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Appendix

Exclusion Diets in IBS Search Strategy

"Database: Embase <1974 to 2017 April 13>, OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials <March 2017>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to April 12, 2017>
Search Strategy:
---
1 exp Irritable bowel syndrome/ (28258)
2 exp Irritable colon/ (28258)
3 (Irritable bowel syndrome or irritable colon* or IBS).tw,kw. (34832)
4 1 or 2 or 3 (41261)
5 exp diet, gluten-free/ (8860)
6 exp gluten free diet/ (8860)
7 ((gluten* adj2 free) or glutens).tw,kw. (11497)
8 exp fructose oligosaccharide/ or exp polyol/ or exp fructose/ or exp galactose oligosaccharide/ (242440)
9 exp diet/ (590580)
10 (FODMAP or FODMAPs or saccharides or oligosaccharide or disaccharide or monosaccharide).tw,kw. (63021)
11 exp diet restriction/ (145695)
12 exp fructan/ (8749)
13 (polyol or polyols or diet restriction or ducto-oligosaccharides or galacto-oligosaccharides or fructans or fructose or galactans or lactose or sorbitol or mannitol or xylitol or maltitol).tw,kw. (166833)
14 exp carbohydrate diet/ or exp Dietary Carbohydrates/ (46682)
15 exp sweetening agent/ (298613)
16 sweetener*.tw,kw. (7427)
17 (diet or diets or dietary or nutrition or food).tw,kw. (1788646)
18 or/5-17 (2589439)
19 4 and 18 (6544)
20 randomized controlled trial.pt. (879623)
21 controlled clinical trial.pt. (183129)
22 random:.mp. (3123681)
23 placebo:.mp. (802774)
24 trial.ab. (1204795)
25 groups.ab. (4274341)
26 double-blind*.mp. or blind*.tw. (936966)
27 clinical trial:.mp. (2709808)
28 or/20-27 (8427422)
29 19 and 28 (2844)
30 remove duplicates from 29 (1998)
31 ((child/ or Pediatrics/ or Adolescent/ or Infant/ or adolescence/ or newborn/) not (adult/ or aged/)) or ((baby or babies or child or children or pediatric* or paediatric* or peadiatric* or

infant* or infancy or neonat* or newborn* or new born* or kid or kids or adolescen* or preschool or pre-school or toddler*) not (aged or adult* or elder* or senior or men or women)).ti. (4352199)
32 ((exp animals/ or exp animal/ or exp nonhuman/ or exp animal experiment/ or animal model/ or animal tissue/ or non human/) not (humans/ or human/)) or ((rats or mice or mouse or cats or dogs or animal* or cell lines) not (human* or men or women)).ti. (10857825)
33 case report/ or case reports/ or (case report or case series).ti. (4192672)
34 note/ or editorial/ or letter/ or Comment/ or news/ (3898425)
35 30 not (31 or 32 or 33 or 34) (1725)

Box 1:Eligibility Criteria

Parallel group randomized controlled trials (or first arm of cross-over)

Adults (participants aged > 17 years)

Diagnosis of IBS based on either a clinician's opinion, or meeting specific diagnostic criteria*.

Compared dietary exclusion of gluten or FODMAPs with placebo diet or usual diet.

Alternatively all patients received GFD or low FODMAP diet and then randomized to challenge or continue on diet.

Minimum duration of therapy and follow up 7 days.

Dichotomous assessment of response to therapy in terms of effect on global IBS symptoms or abdominal pain following therapy.†

*Manning, Kruis score, Rome I, II, III or IV.

†Preferably patient-reported, but if this was not available then as assessed by a physician or questionnaire data.

Table 1: Summary of Trials

Author	Design	Participants	Interventions	Methodology	Outcomes
Biesiekierski 2011	Australian RCT, single center.	Rome III IBS patients intolerant of gluten but celiac excluded. Recruited from newspaper advertisement. 89% female.	Diet spiked with 16g gluten/ day vs. placebo for 4 weeks.	Adequate method of randomization and concealment of allocation. Double-blind. No other IBS medications allowed.	Patients answering "no" to the question "Over the last week were your symptoms adequately controlled?"
Shahbazkhani 2015	Single center Iranian trial	Rome III IBS patients intolerant of gluten but celiac excluded.	Patients randomized to packages containing powdered gluten or gluten free powder for 6 weeks	Unclear method of randomization and concealment of allocation. Double-blind.	"Symptom control" Unclear what these symptoms were but it is implied that this includes stool satisfaction, pain and bloating.
Staudacher 2012	UK RCT, single center.	Rome III IBS. Recruited from secondary care. Bloating and/or diarrhea included, predominant constipation excluded.	Low FODMAPs diet vs. habitual diet for 4 weeks	Method of randomization and concealment of allocation not stated. Open study – patients not blinded (unclear if researchers masked)	GI symptom rating scale. Patients asked "Were your symptoms adequately controlled over the previous week?"

Eswaran 2016	US single center	Rome III (IBS-D)	Low FODMAPs diet vs. modified NICE diet for 4 weeks	Adequate method of randomization and unclear method of concealment of allocation. Dietician and patients not blinded. Unclear if other IBS medications allowed.	Adequate relief overall IBS-D symptoms ≥50% of intervention weeks 3–4; FDA composite endpoint; individual component
McIntosh 2016	Canadian single center	ROME III IBS (all subtypes – predominantly IBS-M and D)	Low FODMAPs diet vs. high FODMAP diet for 3 weeks	Adequate method of randomization and concealment of allocation. Patients not blinded.	IBS-SSS, proportion of patients defined as responders (IBS symptom reduction ≥50)
Bohn 2015	Swedish multicenter study	ROME III IBS (all subtypes)	Low FODMAPS diet versus traditional IBS diet for 4 weeks	Adequate method of randomization and concealment of allocation. Patients not blinded.	Reduction in IBS severity scores ≥50
Halmos 2014	Australian Single center	ROME III	Low FODMAP versus typical diet	Adequate method of randomization and concealment of allocation. Patients not blinded.	Overall improvement in symptoms based on VAS. Secondary outcomes included improvement in pain, bloating, flatus and satisfaction with passage of stool consistency

Hustoft 2017	Norwegian single center study	Rome III IBS, diarrhea predominant or mixed	All received low FODMAPs diet for 3 weeks then randomized to receive supplement of FODMAP or maltodextrin (placebo) for 10 days	Unclear method of randomization or concealment. Double blind	Continued symptom relief
Staudacher 2017	UK, two center study	ROME III IBS (all subtypes)	Low FODMAPs diet versus sham diet with similar number of foods restricted but maintaining same FODMAP intake. 2x2 factorial design also randomized to probiotics versus placebo	Adequate method of randomization and concealment of allocation. Patients not blinded.	Adequate relief of IBS symptoms

Table 2: GRADE Summary of Findings Table Low FODMAP versus Control Diet

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**low FODMAP**	**control**	**Relative (95% CI)**	**Absolute (95% CI)**		
IB S symptoms persist												
7	randomised trials	serious	not serious	not serious	very serious	public ation bias strongly suspected all plausible residual c onfounding would reduc e the demonstrated effect	86/199 (43.2%)	122/198 (61.6%)	**RR 0.69** (0.54 to 0.88)	**191 fewer per 1,000** (from 74 fewer to 283 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
IB S symptoms persist - Low F ODMAP versus alternative diet												
3	randomised trials	serious	not serious	not serious	very serious	public ation bias strongly suspected all plausible residual c onfounding would reduc e the demonstrated effect	68/139 (48.9%)	79/132 (59.8%)	**RR 0.82** (0.66 to 1.02)	**108 fewer per 1,000** (from 12 more to 203 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
IB S symptoms persist - Low F ODMAP versus high F ODMAP												
1	randomised trials	serious	not serious	not serious	not serious	public ation bias strongly suspec ted	7/20 (35.0%)	16/20 (80.0%)	**RR 0.44** (0.23 to 0.83)	**448 fewer per 1,000** (from 136 fewer to 616 fewer)	⨁⨁◯◯ LOW	CRITICAL
IB S symptoms persist - Low F ODMAP versus usual diet												
2	randomised trials	serious	not serious	not serious	serious	public ation bias strongly suspected all plausible residual c onfounding would reduc e the demonstrated effect	9/32 (28.1%)	23/39 (59.0%)	**RR 0.46** (0.25 to 0.84)	**318 fewer per 1,000** (from 94 fewer to 442 fewer)	⨁⨁◯◯ LOW	CRITICAL
IB S symptoms persist - F ODMAP exc lusion then F ODMAP versus plac ebo												
1	randomised trials	serious	serious	not serious	serious	public ation bias strongly suspected all plausible residual c onfounding would reduc e the demonstrated effect	2/8 (25.0%)	4/7 (57.1%)	**RR 0.44** (0.11 to 1.71)	**320 fewer per 1,000** (from 406 more to 509 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

Table 3: GRADE Summary of Findings Table Gluten Free Diet versus Control Diet

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Gluten Free Diet**	**Control Diet**	**Relative (95% CI)**	**Absolute (95% CI)**		
IB S symptoms persist												
2	randomised trials	serious	serious	not serious	very serious	public ation bias strongly suspec ted all plausible residual c onfounding would suggest spurious effec t, while no effec t was observed	16/56 (28.6%)	40/55 (72.7%)	**RR 0.42** (0.11 to 1.55)	**422 fewer per 1,000** (from 400 more to 647 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Table 4: Data Abstraction from Randomized Controlled Trials of Low FODMAP diet and Gluten Free Diet on IBS symptoms

Author	Country	Design	Diet	Participants	Intervention	Methodology	Duration of therapy	IBS Definition	Predominant Stool type	Outcome
Biesiekierski et al., (2011)	Australia	RCT	GFD	Adult patients age 16 years of age and older with IBS that improved on GFD prior to starting study	GFD versus placebo (GFD plus study bread and muffin containing 16g of gluten/day) for 6 weeks	Used computer generated randomization, did not mention allocation ratio, blinding unclear	6 weeks	ROME III	Not specified	Primary outcome global assessment, secondary outcomes change in GI symptoms on VAS and biomarkers
Shahbazkhani et al., (2015)	Iran	RCT	GFD	Adult patients age 16 years of age and older with IBS and newly diagnosed	Patients randomized to packages containing powdered gluten or gluten free powder for 6 weeks	Independent randomization with block allocation. Patients and investigators were blinded.	6 weeks	ROME III	Not specified	Primary outcome was systematic improvement
Bohn et al., (2015)	Sweden	RCT	Low FODMAP	Adult patients aged 18-70 years of age with IBS with an IBS-SSS score >175	Low FODMAP versus traditional IBS diet advise (3 meals and 3 snacks per day with even fiber distribution)	Randomization program with external allocation, blinding was not explicitly explained.	4 weeks	ROME III	Not specified	Primary outcome reduction in IBS-SSS score
Eswaran et al., (2016)	USA	RCT	LOW FODMAP	Adult patients with IBS meeting criteria for IBS-D with abdominal pain >4, daily stool consistency of Bristol Stool Form Scale of >5.	Low FODMAP versus modified NICE guidelines diet	Computer generated randomization with 1:1 allocation. Blinding unclear.	4 weeks	ROME III	IBS-D	Primary outcome >50% reduction in overall IBS symptoms. Secondary outcome FDA composite endpoint (>30% reduction in pain and a reduction in Bristol Stool Score of > 1)
Halmos et al., (2014)	Australia	RCT	Low FODMAP	Adult patients with IBS and healthy controls	Low FODMAP versus typical diet	Computer generated randomization, unclear method of allocation. Assessed if patients could determine which group they were allocated too. Fecal assesses blinded but no other mention of blinding.	21 days	ROME III	Not specified	Primary outcome was overall improvement in symptoms based on VAS. Secondary outcomes included improvement in pain, bloating, flatus and satisfaction with passage of stool consistency
McIntosh et al., (2016)	Canada	RCT	Low FODMAP	Adults greater then 18 years of age and older with IBS for greater then 6 months	High FODMAP versus Low FODMAP	Independent computer generated randomization, allocation in concealed envelopes. Study administrator was blinded	3 weeks	ROME III	IBS-D, IBS-C, IBS-M	Primary outcome was change in symptoms based on IBS-SSS, Change in AUC for lactose breath test

Staudacher et al., (2017)	UK	RCT, 2x2 factorial design	Low FODMAP	Adult patients aged 18-65 years with IBS	Low FODMAP versus sham diet, or Low FODMAP/Probiotics, or LOW FODMAP/Placebo, sham diet/probiotic, sham diet/placebo	Independent randomization, computer generated and 1:1 randomization, stratified by gender. Allocation described.	4 weeks	ROME III	IBS-D, IBS-M, IBS-U	Adequate symptom relief and a 50 point reduction in IBS-SSS
Staudacher et al., (2012)	UK	RCT	Low FODMAP	Adult patients aged 18-65 years with IBS	Low FODMAP versus usual diet	randomized using a random number generator by an independent researcher 1:1 allocation and stratified by sex and presence of diarrhea. Allocation was ensured with sealed numbered envelopes. Blinding unclear.	4 weeks	ROME III	IBS-D	Improvement in symptoms and global assessment
Hustoft et al;., (2017)	Norway	RCT	Low FODMAP	Adult patients with IBS-D or IBS-M	Low FODMAP versus High FODMAP	Randomized according to computer generated list. Allocation sequences was blinded	9 weeks	ROME III	IBS-D, IBS-M	Reduction in IBS-SSS score and global assessment

Figure 1: PRISMA Flow diagram

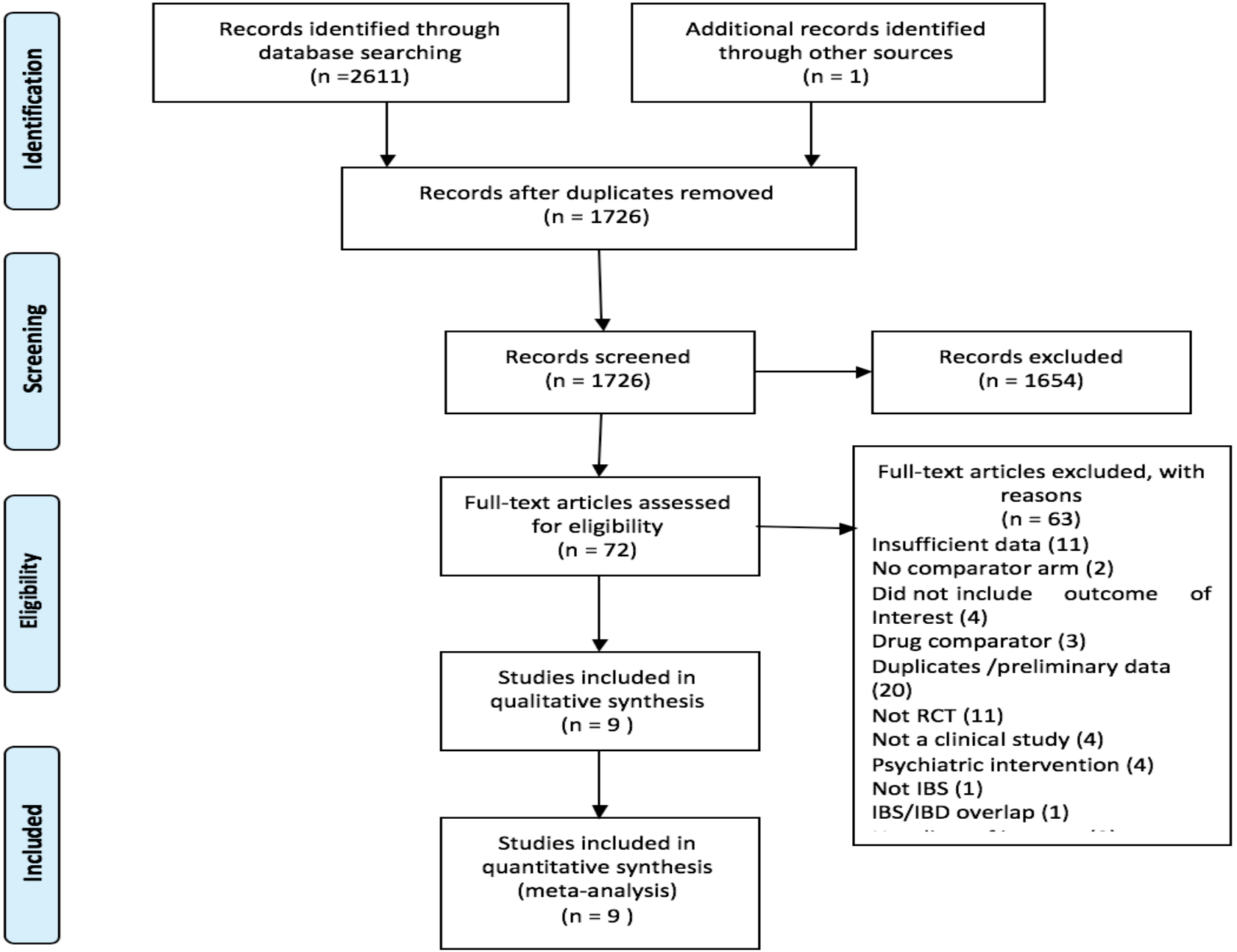

FIGURE 2: Gluten Free diet and IBS symptoms

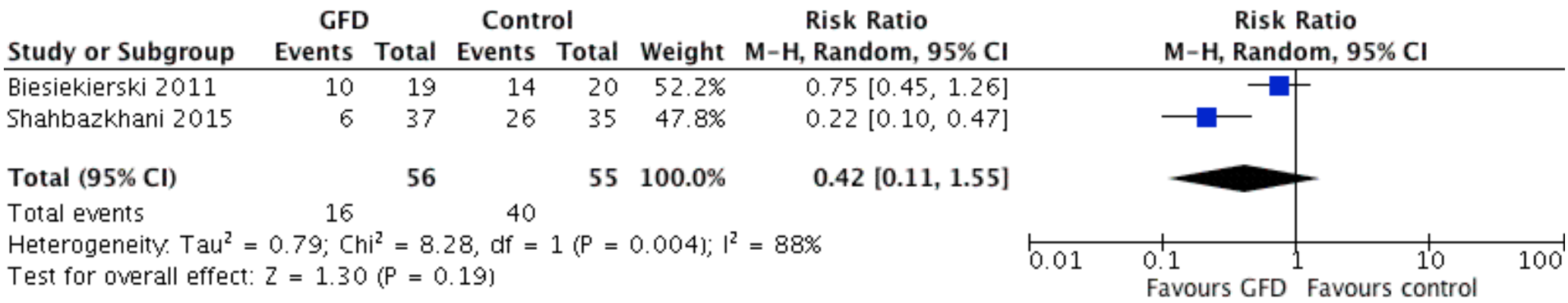

Figure 3 LOW FODMAP DIET AND IBS SYMPTOMS

Study or Subgroup	low FODMAP Events	Total	Control Events	Total	Weight	Risk Ratio Study 111-H, Random, 9S% CI
1.1.1 Low FOOMAP versus alternative diet						
Bohn 2015	19	38	20	37	20.4%	0.93 [0.60, 1.43]
Eswaran 2016	27	50	26	42	26.7%	0.87 [0.62, 1.24)
Staudacher 2017	22	51	33	53	24.3%	0.69 [0.47, 1.01]
Subtotal (9S% CI)		**139**		**132**	**71.4%**	**0.82 (0.66, 1.02)**
Total events	68		79			
Heterogeneity Tau' = 0.00; Chi² = 1.18, df = 2 (P = 0.55); ¡² = 0%						
Test for overall effect: Z = 1.77 (P = 0.08)						
1.1.2 Low FOOMAP versus high FODMAP						
McIntosh 2016	7	20	16	20	11.7%	0.44 [0.23, 0.83)
Subtotal (9S% CI)		**20**		**20**	**11.7%**	**0.44 (0.23, 0.83)**
Total events	7		16			
Heterogeneity Not applicable						
Test for overall effect Z = 2.55 (P = 0.01)						
1.1.3 Low FOOMAP versus usual diet						
Halmos 2014	3	13	6	17	3.9%	0.65 [0.20, 2.13]
Staudacher 2O12	6	19	17	22	10.0%	0.41 [0.20, 0.82)
Subtotal (9S% CI)		**32**		**39**	**13.9%**	**0.46 (0.2S, o.84l**
Total events	9		23			
Heterogeneity Tau'= 0.00; Chi² = 0.45, df = 1 (P = 0.50); ¡² = 0%						
Test for overall effect: Z = 2.52 (P =0.01)						
1.1.4 FODMAP exclusion then FOOMAP versus placebo						
Hustoft 2017	2	8	4	7	3.0%	0.44 [0.11, 1.71)
Subtotal (9S% CI)		**8**		**7**	**3.0%**	**0.44 (0.11, 1.71)**
Total events	2		4			
Heterogeneity Not applicable						
Test for overall effect Z = 1.19 (P = 0.23)						
Total (9S% CI)		**199**		**198**	**100.0%**	**0.69 (0.S4, 0.88)**
Total events	86		122			
Heterogeneity Tau' = 0.03; Chi² = 8.02, df = 6 (P = 0.24); ¡² = 25%						
Test for overall effect: Z = 2.98 (P = 0.003)						
Test for subgroup differences: Chi = 6.26, df = 3 (P = 0.10), ¡² = 52.1%