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Research paper

A healthy dietary pattern is associated with microbiota diversity in recently diagnosed bipolar patients: The Bipolar Netherlands Cohort (BINCO) study

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ABSTRACT

Background: Diet largely impacts the gut microbiota, and may affect mental and somatic health via the gut-brain axis. As such, the relationship between diet and the microbiota in Bipolar Disorder (BD) could be of importance, but has not been studied before. The aim was therefore to assess whether dietary quality is associated with the gut microbiota diversity in patients with recently diagnosed BD, and whether changes occur in dietary quality and microbiota diversity during their first year of treatment.

Methods: Seventy recently (<1 year) diagnosed patients with BD were included in the "Bipolar Netherlands Cohort" (BINCO), and a total of 45 participants were assessed after one year. A 203-item Food Frequency Questionnaire (FFQ) data yielded the Dutch Healthy index (DHD-15), and the microbiota composition and diversity of fecal samples were characterized by 16S rRNA gene amplicon sequencing at baseline and 1-year follow-up. Associations and changes over time were analyzed using multivariate regression analyses and *t*-tests for paired samples.

Results: Included patients had a mean age of 34.9 years (SD ± 11.2), and 58.6 % was female. Alpha diversity (Shannon diversity index), richness (Chao1 index) and evenness (Pielou's Evenness Index) were positively associated with the DHD-15 total score, after adjustment for sex, age and educational level (beta = 0.55; $P < 0.001$, beta = 0.39; $P = 0.024$, beta = 0.54; $P = 0.001$ respectively). The positive correlations were largely driven by the combined positive effect of fish, beans, fruits and nuts, and inverse correlations with alcohol and processed meats. No significant changes were found in DHD-15 total score, nor in microbiota diversity, richness and evenness indexes during one year follow-up and regular treatment.

Conclusion: A healthy and varied diet is associated with the diversity of the microbiota in BD patients. Its potential consequences for maintaining mood stability and overall health should be studied further.

1. Introduction

Bipolar disorder (BD) is a psychiatric disorder characterized by episodes of depressive and (hypo)manic mood states, and affects about 1–2 % of the world population (Grande et al., 2016; McIntyre et al., 2020). Mental well-being in general, like depressive mood states and the quality of life, have been associated with the diversity of the microbiota (Zhernakova et al., 2016; Valles-Colomer et al., 2019). The complex community of microbes in the gastrointestinal tract is a fundamental and necessary component of human physiology, and has systemic effects via

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various 'axes', including the important gut-brain axis. As such, a better understanding of the microbiota composition and diversity, and its plasticity in response to diet in psychopathology, could lead to new insights in the pathophysiology of psychiatric disorders such as BD (Liu et al., 2022).

There is an intricate relationship between dietary quality and the microbiota, where dietary changes confer a strong effect on the microbiota (Jiang et al., 2018; Coello et al., 2019; Sublette et al., 2021; David et al., 2014a; Koponen et al., 2021). For example, the consumption of an aberrant diet induced temporary changes in the abundance of several genera, depending on whether the diet consisted of more plant or animal based products (David et al., 2014b). Moreover, the adherence to a Mediterranean diet, which entails plenty of fruits, vegetables, fibers, and fish, was shown to lead to a more diverse microbiota than the adherence to a Western-style diet, which entails more (saturated) fats, sugars, refined grains, and red meat (Garcia-Mantrana et al., 2018; Hansen et al., 2018). The Mediterranean diet is well-known to lower the risk of cardiovascular morbidity and mortality (Rosato et al., 2019; Tang et al., 2021). Whether this attenuation of cardiovascular risk is due to a mechanism in which microbiota are involved, remains to be elucidated (D. Wang et al., 2021; Vangay et al., 2018). Besides dietary quality, many other factors influence microbiota, among which psychotropic medication. A large in vitro study showed, for example, that antipsychotics confer particularly strong antibiotic-like effects (Maier et al., 2018).

BD patients experience a lower quality of life due to recurrent mood episodes and their consequences. In addition, BD patients have a lower life expectancy partially due to cardiovascular diseases, driven partially by life-style factors (e.g., exercise, smoking and diet) and suicide (Grande et al., 2016; McIntyre et al., 2020). In general, psychiatric patients tend to consume less healthy diets, characterized by an increase in sugar and salt, and a decrease in vegetables, fruit, and fiber intake compared to their age- and sex-matched counterparts not suffering from psychiatric disorders (Bly et al., 2014; Kilbourne et al., 2007; Elmslie et al., 2001; Jacka et al., 2011). Although BD patients also seem to consume poorer quality diets than healthy controls (Elmslie et al., 2001; Jacka et al., 2011), no previous study assessed its relationship with microbiota composition and diversity in BD.

Although psychiatric disorders are considered primarily as diseases of the central nervous system, research has shown a possible interaction with the gut microbiota through the gut-brain axis. In fact, several studies have shown differences in the microbiota when comparing patients with psychiatric disorders and healthy controls (Evans et al., 2017a; Nikolova et al., 2021; Nguyen et al., 2018). However, the few studies that have focused on BD, used cross-sectional designs, which impeded them in detecting potential temporal effects (Jiang et al., 2018; Coello et al., 2019; Nguyen et al., 2018; Rong et al., 2019; Zheng et al., 2020). Microbial diversity was generally lower in BD patients compared to healthy controls, which seemed to be both state and trait dependent (Sublette et al., 2021). Additionally, specific genera were lower in abundance, although these findings were not consistent over the studies (Jiang et al., 2018; Coello et al., 2019; Rong et al., 2019; Zheng et al., 2020). Meanwhile, longitudinal studies in unipolar depression have found possible differences in microbiota of responders and non-responders to treatment (Evans et al., 2017b). Since a lower alpha diversity was found in patients with several psychiatric diseases compared to healthy controls, a more diverse microbiota is generally thought to be of benefit to health (Zhernakova et al., 2016).

The aim of this study was to prospectively investigate the relationship between diet and microbiota in patients with recently diagnosed BD. We aimed to determine: 1) if there is an association between dietary quality and microbiota diversity in recently diagnosed BD, and 2) whether changes occur in dietary quality and microbiota diversity during one year of follow-up. We hypothesized that higher dietary quality would be linked to greater microbiota diversity, and that both dietary quality and microbiota diversity would decline during follow-up (potentially due to psychotropic treatment effects). The current study utilized data from the "Bipolar Netherlands Cohort" (BINCO). In contrast to the rather crude assessments in earlier studies (Jiang et al., 2018; Coello et al., 2019; Kilbourne et al., 2007; Elmslie et al., 2001; Jacka et al., 2011; Rong et al., 2019; Zheng et al., 2020), dietary quality was assessed using a validated 203-item food frequency questionnaire (FFQ) to measure habitual intake over the previous month (Du et al., 2009). In BD patients who provided fecal samples, the diversity of their microbiota was also assessed. Furthermore, the study followed recently diagnosed (<1 year) BD patients during one year, when the assessments were repeated.

2. Participants and methods

2.1. Participants

All data was gathered from participants in the context of the 'Bipolar Netherlands Cohort' (BINCO) study (Koenders et al., 2021), which was initiated to assess possible predictors for the course of disease. Recently diagnosed (<1 year) patients with BD, both type I and type II, from various outpatient clinics in the Netherlands were included in this cohort ($n = 70$). Data and fecal sample collection took place at baseline and after one year follow-up. Microbiota diversity was analyzed in patients who provided both a Food Frequency Questionnaire (FFQ) as well as a corresponding fecal sample at baseline ($n = 39$, Fig. 1). Two participants with implausible total energy intakes (348 kcal/day for a female participant and 617 for a male participant) were excluded according to the guidelines for calculating a valid Dutch healthy diet 2015 (DHD-15) score using total caloric intake as a measure of validity. Five participants provided a stool sample without a (valid) corresponding FFQ at baseline. They were included only in the Bray-Curtis analysis. This resulted in 70 unique participants, of whom 68 provided data at baseline. 39 participants provided combined FFQ and microbiota data at baseline, of whom 21 could be reassessed at follow-up for combined data. Together with two participants who lacked baseline data, combined data for 23 participants was available at follow-up (t2). Thirty-seven participants provided FFQ data both at baseline and follow-up. Microbiome data was available for 43 individuals at baseline and for 27 individuals at follow-up (see Fig. 1).

2.2. Procedure and materials

Participants were interviewed at baseline and at a follow-up visit after one year. The study was conducted in compliance with the Declaration of Helsinki and approved by a central medical ethics committee (Leiden University Medical Centre, The Netherlands, reference number: NL51776.058.14, BINCO) and by the committee at each participating mental health organization (specialized outpatient clinics of PsyQ The Hague and Rotterdam, Zaandam, Beverwijk, and Rivierduinen Leiden). Written informed consent was obtained from all participants.

2.3. Dietary quality data

Dietary data were collected by a 203-item FFQ, an extended version of a reproducible and biomarker validated FFQ (Du et al., 2009). Patients were asked to report the usual intake of foods consumed during the previous month; questions on the frequency, amount, and type of foods and preparation methods were included. The food data were converted into energy and nutrient intake by using the Dutch food composition database. The food items were collapsed into 24 food groups according to criteria derived from the Guidelines Food Choice of the Netherlands Nutrition Center. The calculation of the DHD-15 food scores has been previously reported in more detail (van Lee et al., 2012) and included these 15 food groups: vegetables, fruit, grains, protein-rich plant foods (i.e. legumes), red meat, processed meat, fish, diary, nuts,

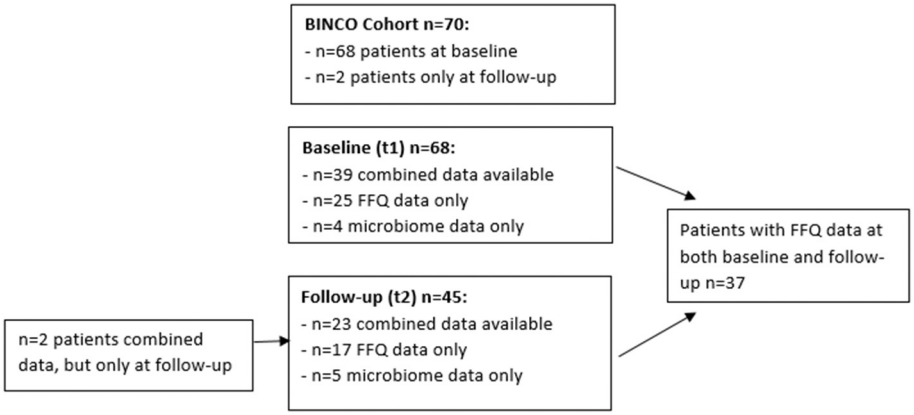

Fig. 1. Flow chart BINCO study into diet and microbiota in participants suffering from BD.
FFQ: Food Frequency Questionnaire.

tea, coffee, fat, sweetened beverages, sodium, and alcohol. The DHD-15 is a measure of how well a person adheres to the Dutch guidelines for a healthy diet that were revised in 2015 (van Lee et al., 2012; Looman et al., 2017; van Lee et al., 2016). The scores range from 0 through 10 and can be calculated from the daily intake of the main food groups from the FFQ, consists of fifteen subscores, each representing a food group. The total sum score ranges from 0 to 150 points; a higher score indicates a better dietary quality (i.e., a better adherence to the Dutch guidelines for a healthy diet with regard to cardiovascular and chronic diseases). Coffee is included as a dichotomous variable in which consumption of filtered coffee is awarded 10 points. Sodium is likely to be underestimated, since the use of extra salt during cooking or eating a meal could not be calculated, neither does the estimation account for differences in sodium in different brands of for example cereal. However, the DHD-15 score adjusts for this by taking a cut off value of 20 % less than the recommended guidelines. The DHD-15 score was deemed unreliable for FFQs with a total calorie-intake of <600 or 800 or >6000 or 8000 for respectively female and male patients, and these participants were excluded with regard to the FFQ data ($n = 2$ one at baseline, $n = 1$ at follow-up).

2.4. Fecal collection and DNA extraction

Fecal samples were collected <48 hours before the study appointment by the participants using a fecal collection kit. Fecal samples were collected by the participants (using fecesvanger.nl) using a small feces container with spoon, which were wrapped and stored in the refrigerator until their visit to the clinic, after which samples were stored at −80 °C until further analysis. A total (t1 and t2) of 71 samples were collected for analysis.

DNA was extracted from 0.1 g of cryopreserved feces and two positive controls (ZymoBiomics Microbial Community Standard (D6300), ZymoResearch, CA, USA) using the Quick-DNA™ Fecal/Soil Microbe Miniprep Kit (ZymoResearch, CA, USA) as described previously (Ducarmon et al., 2020). Negative blanco DNA extractions were included (see Supplementary Fig. S1).

Library preparation, quality control and sequencing were performed by GenomeScan B.V. (Leiden, The Netherlands) using the NEBNext Ultra™ II Q5 Master Mix (New England Biolabs, MA, USA) with 16S rRNA gene V4-specific primers (by GenomeScan B.V.) and the Illumina NovaSeq6000 platform (paired-end, 150 bp), during which two sequencing controls (ZymoBiomics Microbial Community DNA Standard (D6305), ZymoResearch, CA, USA) were included (see Supplementary Fig. S2).

2.5. Mental health assessment

Several questionnaires were assessed during baseline and follow-up visits.

The Clinical Global Impression – Bipolar Disorder (CGI-BD) is a clinical impression scale in which a clinician rates the burden of disease on a Likert scale from 0 to 7 (Busner and Targum, 2007). It consists of three subscales; the first subscale rates burden of disease according to (hypo)manic symptoms, the second subscale according to depressive symptoms, and the third subscale scores according the overall disease burden of disease.

The Quick inventory of depressive symptoms-self report (QIDS-SR) is a 16 item self-report questionnaire that covers 9 domains of depressive symptoms according to the DSM 5 (Rush et al., 2003). Mild depression is diagnosed at 6–10 points, 0–5 points indicate there is no depressive episode. Moderate depression is signified by 11–15 points and severe depression generates a score of 16–21. Patients scoring 22–27 points are considered to suffer from very severe depression. The internal validity is high for the original scale as well as the Dutch translation (Cronbach's alpha 0.86) (Schulte-van Maaren et al., 2013).

The Young Mania Rating Scale (YMRS) assesses (hypo)manic symptoms (Young et al., 1978). This is an 11 item scale, of which four are rated 0 to 8 points covering symptoms of irritability, thought content, aggressive/disruptive behavior and speech. The remaining seven items are rated with scores of 0 to 4. All scores are based on the clinician's impression and the answers of the patient. The YMRS has a maximum of 60 points, all scores above 13 indicating symptoms of hypomania and scores above 20 indicating mania (26–30 moderate and above 38 severe mania). The inter-rater reliability for this questionnaire is high ($r = 0.93$) and the Dutch translation has been validated (Lukasiewicz et al., 2013).

2.6. Covariates

Data on age, smoking, alcohol consumption, educational and civil status was assessed. Body weight and length were measured, yielding the Body Mass Index (BMI).

The use of psychotropic and other medication was dichotomized into use (yes/no) of lithium, antipsychotics, moods stabilizers, antidepressants, benzodiazepines, and supplements. Supplements were scored as being used when the mentioned product was advertised as such or contained at least one vitamin or micronutrient. A participant was considered a user of the medication if they had used the medication during the preceding month.

2.7. Statistical analyses

Baseline characteristics for all 70 participants used in at least one analysis were presented using percentages for categorical variables and mean and standard deviation for continuous variables (Table 1). Baseline variables between participants with follow-up measurements were compared to participants with missing follow-up data using an unpaired *t*-test for the continuous variables and a chi-squared test for the categorical variables.

Raw sequence reads were processed using the QIIME 2 pipeline (v2020–8), with the following settings: forward and reverse read length of 120 bp, quality control using Deblur, and identity level of 100 % (default). Unweighted UniFrac distances were obtained with QIIME2 (v2022–2). The Silva 138SSU Ref database was used for taxonomic classification. The obtained feature table was filtered for features with relative abundance <0.005 % of the total number of reads (Bokulich et al., 2013). Statistical analysis and data visualization were performed in RStudio (R Foundation for Statistical Computing, 2016) (v4.0.4) and SPSS version 25 (SPSS, n.d.) and primarily using the *phyloseq* package (version 1.40.0) (*phyloseq: An R Package for Reproducible Interactive Analysis and Graphics of Microbiome Census Data*, 2013) with the *ggplot2* package (version 3.4.0) (*ggplot2: Elegant Graphics for Data Analysis*, 2016) and *lme4* package (version 1.1–31) (Bates et al., 2015). Richness (Chao1), Shannon diversity and Pielou's Evenness index were computed at OTU level with the *microbiome* package (*Tools for microbiome analysis in R. Microbiome package. Version 1.19.1. Bioconductor*, 2017).

Principal Coordinates Analysis was performed with the *pcoa* function of the *ape* package (version 5.6–2) (*ape 5.0: An Environment for Modern Phylogenetics and Evolutionary Analyses in R*, 2019) with cailliez correction to eliminate negative eigenvalues. Bray-Curtis (computed with the *distance* function) and unweighted UniFrac distance (computed using QIIME 2 v2022–2) were used.

Quality control was based on the positive controls that were included during DNA extraction (PCE) and sequencing (PCS), as well as negative controls that were included during DNA extraction (Supplementary Fig. S1). The mean total reads of the positive controls (1,663,272 ± 44,692) was significantly higher (p = 0.03, Kruskal-Wallis test) compared to the mean total reads of the negative control (3066 ± 369). The negative control primarily contained *Collinsella* with 1295 reads, whereas the median observed reads from *Collinsella* in samples were 43,320. While *Collinsella* has been reported as contaminant in DNA extraction kits (Glassing et al., 2016), it also is a member of the gut microbiota. Given the significantly lower number of total reads in the negative control, and a ~ 30-fold increase in the median reads from *Collinsella* in feces compared to the negative control, we did not consider *Collinsella* as contaminant in the feces.

Additionally, the taxonomic genus composition of the positive controls was compared to the theoretical mock community composition. The eight bacterial genera of the Microbial Community Standard were all identified. The relative abundance of these genera was on average 1.00 ± 0.43 and 1.00-fold different from the theoretical abundances for the two DNA extraction controls and one sequencing control, respectively. This indicates that minor variation is induced by the DNA extraction and sequencing procedures.

We applied a two-step process to analyze the microbiome data, ensuring the comparability of samples despite varying sequencing depths. Initially, we normalized the data by rarefying each sample to the same sequencing depth, specifically to the minimum number of reads found in any of the samples, to mitigate bias introduced by different sequencing depths across samples. Next, diversity for each sample was assessed, including Chao1 richness (the number of different species), the Shannon diversity index for diversity and the Pielou's evenness index for evenness (the distribution of individuals among these species).

Table 1
Baseline characteristics of patients with bipolar disorder, diagnosed less than one year ago with microbiome and DHD-15 data at baseline (n = 39).

Sociodemographic characteristics	
Female sex, n (%)	24 (61.5)
Age, years, mean (SD)	36.3 (10.9)
Level of education	
- Vocational secondary education n, (%)	11 (28.2)
- General secondary education n, (%)	9 (23.1)
- University n, (%)	19 (48.7)
Living without partner (%)	26 (56.7)
Clinical characteristics	
Current smoking, n (%)	16 (41.0)
BMI; mean (SD)	24.4 (4.3)
BMI > 25 kg/m^2 n, (%)	14 (35.9)
Alcohol	
- None	12 (30.8)
- Less than one unit a day	16 (41.0)
- Two or more units per day	1 (2.5)
QIDS baseline; mean (SD)	9.2 (5.7)
YMRS baseline; mean (SD)	3.6 (3.8)
Medication use baseline	
- Lithium n, (%)	20 (51.3)
- Anti-epileptics n, (%)	3 (7.7)
- Anti-psychotics n, (%)	8 (20.5)
- Benzodiazepines n, (%)	11 (28.2)
- Antidepressants n, (%)	8 (20.5)
- Dietary supplements n, (%)	12 (30.8)
Dutch Healthy Diet (DHD-15) index mean, (SD)	84.0 (16.4)

BMI: body mass index. QIDS: Quick Inventory of Depressive Symptoms. YMRS: Young Mania Rating Scale. Dietary supplements; includes use of vitamins and combinations of vitamins and/or minerals.

2.8. Microbiota and dietary quality

Baseline associations between dietary quality (i.e., DHD subscores and total scores) and microbiota diversity and richness were analyzed in scatter plots and Pearson's correlation coefficients, as well as multivariate linear regression analyses. In model one we adjusted all standardized variables for age, sex, and level of education, and in model two additionally for YMRS, QIDS and CGI-BD, smoking, BMI, the use of lithium or a mood stabilizer, and the use of antipsychotics.

Abundance of microbiota family and genus was analyzed at both time points for all available fecal samples and presented for the nine most prevalent families and genera on the group level. Changes over time in patients who contributed data at two waves were analyzed using paired samples *t*-tests. Permutational multivariate analysis of variance was performed to relate variables to overall microbiota composition. The nine most abundant microbiota families and genera were analyzed using multilevel analyses with a random slope for participant, yielding adjusted means and standard errors of proportions.

3. Results

3.1. Study population

The cohort (n = 70) consisted predominantly of females (58.6 %) and the mean age was 34.9 years (SD ±11.2) (Supplementary Table 1). Thirty out of seventy (42.9 %) participants were overweight (BMI > 25 kg/m^2). The average QIDS-SR and YMRS scores indicated no manic state at baseline and on average mild depressive symptoms. Of these 70 participants, 39 provided FFQ data as well as feces samples, as feces samples were analyzed earlier, and some participants had not yet had their second assessment (basic characteristics Table 1). Most participants had completed a form a higher education (62.8 %) and most were living without a partner (55.2 %). Half of the participants were using lithium at baseline (52.9 %). Basic characteristics of patients who were lost to follow-up for combined data of microbiota and FFQ (n = 18) did not differ from patients who continued to participate (n = 21) in sex, age, educational level, smoking status, alcohol consumption, BMI, use of medication or QIDS and YMRS at baseline (Supplementary Table 2).

3.2. Dietary quality is related to microbial diversity in BD patients at baseline

At baseline, microbial diversity (Shannon diversity index), richness (Chao1 richness) and evenness (Pielou's evenness index) were correlated significantly to the DHD-15 total score (Fig. 2). After adjusting for age and sex in linear regression analyses, the association between the DHD-15 total score and diversity, richness and evenness remained statistically significant. Further adjustment for confounders led to the results in Table 2. In both models adjusted for age, sex and educational level the association of the DHD-15 total score and richness and diversity remained significant. The same was seen in model 2, which was additionally adjusted for the use of lithium or mood stabilizing agents, antipsychotics, QIDS, YMRS, GCI, BMI and smoking. The association of the DHD-15 total score and Chao1 richness, Shannon diversity and Pielou's evenness index remained significant. BMI, which showed a narrow distribution in the study population, was not significantly correlated at baseline, neither to either diet (DHD-15 score) nor to any of the three microbiota diversity indexes.

Individual DHD subscores - after adjustment for age and sex - were additionally investigated, showing that the DHD-subscore for fish (beta = 0.45, $p = 0.004$) was significantly associated with Chao1 richness (Fig. 3 top), while the DHD-subscore for legumes and nuts were significantly associated to Shannon diversity and Pielou's evenness index (Fig. 3 middle and bottom). While many other healthy food groups seemed to have positive associations with microbiota diversity, their associations were not statistically significant. Likewise, alcohol, red and processed meat and sodium all showed negative associations, though not statistically significant, with the microbiota diversity indexes at baseline.

3.3. Diet remains stable during one year follow-up in recently diagnosed BD patients

DHD total score and subscores of patients at baseline were compared to scores after one year to assess dietary changes during the one year follow-up of recently diagnosed BD patients. The DHD-15 total score was moderately correlated between baseline and after one year ($n = 37$, $r = 0.52$; $p = 0.001$, Fig. 5). Similarly, the caloric intake of individuals was highly correlated between baseline and after one year (n = 37, $r = 0.61$; $p < 0.001$). DHD-subscores of participants at baseline were compared to DHD-15-subscores after one year (n = 37) and did not change significantly (Supplementary Table 3). The subscore for processed meat decreased (−0.683, 95 % CI: −1.206 to −0.012; $p = 0.046$), indicating participants tended to eat more processed meat after one year than at baseline.

3.4. Microbial changes during BD treatment in relation to diet

The relative abundance of the most abundant genera did not change during the study period of one year (Fig. 4, Supplementary Figs. 1 and 2). This was confirmed in principal coordinates analyses in which no clustering was observed for the two separate time points (Fig. 6). Most abundant were bifidobacteria (proportion of 0.157 (95 % CI: 0.125–0.189) at baseline and 0.128 (95 % CI: 0.089–0.168) at follow-up), followed by *Collinsella* spp. (proportion of 0.119 (95 % CI: 0.087; 0.150) and 0.107 (95 % CI: 0.070; 0.145) respectively). Post hoc analyses of DHD-15 scores correlated to individual families and genera are shown in Supplementary Table 4.

Considering the all three indexes, Chao1 richness was highly correlated for individual measurements between the baseline and 1 year of follow-up ($n = 21$, $r = 0.75$; $p < 0.001$), Shannon diversity was much less stable after 1 year of follow-up (n = 21, $r = 0.32$ $p = 0.12$) (Fig. 5) as was Pielou's evenness index (n = 21, $r = 0.04$ $p = 0.85$). Despite these intrapersonal shifts, the mean diversity over all available subjects did not differ. In exploratory analyses the YMRS tended to be associated with reduced microbiome diversity (Supplementary Table 5).

4. Discussion

In this study we prospectively assessed dietary quality changes in patients recently diagnosed with BD and its potential associations with the composition of microbiota. The DHD-15 total score was positively associated with microbial Shannon diversity, Chao1 richness and Pielou's evenness at baseline, independent of current mood state and medication use, indicating that a healthy diet was associated with a higher richness, diversity and evenness. Neither the overall dietary quality of BD patients nor the microbiota diversity changed significantly during one year of follow-up. We are not aware of previous studies that studied both the microbiota and dietary quality at the same time in BD patients.

That a healthy diet is associated with higher diversity, evenness and richness of the microbiota, is in line with previous studies showing the effects of diet on the microbiota, describing positive effects of overall diets in healthy populations (Garcia-Mantrana et al., 2018; Hansen et al., 2018; C. Wang et al., 2021). The association of an overall healthy diet with all three microbiota indexes after adjustment for several covariates, indicates that dietary quality is an important determinant despite the potential detrimental effects of psychotropics (Maier et al., 2018). The beneficial effect of a healthy diet on cardiovascular disease is an essential part of the management of BD patients, because of the high morbidity and mortality in BD versus the general population (Grande et al., 2016; McIntyre et al., 2020). The risk of cardiovascular disease

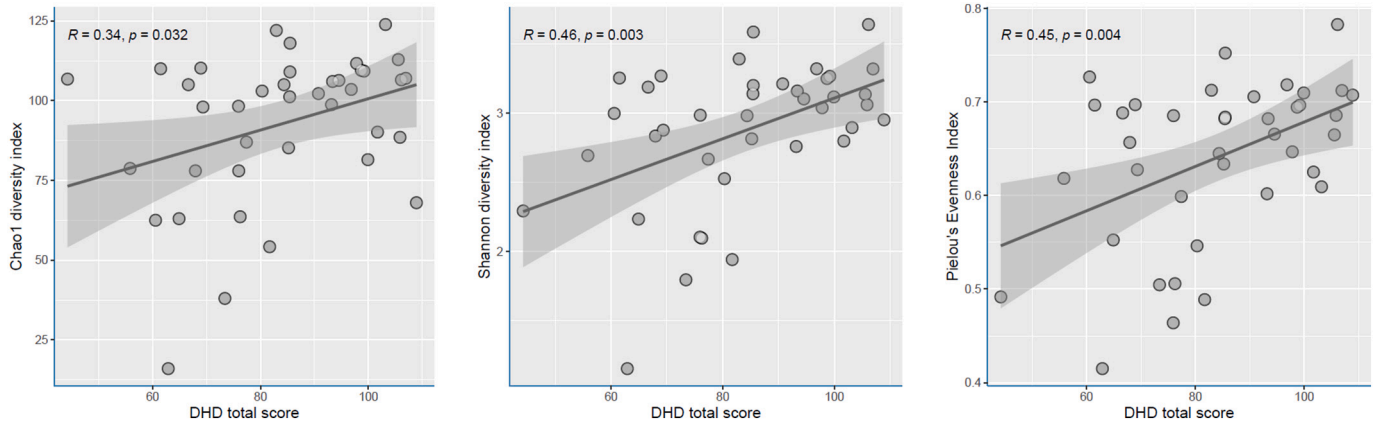

Fig. 2. Pearson's correlation coefficients of the DHD-15 total score with the Chao1 richness, Shannon diversity and Pielou's Evenness Index to indexes for recently diagnosed BD patients at baseline (n = 39). Chao1 (left) indicates richness of microbiota and Shannon diversity index (middle) and Pielou's Evenness (right) index indicate the evenness.

Table 2
Standardized models of DHD-15 total score regression analysis to Chao1, Shannon diversity and Pielou's evenness index for recently diagnosed BD patients at baseline.

DHD total score	Chao1 index		Shannon diversity index		Pielou's evenness index	
	Beta (95 % CI)	P-value	Beta (95 % CI)	P-value	Beta (95 % CI)	P-value
Crude	0.345 (0.032;0.657)	0.032	0.465 (0.170;0.760)	0.003	0.453 (0.156;0.750)	0.004
Model 1	0.391 (0.054;0.728)	0.024	0.546 (0.239;0.852)	<0.001	0.535 (0.226;0.845)	0.001
Model 2	0.432 (0.055;0.809)	0.026	0.621 (0.355;0.886)	<0.001	0.610 (0.360;0.865)	<0.001

Model 1: adjusted for age and sex and educational level.
Model 2: additionally adjusted for use of lithium or other mood stabilizing agents, use of antipsychotics, YMRS total score, QIDS total score, GCI overall disease score, BMI and smoking.

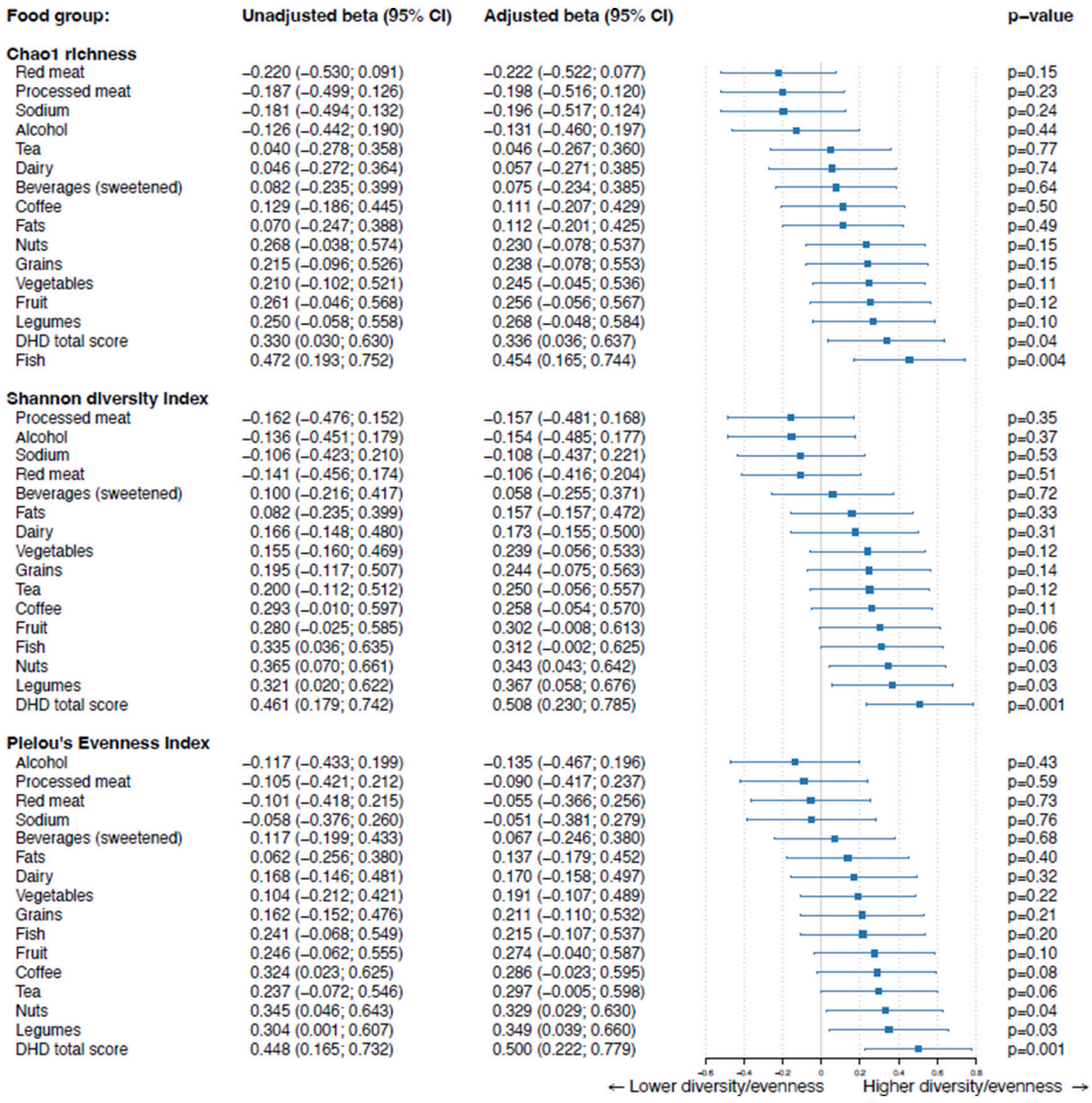

Fig. 3. Cross-sectional forest plots at baseline showing the age- and sex-adjusted standardized beta-coefficients between the fifteen different subscores of the DHD-15 and the Chao1 richness, the Shannon diversity index and Pielou's Evenness Index of all patients who provided both FFQ and microbiome data (n = 39).

may in part be mediated by the gut-brain-axis (Rosato et al., 2019) through the microbiota in BD (McIntyre et al., 2020; Panagiotakos et al., 2007), which is in turn modulated by diet; a diet rich in fruits, nuts, vegetables, legumes and fish being beneficial for the diversity of the microbiota (D. Wang et al., 2021). Since the cardiovascular risk factors need to be managed in patients with BD, diet should take a prominent role in disease management, next to pharmacological interventions.

DHD-subscores that were significantly and positively associated with the microbial diversity and evenness at baseline were nuts and legumes, meaning intake of these food items was associated with higher scores of the Shannon and Pielou's indexes. The intake of both nuts and Legumes has been previously recognized for their role in enhancing microbiota diversity (C. Wang et al., 2021; Tuttolomondo et al., 2019). Fish was positively associated with microbiota richness, which is in line with previous findings (Bolte et al., 2021). However, there are also possible atherosclerotic effects of fish intake through trimethylamine N-oxide (TMAO) which is a product from Trimethylamine (TMA) (Wang et al., 2022). Fish was found to be associated with a lower risk of type 2 diabetes (Panagiotakos et al., 2007; Micha et al., 2017), which is why in the DHD-15 index, orientated to reduce risk of chronic and cardiovascular

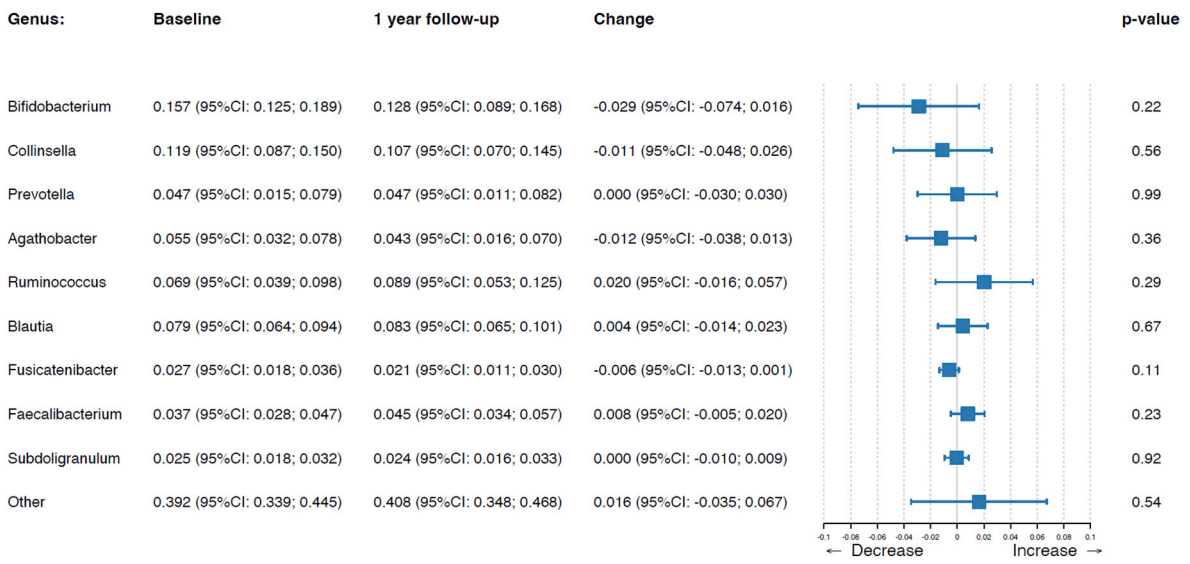

Fig. 4. Forest plot of proportions of genera in stool samples. Baseline and 1 year follow-up were compared, and did not significantly differ for any of the top 9 Genus.

disease, fish consumption is awarded with a higher DHD-score.

Considering diet quality, there have been three previous studies on diet quality in BD patients (Kilbourne et al., 2007; Elmslie et al., 2001; Jacka et al., 2011). Using a variety of less specific dietary indicators, these three studies found an overall less healthy diet in BD patients compared to healthy controls. Patients with BD consumed diets that had higher glycemic loads and were more like the Western-style diet than the controls (Elmslie et al., 2001; Jacka et al., 2011). One of these studies did not find a difference in fruit or vegetable intake, but indicated that intake among all assessed participants was low for both food groups (Kilbourne et al., 2007). Furthermore, participants with BD skipped meals more regularly and reported eating alone more often. However, two of these studies did not include patients with recently diagnosed BD (Kilbourne et al., 2007; Elmslie et al., 2001). A third study did not report on the average duration of BD (Jacka et al., 2011). Furthermore, these previous studies had cross-sectional designs, and did not include data on the microbiota composition. Remarkably, in our study, diet quality did not seem to deteriorate during one year of follow-up, but was slightly lower than the DHD-15 score which was found in a cohort of 885 Dutch men and women without BD between the ages of 20–75. In this cohort reflecting the general population the mean DHD-15 score was 89.2 (SD = 15.4) (Looman et al., 2017) as opposed to the mean score of 84.0 of our cohort. In the general population cohort, men scored significantly lower than women, but were slightly overrepresented (53 %). The current study took place in a cohort with more women (61.5 %) and while there was no significant difference in our small sample ($n = 39$) in DHD-15 scores, women had a higher mean score. Therefore the difference might be larger between the cohorts if they were sex-matched. A longer duration of BD could potentially have led to the results of earlier studies because of the more chronic use of mood stabilizing agents and other psychotropics, or more mood episodes and behavioral and possibly dietary changes. Previous in vitro studies have shown that psychotropics, such as antipsychotics, may decrease microbiota diversity, both in vitro (Maier et al., 2018) as in vivo (Dinan and Cryan, 2018). Aberrant mood states such as depression were also associated with poorer microbiota diversity (Rong et al., 2019; Kurokawa et al., 2021). It is unclear whether depressive symptoms cause a less healthy diet (through loss of appetite and initiative) and therefore less diverse microbiota, or possibly that a less diverse microbiota is the cause of the depressive symptoms such as a loss of initiative and appetite.

Previous studies into the microbiota of BD patients have shown a negative correlation between duration of illness and diversity as well as a difference in abundance of certain microbiota species in BD patients compared to healthy controls (Evans et al., 2017a; Painold et al., 2019). Other studies found no difference in diversity between depressed BD patients or patients with unipolar depression, but concluded that dysbiosis – an imbalance of the microbiota's composition or its functions – could be the driving factor. The abundance of certain genera seemed to be associated with depression (Rong et al., 2019; Jiang et al., 2020). During pharmacological treatment dysbiosis decreased and diversity increased, becoming more like the microbiota of heathy controls (Jiang et al., 2018; Hu et al., 2019). Our results showed no evidence of changes on the group level in microbiota diversity at one year follow-up when it comes to diversity or individual genera. However, in exploratory analyses an increase of the YMRS tended to be associated with a somewhat less healthy dietary intake and reduced microbiome diversity and evenness. Although these were post-hoc analyses and only statistically significant for the Shannon diversity index and Pielou's Evenness index, it could be hypothesized that mania might be more adverse than depression with regard to a diverse and healthy diet and microbiome, which needs to be further investigated.

Our study may yield some clinical implications. Significant dietary and microbiota changes are not seen in this recently diagnosed cohort during one year. Early disease management with a focus on metabolic changes associated with the diet and microbiome might yield benefits, which may be more effective than later interventions. Prebiotics and probiotics (or the combination synbiotics) may help to modulate the microbiota, and are currently being studied as a possible intervention (Liu et al., 2019). Other lifestyle factors should also be included, as patients with BD generally have a higher risk of obesity (Grande et al., 2016; McIntyre et al., 2020; Elmslie et al., 2001), rate of smoking (Grande et al., 2016; McIntyre et al., 2020), and use of alcohol and drugs (Grande et al., 2016; McIntyre et al., 2020) than their healthy counterparts. Such factor may contribute to their increased risk of cardiovascular disease (Grande et al., 2016; McIntyre et al., 2020; Elmslie et al., 2001). Consequently, they have a lower life expectancy on average, which can only in part be ascribed to high suicide rates (Grande et al., 2016; McIntyre et al., 2020).

Strengths of this study are that, to our knowledge, this is the first prospective study into diet quality and microbiota in BD patients. Moreover, patients were rather recently diagnosed with BD, resulting in a homogenous group when it comes to treatment focused on BD. Finally, diet quality was assessed with a validated 203-item questionnaire. There are also some important limitations we need to acknowledge. First, while this study offers some important insights into the early stages of BD, it is important to acknowledge that our findings are limited by the

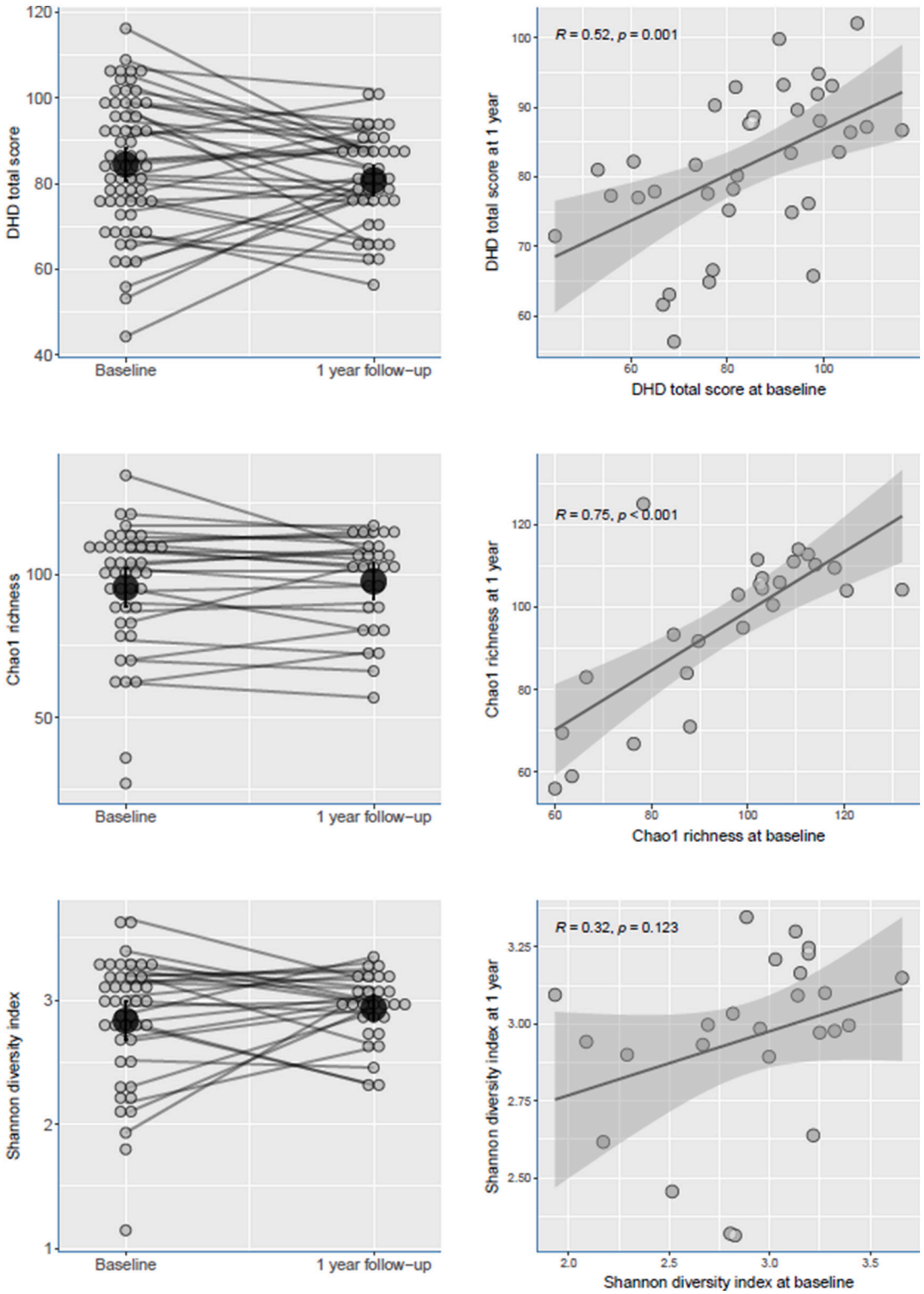

Fig. 5. Change in DHD-total score (Panel A), Chao1 richness (Panel B) and Shannon diversity (Panel C) from baseline to follow-up at one year with the respective p-values (left side). The scatter plots and Pearson's correlation coefficients with respective correlation coefficients and p-values of the respective measures per individual at baseline versus one year follow-up are shown on the right, with their respective means (dark dot) and standard deviations.

absence of matched controls. This restricts our ability to directly compare the differences observed in newly diagnosed BD participants with those in a comparable non-BD group. Second, the sample size was small, which may have increased the risk of type II statistical errors. Third, multiple tests were done and we did not adjusted for multiple testing as our primary aim was to assess the association between diet quality and microbiota diversity, which was statistically significant for both Shannon diversity and Chao1 richness. Fourth, due to the on-going character of the study, there was missing data at follow-up of 46 %, which was largely missingness at random as most had not yet had their

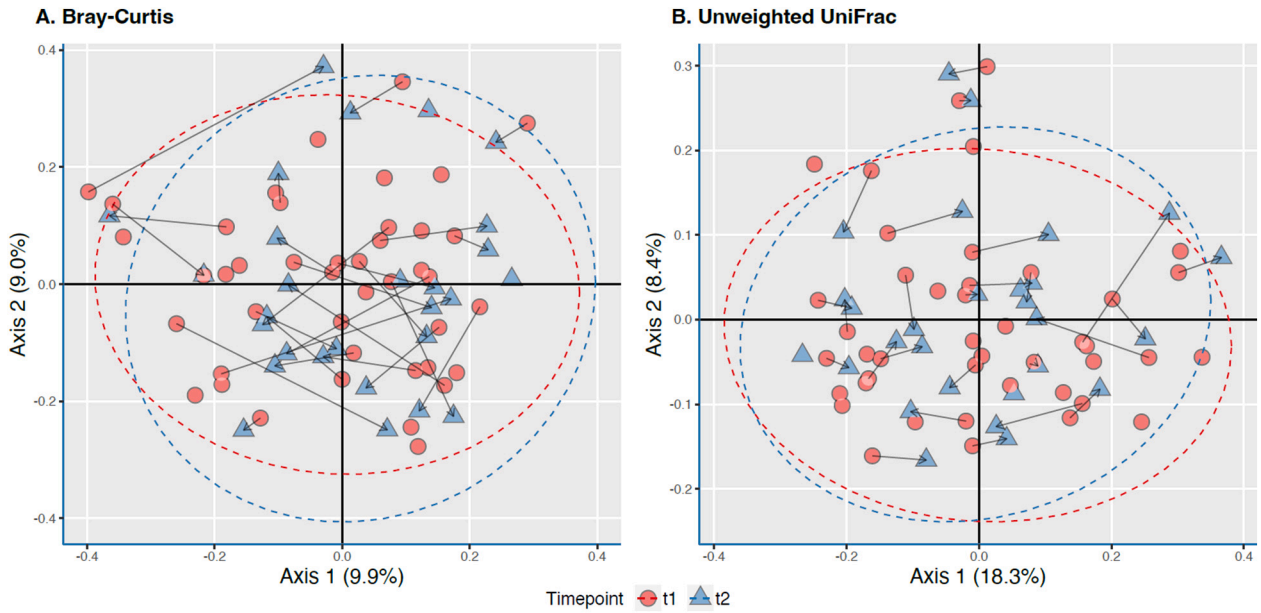

Fig. 6. Principal coordinates analysis using Bray-Curtis dissimilarity indexes (left) and unweighted UniFrac (right) distances for baseline (timepoint t1, red dots) and follow-up (t2, blue triangles) in 39 patients at baseline and 23 patients and 1 year follow-up. The arrows indicate the temporal changes after 1 year in BD patients. Two participants only provided a stool sample at 1 year follow-up, but not at baseline. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

1-year assessment. Fifth, the FFQ was somewhat prone to underestimating sodium intake and scores the use of coffee as a dichotomous variable, not measuring amount of consumption. The FFQ merely assesses intake not dietary habits such as skipping meals and we could not use the DHD-15 to specifically look at fermented products. Thus, more research into the exact mechanism through which factors influence each other is needed. It is also important to acknowledge that our data collection focused not on cardiovascular outcomes, and associations between a broad range of cardiovascular risk factors, dietary habits, and the microbiota, could be an area for future research requiring longer follow-up periods. Furthermore future research could focus on functional outcomes and include assessments of bacterial metabolite concentrations in association with altered abundances.

5. Conclusion

Our main findings were that an overall healthy and diverse diet was associated with a more diverse microbiota in patients with recently diagnosed BD, and that dietary quality did on average not deteriorate significantly during one year of follow-up. Given the high cardiovascular risks associated with BD, attention should be given to diet as a key factor in managing and potentially preventing some of the adverse somatic consequences of this condition. Future studies should compare the diets of BD patients and healthy controls and explore the potential impact of long-term psychotropic treatment and lifestyle changes on the microbiota and mood stability.

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CRediT authorship contribution statement

M.A. Riedinger: Writing – review & editing, Writing – original draft, Visualization, Project administration, Investigation, Formal analysis, Data curation. **R. Mesbah:** Writing – review & editing, Writing – original draft, Project administration, Data curation. **M. Koenders:** Writing – review & editing, Resources, Project administration, Conceptualization. **J.G.E. Henderickx:** Writing – review & editing, Validation, Methodology, Formal analysis. **W.K. Smits:** Writing – review & editing. **E. El Filali:** Writing – review & editing. **J.M. Geleijnse:** Writing – review & editing. **N.J.A. van der Wee:** Writing – review & editing, Supervision. **M. de Leeuw:** Writing – review & editing. **E.J. Giltay:** Writing – original draft, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

All authors declare no conflict of interest.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2024.03.105.

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