

Supplementary Figures

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bonfrate 2020	+	+	+	+	+	+	+
Kajander 2007	?	+	+	+	+	+	?
Staudacher 2012	+	+	?	?	+	+	?
Wilson 2020	+	+	+	?	+	+	+

Figure S1 Risk of bias for treatment studies.

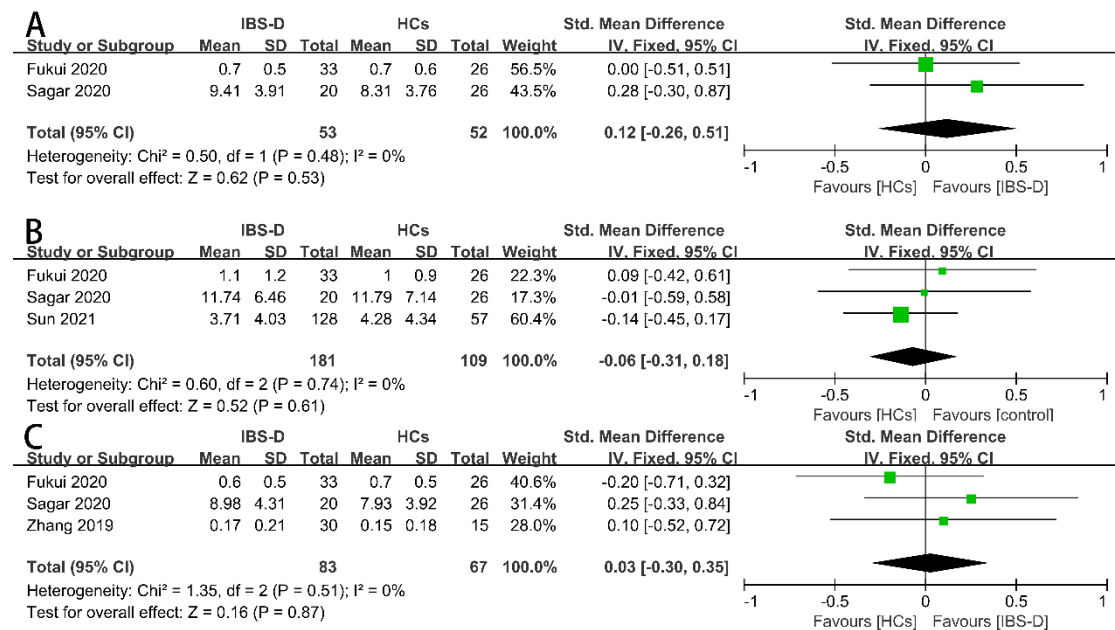


Figure S2 Forest plots of alterations of concentration of fecal SCFAs in IBS-D patients versus HCs: (A) iso-butyrates, (B) valerate, and (C) iso-valerate.

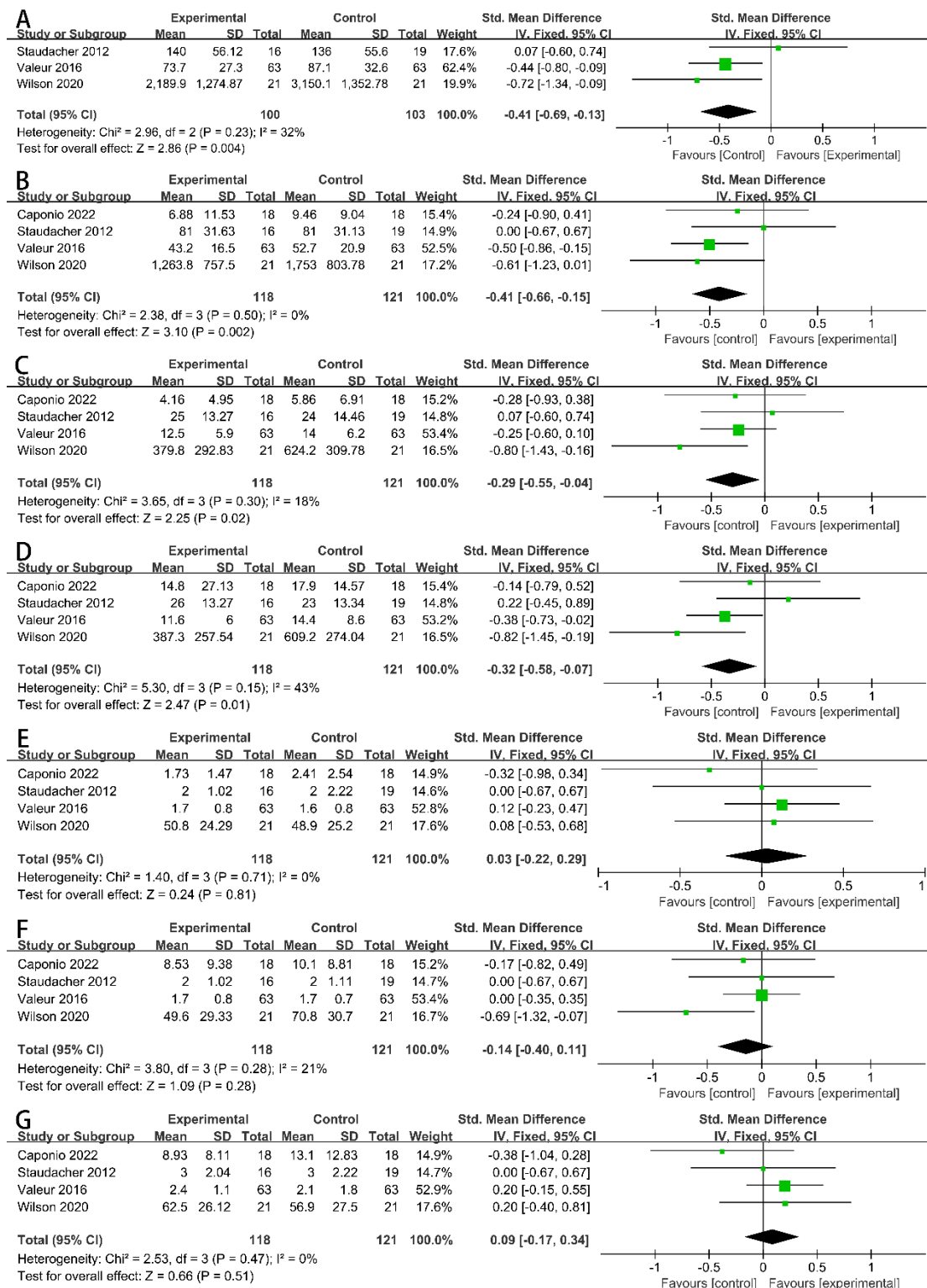


Figure S3 Forest plots of alterations of concentration of fecal SCFAs in IBS patients after diets low in FODMAP treatment: (A) total SCFAs, (B) acetate, (C) propionate, (D) butyrate, (E) iso-butyrate, (F) valerate, and (G) iso-valerate.

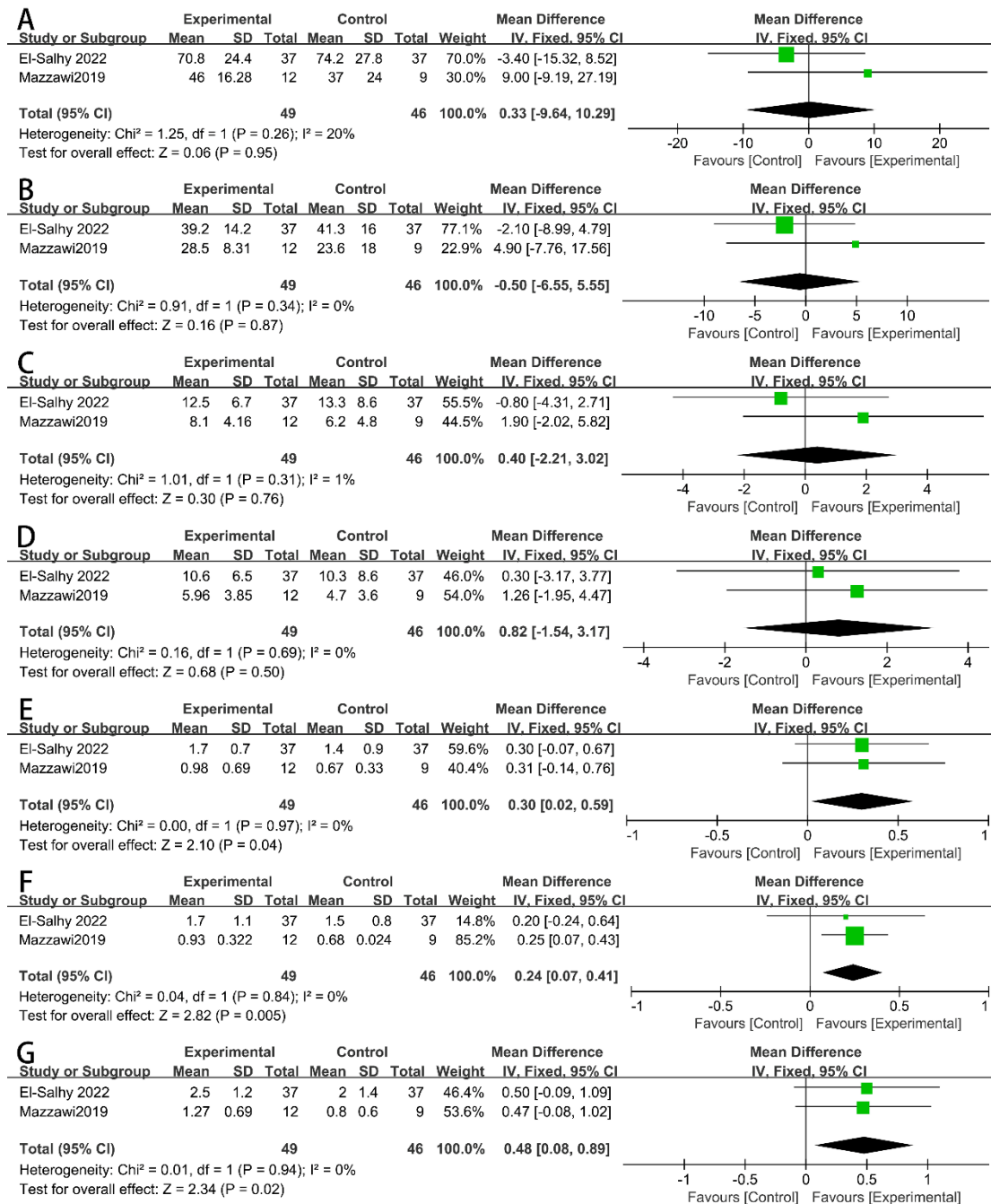


Figure S4 Forest plots of alterations of concentration of fecal SCFAs in IBS patients after FMT treatment: (A) total SCFAs, (B) acetate, (C) propionate, (D) butyrate, (E) iso-butyrate, (F) valerate, and (G) iso-valerate.

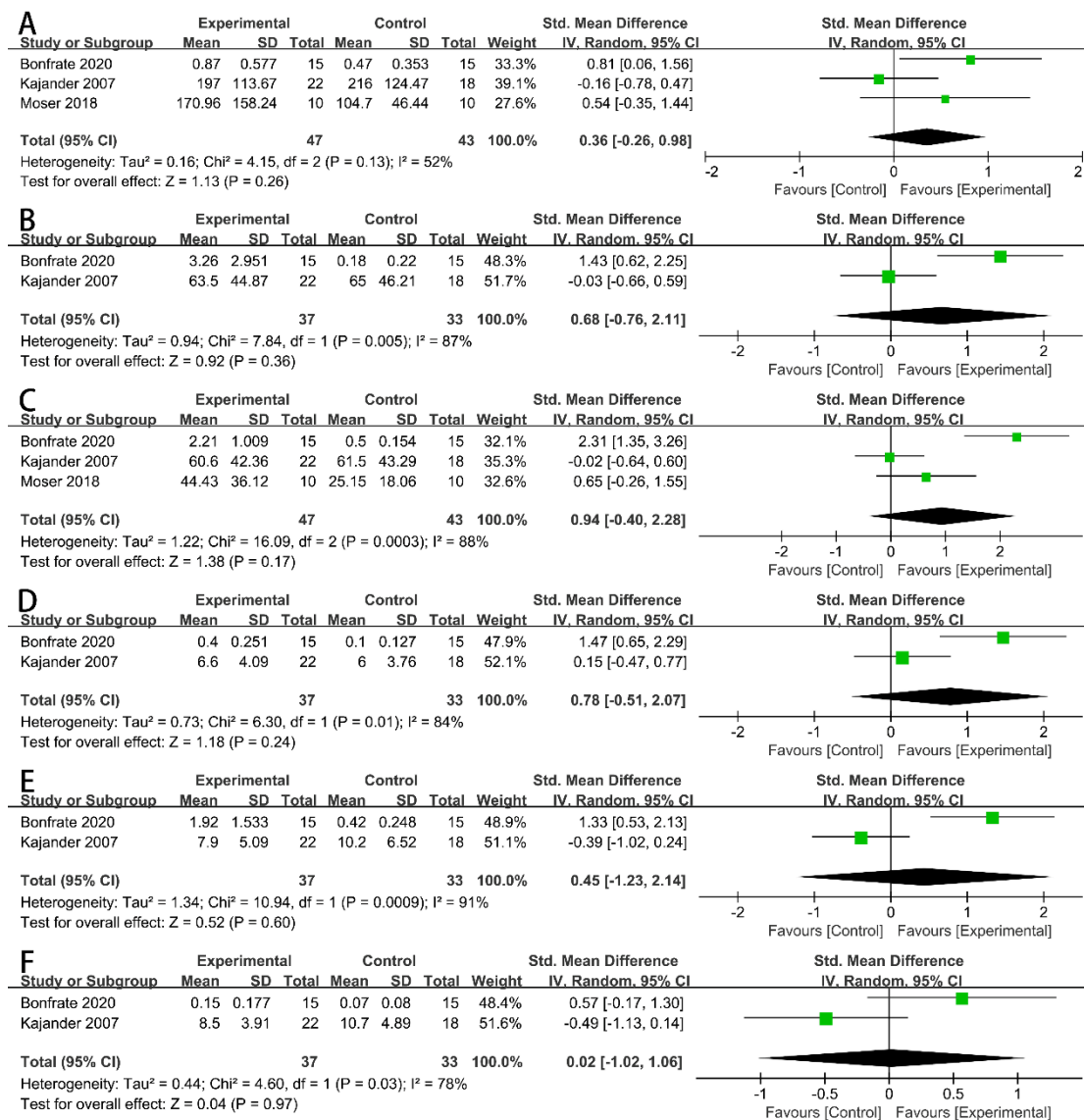


Figure S5 Forest plots of alterations of concentration of fecal SCFAs in IBS patients after probiotics supplementary treatment: (A) total SCFAs, (B) acetate, (C) propionate, (D) butyrate, (E) iso-butyrate, and (F) valerate.

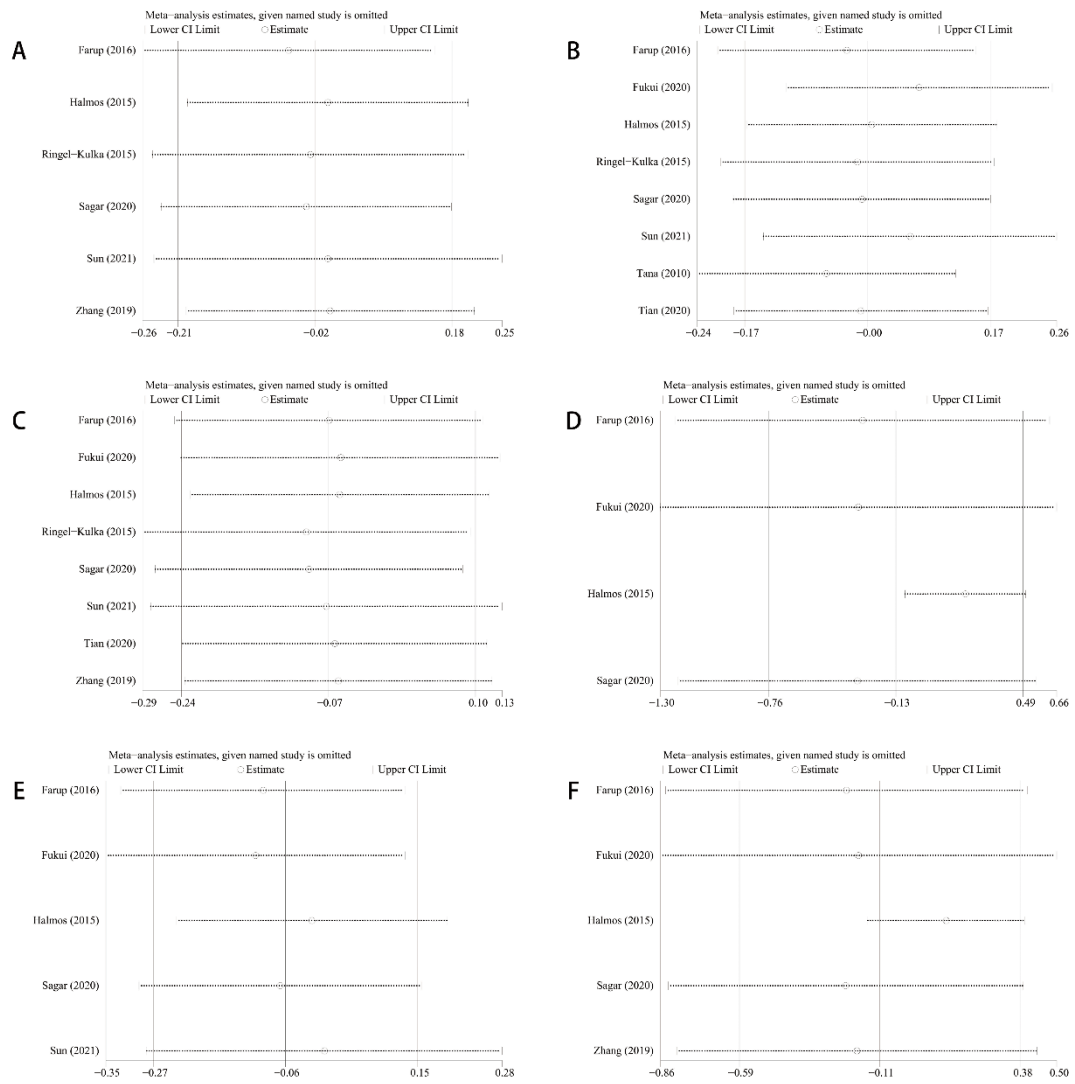


Figure S6 Results of sensitivity analysis: (A)total SCFAs, (B) acetate, (C) butyrate, (D) iso-butyrate, (E) valerate, (F) iso-valerate.

Supplementary Table S1 Characteristics of included case-control studies.

Reference	Year	Country	Diagnostic criteria	IBS/HC	Age (Mean, SD)		Sex (M/F)		Data format	Method
					IBS	HC	IBS	HC		
Farup	2016	Norway	Rome III	25/25	46.2, 12.9	49.2, 14.6	12/13	10/15	Mean, SD	GC
Fukui	2020	Japan	Rome III	85/26	51.3, 15.3	46.2, 10.6	37/48	9/17	Mean, SD	GC-MS
Halmos	2015	Australia	Rome III	27/6	41.9, 19.6	39.4, 36.2	6/21	1/5	Mean, 95% CI	GC
Mortensen	1987	Denmark	No data	18/9	44.9, 11.5	No data	4/14	No data	Mean, SD	GLC
Ringel-Kulka	2015	USA	Rome III	114/33	35.4, 11.3	33.9, 13.0	16/98	4/29	Mean, SD	GC
Sagar	2020	UK	Rome III	20/26	55.4, 13.1	55.4, 13.1	3/17	11/15	Median, IQR	GC
Sun	2021	China	Rome III	162/66	35.5, 11.7	36.7, 11.8	114/48	38/28	Median, IQR	UPLC-MS/MS
Tana	2010	Japan	Rome II	26/26	21.7, 2.0	21.9, 2.9	13/13	13/13	Mean, SD	HPLC
Tian	2020	China	Rome IV	21/14	31.6, 8.9	27.0, 4.4	13/8	8/6	Mean, SD	HS-SPME-GC-MS
Vernia	1987	Italy	No data	38/50	38.2, 14.0	38.2, 12.0	No data	No data	Mean, SD	GLC
Waseem	2023	USA	Rome IV	43/21	No data	32.1, 12.8	10/33	5/16	Median, IQR	HPLC
Zhang	2019	China	Rome IV	30/15	30 (28, 41) [†]	28 (25, 37) [†]	22/8	11/4	Median, IQR	GC-MS

Abbreviations: GC, gas chromatography; GC-MS, gas chromatography-mass spectrometry; GLC, gas-liquid chromatography; UPLC-MS/MS, ultra performance liquid chromatography-tandem mass spectrometry; HPLC, high performance liquid chromatography; HS-SPME-GC-MS, headspace solid-phase microextraction coupled with gas chromatography–mass spectrometry.

[‡]Mean (range) [†]Median (IQR)

Supplementary Table S2 Characteristics of included self-controlled studies and randomized controlled trials

Reference	Year	Country	Treatment	Study design	Diagnostic criteria	Treatment/Control	Age (Mean, SD)		Sex (M/F)		Data format	Method
							Treatment	Control	Treatment	Control		
Caponio	2022	Italy	Low FODMAP diet	Self-controlled study	Rome IV	18/18	42.9, 10.2	42.9, 10.2	4/14	4/14	Mean, SEM	GC
Staudacher	2012	UK	Low FODMAP diet	RCT	Rome III	16/19	36.4, 11.6	35.5, 9.1	5/11	7/12	Mean, 95% CI	GLC
Valeur	2016	Norway	Low FODMAP diet	Self-controlled study	Rome III	63/63	38 (19-67) [†]	38 (19-67) [†]	7/56	7/56	Mean, SD	GC
Wilson	2020	UK	Low FODMAP diet	RCT	Rome III	22/23	38.9, 10.0	30.3, 9.8	9/13	11/12	EMM, SEM	GLC
El-Salhy	2022	Norway	FMT	Self-controlled study	Rome IV	40/40	38.1, 14.4	38.1, 14.4	33/7	33/7	Mean, SD	GC
Mazzawi	2019	Norway	FMT	Self-controlled study	Rome III	13/13	32 (20-44) [†]	32 (20-44) [†]	4/9	4/9	Mean, SEM	GC

Bonfrate	2020	Italy	Probiotics	RCT	Rome IV	15/10	50, 11	46, 10	3/12	4/6	Mean, SD	GC
Kajander	2007	Finland	Probiotics	RCT	Rome I , II	28/27	44 (23-65) [†]	47 (21-65) [†]	9/19	7/20	Mean, 95% CI	GC
Moser	2018	Austria	Probiotics	Self- controlled study	No data	10/10	45.3, 13.8	45.3, 13.8	5/5	5/5	Median, IQR	GC-MS

Abbreviations: EMM, estimated marginal mean

[†]Mean (range)

Supplementary Table S3 Quality assessment of included case-control studies (n=12) using Newcastle-Ottawa Scale (NOS)

Study	Selection (4)				Comparability (2)			Exposure (3)		Total scores
	Adequate definition of cases	Representativeness of the cases	Selection of controls	Definition of controls	Most important factor	Any additional factor	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	
Farup 2016	1		1		1	1	1	1	1	7
Fukui 2020	1	1	1	1	1	1	1	1		8
Halmos 2015	1	1	1	1	1	1	1	1	1	9
Mortensen 1987		1					1	1	1	4
Ringel-Kulka 2015	1	1	1	1	1	1	1	1	1	9
Sagar 2020	1		1		1	1	1	1	1	7
Sun 2021	1	1	1	1	1	1	1	1	1	9
Tana 2010	1	1	1	1	1	1	1	1	1	9
Tian 2020	1	1	1	1	1	1	1	1	1	9
Vernia 1987		1			1		1	1	1	5

Waseem 2023	1	1	1			1	1	1	1	7
Zhang 2019	1	1	1	1	1	1	1	1	1	9

Supplementary Table S4 Results of Egger's test

	Bias Coef.	Bias 95% Conf. Interval	Slope Coef.	Slope 5% Conf. Interval	P > t
Total SCFAs	-0.3976121	-2.895238, 2.100014	0.0738562	-0.5275169, 0.6752294	0.681
Acetate	1.394528	-2.003903, 4.792959	-0.3301604	-1.161407, 0.5010865	0.354
Propionate	-0.9793771	-5.131996, 3.173241	0.5184281	-0.5032637, 1.54012	0.585
Butyrate	-0.6861996	-2.155867, 0.7634681	0.0924434	-0.2675218, 0.4524086	0.287
Iso-butyrate	-6.271296	-16.47342, 3.930824	1.81723	-1.152308, 4.786768	0.118
Valerate	-0.822878	-5.607888, 3.962132	0.1241238	-1.020154, 1.268402	0.622
Iso-valerate	-5.152876	-13.4714, 3.165648	1.478465	-0.9797311, 3.9797311	0.143

Supplementary Table S5 Results of Sensitive Analysis

	Study omitted	Estimate	[95% Conf. Interval]	
Total SCFAs	Farup (2016)	-0.0537573	-0.25909933	0.15158476
	Halmos (2015)	0.00141935	-0.19591708	0.19875577
	Ringel-Kulka (2015)	-0.02297872	-0.24503924	0.19908179
	Sagar (2020)	-0.02880018	-0.23291819	0.17531782
	Sun (2021)	0.001686	-0.24318291	0.24655491
	Zhang (2019)	0.00478731	-0.19785017	0.20742479
Acetate	Farup (2016)	-0.03316492	-0.21108778	0.14475794
	Fukui (2020)	0.06623571	-0.11704095	0.24951237
	Halmos (2015)	0.00102529	-0.17166284	0.17371342
	Ringel-Kulka (2015)	-0.01878201	-0.20726389	0.16969988
	Sagar (2020)	-0.0122573	-0.18939728	0.16488266
	Sun (2021)	0.05373727	-0.14802383	0.25549838
	Tana (2010)	-0.06147144	-0.23948076	0.11653788
	Tian (2020)	-0.01399851	-0.18906529	0.16106826

Butyrate	Farup (2016)	-0.07053811	-0.25016567	0.109089943
	Fukui (2020)	-0.05677766	-0.24205351	0.1284982
	Halmos (2015)	-0.0579998	-0.23211952	0.1161199
	Ringel-Kulka (2015)	-0.09666561	-0.28707302	0.09374181
	Sagar (2020)	-0.09367953	-0.27238676	0.08502769
	Sun (2021)	-0.0734707	-0.27767083	0.13072941
	Tian (2020)	-0.06368819	-0.24028113	0.11290476
	Zhang (2019)	-0.05968299	-0.23742168	0.11805569

continued table

Iso-butyrate	Farup (2016)	-0.29769403	-1.2220086	0.62662053
	Fukui (2020)	-0.31816927	1.2968056	0.66046709
	Halmos (2015)	0.2100735	-0.08796672	0.50811374
	Sagar (2020)	-0.32388538	-1.2096269	0.56185609
Valerate	Farup (2016)	-0.09725261	-0.3236132	0.12910797
	Fukui (2020)	-0.10922406	-0.34730831	0.12886019
	Halmos (2015)	-0.01943739	-0.23485042	0.19597563
	Sagar (2020)	-0.06992291	-0.29455686	0.15471104
	Sun (2021)	0.00018424	-0.28248942	0.28285789
Iso-valerate	Farup (2016)	-0.21922472	-0.83820349	0.39975408
	Fukui (2020)	-0.17798761	-0.85600758	0.50003237
	Halmos (2015)	0.12230266	-0.14616375	0.39076906
	Sagar (2020)	-0.22224794	-0.82904285	0.38454697
	Zhang (2019)	-0.18330897	-0.80001092	0.433393

Supplemental methods. Full electronic search strategy for each database.

1) PubMed search strategy

#1 "SCFA"[All Fields] OR ("fatty acids, volatile"[MeSH Terms] OR ("fatty"[All Fields] AND "acids"[All Fields] AND "volatile"[All Fields]) OR "volatile fatty acids"[All Fields] OR ("short"[All Fields] AND "chain"[All Fields] AND "fatty"[All Fields] AND "acids"[All Fields]) OR "short chain fatty acids"[All Fields]) OR ("acetalization"[All Fields] OR "acetalizations"[All Fields] OR "acetalized"[All Fields] OR "acetals"[MeSH Terms] OR "acetals"[All Fields] OR "acetal"[All Fields] OR "acetates"[MeSH Terms] OR "acetates"[All Fields] OR "acetate"[All Fields] OR "acetic"[All Fields]) OR ("propionates"[MeSH Terms] OR "propionates"[All Fields] OR "propionate"[All Fields] OR "propionic"[All Fields] OR "propionics"[All Fields]) OR ("butyrates"[MeSH Terms] OR "butyrates"[All Fields] OR "butyrate"[All Fields] OR "butyric"[All Fields]) OR ("valerates"[MeSH Terms] OR "valerates"[All Fields] OR "valerate"[All Fields] OR "valeric"[All Fields]) **538776**

#2 "IBS"[All Fields] OR ("irritable bowel syndrome"[MeSH Terms] OR ("irritable"[All Fields] AND "bowel"[All Fields] AND "syndrome"[All Fields]) OR "irritable bowel syndrome"[All Fields]) **27503**

#3 #1 AND #2 **570**

#4 #3 NOT ("meta analysis"[Publication Type] OR "review"[Publication Type] OR "systematic review"[Filter]) **446**

#5 #4 AND ((fft[Filter]) AND ((humans[Filter]) AND (english[Filter]))) **181**

2) Web of Science search strategy

#1 TS=(SCFA) OR TS=(SCFAs) OR TS=(short chain fatty acids) OR TS=(volatile fatty acids) OR TS=(acetate) OR TS=(acetic acid) OR TS=(propionate) OR TS=(propionic acid) OR TS=(propanoic acid) OR TS=(butyrate) OR TS=(butyric acid) OR TS=(butanoic acid) OR TS=(isobutyric acid) OR TS=(valerate) OR TS=(valeric acid) OR TS=(pentanoic acid) OR TS=(isovaleric acid) **710325**

#2 TS=(irritable bowel syndrome) OR TS=(IBS) **38867**

#3 #1 AND #2 1093

#4 #3 and Review Article or Meeting or Editorial Material or Book or Letter or Case Report (Exclude – Document Types) 600

#5 #4 and Humans (MeSH Headings) and English (Languages) 256

3) Embase search strategy

#1 'short chain fatty acid' OR 'short chain fatty acid'/exp OR 'short chain fatty acids' OR ('short' AND 'chain' AND 'fatty' AND ('acid' OR 'acid'/exp OR 'acids' OR 'acids'/exp)) OR 'scfa' OR 'scfas' OR 'volatile fatty acid' OR 'volatile fatty acids' OR ('volatile' AND 'fatty' AND ('acid' OR 'acid'/exp OR 'acids' OR 'acids'/exp)) OR 'acetate' OR 'acetate'/exp OR 'acetates' OR 'acetates'/exp OR ('acetic' AND ('acid' OR 'acid'/exp OR 'acids' OR 'acids'/exp)) OR 'propionate' OR 'propionate'/exp OR 'propionates' OR 'propionates'/exp OR ('propionic' AND ('acid' OR 'acid'/exp OR 'acids' OR 'acids'/exp)) OR ('propanoic' AND ('acid' OR 'acid'/exp OR 'acids' OR 'acids'/exp)) OR 'butyrate' OR 'butyrate'/exp OR 'butyrates' OR 'butyrates'/exp OR ('butyric' AND ('acid' OR 'acid'/exp OR 'acids' OR 'acids'/exp)) OR 'isobutyrate' OR 'isobutyrate'/exp OR 'isobutyrate' OR 'isobutyrate'/exp OR ('isobutyric' AND ('acid' OR 'acid'/exp OR 'acids' OR 'acids'/exp)) OR ('butanoic' AND ('acid' OR 'acid'/exp OR 'acids' OR 'acids'/exp)) OR 'valerate' OR 'valerate'/exp OR 'valerates' OR 'valerates'/exp OR (('valeric' OR 'valeric'/exp) AND ('acid' OR 'acid'/exp OR 'acids' OR 'acids'/exp))

OR 'acids'/exp)) OR 'isovalerate' OR 'isovalerate'/exp OR 'isovalerates' OR
'isovalerates'/exp OR ('isovaleric' AND ('acid' OR 'acid'/exp OR 'acids' OR
'acids'/exp)) OR ('pentanoic' AND ('acid' OR 'acid'/exp OR 'acids' OR 'acids'/exp))

596686

#2 'irritable bowel syndrome' OR 'irritable bowel syndrome'/exp OR ('irritable' AND
(('bowel' OR 'bowel'/exp) AND 'syndrome') OR 'ibs' **47877**

#3 #1 AND #3 1301

#4 #3 AND 'article'/it 601

#5 #4 AND 'human'/de AND [adult]/lim AND [english]/lim 164

181+256+164 = 601 records in total.