Endometriosis and Irritable Bowel Syndrome: a Systematic Review and Meta-analysis.

Running title: Endometriosis and Irritable Bowel Syndrome

Keywords: endometriosis, Irritable bowel syndrome, systematic review, meta-analysis

Abstract

Background: Irritable bowel disease and endometriosis are two common diseases characterized by chronic inflammation state and recurrent abdominal pain. As consequence of sharing of symptoms and of chronic inflammation, endometriosis and IBS may coexist and be misdiagnosed and this leads to delays in diagnosis, mismanagement, and unnecessary testing.

In recent years, some studies have found higher risk of IBS in women with endometriosis, compared to women without endometriosis.

Aims: To provide a general overview, we performed a systematic review and a meta-analysis on published data on this issue.

Materials and Methods: A systematic literature search selection process, 11 studies were identified for the current study: two prospective and two retrospective cohort studies, four case-control studies, one cross-sectional studies and two clinical series.

Results: When we meta-analysed data about prevalence of IBS in women with endometriosis, the overall OR (95%CI), compared to women without endometriosis was 3.26 (1.97-5.39) with no statistically significant heterogeneity. All of three studies considering the incidence of IBS in women with a previous diagnosis of endometriosis, showed about 2 fold greater risk among women with enndometriosis than women without. Likewise, in the random effects model of the meta-analysis, the overall OR of history of IBS in women with endometriosis was 3.10 (95% CI 2.06-4.67), with no heterogeneity between three studies considered.

Conclusion: This meta-analysis provides epidemiological evidence of a link between endometriosis and IBS, highlighting two or more times higher risk of IBS in women with endometriosis compared to women without the condition.

Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder, characterized mainly by chronic inflammation state and recurrent abdominal pain. Based on 55 studies included in a meta-analysis involving 83330 women, the pooled IBS prevalence according to female gender was 14% (95% CI, 11.0%–16.0%)[1]. There is no invasive diagnostic test for IBS: the diagnosis is based on the presence of symptoms. Classical symptoms of IBS are abdominal pain and discomfort with changes in bowel habits in the absence of organic disease. A panel of international experts in the field of functional gastrointestinal disorders has developed the Rome criteria with subsequent several revisions in order to obtain a useful common criterion to clinically diagnose IBS[2].

Endometriosis is a chronic inflammatory disease characterized by the presence of endometrium tissue outside the uterine cavity. Symptoms typically include abdominal pain, dysmenorrhea and dyspareunia and can significantly compromised the quality of life of affected women. The pathogenesis of endometriosis is clearly defined not yet, but endometriosis is considered a multifactorial disorder where chronic inflammation is created and maintained by multiple factors, where secretion of cytokines and increased mast cells number play a role[3].

As consequence of sharing of symptoms and of chronic inflammation, endometriosis and IBS may coexist and be misdiagnosed, even among experienced gynecologists and this leads to delays in diagnosis, mismanagement, and unnecessary testing.

In recent years, some studies have found higher risk of IBS in women with endometriosis, compared to women without endometriosis[4,5,6]. To provide a general overview of available evidence about the relation between endometriosis and IBS we performed a systematic review and a meta-analysis on published data on this issue.

Methods

A systematic literature search was performed using the electronic databases MEDLINE and EMBASE from 1990 to November 2019. The search terms “endometriosis” and “irritable bowel syndrome” were used as a combination of free text and as Medical Subject Heading (MeSH) terms. Two authors (F.C. and S.C.) reviewed the papers and independently selected the articles eligible for the systematic review and discrepancies were resolved by discussion. Furthermore, they reviewed reference lists of the retrieved papers to identify any potential additional studies that could be included. If multiple published reports from the same study were available, only the one

with the most detailed information was included. Studies were selected for the review if they met all of the following criteria:

- study reporting original data;
- diagnosis of endometriosis and IBS was defined;
- estimates of the association between IBS and endometriosis or number or percentage of subjects with endometriosis and with or without IBS diagnosis;
- full-length articles, published in English.

For each study, the following information was collected: first author's last name; year of publication; country of origin; study design; number of subjects; age, if available; relative risks (RR), hazard ratios or odds ratios (OR) of endometriosis and corresponding 95% confidence intervals (CI) for IBS or frequency distribution to calculate them; covariates adjusted in the statistical analysis.

We combined the OR estimates from each study and computed unadjusted OR from the exposure distributions of cases and controls as reported in the publications when adjusted estimates were not available. We obtained the summary estimates of the OR for IBS in patients with endometriosis versus patients without, using the random-effect models. Sensitivity analysis was also performed.

We assessed the heterogeneity among studies using the $\chi 2$ test[7] and quantified it using the I2 statistic, which represents the percentage of the total variation across studies that is attributable to heterogeneity rather than chance[8]. Results were defined as heterogeneous for P values less than 0.10[7].

Information on the methodological quality of included studies was assessed based on the Methodological Index for Non-Randomised Studies (MINORS), a validated instrument that is designed for assessment of methodological quality of non-randomized studies[9]. Briefly, for non comparative studies, it uses eight pre-defined items and the maximum score is 16. For comparative studies, the global ideal score is 24, based on 12 items.

All analyses were performed using Review Manager (RevMan; computer program, version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2014).

Results

Fig.1 shows PRISMA flow diagram of the literature search and selection process: 298 records identified through Medline/Embase database searching, after duplicates removed, were reviewed.

After the exclusion of 272 records, 26 articles were fully reviewed and a total of 11 studies were identified for the current study.

The main methodological characteristics of identified papers are presented in Table 1: we selected two prospective studies[10,11], two retrospective cohort studies[5,12], four case-control studies[4,6,13,14], one cross-sectional studies[15] and two clinical series, consecutive women underwent laparoscopy[16] and consecutive women referred to IBS center[17]. Two studies were conducted in the USA, two in the UK, three in Europe (Netherlands, Denmark and Sweden), one in New Zealand, one in Australia, one in Taiwan and one in Egypt.

Frequency (prevalence) of IBS in women with endometriosis without comparison group

Three studies have considered the frequency of IBS in clincal data of women with endometriosis.

In a Canadian cohort of 373 women with endometriosis, 52% had a diagnosis of IBS according to the Rome III criteria and women with a history of minimal-mild endometriosis had more severe IBS symptoms compared with women with a history of moderate-severe endometriosis[11].

In a prospective study, in 98 women with endometriosis laparoscopically confirmed, 15 women also had IBS, diagnosed with Rome III criteria[10]. In a series of 290 women with a diagnosis of endometriosis confirmed on histology, 60 (20.7%) women had previously been diagnosed with IBS, but it was not specified the criteria used for the IBS diagnosis[16].

Frequency (prevalence) of IBS in women with endometriosis compared to women without endometriosis

Three case-control studies and one cross-sectional study[4,6,14,15] reported the prevalence of IBS in women with and without endometriosis.

In a British national case-control study (data retrieved from the General Practice Research Database) the risk of IBS diagnosis was 2.6 (95% CI: 2.3-3.0) when compared to the controls[4].

In a smaller British case-control study on visceral hypersensitivity, in 40 patients with laparoscopically confirmed endometriosis, 60% had Rome III positive, compared to 0% in women without endometriosis[14]. In Sweden case-control study, IBS had shown to be associated with endometriosis and the adjusted OR was 2.58 (95% CI: 1.01-6.63)[6].

In the Danish cross-sectional study, 59.8% of women with endometriosis had IBS diagnosis based on the Rome III diagnostic criteria, compared to 28.4% of women without endometriosis. When the analysis was restricted to women without bowel involved endometriosis the proportion of IBS

(ROME III diagnostic criteria) was higher in women with endometriosis, compared to women without endometriosis (OR 5.16, 95%CI 2.58-10.30)[15].

In the random effects model of the meta-analysis, the overall OR (95%CI) of IBS in women with endometriosis, compared to women without endometriosis was 3.26 (1.97-5.39) with no statistically significant heterogeneity. When, in sensitivity analysis, study of Issa et al. [14] was excluded, the overall OR remained 2.72 (2.24-3.31) (Fig 2).

Diagnosis (incidence) of IBS in women with previous diagnosis of endometriosis.

Three studies have considered the incidence of IBS in women with a previous diagnosis of endometriosis.

In the British national case-control study, when the analysis was restricted to women with IBS diagnosis after the earliest date of endometriosis diagnosis and without a previous IBS diagnosis, endometriosis was associated to IBS (OR 2.5 - 95% CI: 2.2-2.8)[4].

In a retrospective study, based on a cohort from National Health Insurance in Taiwan, the hazard ratio of IBS diagnosis was 1.94 fold (95%CI 1.68-2.25) higher for patients with endometriosis than for patients without endometriosis. After adjustment for urbanization level, monthly income, residential region and comorbidities, the hazard ratio within the 5 years follow-up period was 1.79 times (95% CI 1.55-2.07) greater among women with endometriosis than the comparison patients[5].

In American cohort of women[12], where the data were extracted from a database of insurance claims, cases were women with clinical diagnoses of endometriosis (recorded using codes from the International Classification of Diseases, ICD9) on 2 or more outpatient claims or 1 or more inpatient claim, whereas controls patients had no claims with an endometriosis diagnosis during the same 2006-2015 period: the hazard ratio for developing IBD among endometriosis patients compared to controls was 3.4 (95% CI 3.0-3.8). When cases were restricted to women with laparoscopically confirmed endometriosis, the adjusted hazard ratio was 2.9 (95% CI 2.5-3.5). Having only data expressed as hazard ratio, we can not include this study in the meta-analysis.

In the random effects model of the meta-analysis, the summary OR from two studies[4,5] of incidence of IBS subsequent endometriosis diagnosis was 2.11 (95% CI 1.83-2.43), compared to women without endometriosis, with no statistically significant heterogeneity (data not shown).

History of IBS in women with endometriosis.

Three studies have investigated the presence of a history of IBS in women with a diagnosis of endometriosis. In the previous quote British national case-control study, when the analyses included only women with an IBS diagnosis referred to the period before the first diagnosis of endometriosis, the OR for IBS in women with endometriosis was 3.5 (95% CI 3.1-3.9), compared to women without the condition[4].

In the Danish cross-sectional study, the OR of having a history of IBS in women with endometriosis (adjusted for age, education and gastroenterological comorbidity), was 4.48 (95%CI 1.81-11.06), compared to women without endometriosis[15].

In Egyptian case-control study, significantly higher proportion of women with endometriosis than controls (29.1% vs 16.6%, P <.01) reported a history of IBS[13].

In the random effects model of the meta-analysis, the overall OR of history of IBS in women with endometriosis was 3.10 (95% CI 2.06-4.67), with no heterogeneity between studies (Fig 3).

Frequency of concurrent endometriosis in women with IBS

A retrospective analysis of 160 women with a confirmed diagnosis of IBS (Rome III positive) attending a specialist IBS service in New Zealand, 59 (37%) were found to have reported a history or recent diagnosis of endometriosis[17].

Discussion

The present meta-analysis confirms evidence of the association between IBS and endometriosis, analyzed as prevalence, incidence and history of IBS in women with endometriosis: the frequency of IBS was higher in women with endometriosis compared to women without endometriosis in all studies where this comparison was analyzed[4-6,12-15], also though with different percentage values, even comparing the values within the same type of studies.

Few data are available in the relation between severity and site of endometriosis and IBS, but the Canadian study reported higher IBS severity score in women with a history of minimal to mild endometriosis, compared with women with moderate to severe disease[11].

Potential bias should be considered. There are no specific tests for IBS[2]. The diagnosis is mainly based on the presence of symptoms. The development of ROME criteria has produced an internationally recognized diagnostic criterion, but not all of the studies used this diagnostic tool[2,18]. Moreover, using data from public databases (for instance, data from Insurance claims) the

prevalence of IBS could be underestimated. As regards endometriosis, the gold standard for diagnosis is based on laparoscopy, but due to its invasiveness, in the clinical practice is limited to selected patients, thus not all of the studies reported histologically confirmed diagnosis of endometriosis.

Another limitation could be that not all of the studies distinguish the location of the endometriotic tissue, but the Danish study reported an increased risk of IBS still present even when women with bowel endometriosis were excluded from the analyses[15].

Because the symptoms overlap, there is a risk of misdiagnosis between the two conditions. In fact, it is conceivable that in women with endometriosis the diagnosis of IBS can be less probable due to misclassification of symptoms and consequently give an underestimate of the association. Otherwise, it is possible that physicians, awarded about the association between endometriosis and IBS, may search more carefully IBS in women with endometriosis and vice versa. This kind of bias should tent to overestimate the association. Thus this potential diagnostic bias should be considered in the interpretation of the association between IBS and endometriosis.

Furthermore, given the use of observational data, we can not establish whether the association between endometriosis and IBS is causal and in several published studies the information on the temporal sequence of these pathologies is lacking. In the two studies that have considered the incidence of IBS[4,5], women with endometriosis are more likely to have a subsequent diagnosis of IBS then women without endometriosis, but this association should be interpreted with caution with regards to causality.

The association between endometriosis and IBS could be the result of shared risk and pathogenic factors, such as chronic inflammatory process and increased presence of mast cells[19,20]. The research on inflammation in endometriosis almost completely mirrors that observed in IBS. The activation of mast cells and their degranulation, with subsequent release of lymphokines, tumor necrosis factor-α in the interstitial tissue, has been reported in both conditions[21]. The presence of pro-inflammatory cytokines promotes the persistence of a situation of chronic inflammation. Considering the pathophysiological mechanism common to both IBS and endometriosis, in presence of severe pelvic pain, the possible diagnosis of these two pathologies needs to be investigated.

Despite these limitations, this meta-analysis provides epidemiological evidence of a link between endometriosis and IBS, highlighting two or more times higher risk of IBS in women with endometriosis compared to women without the condition.

Figure 1. PRISMA flow diagram of the literature search and selection process.

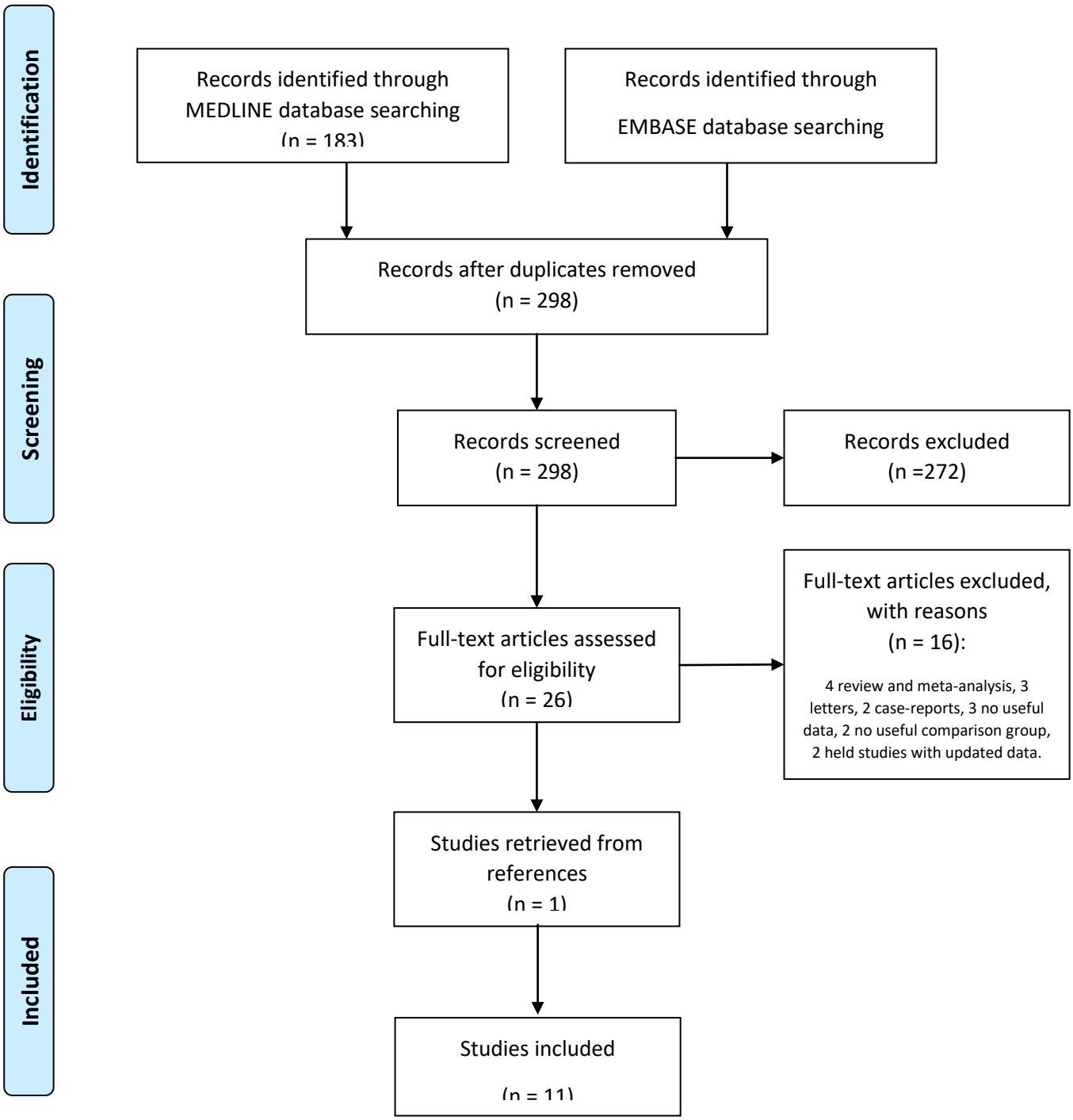

Figure 2. Study specific and summary OR of IBS prevalence in women with endometriosis compared with controls

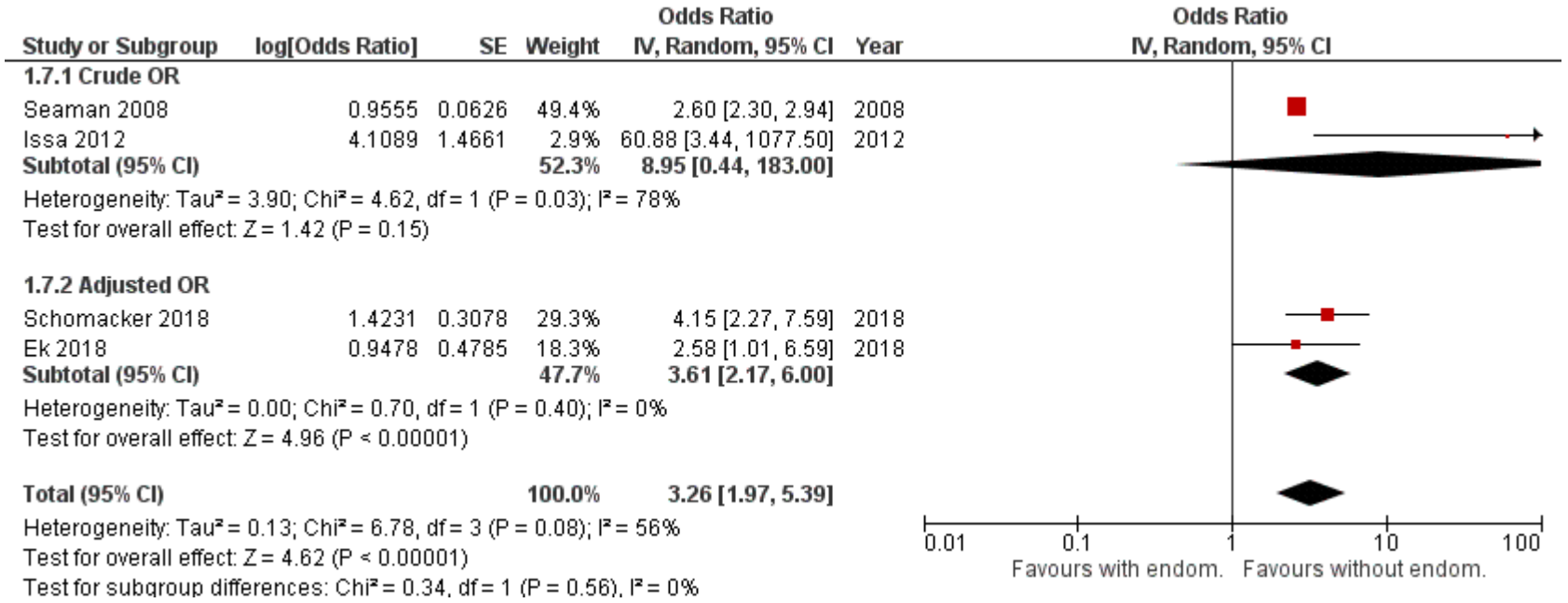

Figure 3. Study specific and summary OR of history of IBS in women with endometriosis compared with controls

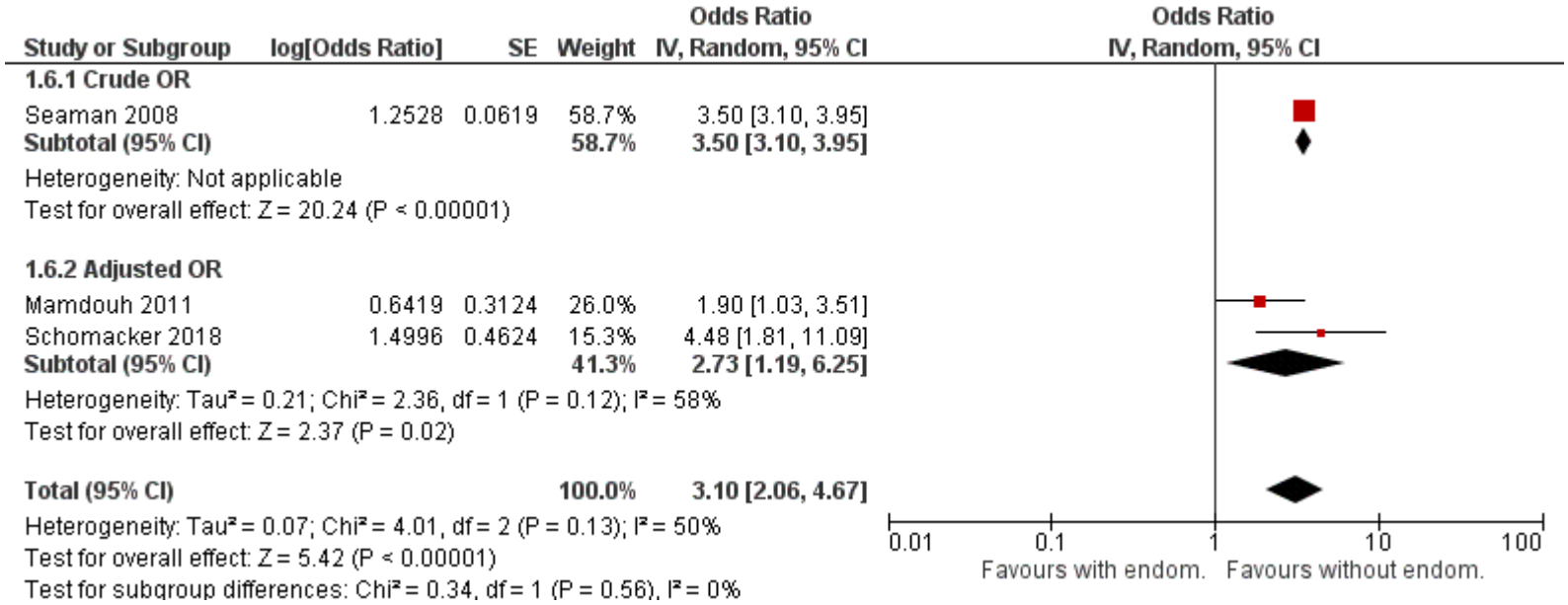

Table 1. Characteristic of the selected studies on the association of Irritable Bowel Syndrome (IBS) and endometriosis

Author, Year	**Year of recruitment**	**Country**	**Study design**	**Endometriosis diagnosis**	**IBS diagnosis**	**No. of patients with endometriosis**	**Age and/or range (y)**	**No. of patients controls**	**Age** mean range (y)	**MINORS score**
Seaman et al. 2008	1992-2001	UK	national case-control study†	code for endometriosis	clinical symptoms + IBS specific drugs (antispamodic, antimotility and laxative)	5540	15-55	21239	15-55	18
Maroun et al., 2009	2000-2004	Australia	consecutive women underwent laparoscopy	suspected endometriosis	the diagnostic criteria were not specified	290	(16-54) 31,1 ±7,4			11
Meurs-Szojda et al.,2010	2006-2007	Netherlands	prospective study	confirmed endometriosis	ROME III	98	34 (22-51)	15[#]		10
Mamdouh et al., 2011	2005-2007	Egypt	case-control study	endometriosis laparoscopically confirmed	the diagnostic criteria were not specified	110	27.9 ± 6.8 (16-43)	220	27.4 ± 6.4 (16-43)	17
Issa et al., 2012		UK	case-control study	endometriosis laparoscopically confirmed	ROME III	40	19-48	24	34.3 (20-54)	16
WU et al., 2015	2000-2005	Taiwan	retrospective population based cohort study (from National Health Insurance Programme)	ICD-9 codes: 617.X at least twice in the same years and assigned by a gynaecologist	ICD-9 code:564.1 (after index date*)	6076	25-54	30380	25-54	20
Moore et al.,2017	2009-2013	New Zealand	consecutive women referred to IBS clinic	endometriosis laparoscopically confirmed	ROME III	59[#]	28 (16-65)	101	38 (13-84)	14

Lee et al., 2018	2013-2015	Canada	Prospective cohort of women with endometriosis	endometriosis surgically confirmed	ROME III	373	35.0 ± 7.3	194[#]		10
Schomacker et al., 2018		Denmark	cross-sectional study	endometriosis laparoscopically confirmed and/or based on MRI	ROME III and prior diagnosis	254	38.8	102	37.9	17
Surrey et al.,2018	2006-2015	USA	Retrospective cohort study (from Insurance claims database)	ICD-9 codes: 617.X on ≥1 inpatient or ≥2 outpatient claims. Laparoscopically confirmed		24564	36.4±8.4 (18-49)	6141	36.5±8.2 (18-49)	18
EK et al., 2018	2013-2017	Sweden	case-control study	ICD-10 N80 confirmed by laparotomy or laparoscopy	IBS diagnosed by a physician. VAS-IBS	172	38 (32-43)	117	42 (28-52)	15

†: data from UK General Practice Research Database (GPRD)

* The index date was defined as the earliest date of endometriosis diagnosis

patients with concurrent IBS and endometriosis

MRI: Magnetic Resonance Imaging

VAS-IBS: Visual Analogue Scale for Irritable Bowel Syndrome

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