SUPPLEMENTARY MATERIAL

Search strategy

The search strategy was designed and conducted by an experienced librarian (LCH, Mayo Clinic) with input from one of the researchers (NH).

A comprehensive search of several databases from inception to March 18, 2020, limited to English language only, and excluding animal studies, was conducted. The databases included Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily, Ovid Embase, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. Controlled vocabulary supplemented with keywords was used to search for studies describing disturbances in the gastrointestinal barrier function in patients with irritable bowel syndrome.

Search strategy in OVID

#	Searches
1	Irritable Bowel Syndrome/
2	"irritable bowel".mp.
3	irritable colon/
4	(colon* adj (spasm or spastic or irritable)).mp.
5	("irritable colon syndrome" or "mucous colitis").mp.
6	or/1-5
7	Permeability/
8	((gut or colon* or gastric* or gastro* or intestin* or duoden* or epitheli*) adj10 (permeab* or hyperpermeab* or barrier* or wall)).mp.
9	"leaky gut".mp.
10	or/7-9
11	6 and 10
12	Gastrointestinal Tract/pa
13	exp Intestines/pa
14	gastrointestinal tract/
15	exp pathology/
16	14 and 15
17	12 or 13 or 16
18	6 and 17
19	exp Intercellular Junctions/
20	Myosin Light Chains/
21	Myosin-Light-Chain Kinase/
22	exp Tight Junction Proteins/
23	((intercellular or cell* or anchoring or adherens) adj (junction* or connection or bridge)).mp.
24	("tight junction*" or claudin* or occludin* or occluden* or "adherens junction*" or cadherin or desmosomes or hemidesmosome* or mucin or MLCK or "myosin light chain*" or "myosin-light chain").mp.
25	or/19-24
26	6 and 25

27	11 or 18 or 26
28	((alpaca or alpacas or amphibian or amphibians or animal or animals or antelope or armadillo or armadillos or avian or baboon or baboons or beagle or beagles or bee or bees or bird or birds or bison or bovine or buffalo or buffaloes or buffalos or "c elegans" or "Caenorhabditis elegans" or camel or camels or canine or canines or carp or cats or cattle or chick or chicken or chickens or chicks or chimp or chimpanze or chimpanzees or chimps or cow or cows or "D melanogaster" or "dairy calf" or "dairy calves" or deer or dog or dogs or donkey or donkeys or drosophila or "Drosophila melanogaster" or duck or duckling or ducklings or ducks or equid or equids or equine or equines or feline or felines or ferret or ferrets or finch or finches or fish or flatworm or flatworms or fox or foxes or frog or frogs or "fruit flies" or "fruit fly" or "G mellonella" or "Galleria mellonella" or geese or gerbil or gerbils or goat or goats or goose or gorilla or gorillas or hamster or hamsters or hare or hares or heifer or heifers or horse or horses or insect or insects or jellyfish or kangaroo or kangaroos or kitten or kittens or lagomorph or lagomorphs or lamb or lambs or llama or llamas or macaque or macaques or macaw or macaws or marmoset or marmosets or mice or minipig or minipigs or mink or minks or monkey or monkeys or mouse or mule or mules or nematode or nematodes or octopus or octopuses or orangutan or "orang-utan" or orangutans or "orang-utans" or oxen or parrot or parrots or pig or pigeon or pigeons or piglet or piglets or pigs or porcine or primate or primates or quail or rabbit or rabbits or rat or rats or reptile or reptiles or rodent or rodents or ruminant or ruminants or salmon or sheep or shrimp or slug or slugs or swine or tamarin or tamarins or toad or toads or trout or urchin or urchins or vole or voles or waxworm or waxworms or worm or worms or xenopus or "zebra fish" or zebrafish) not (human or humans or patient or patients)).ti,ab,hw,kw.
29	27 not 28
30	29 not ((exp animals/ or exp nonhuman/) not exp humans/)
31	(letter or conference abstract or editorial or erratum or note or addresses or autobiography or bibliography or biography or blogs or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts).mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, sh, kw, tx, ct, tn, dm, mf, dv, dq]
32	30 not 31
33	limit 32 to english language [Limit not valid in CDSR; records were retained]
34	remove duplicates from 33

Search strategy in Scopus

#	Searches
1	TITLE-ABS-KEY ("irritable bowel")
2	TITLE-ABS-KEY ((colon* W/1 (spasm OR spastic OR irritable)))
3	TITLE-ABS-KEY ("irritable colon syndrome" OR "mucous colitis")
4	#1 or #2 or #3
5	TITLE-ABS-KEY (((gut OR colon* OR gastric* OR gastro* OR intestin* OR duoden* OR epitheli*) W/10 (permeab* OR hyperpermeab* OR barrier* OR wall)))
6	TITLE-ABS-KEY ("leaky gut")
7	#5 or #6
8	#4 and #7
9	TITLE-ABS-KEY (((intercellular OR cell* OR anchoring OR adherens) W/2 (junction* OR connection OR bridge)))

10	TITLE-ABS-KEY (("tight junction*" OR claudin* OR occludin* OR occluden* OR "adherens junction*" OR cadherin OR desmosomes OR hemidesmosome* OR mucin OR mlck OR "myosin light chain*" OR "myosin-light chain"))
11	#9 or #10
12	#4 and #11
13	#8 or #12
14	INDEX(embase) OR INDEX(medline) OR PMID(0* OR 1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9*)
15	#13 and not #14
16	DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh) OR DOCTYPE(ch)
17	#15 and not #16
18	LANGUAGE(english)
19	#17 and #18

Supplementary table 1: quality assessment

	Aims	Study design	Sample size justification	Target population	Sample selection	Selection process	Non-responders	Measurement validity	Measurement reliability	Statistics	Overall methods	Basic data	Response rate	Non-responders 2	Internal consistency	Overall results	Conclusions	Limitations	Conflicts of interest	Ethical approval	
Reference	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**	**Q10**	**Q11**	**Q12**	**Q13**	**Q14**	**Q15**	**Q16**	**Q17**	**Q18**	**Q19**	**Q20**	**Total score**
In vivo studies – adults																					
Lobley et al, 1990 [1]	1	1	0	1	1	0	0	1	1	1	1	1	0	0	1	1	1	0	1	1	13
Paganelli et al, 1990 [2]	1	1	0	1	1	0	1	1	1	0	0	1	0	0	1	1	1	0	0	0	11
Spiller et al, 2000 [3]	1	1	0	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	16
Marshall et al, 2004 [4]	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	1	1	0	1	1	17
Dunlop et al, 2006 [5]	1	1	0	1	1	0	0	1	1	1	1	1	0	0	1	1	1	1	1	1	15
Zeng et al, 2008 [6]	1	1	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	17
Park et al, 2009 [7]	1	1	0	1	0	0	0	1	0	1	0	1	0	0	1	1	1	0	0	1	10
Zhou et al, 2009 [8]	1	1	0	1	0	0	0	1	1	1	0	1	0	0	1	1	1	0	1	1	12
Kerckhoffs et al, 2010 [9]	1	1	0	1	0	0	0	1	1	1	1	1	1	0	1	1	1	0	1	1	14
Zhou et al, 2010 [10]	1	1	0	1	1	0	0	1	1	1	0	1	0	0	1	1	1	0	1	1	13
Gecse et al, 2011 [11]	1	1	0	1	1	0	0	1	1	1	1	1	0	0	1	1	1	1	1	1	15
Mattioli et al, 2011 [12]	1	1	0	1	0	0	0	1	1	1	1	1	0	0	1	1	1	0	1	1	13
Rao et al, 2011 [13]	1	1	1	1	1	0	0	1	1	1	1	1	0	0	1	1	1	0	1	1	15
Vazquez et al, 2012 [14]	1	1	1	1	0	0	0	1	1	1	1	1	0	0	1	1	1	1	1	1	15
Del Valle-Pinero et al, 2013 [15]	1	1	0	1	1	0	0	1	1	1	1	1	0	0	1	1	1	1	1	0	14
Swan et al, 2013 [16]	1	1	1	1	1	0	0	1	1	1	1	1	0	0	1	1	1	0	1	1	15
Camilleri et al, 2014 [17]	1	1	0	1	1	1	0	1	1	1	0	1	0	0	1	0	1	1	1	1	14
Keszthelyi et al, 2014 [18]	1	1	1	1	1	0	0	1	1	1	1	1	0	0	1	1	1	1	1	1	16
Mujagic et al, 2014 [19]	1	1	0	1	1	0	0	1	1	1	1	1	1	0	1	1	1	1	1	1	16
Zhou et al, 2015 [20]	1	1	0	1	1	0	1	1	1	1	0	1	0	0	1	1	1	0	1	1	14
Jarrett et al, 2016 [21]	1	1	0	1	0	0	1	1	1	1	1	1	0	0	1	1	1	1	1	1	15
Li et al, 2016 [22]	1	1	0	1	1	0	0	1	1	1	1	1	0	0	1	1	1	1	1	1	15
Peters et al, 2017 [23]	1	1	1	1	1	0	0	1	1	1	1	1	0	0	1	1	1	0	1	1	15
Russo et al, 2017 [24]	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	19
Valentin et al, 2017 [25]	1	1	1	1	1	0	0	1	1	1	1	1	1	0	1	1	1	1	1	1	17
Linsalata et al, 2018 [26]	1	1	0	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	18
Russo et al, 2018 [27]	1	1	0	1	1	1	1	1	1	1	1	1	1	0	1	0	1	1	1	1	17
In vivo studies – children																					

Shulman et al, 2008 [28]	1	1	0	1	1	0	0	1	1	1	1	1	0	0	1	1	1	1	1	1	15
Francavilla et al, 2010 [29]	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	19
Gervasoni et al, 2016 [30]	1	1	0	1	0	0	0	1	1	1	0	1	0	0	1	1	1	0	1	1	12
Shulman et al, 2020 [31]	1	1	1	1	1	0	0	1	1	1	0	1	0	0	1	1	1	1	1	1	15
In vitro studies – biopsies																					
Piche et al, 2009 [32]	1	1	0	1	1	1	0	1	1	1	1	1	0	0	1	1	1	0	1	1	15
Coeffier et al, 2010 [33]	1	1	0	1	1	0	0	1	1	1	1	1	0	0	1	1	1	1	1	1	15
Lee et al, 2010 [34]	1	1	0	1	1	0	0	1	1	1	1	1	0	0	0	1	1	1	0	1	13
Bertiaux-Vandaele et al, 2011 [35]	1	1	0	1	1	0	1	1	1	1	1	1	0	0	1	1	1	1	1	1	16
Martinez et al, 2012 [36]	1	1	0	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	16
Vivinus-Nebot et al, 2012 [37]	1	1	0	1	1	1	0	1	1	1	1	1	0	0	1	1	1	0	1	1	15
Lee et al, 2013 [38]	1	1	0	1	1	0	0	1	1	1	1	1	0	0	1	1	1	1	1	1	15
Martinez et al, 2013 [39]	1	1	0	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	16
Turcotte et al, 2013 [40]	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1	18
Wilcz-Villega et al, 2013 [41]	1	1	0	1	0	0	0	1	1	1	1	1	0	0	1	1	1	1	1	1	14
Camilleri et al, 2014 [42]	1	1	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	17
Nebot-Vivinus et al, 2014 [43]	1	1	0	1	1	0	0	1	1	1	1	0	0	0	1	1	1	1	1	1	14
Vivinus-Nebot et al, 2014 [44]	1	1	0	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	16
Wilcz-Villega et al, 2014 [45]	1	1	0	1	1	1	0	1	1	1	1	1	0	0	0	1	1	0	1	1	14
Camilleri et al, 2015 [46]	1	1	0	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	16
Cheng et al, 2015 [47]	1	1	0	1	1	0	0	1	1	1	1	1	0	0	1	1	1	0	1	1	14
Zhen et al, 2015 [48]	1	1	0	1	1	0	0	1	1	1	1	1	0	0	1	1	1	1	1	1	15
Tulic et al, 2016 [49]	1	1	0	1	0	0	0	1	1	1	1	1	0	0	1	1	1	1	1	1	14
Bednarska et al, 2017 [50]	1	1	0	1	1	0	0	1	1	1	1	1	0	0	1	1	1	0	1	1	14
Ishimoto et al, 2017 [51]	1	1	0	1	1	0	0	1	1	1	1	1	0	0	1	1	1	1	1	1	15
Martinez et al, 2017 [52]	1	1	0	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	16
Barbaro et al, 2018 [53]	1	1	0	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	16
Lee et al, 2019 [54]	1	1	0	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	16
Rodino-Janeiro et al, 2018 [55]	1	1	0	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	16
Videlock et al, 2018 [56]	1	1	1	1	1	0	0	1	1	1	1	1	0	0	1	1	1	1	1	1	16
Fritscher-Ravens et al, 2019 [57]	1	1	1	1	1	0	0	1	1	1	1	1	0	0	1	1	1	1	1	1	16
Witt et al, 2019 [58]	1	1	0	1	1	0	0	1	1	1	1	1	0	0	1	1	1	1	1	1	15
Zhao et al, 2019 [59]	1	1	0	1	1	0	0	1	1	1	1	1	0	0	1	1	1	1	1	1	15
Katinios et al, 2020 [60]	1	1	0	1	1	0	0	1	1	1	1	1	0	0	1	1	1	1	1	1	15
In vitro studies – fecal																					
Gecse et al, 2008 [61]	1	1	0	1	1	0	0	1	1	1	1	1	0	0	1	1	1	0	1	1	14
Annahazi et al, 2013 [62]	1	1	0	1	1	0	0	1	1	1	1	1	1	0	0	1	1	0	1	1	14
Crouzet et al, 2013 [63]	1	1	0	1	0	0	0	1	1	1	1	1	0	0	1	1	1	0	1	1	13
De Palma et al, 2017 [64]	1	1	1	1	1	0	0	1	1	1	1	1	0	0	1	1	1	1	1	1	16

Edogawa et al, 2019 [65]	1	1	0	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	16
Han et al, 2019 [66]	1	1	0	1	1	0	0	1	1	1	1	0	0	0	1	1	1	1	1	14

Supplementary table 2: patient characteristics across studies

Reference	Country	Diagnostic criteria	Group	N	Female gender (N (%))	Age (yr)	BMI (kg/m²)	Anxiety and depression	Symptomatology	Quality of Life
In vivo studies – adults										
Lobley et al, 1990 [1]	United Kingdom	Clinical diagnosis	IBS [§]	40	87 (61%)	16 – 81[a]	ND	ND	ND	ND
			HV	40	13 (33%)	20 – 50[a]	ND	ND	ND	ND
Paganelli et al, 1990 [2]	Italy	Clinical diagnosis	IBS-D, DSCG	7	6 (86%)	39.4 ± 16.6[b]	ND	ND	ND	ND
			IBS-D, placebo	7	5 (71%)	33.9 ± 7.5[b]	ND	ND	ND	ND
			HV	10	ND	ND	ND	ND	ND	ND
Spiller et al, 2000 [3]	United Kingdom	Rome I	IBS	10	6 (60%)	ND	ND	ND	ND	ND
			HV	10	ND	25 (22 – 45)[c]	ND	ND	ND	ND
Marshall et al, 2004 [4]	Canada	Rome I	IBS	132	81 (61%)	44.7 (16 – 84)[d]	ND	ND	ND	ND
			HV	86	52 (60%)	48.9 (17 – 84)[d]	ND	ND	ND	ND
Dunlop et al, 2006 (part 1) [5]	United Kingdom	Rome II	PI-IBS-D	15	7 (47%)	38.5 ± 10.1[b]	ND	HADS: Anxiety 8.5 ± 4.6[b] Depression 5.3 ± 3.6[b]	GSRS: Abdominal pain 11 (8 – 12)[c] Indigestion 13 (7 – 17)[c] Constipation 6 (5 – 8)[c] Diarrhea 10 (7 – 15)[c]	IBS-QOL: Bowel symptoms 41 (34 – 54)[c] Activity limitation 15 (14 – 16)[c] Fatigue 15 (11 – 18)[c] Emotional function 26 (13 – 35)[c]
			IBS-C	15	15 (100%)	35.1 ± 11.2[b]	ND	HADS: Anxiety 10.3 ± 4.9[b] Depression 5.5 ± 4.1[b]	GSRS: Abdominal pain 9 (7 – 13)[c] Indigestion 14 (11 – 19)[c] Constipation 14 (9 – 17)[c] Diarrhea 6 (4 – 6)[c]	IBS-QOL: Bowel symptoms 49 (45 – 57)[c] Activity limitation 14 (8 – 17)[c] Fatigue 11 (8 – 17)[c] Emotional function 28 (17 – 33)[c]
			HV	15	10 (67%)	35.9 ± 10.0[b]	ND	HADS: Anxiety 4.5 ± 3.1[b] Depression 2.5 ± 2.0[b]	GSRS: Abdominal pain 4 (3 – 5)[c]	IBS-QOL: Bowel symptoms 14 (12 – 16)[c]

									Indigestion 6 (4 – 7)[c] Constipation 3 (3 – 4)[c] Diarrhea 3 (3 – 3)[c]	Activity limitation 6 (3 – 8)[c] Fatigue 4 (4 – 4)[c] Emotional function 28 (17 – 33)[c]
Dunlop et al, 2006 (part 2) [5]	United Kingdom	Rome II	PI-IBS-D	15	7 (47%)	36.6 ± 13.9[b]	ND	ND	ND	ND
			Non PI-IBS-D	15	6 or 7 (45%)	39.5 ± 10.4[b]	ND	ND	ND	ND
			HV	12	6 (50%)	35.3 ± 5.9[b]	ND	ND	ND	ND
Zeng et al, 2008 [6]	China	Rome II	IBS-D, probiotics	14	4 (29%)	44.6 ± 12.4[b]	ND	ND	GSRS: 9.6 ± 1.1[b]	ND
			IBS-D, placebo	15	6 (40%)	45.8 ± 9.2[b]	ND	ND	GSRS: 9.6 ± 1.2[b]	ND
			HV	12	9 (75%)	44.4 ± 12.8[b]	ND	ND	ND	ND
Park et al 2009 [7]	South Korea	Rome II	IBS	38	20 (52%)	40.2 ± 2.6[b]	ND	STAI-S: 43.6 ± 1.8[b] STAI-T: 44.3 ± 1.7[b] BDI: 12.6 ± 1.5[b]	ND	ND
			HV	12	5 (42%)	37.8 ± 2.6[b]	ND	STAI-S: 37.5 ± 2.1[b] STAI-T: 38.6 ± 1.1[b] BDI: 7.0 ± 41.4[b]	ND	ND
Zhou et al, 2009 [8]	USA	Rome III	IBS-D	54	41 (76%)	29.5 ± 7.3[b]	ND	Exclusion if on SSRIs, TCAs in prior 3 weeks	FBDSI, increased IP: 100.8 ± 5.4[b] FBDSI, normal IP: 51.6 ± 12.7[b]	ND
			HV	22	16 (72%)	28.3 ± 5.3[b]	ND	Exclusion if on SSRIs, TCAs in prior 3 weeks	FBDSI: 6.1 ± 5.6[b]	ND
Kerckhoffs et al, 2010 [9]	The Netherlands	Rome II	IBS	14	10 (71%)	41 (21 – 63)[d]	ND	ND	ND	ND
			HV	15	8 (53%)	31 (21 – 55)[d]	ND	ND	ND	ND
Zhou et al, 2010 [10]	USA	Rome III	IBS-D	19	19 (100%)	27 ± 3.3[b]	ND	ND	ND	ND

			HV	10	10 (100%)	29 ± 5.2[b]	ND	ND	ND	ND
Gecse et al, 2011 [11]	Hungary	Rome III	IBS-C	12	10 (83%)	56 (37 – 65)[c]	ND	ND	ND	ND
			IBS-D	18	12 (67%)	49 (25 – 68)[c]	ND	ND	ND	VAS: 45 ± 5[b]
			HV	10	8 (80%)	49 (38 – 65)[c]	ND	ND	ND	ND
Mattioli et al, 2011 [12]	Italy	Rome III	IBS-C	32	21 (66%)	48.6 ± 15.4[b]	23.7 ± 3.9[b]	ND	ND	ND
			HV	23	15 (65%)	40.5 ± 14.0[b]	22.6 ± 3.9[b]	ND	ND	ND
Rao et al, 2011 [13]	USA	Rome III	IBS-D	12	12 (100%)	42.4 ± 3.0[b]	30.9 ± 1.8[b]	ND	ND	ND
			HV	12	11 (92%)	37.4 ± 2.6[b]	24.4 ± 0.8[b]	ND	ND	ND
Vazquez-Roque et al, 2012 [14]	USA	Rome II	IBS-D, HLA-DQ2/8 positive	23	Total IBS: 43 (96%)	41.5 ± 3.0[b]	30.3 ± 1.7[b]	ND	Bowel disease questionnaire symptom score 0.422 ± 0.295[b]	ND
			IBS-D, HLA-DQ2/8 negative	22	Total IBS: 43 (96%)	44.5 ± 2.5[b]	30.7 ± 2.2[b]	ND	Bowel disease questionnaire symptom score 0.422 ± 0.295[b]	ND
			HV	12	11 (92%)	37.4 ± 2.6[b]	24.4 ± 0.8[b]	ND	ND	ND
Del Valle-Pinero et al, 2013 [15]	USA	Rome III	IBS	20	12 (60%)	26.7 ± 6.9[b]	24.5 ± 3.8[b]	ND	ND	ND
			HV	39	19 (49%)	27.5 ± 7.0[b]	24.8 ± 5.3[b]	ND	ND	ND
Swan et al, 2013 [16]	United Kingdom	Rome II	IBS-C	18	16 (89%)	40.6 ± 2.3[b]	ND	HADS: Anxiety 8.0 (5.0 – 10.0)[c] Depression 4.0 (2.0 – 5.0)[c]	PHQ12SSS: 7.8 (6.3 – 9.0)[c]	ND
			IBS-D	37	25 (68%)	40.6 ± 2.3[b]	ND	HADS: Anxiety 7.0 (4.0 – 11.5)[c] Depression 4.0 (2.0 – 5.0)[c]	PHQ12SSS: 8.0 (5.0 – 11.0)[c]	ND
			HV	26	17 (65%)	35.0 ± 2.7[b]	ND	HADS: Anxiety 4.0 (2.5 – 5.5)[c] Depression 1.0 (1.0 – 2.0)[c]	PHQ12SSS: 3.0 (1.0 – 4.0)[c]	ND
Camilleri et al, 2014 [17]	USA	Rome III	IBS-C		30 (100%)	44.6 ± 1.1[b]	26.6 ± 0.8[b]	HADS: Anxiety 2.8 ± 0.5[b]	ND	Psychosomatic symptom score: 0.4 ± 0.06[b]

								Depression 0.9 ± 0.2[b]		
			IBS-D	64	59 (92%)	41.9 ± 1.5[b]	29.7 ± 0.9[b]	HADS: Anxiety 4.0 ± 0.5[b] Depression 1.6 ± 0.2[b]		Psychosomatic symptom score: 0.5 ± 0.04[b]
			HV	30	22 (73%)	39.3 ± 2.1[b]	24.5 ± 0.7[b]	HADS: Anxiety 2.1 ± 0.3[b] Depression 0.4 ± 0.1[b]		Psychosomatic symptom score: 0.2 ± 0.04[b]
Keszthelyi et al, 2014 [18]	The Netherlands	Rome III	IBS	15	8 (53%)	33 ± 17[e]	24 ± 4[e]	Exclusion if presence of psychiatric disorders or on treatments for those	ND	ND
			HV	15	10 (67%)	44 ± 13[e]	27 ± 5[e]	Exclusion if presence of psychiatric disorders or on treatments for those	ND	ND
Mujagic et al, 2014 [19]	The Netherlands	Rome III	IBS-C	21	13 (62%)	47.5 ± 3.6[e]	25.0 ± 0.9[e]	HADS: Anxiety ≥ 8 in 7 (35%) Depression ≥ 8 in 4 (21%)	GSRS: Abdominal pain 3.3 ± 0.3[e] Indigestion 3.9 ± 0.3[e] Constipation 3.9 ± 0.3[e] Diarrhea 2.8 ± 0.3[e]	ND
			IBS-D	34	19 or 20 (57%)	45.0 ± 2.4[e]	25.6 ± 1.2[e]	HADS: Anxiety ≥ 8 in 15 or 16 (46%) Depression ≥ 8 in 9 or 10 (29%)	GSRS: Abdominal pain 3.3 ± 0.2[e] Indigestion 4.2 ± 0.2[e] Constipation 2.7 ± 0.2[e] Diarrhea 4.0 ± 0.2[e]	ND

			IBS-M	30	21 (70%)	42.2 ± 3.1[e]	25.4 ± 0.7[e]	HADS: Anxiety ≥ 8 in 11 or 11 (36%) Depression ≥ 8 in 5 or 6 (17%)	GSRS: Abdominal pain 3.2 ± 0.2[e] Indigestion 4.2 ± 0.2[e] Constipation 3.8 ± 0.2[e] Diarrhea 3.7 ± 0.3[e]	ND
			HV	94	55 (59%)	45.0 ± 2.0[e]	23.8 ± 0.5[e]	HADS: Anxiety ≥ 8 in 11 or 12 (12%) Depression ≥ 8 in 7 or 8 (8%)	GSRS: Abdominal pain 1.6 ± 0.1[e] Indigestion 1.9 ± 0.1[e] Constipation 1.6 ± 0.1[e] Diarrhea 1.4 ± 0.1[e]	ND
Zhou et al, 2015 [20]	USA	Rome III	IBS-C	74	54 (73%)	30.4 ± 4.3[b]	ND	ND	ND	ND
			IBS-D	109	75 (69%)	28.6 ± 2.9[b]	ND	ND	ND	ND
			HV	36	26 (72%)	31.5 ± 3.6[b]	ND	ND	ND	ND
Jarrett et al, 2016 [21]	USA	Rome III	IBS	85	75 (88%)	39.2 ± 15.3[b]	ND	Exclusion if presence of current mental health disorders	ND	70.3 ± 14.2[b]
Li et al, 2016 [22]	China	Rome III	IBS-D	40	16 (40%)	37.3 ± 12.1[b]	22.4 ± 3.1[b]	HADS, increased sIP: Total 16.0 ± 8.1[b] Anxiety 8.1 ± 4.3[b] Depression 7.9 ± 4.7[b] HADS, normal sIP: Total 10.1 ± 5.9[b] Anxiety 6.3 ± 3.3[b] Depression 4.1 ± 2.6[b]	GSRS, increased sIP: Mild (42%); Moderate (42%); Severe (16%) GSRS, normal sIP: Mild (62%); Moderate (33%); Severe (5%)	IBS-QOL, increased sIP: 68.2 ± 19.0[b] IBS-QOL, normal sIP: 79.7 ± 14.3[b]
			HV	10	4 (40%)	36.5 ± 14.1[b]	21.5 ± 1.8[b]	ND	ND	ND
Peters et al, 2017 [23]	USA	Rome III	IBS-C	19	19 (100%)	45.4 ± 2.8[e]	-	HADS: Anxiety 3.4 ± 0.5[e]	SSS: 207 ± 18[e]	IBS-QOL 32.3 ± 2.6[e]

								Depression 1.1 ± 0.4[e]		
			HV	18	18 (100%)	43.1 ± 2.8[e]	-	HADS: Anxiety 2.6 ± 0.5[e] Depression 0.4 ± 0.4[e]	-	-
Russo et al, 2017 [24]	Italy	Rome III	IBS-D	28	26 (93%)	40.8 ± 2.3[e]	23.5 ± 0.7[e]	Exclusion if presence major psychiatric disorders	Inclusion if GSRS-IBS ≥ 3.0	ND
			HV	19	13 (68%)	39.7 ± 3.3[e]	25.0 ± 1.0[e]	Exclusion if presence of major psychiatric disorders	ND	ND
Valentin et al, 2017 [25]	USA	Rome III	IBS-D	15	13 (87%)	40.3 ± 2.3[b]	34.3 ± 3.0[b]	Exclusion if presence of uncontrolled psychiatric disorder	ND	
			HV	12	ND	ND	ND	ND	ND	ND
Linsalata et al, 2018 [26]	Italy	Rome III	IBS-D	39	33 (85%)	40.1 ± 12.2[b]	23.9 ± 3.3[b]	Exclusion if presence of major psychiatric disorders	GSRS: Abdominal pain 14 (6 – 25)[c] Indigestion 19 (7 – 38)[c] Diarrhea 5 (3 – 21)[c]	ND
			HV		13 (65%)	39.7 ± 7.2[b]	23.8 ± 2.9[b]	Exclusion if presence of major psychiatric disorders	GSRS: Abdominal pain 6 (0 – 6)[c] Indigestion 6 (6 – 6)[c] Diarrhea 3 (3 – 3)[c]	ND
Russo et al, 2018 [27]	Italy	Rome III	IBS-D	34	30 (88%)	41.2 ± 2.1[e]	25.1 ± 0.9[e]	Exclusion if presence of major psychiatric disorders	GSRS: Abdominal pain 13 (6 – 25)[c] Indigestion 19 (7 – 38)[c]	ND

									Diarrhea 5 (3 – 21)[c]	
			HV	17	12 (71%)	39.5 ± 2.9[e]	24.3 ± 0.4[e]	Exclusion if presence of major psychiatric disorders	GSRS: Abdominal pain 6 (6 – 6)[c] Indigestion 6 (6 – 6)[c] Diarrhea 3 (3 – 3)[c]	ND
In vivo studies – children										
Shulman et al, 2008 [28]	USA	Rome II	IBS or FAP	93	65 (71%)	8.2 ± 1.4[b]	ND	ND	ND	ND
			HV	52	39 (73%)	8.5 ± 1.3[b]	ND	ND	ND	ND
Francavilla et al, 2010 [29]	Italy	Rome II	IBS or FAP, treated with LGG [§§]	67	24 (36%)	6.5 ± 2.1[b]	ND	ND	ND	School absenteeism
			IBS or FAP, treated with placebo [§§]	69	23 (33%)	6.3 ± 2.0[b]	ND	ND	ND	School absenteeism
			HV	55	25 (45%)	5 – 12[a]	ND	ND	ND	ND
Gervasoni et al, 2016 [30]	Italy	Rome III	IBS	15	7 (47%)	5 – 16[a]	ND	ND	ND	ND
			HV	10	6 (60%)	5 – 16[a]	ND	ND	ND	ND
Shulman et al, 2020 [31]	USA	Rome III	IBS	95	59 (62%)	9.4 ± 1.5[b]	ND	ND	ND	ND
			FAP	25	15 (60%)	9.2 ± 1.7[b]	ND	ND	ND	ND
			HV	60	10 (40%)	9.7 ± 1.6[b]	ND	ND	ND	ND

[a] range; [b] mean ± standard deviation; [c] median (range); [d] mean (range); [e] mean ± standard error of the mean.

[§] Characteristics of overall patient population, describing patients with several GI diseases (n = 143), 28% is IBS.

[§§] Only 54 out of 136 children with IBS or FAP completed IP measurements (40%).

BDI, Beck depression inventory; BMI, body mass index; DSCG, disodium cromoglycate; FAP, functional abdominal pain; FBDSI, functional bowel disorder severity index; GSRS, gastrointestinal symptom rating scale; HADS, hospital anxiety and depression scale; HLA-DQ2/8, human leukocyte antigen serotype 2 and/or 8; HV, healthy volunteer; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrhea; IBS-QOL, irritable bowel syndrome - quality of life; IP, intestinal permeability; LGG, *Lactobacillus rhamnosus GG*; ND, not described; PHQ12SSS, patient health questionnaire 12 somatic symptom scale; PI-IBS, post-infection irritable bowel syndrome; sIP, small intestinal permeability; SSRI, selective serotonin reuptake inhibitor; SSS, symptom severity scale; STAI-S, state-trait anxiety inventory – state component; STAI-T, state-trait anxiety inventory – trait component; TCA, tricyclic antidepressants; VAS, visual analogue scale

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