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Poor intake of vitamins and minerals is associated with symptoms among patients with irritable bowel syndrome

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extraintestinal symptoms, fatigue, fatty acids, gastrointestinal symptoms, irritable bowel syndrome (IBS), minerals, starch- and sucrose-reduced diet (SSRD), vitamins.

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Abstract

Background and Aim: Poor food habits with insufficient intake of micronutrients have been described in irritable bowel syndrome (IBS), which could be of importance for development of gastrointestinal and extraintestinal symptoms. The study aims were to examine intake and plasma/serum levels of micronutrients in IBS and whether these factors were associated with symptoms and restrictions and to study the effects of a starch- and sucrose-reduced diet (SSRD).

Methods: One hundred five patients with IBS or functional gastrointestinal disorder (FGID) according to Rome IV criteria were included to SSRD/controls for 4 weeks. Patients completed a study questionnaire about lifestyle habits, medical health, IBS-symptom severity score (IBS-SSS), visual analog scale for IBS (VAS-IBS), and diary books before and after study start. Plasma/serum levels of micronutrients were analyzed at baseline.

Results: Intake of micronutrients at baseline was lower than recommended according to national guidelines. Gastrointestinal symptoms were inversely associated with intake and plasma levels of iron. Extraintestinal symptoms and fatigue inversely associated with intake of vitamin B6, phosphorus, magnesium, and iodine, as was plasma levels of iron, and positively associated with plasma iron-binding capacity. Fatigue was also inversely associated with calcium, iron, and zinc intakes. Plasma ferritin was lower in participants on restrictions. SSRD increased the intake of several vitamins, selenium, and fat, whereas sodium intake was decreased, with markedly reduced symptoms.

Conclusion: Irritable bowel syndrome patients had low intake of micronutrients at baseline, which associated inversely with total IBS-SSS, extraintestinal IBS-SSS, and fatigue. SSRD increased the intake of several micronutrients, which correlated weakly with symptom improvement.

Introduction

Irritable bowel syndrome (IBS) is the most common functional gastrointestinal disorder (FGID).[1] The etiology is unknown, but female sex, dietary habits, and psychological factors have been discussed as risk factors for the disease.[1] Depression, anxiety, and concomitant pain from other organs are common diseases found to be associated with IBS.[2–4]

A recently performed dietary intervention with a starch- and sucrose-reduced diet (SSRD) markedly improved gastrointestinal (GI) symptoms, extraintestinal symptoms, and psychological well-being.[5,6] One additional finding was that patients with IBS/FGID had a low intake and circulating levels of several micronutrients.[5,7] The findings of poor food habits in IBS with higher amount of processed food have been described previously.[8–10] The lower intake of fruits, vegetables, and micronutrients may be explained by a history of several diets to avoid abdominal pain and symptoms.[10,11] Dietary interventions with low levels of fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) may lead to malnutrition if strictly adhered to for a longer time.[10,12] A low nutritional intake for several years may be of importance to develop cognitive failure, mental illness, and several organic conditions, where vitamin B deficiency is one of the most well-known vitamins of importance.[13–15] Vitamin D deficiency has been suggested to trigger both IBS and mental illness,[16,17] and be of importance for central hypersensitivity.[18] On the other hand, chronic fatigue could not be associated with vitamin D deficiency because many of the patients were taking vitamin D supplements.[19] Iron deficiency and anemia are well-known causes of chronic fatigue.[20]

Our hypothesis was that IBS patients have low intake of vitamins and minerals, which could have importance for the development and experience of symptoms and psychological well-being in the disease. Furthermore, it is important to evaluate the effect of a new dietary regime on intake of important micronutrients and fatty acid composition. The primary aim of the present study was to examine baseline data regarding intake and plasma/serum levels of micronutrients in IBS and whether these factors were associated with symptoms and various restrictions. The secondary aim was to examine effects of SSRD on the intake of micronutrients, fatty acids, and symptoms.

Material and methods

This study was performed in accordance with the declaration of Helsinki and approved by the Ethical Review Board of Lund University (2017/171 and 2017/810). All subjects gave their written, informed consent before inclusion. The study was registered at ClinicalTrials.gov data base (NCT03306381).

Patients. The inclusion criteria for this 4-week open dietary intervention were a diagnosis of IBS, age 18–70 years, and Northern European heritage. Exclusion criteria were insufficient symptoms, that is, < 175 scores on irritable bowel syndrome-symptom severity score (IBS-SSS),[21] presence of any organic GI disease, severe organic and psychiatric diseases, or on gluten-free-, vegan-, low FODMAP-, or low carbohydrate high fat (LCHF) diets (Figs S1 and S2).

Region Skåne provided one registry over all subjects who had received an IBS diagnosis (K58.0 or K58.9 according to the International Statistical Classification of Diseases and Related Health Problems – ICD-10) in primary healthcare centers (PCC) during 2015–2017. Another registration was provided from the Department of Gastroenterology and Hepatology during 2016–2017.

In total, 1039 and 640 unique IBS patients from PCC and the tertiary center, respectively, were identified. Invitation letters were randomly sent to 528 and 151 patients, followed by a phone call a couple of weeks later. After further information, 145 patients who suffered from abdominal pain at least once weekly along with altered bowel habits were willing to participate (112 patients [77%] from PCC; 34 men [23%]) After acceptance to participate, 40 patients (11 men [28%]) were excluded because they did not show up or were not willing to participate at later time point (n = 18), had mild symptoms with < 175 scores of the IBS-SSS (n = 14), wrong diagnoses (n = 5), or were already on a diet listed in the exclusion criteria (n = 3). Thus, 105 patients (23 men [22%]) were finally included in the study (77 patients [73%] from PCC), corresponding to 15% inclusion rate. Of these, 97 participants completed the study (Fig. S2).

Dietary advice. The patients were instructed to hold a diet with starch and sucrose restriction, according to the advice given to patients with congenital sucrase-isomaltase deficiency (CSID).[22] Briefly, all forms of sucrose-containing food, for example, candies, cakes, jam, and juice, should be excluded, and replaced by nuts in the case of sweet cravings. The starch content was reduced with less intake of cereals, but more intake of meat, fish, egg, and dairy products. Fruits and vegetables with low starch content were recommended (Tables S1 and S2). The content of gluten and lactose were un-restricted. Fiber-rich bread, raw rice, and fiber-rich pasta were preferred instead of white bread and ordinary rice and pasta, to delay the nutrient transport through the GI tract. Participants were still recommended to restrict their intake of fiber-rich cereals to a maximum of one serving per day. Participants in the control group were urged not to make any changes to their ordinary diet.

All participants were encouraged to continue with their ordinary energy intake, degree of physical activity, and medications. The participants could reach the study staff by telephone or email, whenever they wanted during the study.

Questionnaires. Patients completed a study questionnaire before study start. Before and afterwards, patients completed a 4-day food diary (also in the middle of the study); the Rome IV questionnaire;[23] the IBS-SSS;[21] and the visual analog scale for IBS (VAS-IBS)[24] (Fig. S1).

Study questionnaire. A study questionnaire about sociodemographic factors, family history, lifestyle habits, medical health, and pharmacological treatment was completed.

Food diaries. Participants registered all consumed foods in a free-writing structure, with information on time/type of food intake and GI symptoms in relation to food intake. They reported the amount and/or volume of each food item, including the percentage of fat in dairy products, fiber in bread products, and cacao in chocolate, as well as type of soda (sugar-free or regular) consumed. The product manufacturer was given when applicable, for example, for brands of bread, butter, and muesli. The product name and ingredient list for pre-maid dishes was reported. Calculations of the total amounts of macro- and micronutrients were performed from day 2 of the 4-day registrations from start and end of the study by a nutritionist, using the AIVO Diet computer program from the National Food Agency, Sweden.[25] The percentages of participants who had an intake of micronutrients equal to or above the average intake requirement (AR) of 50% of the population were calculated based on the 2012 Nordic nutrition recommendations when available.[26]

Rome IV questionnaire. The Rome IV questionnaire was developed to diagnose FGID.[23] Questions No 40–48 in the Swedish version of the questionnaire was used, after having received license from The Rome Foundation, Inc. Raleigh, NC, USA.

Irritable bowel syndrome-symptom severity score. IBS-SSS estimates abdominal pain, abdominal distension, satisfaction with bowel habits, and the impact of bowel habits on daily life using visual analog scales (VAS) ranging from absent (0 mm) to very severe (100 mm) symptoms. The number of days with abdominal pain in the last 10 days was reported. The maximum achievable score is 500. Scores ranging 75–174 indicate mild disease, 175–299 indicate moderate disease, and ≥ 300 indicate severe disease. The extraintestinal symptoms nausea, difficulties to eat a whole meal, reflux, belching, headache, back pain, leg pain, muscle/joint pain, urinary urgency, and fatigue were estimated on VAS scales. The maximal achievable score is 500, after dividing the sum score with a factor of two.[21]

Visual analog scale for irritable bowel syndrome. The VAS-IBS is a validated questionnaire covering abdominal pain, diarrhea, constipation, bloating and flatulence, vomiting and nausea, psychological well-being, and intestinal symptoms' influence on daily life, ranging from absent (0 mm) to very severe (100 mm) symptoms. The item psychological well-being has been shown to closely correlate with anxiety in close relations, self-esteem, and coping skills.[24] The values are inverted from the original format and validated to measure changes over time.[27,28]

Laboratory analyses. Cobalamin, folate, ferritin, iron, total iron-binding capacity (TIBC) in plasma, and 25-hydroxy (25-OH) in serum, were analyzed at baseline according to clinical routines at the Department of Clinical Chemistry.[29]

Statistical analyses. The statistical calculations were performed in IBM SPSS, version 26. Data were not normally distributed according to the Kolmogorov–Smirnov test and presented as median (interquartile ranges) or number (percentages). Changes of data between week 4 and baseline were calculated. Mann–Whitney *U* test, Wilcoxon's test, and Spearman's test were used for continuous variables and Fisher's exact test was used for dichotomous variables.

Baseline data was calculated by generalized linear model to (i) examine associations between intake of vitamins, minerals, and fat (predictors) and total IBS-SSS (tIBS-SSS), extraintestinal IBS-SSS, abdominal pain, fatigue, intestinal symptoms' influence on daily life, and psychological well-being (dependent variables) and (ii) examine associations between intake or plasma/serum levels of micronutrients (dependent variables) and current restrictions (predictor). Calculations were adjusted for sex and presented as β and 95% confidence interval (CI). *P*-value < 0.05 was considered statistically significant.

Table 1 Participant characteristics

	Intervention group (*N* = 80)		Control group (*N* = 25)		
	Median (IQR)	*N* (%)	Median (IQR)	*N* (%)	*P*-value
Age (years)	48 (37–57)		35 (29–50)		0.028
Body mass index (kg/m^2)	24.7 (22.3–28.9)		23.6 (21.4–26.5)		0.193
Sex (women/men)		60/20		22/3	0.267
Current restriction		51/78		17/25	1.000
Physical activity per week					0.838
None		9 (12)		2 (8)	
< 30 min		19 (24)		5 (20)	
30–60 min		12 (13)		4 (16)	
60–120 min		20 (26)		6 (24)	
>120 min		18 (23)		8 (32)	
Subgroups (*Missing value*)		2		0	0.294
IBS-D		23 (30)		3 (12)	
IBS-M		29 (36)		8 (32)	
IBS-C		13 (17)		7 (28)	
Unspecified IBS		2 (3)		1 (4)	
Non-IBS FGID		11 (14)		6 (24)	
		P-value*		*P*-value*	
Total IBS-SSS					
Baseline	306 (250–356)		310 (247–351)		0.820
4 weeks	156 (88–250)	< 0.001	300 (233–331)	0.248	< 0.001
Total extraintestinal IBS-SSS					
Baseline	184 (125–254)		197 (106–257)		0.765
4 weeks	98 (61–174)	< 0.001	169 (107–208)	0.231	0.017
Abdominal pain					
Baseline	52 (37–65)		49 (27–63)		0.441
4 weeks	24 (6–43)	< 0.001	50 (32–63)	0.650	< 0.001
Fatigue					
Baseline	64 (46–87)		67 (39–91)		0.880
4 weeks	48 (22–71)	< 0.001	65 (41–83)	0.794	0.033
Intestinal symptoms influence on daily life					
Baseline	72 (52–86)		68 (53–78)		0.539
4 weeks	35 (20–66)	< 0.001	65 (51–82)	0.732	< 0.001
Psychological well-being					
Baseline	50 (24–69)		47 (24–71)		0.950
4 weeks	36 (13–53)	< 0.001	48 (32–60)	0.732	0.092

Six missing values in the intervention group and two in the control group regarding symptoms at week 4. *N* (%) = number and per cent, IBS = irritable bowel syndrome, IBS-D = diarrhea-predominant IBS, IBS-M = mixed IBS, IBS-C = constipation-predominant IBS, FGID = functional gastrointestinal disorder. Symptoms the past 2 weeks, at baseline and at the end of the study, were assessed by the irritable bowel syndrome-symptom severity score (IBS-SSS)[21] and the visual analog scale for irritable bowel syndrome (VAS-IBS) where 0 mm means no symptoms and 100 mm means maximal symptoms.[24,27,28] IBS subgroup diagnosis based on Rome IV criteria.[1,23] Values are given as median and interquartile range (IQR). Mann–Whitney *U* test, Fisher's exact test, or Wilcoxon's test.

*$P < 0.05$ was considered statistically significant.

Results

Baseline data

Basic characteristics. The IBS patients (n = 105) had a median age of 46 (34–57) years and body mass index (BMI) of 24.5 (22.4–27.7) kg/m^2 (range 16.0–39.8 kg/m^2). The disease duration was 18.5 (10.0–29.0) years (range 3.0–60.0 years). The age was higher in the intervention than in the control group, whereas BMI, sex distribution, and physical activity did not differ between groups (Table 1). Six participants (5.7%) were regular smokers, and 13 participants (12.4%) were snuff users. Forty-six participants (43.5%) drank less than 1 glass of alcohol/week, whereas 40 (38.1%) drank 1–4 standard glasses/week. Sixty-two participants (59.0%) were married or cohabited. Half of them (n = 52; 49.5%) had a university degree, 23 (21.9%) had an education of 1 year after secondary school, and 23 (21.9%) had secondary school as the highest education. About half of them (n = 53; 50.5%) worked full time whereas 19 (18.1%) worked 50–99%, 16 (15.2%) were retired, and a few were studying (n = 5), on sick leave (n = 5), unemployed (n = 3), or on parental leave (n = 1).

According to tIBS-SSS, 48 participants (47.6%) had moderate, and 55 participants (52.4%) had severe disease. IBS subgroups did not differ between the intervention and control group (Table 1).

The most common comorbidity was allergy, hypothyroid disease, and asthma. Antidepressant drugs, levothyroxine, and laxatives were the most common drugs (Table S3). Five patients had lactose intolerance. Altogether, 16 participants had any kind of psychiatric diagnosis. Only three used birth control medications.

Table 2 Vitamin intake at baseline and at the end of the 4-week SSRD study

	Intervention group (N = 80*)			Control group (N = 25**)			
Variable	Median (IQR)	% of patients ≥AR	*P*-value	Median (IQR)	% of patients ≥AR	*P*-value	*P*-value
Retinol (μg)							
Baseline	326 (180–460)			276 (136–354)			0.117
4 weeks	352 (218–520)		0.082	370 (230–533)		0.028	0.892
Vitamin A (μg)							
Baseline	510 (334–798)			383 (262–541)			0.143
4 weeks	443 (274–708)		0.492	438 (251–646)		0.799	0.673
Vitamin D (μg)							
Baseline	3.5 (1.7–5.9)	16		2.4 (1.8–4.1)	4		0.127
4 weeks	4.7 (2.2–9.8)	30	0.007	4.0 (2.8–5.7)	12	0.008	0.501
Vitamin E (mg)							
Baseline	9.7 (6.6–14.0)			9.0 (5.6–13.0)			0.307
4 weeks	13.3 (8.8–20.8)		0.001	10.2 (6.2–14.1)		0.187	0.060
Thiamine (mg)							
Baseline	1.0 (0.8–1.3)	63		0.9 (0.6–1.3)	52		0.182
4 weeks	1.0 (0.6–1.6)	41	0.937	0.8 (0.6–1.2)	36	0.176	0.262
Riboflavin (mg)							
Baseline	1.3 (1.0–1.5)	55		1.0 (0.8–1.5)	36		0.090
4 weeks	1.4 (1.1–1.8)	61	0.227	1.2 (0.8–1.6)	44	0.349	0.099
Niacin (mg)							
Baseline	6 (11–23)	63		14 (10–20)	64		0.315
4 weeks	17 (11–25)	63	0.895	14 (11–23)	52	0.905	0.519
Vitamin B6 (mg)							
Baseline	1.5 (1.2–2.0)	75		1.4 (0.9–1.9)	64		0.198
4 weeks	1.6 (1.0–2.0)	66	0.586	1.4 (1.1–2.1)	68	0.939	0.750
Folacin (μg)							
Baseline	226 (171–296)	61		238 (148–279)	56		0.524
4 weeks	282 (193–417)	66	0.036	229 (131–351)	52	0.333	0.153
Vitamin B12 (μg)							
Baseline	3.1 (2.1–4.9)	90		2.4 (1.6–4.4)	84		0.169
4 weeks	4.2 (2.8–6.9)	88	0.030	3.0 (2.1–4.5)	76	0.673	0.018
Vitamin C (mg)							
Baseline	69 (28–106)	63		54 (24–74)	52		0.201
4 weeks	88 (31–144)	59	0.071	47 (22–98)	40	0.892	0.023

SSRD = starch- and sucrose-reduced diet, AR = the nutrient intake level meeting the requirements of 50% of the population.[26] Nutrient levels were calculated from a single day (day 2) of 4-day food diary registrations; before and at the end of the 4-week SSRD intervention. Calculations were performed with the AIVO Diet computer program.[25] Values are presented as median and interquartile ranges (IQR). Comparisons within groups were performed by Wilcoxon's test and between groups were performed by Mann–Whitney U test. $P < 0.05$ was considered statistically significant.
*Two missing values (mv) at baseline and six mv at week 4.
**Three mv at 4 weeks.

Dietary intake. Overall, the intake of vitamins and minerals was low at baseline. Several micronutrients were ingested in small amounts around or below 50% of AR, for example, vitamin D, several vitamin B compounds, iron, and selenium (Tables 2 and 3). Folacin intake differed between IBS-C and IBS-D (262 [174–348] *vs* 188 [155–225] μg; $P = 0.028$).

More women ($n = 58$, 70.7% of women) than men ($n = 10$, 43.5% of men) were on a current restriction at baseline ($P = 0.043$). The most common restrictions were lactose-reduced ($n = 40$), gluten-reduced ($n = 25$), and/or vegetarian restrictions ($n = 12$), sometimes in combination. Women had a lower daily intake of niacin ($P = 0.016$), and higher of folacin ($P = 0.020$), compared with men. Patients on a current restriction had lower niacin intake and higher folacin intake compared with no restriction (Table S4), but adjustment for sex abolished differences for both ($P = 0.169$ *vs* $P = 0.854$). Patients who had tested low FODMAP previously ($n = 11$), did not differ in any intakes compared with others (data not shown).

The foods that most often triggered onset of symptoms were gluten-free/gluten-containing bread (*number of participants* = 31), candies/cakes ($n = 26$), coffee ($n = 11$), pizza and/or hamburger ($n = 10$), pasta ($n = 8$), cabbage ($n = 7$), fruits ($n = 6$), onion ($n = 5$), and beans ($n = 4$).

Circulating levels of micronutrients. Several participants had values outside (above or below) the laboratory reference values of cobalamin ($n = 16$ [2 below]), folate ($n = 4$ below), ferritin ($n = 30$ [8 below]), iron ($n = 10$ [9 below]), TIBC ($n = 11$ [2 below]), and vitamin D ($n = 81$ below). Participants with IBS-D had higher ferritin levels compared with IBS-C (123 [56–256] *vs* 52 [35–102] μg/L; $P = 0.014$) and those with psychiatric diagnoses had higher plasma levels of TIBC compared with those without any diagnosis (70 [63–77] *vs* 62 [58–70] μmol/L; $P = 0.031$).

Ferritin levels were lower in women than in men ($P < 0.001$) and inversely associated with being on a current restriction (Table S5), whereas a history of low FODMAP did not affect any levels (data not shown).

Associations of micronutrients with symptoms and well-being. There was an inverse association between tIBS-SSS and iron intake and iron plasma levels, and a positive

Table 3 Mineral intake at baseline and at the end of the 4-week SSRD study

	Intervention group ($N = 80$*)			Control group ($N = 25$**)			
Variable	Median (IQR)	% of patients ≥ AR	*P*-value	Median (IQR)	% of patients ≥ AI	*P*-value	*P*-value
Sodium (mg)							
Baseline	2419 (1886–3153)			2205 (1911–3282)			0.965
4 weeks	1866 (1215–2768)		0.001	2187 (1266–2650)		0.050	0.687
Potassium (mg)							
Baseline	2506 (2048–3243)			2435 (1782–3183)			0.835
4 weeks	2560 (1760–3168)		0.652	2466 (1715–3204)		0.633	0.800
Phosphorus (mg)							
Baseline	1134 (941–1456)	96		981 (815–1386)	100		0.169
4 weeks	1301 (1017–1586)	93	0.067	1082 (821–1391)	88	0.799	0.075
Calcium (mg)							
Baseline	759 (500–954)	74		685 (450–964)	68		0.718
4 weeks	796 (552–1021)	76	0.869	782 (386–1120)	60	0.633	0.648
Magnesium (mg)							
Baseline	261 (203–354)			253 (202–324)			0.407
4 weeks	284 (201–422)		0.558	280 (184–378)		0.842	0.563
Iodine (μg)							
Baseline	103 (77–143)	50		97 (53–141)	44		0.517
4 weeks	120 (72–157)	53	0.956	106 (82–138)	52	0.905	0.626
Selenium (μg)							
Baseline	34 (22–54)	56		27 (18–40)	40		0.158
4 weeks	47 (33–71)	71	0.003	33 (22–50)	52	0.325	0.025
Iron (mg)							
Baseline	8.2 (6.1–10.5)	51		7.6 (4.6–9.0)	32		0.096
4 weeks	7.5 (5.8–10.4)	45	0.436	7.1 (5.6–9.3)	32	0.679	0.620
Zinc (mg)							
Baseline	8.0 (6.3–9.9)	86		6.5 (5.4–9.1)	80		0.049
4 weeks	8.9 (6.8–11.4)	81	0.163	7.5 (6.0–10.0)	80	0.616	0.084

SSRD = starch- and sucrose-reduced diet, AR = the nutrient intake level meeting the requirements of 50% of the population.[26] Nutrient levels were calculated from a single day (day 2) of 4-day food diary registrations; before and at the end of the 4-week SSRD intervention. Calculations were performed with the AIVO Diet computer program.[25] Values are presented as median and interquartile ranges (IQR). Comparisons within groups were performed by Wilcoxon's test and between groups were performed by Mann–Whitney *U* test. $P < 0.05$ was considered statistically significant.

*Two missing values (mv) at baseline and six mv at week 4.

**Three mv at 4 weeks.

association between tIBS-SSS and plasma levels of vitamin D and cobalamin (Table 4).

Extraintestinal symptoms were inversely associated with intakes of vitamin B6, phosphorus, magnesium, and iodine, and plasma levels of iron, and positively associated with plasma TIBC levels (Table 5, Fig. 1).

Fatigue was inversely associated with intakes of vitamin B6, phosphorus, calcium, magnesium, iodine, iron, and zinc, and tended to be inversely associated with intakes of thiamine (β: −9.804; 95% CI: −20.356 to 0.748; $P = 0.069$), folacin (β: −0.029; 95% CI: −0.060 to 0.003; $P = 0.076$), and vitamin C (β: −0.067; 95% CI: −0.144 to 0.010; $P = 0.089$). Plasma levels of iron was inversely associated with fatigue and the intestinal symptoms' influence on daily life, whereas TIBC was positively associated with fatigue and impaired psychological well-being (Table 4, Fig. 2). No associations were found between intake of micronutrients regarding abdominal pain, intestinal symptoms' influence on daily life, and psychological well-being (data not shown).

Table 4 Statistically significant associations between symptoms and intake or plasma/serum levels of micronutrients at baseline

	β	95% CI	*P*-value
Total IBS-SSS			
Iron	−5.048	−9.047 to −1.048	0.013
P-Iron	−3.459	−5.560 to −1.358	0.001
P-Cobalamins	0.081	0.025–0.148	0.015
S-Vitamin D 25-OH	0.756	0.051–1.460	0.036
Total Extraintestinal IBS-SSS			
Vitamin B6	−20.762	−38.641 to −2.882	0.023
Phosphorus	−0.042	−0.082 to −0.002	0.041
Magnesium	−0.112	−0.215 to −0.010	0.032
Iodine	−1.171	−0.346 to 0.003	0.054
P-Iron	−3.312	−5.789 to −0.835	0.009
P-TIBC	2.862	1.372–4.353	< 0.001
Fatigue			
Vitamin B6	−6.068	−12.011 to −0.125	0.045
Phosphorus	−0.021	−0.033 to −0.008	0.002
Calcium	−0.012	−0.024–0.000	0.043
Magnesium	−0.052	−0.085 to −0.019	0.002
Iodine	−0.060	−0.118 to −0.003	0.041
Iron	−2.435	−3.871 to −0.998	0.001
Zinc	−1.671	−3.196 to −0.146	0.032
P-Iron	−1.066	−1.889 to −0.243	0.011
P-TIBC	1.002	0.513–1.492	< 0.001
Intestinal symptoms influence on daily life			
P-Iron	−0.726	−1.388 to −0.065	0.031
Psychological well-being			
P-TIBC	0.670	0.172–1.168	0.008

β = beta-value, CI = confidence interval, P = plasma, S = serum, TIBC = total iron-binding capacity. Symptoms the past 2 weeks were assessed by the irritable bowel syndrome-symptom severity score (IBS-SSS)[21] and the visual analog scale for irritable bowel syndrome (VAS-IBS) where 0 mm means no symptoms and 100 mm means maximal symptoms.[24,27,28] Generalized linear model adjusted for sex. Values are presented as β and 95% CI. $P < 0.05$ was considered statistically significant.

Table 5 Statistically significant correlations between changes in fat intake and symptoms during the SSRD study

Change in variable (Δ-value)	Fat (E%)	Saturated fat (g)	Poly-unsaturated fat (E%)
Total IBS-SSS	*rs* = −209 *P* = 0.043		*rs* = −0.305 *P* = 0.003
Total extraintestinal IBS-SSS		*rs* = 0.206 *P* = 0.046	*rs* = −0.209 *P* = 0.044
Fatigue			*rs* = −0.219 *P* = 0.032
Intestinal symptoms influence on daily life			rs = −0.315 *P* = 0.002
Psychological well-being			*rs* = −0.241 *P* = 0.018

E% = energy percentage, SSRD = starch- and sucrose-reduced diet. Symptoms the past 2 weeks, at baseline and at the end of the study, were assessed by the irritable bowel syndrome-symptom severity score (IBS-SSS)[21] and the visual analog scale for irritable bowel syndrome (VAS-IBS) where 0 mm means no symptoms and 100 mm means maximal symptoms.[24,27,28] Δ-values (difference 4 weeks-baseline) were calculated and correlated by Spearman's correlation test. $P < 0.05$ was considered statistically significant.

SSRD intervention. During the intervention, all the symptoms were reduced, and psychological well-being was improved (Table 1). The intake was increased regarding vitamin B12, D and E, folacin, and several minerals although only significantly for selenium, whereas the sodium intake was decreased. Vitamin C intake tended to be increased. Vitamin D intake was increased both in the control and intervention group during the trial (Tables 2 and 3). When comparing levels between the groups, there was slightly higher zinc intake at baseline, and selenium and phosphorus intake after 4 weeks, in the intervention group compared with the control group (Table 3).

The changes in intakes (Δ-values) of folacin ($rs = (-0.219)$; $P = 0.033$) and selenium ($rs = (-0.239)$; $P = 0.020$) during the study correlated with the reduced influence of intestinal symptoms' on daily life. The increased vitamin E intake correlated with the reduced tIBS-SSS ($rs = (-0.224)$; $P = 0.030$).

At baseline, the E% of saturated fat was associated with abdominal pain (β:1.255, 95% CI: 0.456–2.055; $P = 0.002$). The fat intake was increased during the intervention, especially poly- and monounsaturated fat (Table S6). Increased intake of E% poly-unsaturated fat correlated with both reduced GI and extraintestinal symptoms (Table 5).

Discussion

The main findings in the present study were that IBS patients had an overall low intake of vitamins and mineral at baseline. The intakes associated inversely with tIBS-SSS, extraintestinal IBS-SSS, and fatigue. The SSRD intervention increased the intake of several micronutrients and unsaturated fat but lowered the sodium intake.

Previous studies have shown that IBS patients had lower intakes of fibers and vegetables, but higher intake of sugar and processed/ultra-processed food compared with the general population and dietary guidelines,[8,9,30] and a large portion of patients had

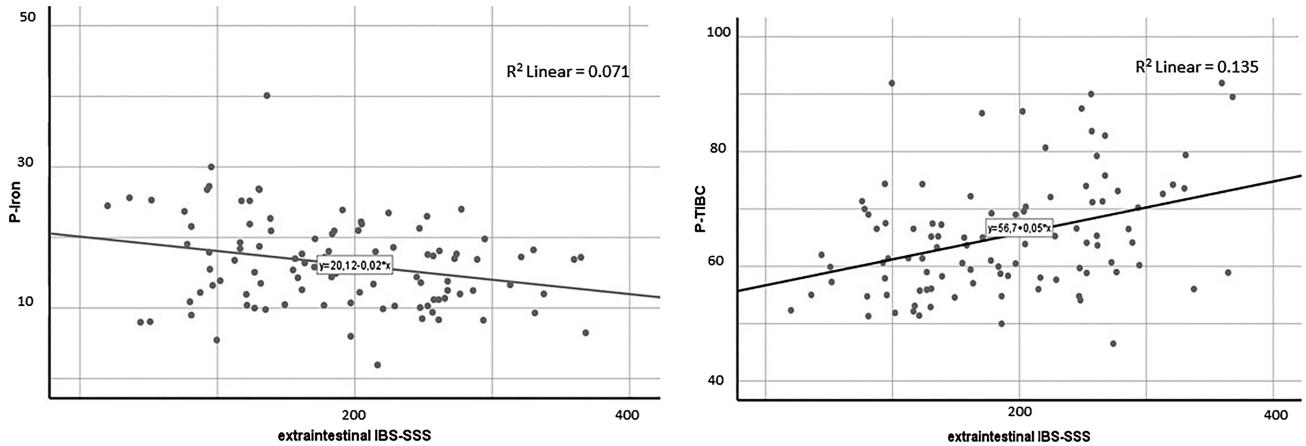

Figure 1 The correlations at baseline between plasma levels of iron and total iron-binding capacity (TIBC) and extraintestinal symptoms assessed by irritable bowel syndrome-symptom severity score (IBS-SSS).[21] 0 mm means no symptoms and 100 mm means maximal symptoms. Spearman's correlation test. $P < 0.05$ was considered statistically significant.

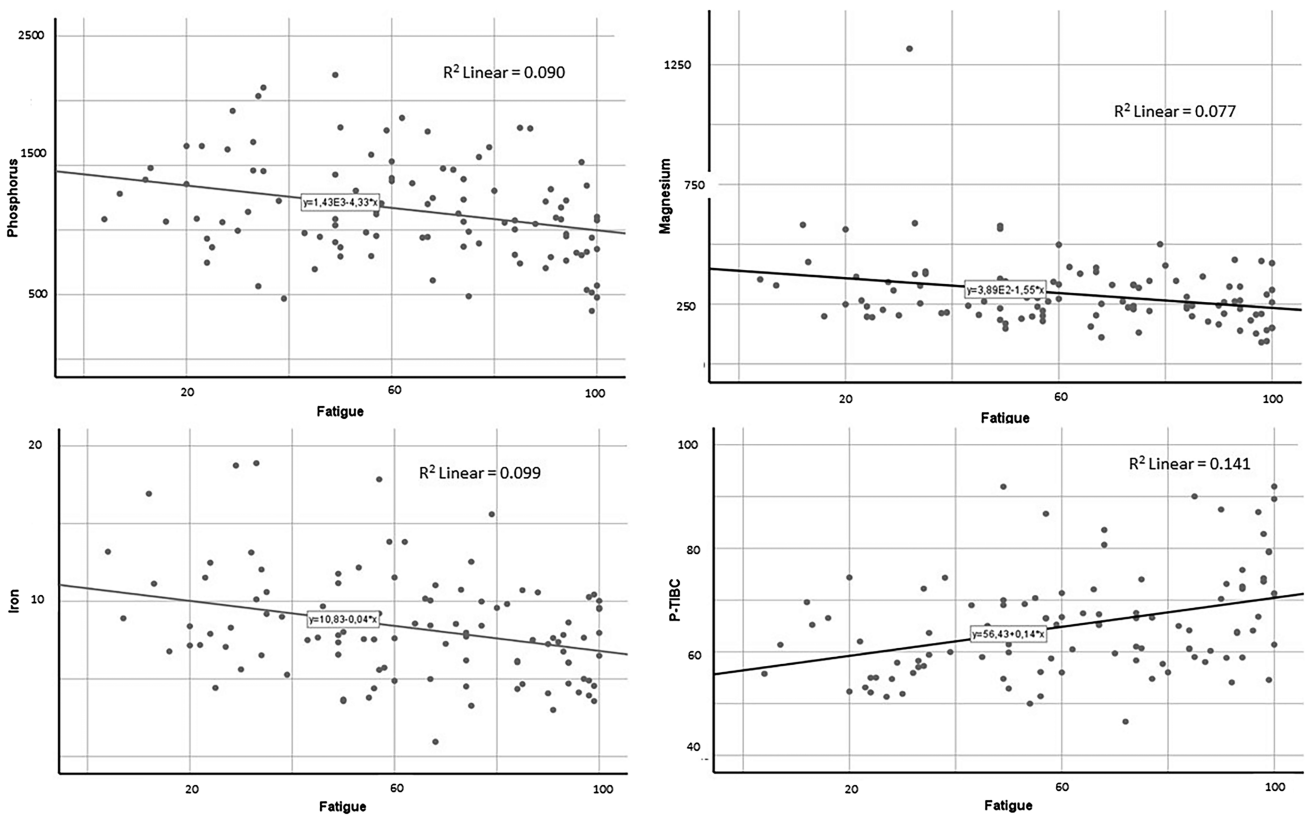

Figure 2 The correlations at baseline between intake of phosphorus, magnesium, and iron, and plasma levels of total iron-binding capacity (TIBC) and fatigue assessed by irritable bowel syndrome-symptom severity score (IBS-SSS).[21] 0 mm means no symptoms and 100 mm means maximal symptoms. Calculations of nutrients were performed with the AIVO Diet computer program.[26] Spearman's correlation test. $P < 0.05$ was considered statistically significant.

insufficient micronutrient intake.[10,11,31] Lower adherence to dietary guidelines in the general population predicted a higher risk of all-cause mortality.[32] In accordance, we have previously published the high intake of processed and ultra-processed food in the current study population at baseline,[5] and that the reduced intake of carbohydrates, disaccharides, and starch in SSRD correlated with reduced GI and extraintestinal symptoms.[5–7] Furthermore, increased intakes of vitamin E, folacin, and selenium, as well as poly-unsaturated fatty acids, also correlated with reduced symptoms during the intervention. Thus, a causality between poor dietary intake and symptoms may be assumed, because previous analysis of plasma metabolomics demonstrated good compliance to the SSRD.[33]

Somatic pain and chronic fatigue are well-known so called extraintestinal symptoms in IBS.[2,3] The pathophysiology behind both GI and extraintestinal symptoms is unknown, but concomitant visceral and somatic hypersensitivity has been discussed with cross sensitization.[34] Vitamins and minerals act as cofactors in multiple processes in the cells.[35] Impaired cognitive and psychological functions, mental and physical fatigue, weakness, somatic pain, and neuropathy are well-known complications to malnutrition with deficiency of vitamins and minerals.[13–17] Vitamin D deficiency is of importance for central hypersensitization.[18] Iron deficiency is well-known to be associated with chronic fatigue,[20] reduced working capacity,[36] cognitive decline,[37] impaired thermoregulation,[38] and dysregulation of immune and thyroid function.[38,39]

In the current study, both intake and plasma levels of iron at baseline were inversely associated with GI symptoms, their influence on daily life, extraintestinal symptoms, and fatigue, whereas plasma levels of TIBC were associated with extraintestinal symptoms, fatigue, and impaired psychological well-being. Thus, although no causality can be proved, iron deficiency may be of importance both for symptoms and psychological well-being in IBS. Diverse dietary regimes, including vegan/vegetarian diets, may contribute to iron deficiency,[12,40] as was observed with low ferritin levels in those on current restriction. Another cause to iron deficiency may be nonsteroidal anti-inflammatory drugs (NSAID) or proton pump inhibitors;[41] drug treatments that may be over-represented in IBS.[42,43] Further research within this field is necessary to exclude malnutrition in the pathophysiology behind comorbidity in IBS. No examinations were performed in the current study to diagnose malnutrition, but assessment of diary protocols, malnutrition, and circulating micronutrient levels could be valuable in the daily care of this disease entity when insufficient intake is suspected.

There was no association between tIBS-SSS and intake of vitamin D and cobalamins, but plasma levels of these vitamins were associated with tIBS-SSS. Although the intake of vitamin D was low, several of the participants compensated this by medication of vitamin D, possibly most often among those with severe disease, because dairy products and fat intake may provoke GI symptoms.[44]

The current study suggests overall poor food habits in IBS, independently on a specific restriction or not, in accordance with the literature.[8–11,30,31] Poor food habits may cause symptoms but may also depend on avoidance of varying foods as self-testing of the patients. Advanced dietary regimes demand supervision by a skilled dietician and patients to have the ability to understand complex informative texts, with risks of social stigmata and poor quality of life.[44] Strict exclusion diets may lead to malnutrition and development of eating disorders.[10–12,31,44] SSRD has the advantage of being simple to follow and being an easy tool for the primary healthcare providers, because just reduction of bread intake and exchange of sweetened and processed/ultra-processed food to increased intakes of vegetables, fruits, fish, and dairy products seems to be enough for several of the participants.[5] Thus, exchange of food that most often triggered symptom onset. It remains to determine whether the correlations between improved food intake and reduced symptoms are due to micronutrients or fatty acids *per se* or represents reduced amount of processed food. The lower sodium intake may be explained by avoidance of processed/ultra-processed food and is of importance for the general health in several aspects.[45,46] No eating disorders was observed to develop during the study and the psychological well-being was improved.

There are several limitations of this study. Micronutrient intake was only calculated for 1 day before and after the study start. However, the dietician estimated that the nutrient intake was similar from day to day (altogether 12 days of complete diary registration), and the values are in line with the overall low intake of fruits, berries, vegetables and dairy products and plasma/serum levels of micronutrients at the study start.[5,7] The report of depression, chronic fatigue, panic attacks, and burnout were self-reported. No specific questionnaire was completed to define mental illness except the psychological well-being item of VAS-IBS, which has been validated against other questionnaires.[24] Patients included had moderate to severe IBS, so the results may not be extrapolated to mild IBS disease.

In conclusion, IBS patients reported low intake of several vitamins and minerals, and the low intake and plasma/serum levels were associated with GI symptoms, but most of all with extraintestinal symptoms and fatigue. SSRD improved dietary intake. The role of malnutrition must be further explored in IBS and associated comorbidity.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Recommendations of fruit intake according to a starch- and sucrose-reduced diet.
Table S2. Recommendations of vegetable and legume intake according to a starch- and sucrose-reduced diet.
Table S3. Comorbidity and drug treatment in the IBS patients.
Table S4. The intake of micronutrients dependent on current restriction at baseline.
Table S5. The association of any current restriction on plasma/serum levels of micronutrients at baseline.
Table S6. Fat intake at baseline and at the end of the 4-week SSRD intervention.
Figure S1. Flow chart over inclusion and exclusion criteria and the process for inclusion of patients with irritable bowel syndrome (IBS) in the 4-week starch- and sucrose-reduced diet (SSRD) trial.
Figure S2. The CONSORT flow chart over the 4-week starch- and sucrose-reduced diet (SSRD) trial.