer, respectively (Table 1). Any postoperative complications occurred in 368 patients (30%), surgical complications occurred in 219 patients (18%), and anastomotic leakage was reported for 100 of 1098 patients (9%) having an anastomosis and data on anastomotic leakage available. Compared with patients with uncomplicated recovery, patients with any complications were more often men (71% compared with 60%), diagnosed with rectal cancer (45% compared with 29%), had received neoadjuvant radiotherapy or chemoradiotherapy (32% compared with 18%), had received a low anterior resection (42% compared with 29%), and had a worse preoperative physical health status (ASA-score of I: 22% compared with 35%) (Table 1). Patients with complications also more often got a stoma during surgery (44% compared with 21%) and stayed longer in the hospital [median (Q1–Q3), 11 (7–18) d compared with 5 (4–6) d] compared with patients with uncomplicated recovery (Table 1). Cancer stage and other disease-related factors were comparable between the patients with and without postoperative complications.

Preoperative plasma SCFA and BCFA levels

Plasma SCFA and BCFA levels were measured in blood samples taken around time of diagnosis, i.e., before surgery. The median (Q1–Q3) time between blood collection and surgical procedure was 8 (2–18) d. Distributions of the plasma SCFA and BCFA levels and Spearman correlations across metabolites are depicted in Figure 2. Remarkably, all metabolites were positively correlated with each other, with the strongest correlations observed among the various BCFAs (r ranging from 0.48 to 0.79). Acetate appeared only weakly correlated with the other SCFAs propionate and isovalerate ($r = 0.34$, $r = 0.20$, respectively). This observation could be explained by the majority of gut microbial species being able to produce acetate, whereas production of other investigated metabolites is restricted to specific microbial groups [16]. Valerate correlated modestly with the SCFAs propionate and butyrate ($r = 0.62$, $r = 0.74$, respectively), but also with BCFAs (r ranging from 0.34 to 0.59).

Plasma SCFA and BCFA levels in relation to postoperative complications

Preoperative plasma acetate levels were lower in patients who subsequently developed postoperative complications compared with patients without complications [median (Q1–Q3), 30.1 (23.3–40.2) μmol/L compared with 28.4 (21.8–37.1) μmol/L; $P = 0.005$] (Figure 3). In contrast, plasma isovalerate levels were higher in patients who developed complications compared with those without

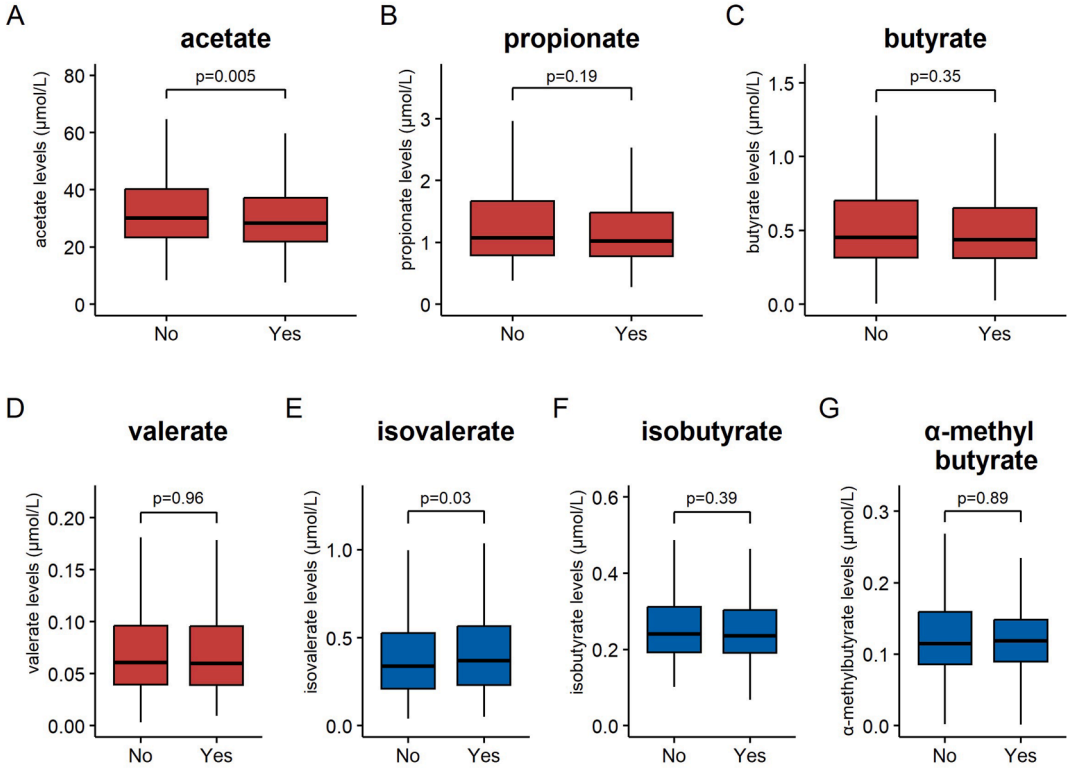


FIGURE 3. (A–G) Box plots for preoperative plasma levels of short-chain fatty acids (red) and branched-chain fatty acids (blue) of patients with ($n = 368$) and without ($n = 852$) any postoperative complications. Box plots show the median, first and third quartiles, and whiskers representing values within 1.5 times the interquartile range. Differences between groups were tested using Mann-Whitney U tests.

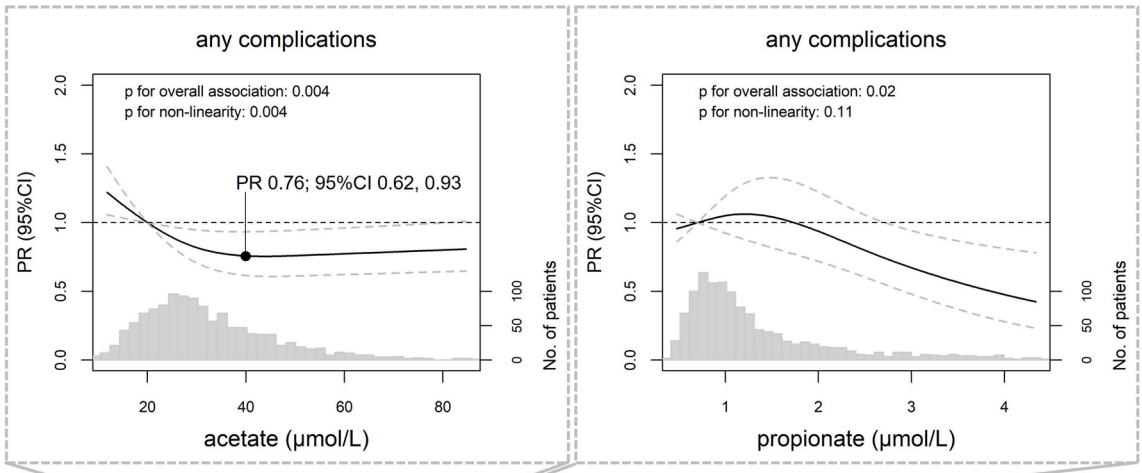
complications [median (Q1–Q3), 0.37 (0.23–0.57) μmol/L compared with 0.34 (0.21–0.53) μmol/L; $P = 0.03$]. No statistically significant differences were found for the other investigated metabolites (Figure 3).

Next, associations between metabolite levels and risk of any or surgical postoperative complications, as well as anastomotic leakage, were investigated. First, we used multivariable-adjusted restricted cubic splines to evaluate linearity of the associations (Figure 4A and Supplemental Figures 1 and 2). All associations appeared to be linear, apart from the association between acetate and any complications ($P_{\text{non-linearity}} = 0.004$). The corresponding restricted cubic spline initially shows a risk reduction compared with the reference of 20.0 μmol/L (median of first tertile) and flattening of the curve for acetate levels above ~40 μmol/L. Plasma acetate levels of 40.0 μmol/L were associated with a 24% lower risk of complications (PR: 0.76; 95% CI: 0.62, 0.93) compared with the reference of 20.0 μmol/L (Figure 4A). For the remaining metabolites, multivariable-adjusted Cox proportional hazards regression analyses were performed to evaluate associations with postoperative outcomes. These analyses showed that higher preoperative plasma levels of propionate were associated with a lower risk of any complications ($PR_{\text{per1μmol/L}}$ 0.84; 95% CI: 0.73, 0.96) (Figure 4B). A similar pattern was observed for surgical complications, with inverse associations for acetate and propionate ($PR_{\text{per20μmol/L}}$ 0.73; 95% CI: 0.60, 0.93; and $PR_{\text{per1μmol/L}}$ 0.83; 95% CI: 0.69, 1.00; respectively) (Figure 4B). Higher preoperative levels of propionate and valerate were associated with a lower risk of having an anastomotic leakage ($PR_{\text{per1μmol/L}}$ 0.68; 95% CI: 0.50, 0.93; and $PR_{\text{per0.1μmol/L}}$ 0.65; 95% CI: 0.42, 1.00; respectively) (Figure 4B).

Plasma SCFA and BCFA levels and length of hospital stay

We also investigated whether preoperative metabolite levels were associated with length of hospital stay, as indicator of postoperative recovery [30,31], using multivariable-adjusted linear regression analyses. Higher plasma levels of acetate and propionate were associated with a statistically significantly shorter duration of hospital stay ($beta_{\text{perdoubling}}$ –0.09; 95% CI: –0.17, –0.01; and $beta_{\text{perdoubling}}$ –0.14; 95% CI: –0.21, –0.07; respectively) (Figure 5). Higher plasma levels of isovalerate were associated with a statistically significantly longer duration of hospital stay ($beta_{\text{perdoubling}}$ 0.06; 95% CI: 0.00, 0.11). No statistically significant associations were found for the other investigated metabolites (Figure 5).

A



B

	acetate per 20 μmol/L	propionate per 1 μmol/L	butyrate per 0.5 μmol/L	valerate per 0.1 μmol/L	isovalerate per 0.5 μmol/L	isobutyrate per 0.1 μmol/L	α-methyl butyrate per 0.1 μmol/L
any complications	NA	0.84 (0.73, 0.96)	0.96 (0.87, 1.06)	1.01 (0.88, 1.16)	1.09 (0.92, 1.30)	0.96 (0.88, 1.05)	0.92 (0.78, 1.09)
surgical complications	0.75 (0.60, 0.93)	0.83 (0.69, 1.00)	0.98 (0.87, 1.11)	0.97 (0.80, 1.17)	1.11 (0.89, 1.39)	0.98 (0.87, 1.10)	0.91 (0.73, 1.14)
anastomotic leakage	0.80 (0.58, 1.10)	0.68 (0.50, 0.93)	0.73 (0.52, 1.04)	0.65 (0.42, 1.00)	1.19 (0.87, 1.61)	0.86 (0.69, 1.06)	0.84 (0.59, 1.19)

FIGURE 4. Associations between preoperative plasma levels of short-chain fatty acids and branched-chain fatty acids and risk of any postoperative complications, surgical postoperative complications, and anastomotic leakage. (A) Graphs depict restricted cubic splines (solid lines) and corresponding 95% CIs (dashed lines). The reference was set at the median of the first tertile of the metabolite levels. Knots were located at the 10th, 50th and 90th percentile, and graphs were truncated at the first and 99th percentile. Only the splines showing statistically significant associations for postoperative complications are shown here. Plots for the other metabolites, as well as other outcomes (surgical complications and anastomotic leakage), are shown in Supplemental Figures 1 and 2. (B) Prevalence ratios and 95% CIs from Cox proportional hazards regression analyses with continuous increment are presented in the table. NA: not applicable, because the association between acetate and any complications appeared to be nonlinear, the prevalence ratio and 95% CI were calculated based on the data of the restricted cubic spline (also depicted in the spline). Both restricted cubic splines and Cox regression models were adjusted for age at diagnosis (continuous in years), sex (female, male), tumor location (colon, rectum), smoking status (current, former, never), and preoperative physical health status of the patient based on American Society of Anesthesiologists classification (I, II, III–IV). Numbers of cases/total number of patients included in the analyses are: any complications, 350/1186; surgical complications, 208/1176; anastomotic leakage, 93/1067. CI, confidence interval; PR, prevalence ratio.

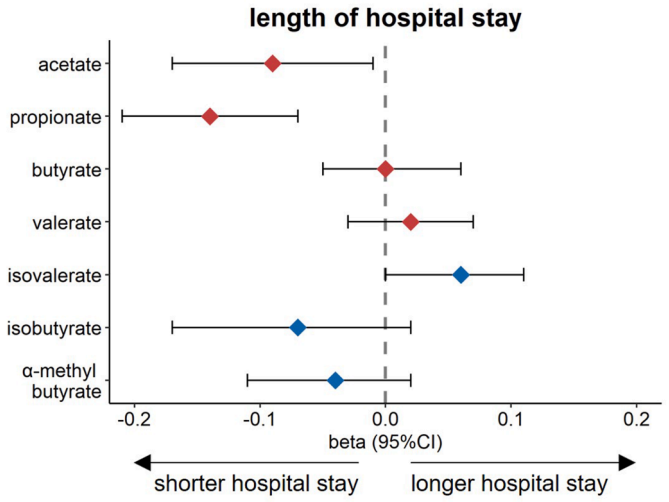


FIGURE 5. Forest plot showing the associations between preoperative plasma levels of short-chain fatty acids (red) and branched-chain fatty acids (blue) and log2-transformed length of hospital stay in patients with colorectal cancer. Metabolites are modeled per doubling in metabolite level. A total of 1162 patients were included in the analyses. Linear regression models were adjusted for age at diagnosis (continuous in years), sex (female, male), tumor location (colon, rectum), smoking status (current, former, never), surgical approach (open, laparoscopic), and preoperative physical health status of the patient based on American Society of Anesthesiologists classification (I, II, III–IV). CI, confidence interval.

Group distinction based on total SCFA levels and total BCFA levels

We hypothesized that the balance between gut microbial saccharolytic and proteolytic fermentation products, and thereby the balance between total plasma SCFA levels and BCFA levels may be relevant for postoperative recovery. Hence, we classified patients based on *1*) total SCFA levels below and above median level of the study population ($median_{TotalSCFA}$ = 31.4 μmol/L), and *2*) total BCFA levels below and above median level of the study population ($median_{TotalBCFA}$ = 0.73 μmol/L). This resulted in 4 groups indicating whether patients had either low or high SCFA levels in combination with low or high BCFA levels. Box plots depicting total SCFA and total BCFA levels per group are shown in Figure 6A–D. Personal and clinical characteristics of the population according to these SCFA/BCFA profiles are shown in Supplemental Table 1. No differences in lifestyle and clinical factors were observed between the groups.

Associations between the SCFA/BCFA profiles and the risk of any complications, surgical complication, anastomotic leakage as well as length of hospital stay were investigated using multivariable-adjusted regression analyses (Figure 6E–H). Compared with the low SCFA/low BCFA group, having low SCFA levels combined with high BCFA levels was associated with an increased risk of complications (any complications: PR: 1.35; 95% CI: 1.02, 1.80). In contrast, having high SCFA levels combined with low BCFA levels was associated with a decreased risk of complications, especially for surgical complications (any complications: PR: 0.79; 95% CI: 0.57, 1.08; surgical complications: PR: 0.59; 95% CI: 0.36, 0.94). Being in this high SCFA/low BCFA group was also associated with a shorter hospital stay compared with the reference group (beta –0.17; 95% CI: –0.32, –0.02). Having high SCFA levels combined with high BCFA levels was not associated with the risk of complications (for any complications PR: 0.88; 95% CI: 0.67, 1.17) compared with the reference group. To summarize, the combination of high SCFA levels and low BCFA levels was associated with the lowest risk of complications, suggesting that this combination may be most optimal to support postoperative recovery.

Discussion

In this study, we characterized SCFA and BCFA levels in preoperative plasma samples of patients with CRC and investigated whether levels of these microbial-derived metabolites were associated with the risk of complications after CRC surgery. Higher circulating SCFA levels, especially acetate and propionate, were associated with a lower risk of postoperative complications and shorter hospital stay after CRC surgery. Also, higher levels of the SCFAs propionate and valerate were associated with a lower risk of an anastomotic leakage after CRC surgery. The combination of low total SCFA levels and high total BCFA levels was associated with a higher risk of postoperative complications. Patients with a combination of high total SCFA levels and low total BCFA levels had the most favorable profile regarding postoperative recovery.

To the best of our knowledge, this is the first study showing that plasma SCFA and BCFA levels are linked to postoperative complications in patients with CRC. In line with our findings, a study among patients with esophageal cancer who received synbiotics before and after esophagectomy found that preoperative fecal levels of acetate and propionate were lower in patients with postoperative infectious complications (n = 10) compared with those with uncomplicated recovery (n = 45) [37]. Likewise, preoperative fecal levels of acetate and butyrate were lower in 13 patients with infectious complications compared with 31 patients without complications after hepatectomy with bile duct resection for biliary malignancies [38].

In rodent studies, administration of SCFAs, mostly via colonic infusions of butyrate, improved anastomotic strength and colonic healing after colonic surgery by enhancing re-epithelialization of the gut epithelial lining and promoting collagen synthesis and collagen maturation [21]. In line with these findings, we observed that higher plasma levels of SCFAs were associated with a lower risk of postoperative complications, including anastomotic leakage. However, we did not observe an association between plasma butyrate levels and postoperative complications. It has been estimated that only 2% of butyrate produced in the colon can be detected in the systemic circulation (compared with 36% and 9% for acetate and propionate, respectively) [39], so colonic butyrate production is not well reflected in plasma, which may explain the failure to detect an association in our study.

The inverse association between SCFAs and postoperative complications might be explained by the biological function of these microbial-derived metabolites. It has been suggested that SCFAs support gut barrier function via improved production of mucus and antimicrobial peptides as well as regulation of tight junctions between colonocytes [17,19]. Furthermore, SCFAs inhibit intestinal proinflammatory cytokine production upon bacterial LPS exposure and regulate intestinal T-cell differentiation, which is deemed essential for effective immune responses [16,19,40]. Next to the potential local effects of SCFAs, these metabolites could also induce systemic effects as a fraction appears in the systemic circulation [16,39,41].

We observed that high BCFAs levels combined with low SCFA levels were associated with a higher risk of postoperative complications. Also, higher levels of isovalerate were associated with longer hospital stay. Evidence on the (patho)physiological effects of BCFAs is scarce [15,24]. A study in mice showed that a high-protein diet impaired hepatic insulin sensitivity, which might be attributed to an increased

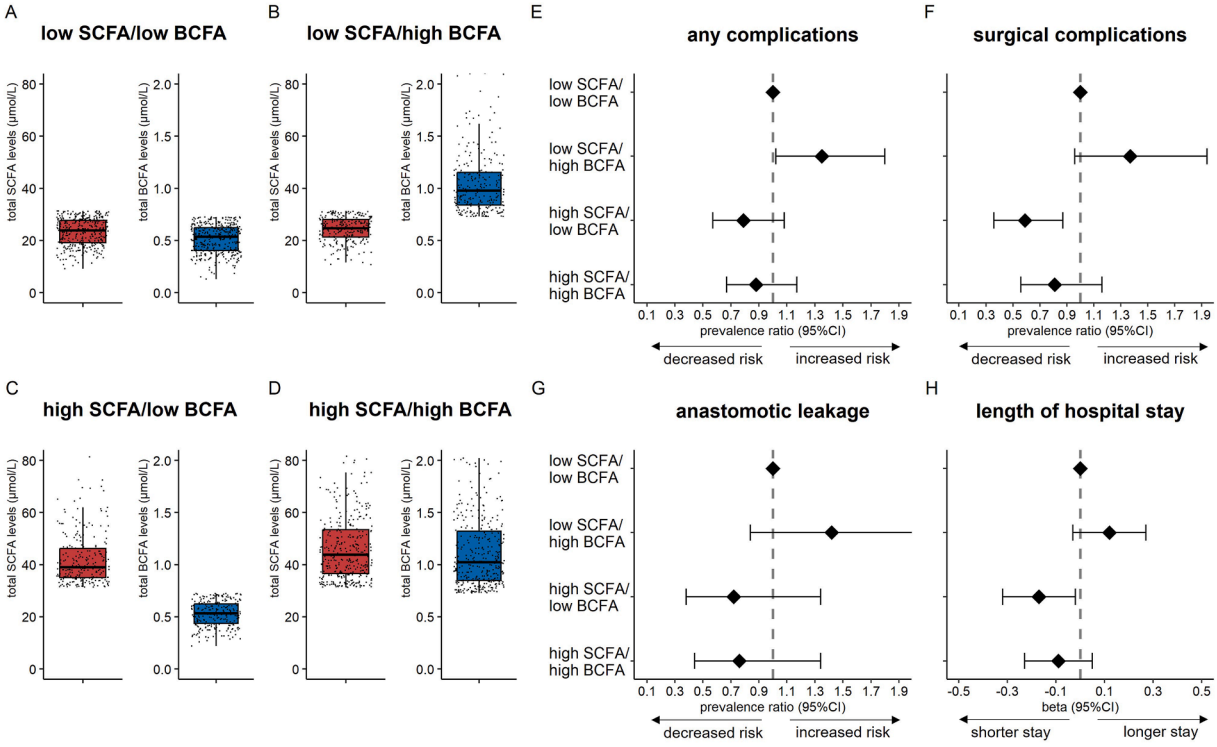


FIGURE 6. (A–D) Box plots showing preoperative plasma levels of total short-chain fatty acids (SCFAs, red) and total branched-chain fatty acids (BCFAs, blue) per SCFA/BCFA profile. Groups were made based on whether patients had total SCFA levels and total BCFA levels above or below the median level of the study population. Median total SCFA concentration was 31.4 µmol/L and median total BCFA concentration was 0.73 µmol/L. Box plots show the median, first, and third quartiles, whiskers representing values within 1.5 times the interquartile range, and values of individual patients are plotted as jitter (smallest and largest values are 1.5 box lengths away from 25th and 75th percentile). (E–H) Forest plots showing the associations between SCFA/BCFA profiles and any postoperative complications, surgical postoperative complications, anastomotic leakage, and length of hospital stay. The low SCFA/low BCFA group was used as a reference. Cox and linear regression models were adjusted for age at diagnosis (continuous in years), sex (female, male), tumor location (colon, rectum), smoking status (current, former, never), and preoperative physical health status of the patient based on American Society of Anesthesiologists classification (I, II, III–IV). Analyses for length of hospital stay were also adjusted for surgical approach (open, laparoscopic). CI, confidence interval.

production of the BCFAs isobutyrate and isovalerate, although other mechanistic routes cannot be excluded [42]. Besides, higher BCFA levels, resulting from increased proteolytic fermentation, might be accompanied by higher levels of phenols, amines, hydrogen sulfide, and p-cresol [15,22,23]. These proteolytic fermentation products are known to have proinflammatory and genotoxic effects on colonic cells and impair gut barrier function [23,25], which may also explain the positive association observed for BCFAs and postoperative complications.

Our findings may suggest that having high SCFA levels could attenuate the higher risk of complications seen for patients with high BCFA levels in combination with low SCFA levels. Although speculative, it supports the hypothesis that promoting microbial saccharolytic fermentation over proteolytic fermentation is beneficial for postoperative recovery of colorectal surgery (Figure 7). This hypothesis may raise concerns about the emphasis on high-protein intake before CRC surgery [43–45], especially in the case of low intake of fiber, as higher protein inflow in the colon may result in increased microbial proteolytic fermentation [23,46,47]. Higher intakes of dietary fiber are known to promote microbial saccharolytic fermentation and thereby SCFA production, and decrease proteolytic fermentation including BCFA production [22,25,48]. Earlier work in the COLON study has shown that higher dietary fiber intake before surgery was associated with a lower risk of postoperative complications in patients with CRC [6], which may be speculatively explained by increased microbial saccharolytic fermentation with higher fiber intakes. Earlier studies observed lower fecal SCFA levels in patients with CRC compared with healthy controls [49,50], and fecal SCFA levels further decreased after CRC surgery [51]. In addition, adherence to the recommendations on dietary fiber intake is low (9%) among patients with CRC [6], indicating that increasing fiber intake is a promising strategy to optimize preoperative SCFA levels to support postoperative recovery.

Limitations of this study include the relatively modest number of events, especially for anastomotic leakage, which may have reduced statistical power and hampered further subgroup analyses. Because of the observational nature of this study, reverse causation and residual confounding cannot be fully ruled out, even though we considered several relevant clinical or lifestyle variables in the analyses. Noteworthy, plasma levels of acetate mostly originate from intestinal absorption of acetate produced by microbial fermentation, but small amounts of acetate might also be endogenously produced in the hepatocytes (e.g., from acetyl-CoA) [52,53]. Our blood samples were collected in a nonfasted way, which may have impacted plasma levels of SCFA and BCFA [54]. However, because the impact of recent dietary intake is most likely nondifferential for patients who subsequently developed complications compared with those who did not, this would not have affected the observed associations. It should also be noted that our findings concern patients with nonmetastatic CRC, so it needs to be confirmed to what extent these findings also apply to patients with metastatic CRC undergoing surgery. Moreover, as the cohort study specifically focused on lifestyle, it is possible that more

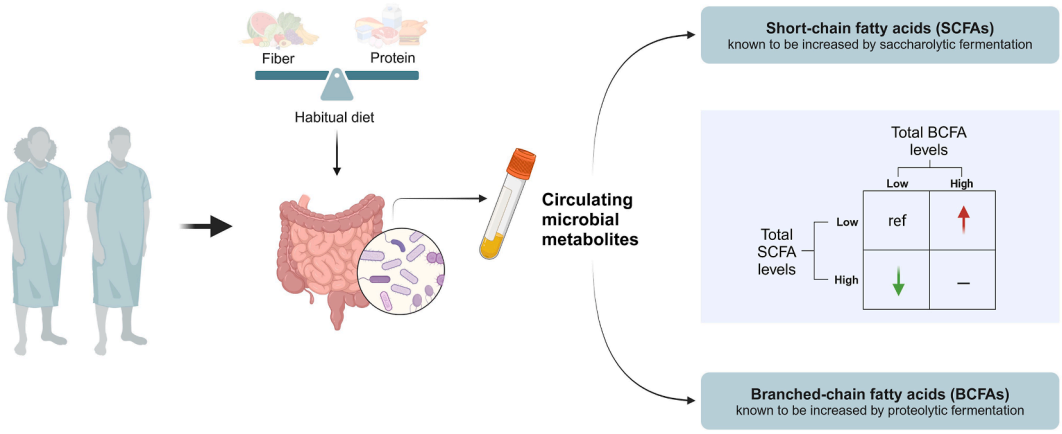


FIGURE 7. Hypothesized model describing the potential relation between short-chain fatty acids (SCFAs), branched-chain fatty acids (BCFAs), and risk of complications after surgery in patients with colorectal cancer. Higher preoperative plasma BCFA levels, especially combined with lower SCFA levels, might be associated with an increased risk of postoperative complications (indicated with a red arrow). In contrast, higher preoperative plasma SCFA levels, especially combined with lower BCFA levels, might be associated with a reduced risk of postoperative complications (indicated with a green arrow). Our findings may suggest that increased gut microbial saccharolytic fermentation is preferred over proteolytic fermentation to support recovery after surgery and prevent postoperative complications in patients with colorectal cancer. Figure created with BioRender.com.

health-conscious patients were more eager to participate, possibly limiting generalizability of the findings.

Strengths of this study include the prospective design and adjustment for lifestyle and clinical factors related to complications after CRC surgery. Moreover, this is the first clinical study investigating SCFAs and BCFAs in the context of recovery after CRC surgery, which adds relevant leads for biological mechanisms linked to postoperative complications, which might be targeted in future prehabilitation programs.

To conclude, we observed that higher circulating levels of SCFAs before surgery were associated with a lower risk of postoperative complications in patients with CRC. High levels of BCFAs combined with low SCFA levels were associated with a higher risk of complications. These findings imply that microbial fermentation processes may be linked to postoperative recovery. Because plasma SCFA levels can be potentially increased by the intake of dietary fiber, targeted strategies to promote dietary fiber intake could be of interest for nutritional prehabilitation. Future nutritional intervention studies are needed to investigate to what extent changes in dietary fiber and protein intake can modulate production of microbial metabolites in the time between diagnosis and surgery, and whether those interventions indeed translate into lower complication rates in patients with CRC.

Acknowledgments

We thank all participants, the involved coworkers in the participating hospitals, and the COLON investigators at Wageningen University & Research. We also thank the registration team of the Netherlands Comprehensive Cancer Organisation (IKNL) for the collection of data for the Netherlands Cancer Registry.

Author contributions

The authors responsibilities were as follows – NK-D, EGZ, EC, EK, DEK: designed the research; NK-D, RMW, FJBvD, EK, DEK: obtained funding for any aspect of the research; NK-D, RMW, FJBvD, NTvH, FMK, AU, AMcC, PMU, JHWdW, EK, DEK: contributed to data collection; NK-D: performed formal analysis and wrote the draft of the paper; and all authors: contributed to the study and have read and approved the final manuscript.

Conflict of interest

The authors declare no conflicts of interest.

Funding

Research presented in this article was financially supported by the VLAG Graduate School of Wageningen University, Gelderse Vallei Hospital (Research Fund 2022) and the Dutch Research Council (016.Veni.188.082). The COLON study (COlorectal cancer: Longitudinal, Observational study on Nutritional and lifestyle factors) was financially supported by Wereld Kanker Onderzoek Fonds (WKOF) & World Cancer Research Fund International (WCRF International) as well as by funding (2014/1179, IIG_FULL_2021_022, IIG_FULL_2021_023, and IIG_FULL_2023_017) obtained from the Wereld Kanker Onderzoek Fonds (WKOF) as part of the World Cancer Research Fund International grant programme; Alpe d'Huzes/Dutch Cancer Society (UM 2012-5653, UW 2013-5927, UW 2015-7946); and ERA-NET on Translational Cancer Research (TRANSCAN: Dutch Cancer Society (UW2013-6397, UW2014-6877) and the Netherlands Organization for Health Research and Development (ZonMw), the Netherlands) and the Regio Deal Foodvalley (162135). The funding parties had no role in the collection, analysis, and interpretation of the data, writing of the report, or decision to submit the article for publication.

Data availability

Because the data consist of identifying patient information, some access restrictions apply and the data can therefore not be made publicly available. Data will be shared with permission from the steering committee of the COLON study. Requests for data can be sent to Dieuwertje E. Kok, Division of Human Nutrition and Health, Wageningen University & Research, The Netherlands (e-mail: dieuwertje.kok@wur.nl).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2025.10.001.

References

[1] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, et al., Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 71 (3) (2021) 209–249.

[2] N.P.M. Brouwer, A.C.R.K. Bos, V.E.P.P. Lemmens, P.J. Tanis, N. Hugen, I. D. Nagtegaal, et al., An overview of 25 years of incidence, treatment and outcome of colorectal cancer patients, Int. J. Cancer. 143 (11) (2018) 2758–2766.

[3] L.C.F. De Nes, G. Hannink, J. T'Lam-Boer, N. Hugen, R.H. Verhoeven, J.H. W. de Wilt, Postoperative mortality risk assessment in colorectal cancer: development and validation of a clinical prediction model using data from the Dutch ColoRectal Audit, BJS Open 6 (2) (2022) zrac014.

[4] C.L. Downey, J. Bainbridge, D.G. Jayne, D.M. Meads, Impact of in-hospital postoperative complications on quality of life up to 12 months after major abdominal surgery, Br. J. Surg. 110 (9) (2023) 1206–1212.

[5] L. Loogman, L.C.F. De Nes, T.C. Heil, D.E.G. Kok, R.M. Winkels, E. Kampman, et al., The association between modifiable lifestyle factors and postoperative complications of elective surgery in patients with colorectal cancer, Dis. Colon Rectum 64 (11) (2021) 1342–1353.

[6] D.E. Kok, M.N.N. Arron, T. Huibregtse, F.M. Kruyt, D.J. Bac, HK van Halteren, et al., Association of habitual preoperative dietary fiber intake with complications after colorectal cancer surgery, JAMA Surg 156 (9) (2021) 1–10.

[7] S. Boatman, T. Kaiser, H. Nalluri-Butz, M.H. Khan, M. Dietz, J. Kohn, et al., Diet-induced shifts in the gut microbiota influence anastomotic healing in a murine model of colonic surgery, Gut Microbes 15 (2) (2023) 2283147.

[8] R. Keskey, E. Papazian, A. Lam, T. Toni, S. Hyoju, R. Thewissen, et al., Defining microbiome readiness for surgery: dietary prehabilitation and stool biomarkers as predictive tools to improve outcome, Ann. Surg. 276 (5) (2022) e361–e369.

[9] S.K. Hyoju, C. Adriaansens, K. Wienholts, A. Sharma, R. Keskey, W. Arnold, et al., Low-fat/high-fibre diet prehabilitation improves anastomotic healing via the microbiome: an experimental model, Br. J. Surg. 107 (6) (2020) 743–755.

[10] R. Hajjar, M. Oliero, T. Cuisiniere, G. Fragoso, A. Calvé, S. Djediai, et al., Improvement of colonic healing and surgical recovery with perioperative supplementation of inulin and galacto-oligosaccharides, Clin. Nutr. 40 (6) (2021) 3842–3851.

[11] J.C. Alverdy, S.K. Hyoju, M. Weigerinck, J.A. Gilbert, The gut microbiome and the mechanism of surgical infection, Br. J. Surg. 104 (2) (2017) e14–e23.

[12] R. Bachmann, D. Leonard, N. Delzenne, A. Kartheuser, P.D. Cani, Novel insight into the role of microbiota in colorectal surgery, Gut 66 (4) (2017) 738–749.

[13] S. Gaines, C. Shao, N. Hyman, J.C. Alverdy, Gut microbiome influences on anastomotic leak and recurrence rates following colorectal cancer surgery, Br. J. Surg. 105 (2) (2018) e131–e141.

[14] H.J. Flint, K.P. Scott, P. Louis, S.H. Duncan, The role of the gut microbiota in nutrition and health, Nat. Rev. Gastroenterol. Hepatol. 9 (10) (2012) 577–589.

[15] K. Oliphant, E. Allen-Vercoe, Macronutrient metabolism by the human gut microbiome: major fermentation by-products and their impact on host health, Microbiome 7 (1) (2019) 1–15.

[16] A. Koh, F. De Vadder, P. Kovatcheva-Datchary, F. Bäckhed, From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites, Cell 165 (6) (2016) 1332–1345.

[17] K. Makki, E.C. Deehan, J. Walter, F. Bäckhed, The impact of dietary fiber on gut microbiota in host health and disease, Cell Host Microbe 23 (6) (2018) 705–715.

[18] B. van der Hee, J.M. Wells, Microbial regulation of host physiology by short-chain fatty acids, Trends Microbiol 29 (8) (2021) 700–712.

[19] E.E. Blaak, E.E. Canfora, S. Theis, G. Frost, A.K. Groen, G. Mithieux, et al., Short chain fatty acids in human gut and metabolic health, Benef. Microbes. 11 (5) (2020) 411–455.

[20] C.M. van der Beek, C.H.C. Dejong, F.J. Troost, A.A.M. Masclee, K. Lenaerts, Role of short-chain fatty acids in colonic inflammation, carcinogenesis, and mucosal protection and healing, Nutr. Rev. 75 (4) (2017) 286–305.

[21] A.C.L. Wildeboer, C.P.M. van Helsdingen, C.G. Gallé, R.B.M. de Vries, J.P. M. Derikx, N.D. Bouvy, Enhancing intestinal anastomotic healing using butyrate: systematic review and meta-analysis of experimental animal studies, PLOS ONE 18 (6) (2023) e0286716.

[22] L.A. David, C.F. Maurice, R.N. Carmody, D.B. Gootenberg, J.E. Button, B. E. Wolfe, et al., Diet rapidly and reproducibly alters the human gut microbiome, Nature 505 (7484) (2014) 559–563.

[23] W.R. Russell, S.W. Gratz, S.H. Duncan, G. Holtrop, J. Ince, L. Scobbie, et al., High-protein, reduced-carbohydrate weight-loss diets promote metabolite profiles likely to be detrimental to colonic health, Am. J. Clin. Nutr. 93 (5) (2011) 1062–1072.

[24] D. Rios-Covian, S. González, A.M. Nogacka, S. Arboleya, N. Salazar, M. Gueimonde, et al., An overview on fecal branched short-chain fatty acids along human life and as related with body mass index: associated dietary and anthropometric factors, Front. Microbiol. 11 (2020) 973.

[25] C.K. Yao, J.G. Muir, P.R. Gibson, Review article: insights into colonic protein fermentation, its modulation and potential health implications, Aliment. Pharmacol. Ther. 43 (2) (2016) 181–196.

[26] R.M. Winkels, R.C. Heine-Bröring, M. van Zutphen, S. van Harten-Gerritsen, D.E.G. Kok, F.J.B. van Duijnhoven, et al., The COLON study: Colorectal cancer: Longitudinal, Observational study on Nutritional and lifestyle factors that may influence colorectal tumour recurrence, survival and quality of life, BMC Cancer 14 (1) (2014) 374.

[27] M. Thing, M.P. Werge, N. Kimer, L.E. Hetland, E.B. Rashu, P. Nabilou, et al., Targeted metabolomics reveals plasma short-chain fatty acids are associated with metabolic dysfunction-associated steatotic liver disease, BMC Gastroenterol 24 (1) (2024) 43.

[28] R. Wei, J. Wang, E. Jia, T. Chen, Y. Ni, W. Jia, GSimp: a Gibbs sampler based left-censored missing value imputation approach for metabolomics studies, PloS. Comput. Biol. 14 (1) (2018) e1005973.

[29] N.J. Van Leersum, H.S. Snijders, D. Henneman, N.E. Kolfschoten, G. A. Gooiker, M.G. Ten Berge, et al., The Dutch surgical colorectal audit, Eur. J. Surg. Oncol. 39 (10) (2013) 1063–1070.

[30] C.R. Sabajo, D.W.G. ten Cate, M.H.M. Heijmans, C.T.G. Koot, L.V.L. van Leeuwen, G.D. Slooter, Prehabilitation in colorectal cancer surgery improves outcome and reduces hospital costs, Eur. J. Surg. Oncol. 50 (1) (2024) 107302.

[31] L. Anthuber, F. Sommer, S. Wolf, D. Vlasenko, M. Hoffmann, T.T. Arndt, et al., Influence of perioperative step volume on complication rate and length of hospital stay after colorectal cancer surgery (IPOS trial): study protocol for a randomised controlled single-centre trial at a German university hospital, BMJ Open 13 (12) (2023) e076298.

[32] G.C.W. Wendel-Vos, A.J. Schuit, W.H.M. Saris, D. Kromhout, Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity, J. Clin. Epidemiol. 56 (12) (2003) 1163–1169.

[33] I.S. Bakker, I. Grossmann, D. Henneman, K. Havenga, T. Wiggers, Risk factors for anastomotic leakage and leak-related mortality after colonic cancer surgery in a nationwide audit, Br. J. Surg. 101 (4) (2014) 424–432.

[34] H. Nasser, T. Ivanics, S. Leonard-Murali, A. Stefanou, Risk factors for surgical site infection after laparoscopic colectomy: an NSQIP database analysis, J. Surg. Res. 249 (2020) 25–33.

[35] C.C. Margadant, E.R.J. Bruns, D.A.M. Sloothaak, P. van Duijvendijk, A. F. van Raamt, H.J. van der Zaag, et al., Lower muscle density is associated with major postoperative complications in older patients after surgery for colorectal cancer, Eur. J. Surg. Oncol. 42 (11) (2016) 1654–1659.

[36] A.C.M. Cuijpers, B.C. Bongers, A.F.J.M. Heldens, M.J.L. Bours, N.L.U. van Meeteren, L.P.S. Stassen, et al., Aerobic fitness and muscle density play a vital role in postoperative complications in colorectal cancer surgery, J. Surg. Oncol. 125 (6) (2022) 1013–1023.

[37] M. Motoori, K. Tanaka, K. Sugimura, H. Miyata, T. Saito, Y. Miyazaki, et al., Impact of preoperative fecal short chain fatty acids on postoperative infectious complications in esophageal cancer patients, BMC Gastroenterol 20 (1) (2020) 74.

[38] Y. Yokoyama, T. Mizuno, G. Sugawara, T. Asahara, K. Nomoto, T. Igami, et al., Profile of preoperative fecal organic acids closely predicts the incidence of postoperative infectious complications after major hepatectomy with extrahepatic bile duct resection: importance of fecal acetic acid plus butyric acid minus lactic acid gap, Surgery 162 (4) (2017) 928–936.

[39] E. Boets, S.V. Gomand, L. Deroover, T. Preston, K. Vermeulen, V. De Preter, et al., Systemic availability and metabolism of colonic-derived short-chain fatty acids in healthy subjects: a stable isotope study, J. Physiol. 595 (2) (2017) 541–555.

[40] W. Yang, T. Yu, X. Huang, A.J. Bilotta, L. Xu, Y. Lu, et al., Intestinal microbiota-derived short-chain fatty acids regulation of immune cell IL-22 production and gut immunity, Nat. Commun. 11 (1) (2020) 4457.

[41] G. den Besten, K. Van Eunen, A.K. Groen, K. Venema, D.J. Reijngoud, B. M. Bakker, The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism, J. Lipid Res. 54 (9) (2013) 2325–2340.

[42] B.S.Y. Choi, N. Daniel, V.P. Houde, A. Ouellette, B. Marcotte, T.V. Varin, et al., Feeding diversified protein sources exacerbates hepatic insulin resistance

via increased gut microbial branched-chain fatty acids and mTORC1 signaling in obese mice, Nat. Commun. 12 (1) (2021) 3377.
[43] S. Van Rooijen, F. Carli, S. Dalton, G. Thomas, R. Bojesen, M. Le Guen, et al., Multimodal prehabilitation in colorectal cancer patients to improve functional capacity and reduce postoperative complications: the first international randomized controlled trial for multimodal prehabilitation, BMC Cancer 19 (1) (2019) 98.
[44] A. Bausys, M. Kryzauskas, V. Abeciunas, A.E. Degutyte, R. Bausys, K. Strupas, et al., Prehabilitation in modern colorectal cancer surgery: a comprehensive review, Cancers (Basel) 14 (20) (2022) 5017.
[45] C. Gillis, K. Buhler, L. Bresee, F. Carli, L. Gramlich, N. Culos-Reed, et al., Effects of nutritional prehabilitation, with and without exercise, on outcomes of patients who undergo colorectal surgery: a systematic review and meta-analysis, Gastroenterology 155 (2) (2018) 391–410.e4.
[46] I. Attaye, P.B. Lassen, S. Adriouch, E. Steinbach, R. Patiño-Navarrete, M. Davids, et al., Protein supplementation changes gut microbial diversity and derived metabolites in subjects with type 2 diabetes, iScience 26 (8) (2023) 107471.
[47] F. Blachier, M. Beaumont, K.J. Portune, N. Steuer, A. Lan, M. Audebert, et al., High-protein diets for weight management: interactions with the intestinal microbiota and consequences for gut health. A position paper by the my new gut study group, Clin. Nutr. 38 (3) (2019) 1012–1022.
[48] S.K. Gill, M. Rossi, B. Bajka, K. Whelan, Dietary fibre in gastrointestinal health and disease, Nat. Rev. Gastroenterol. Hepatol. 18 (2) (2021) 101–116.
[49] E. Niccolai, S. Baldi, F. Ricci, E. Russo, G. Nannini, M. Menicatti, et al., Evaluation and comparison of short chain fatty acids composition in gut diseases, World J. Gastroenterol. 25 (36) (2019) 5543–5558.
[50] H.M. Chen, Y.N. Yu, J.L. Wang, Y.W. Lin, X. Kong, C.Q. Yang, et al., Decreased dietary fiber intake and structural alteration of gut microbiota in patients with advanced colorectal adenoma, Am. J. Clin. Nutr. 97 (5) (2013) 1044–1052.
[51] S. Ohigashi, K. Sudo, D. Kobayashi, T. Takahashi, K. Nomoto, H. Onodera, Significant changes in the intestinal environment after surgery in patients with colorectal cancer, J. Gastrointest, Surg. 17 (9) (2013) 1657–1664.
[52] J.R. Moffett, N. Puthillathu, R. Vengilote, D.M. Jaworski, A.M. Namboodiri, Acetate revisited: a key biomolecule at the nexus of metabolism, epigenetics and oncogenesis—part 1: acetyl-coa, acetogenesis and acyl-coa short-chain synthetases, Front. Physiol. 11 (2020) 580167.
[53] J.G. Bloemen, K. Venema, M.C. van de Poll, S.W. Olde Damink, W. A. Buurman, C.H. Dejong, Short chain fatty acids exchange across the gut and liver in humans measured at surgery, Clin. Nutr. 28 (6) (2009) 657–661.
[54] A. Nogal, F. Asnicar, A. Vijay, A. Kouraki, A. Visconti, P. Louca, et al., Genetic and gut microbiome determinants of SCFA circulating and fecal levels, postprandial responses and links to chronic and acute inflammation, Gut Microbes 15 (1) (2023) 2240050.