

Review Article

The association between BMI and risk of endometriosis-a meta-analysis

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Abstract: Objective: The objective of this meta-analysis was to systematically assess the association between BMI and endometriosis. Methods: Relevant studies were identified through searching PubMed, Embase and Cochrane databases before August 2014. A random-effects model was derived to composite the pooled HR or OR. Results: 13 articles included in the final meta-analysis. When considering BMI as a continuous variable, pooled analysis indicated the risk of endometriosis was inversely associated with BMI (OR=0.95, 95% CI: 0.92-0.98), but a significant heterogeneity was observed. When excluded one study with HR, the heterogeneity of pooled OR decreased. When considering BMI as a category variable, the pooled analysis presented an OR of 0.61 (95% CI 0.44 to 0.85). In subgroup with a BMI cutoff value from 21 to 23, the heterogeneity decreased to 0.0%. Conclusion: Our subgroup analysis indicated that the risk of endometriosis seems to be inversely associated with BMI. But the precise relationship needs further verification research in the future.

Keywords: BMI, endometriosis, meta-analysis, HR (Hazard Ratio), OR (Oddis Ratio)

Introduction

Endometriosis has been clinically recognized since 1860 [1]. The prevalence of endometriosis has been estimated to affect 10% to 15% of women of reproductive age [2, 3], and 35% to 50% of women with pelvic pain, infertility, or both [4]. Overweight or obesity is a big burden for public health in developed nations including Europe and America and tendency is increasing in developing nations. Obesity is known to be associated with increased risks of high blood pressure, heart disease [5], osteoarthritis [6], type 2 diabetes [7] and cancers [8, 9]. Studies have described the relation between body mass index (BMI) and endometriosis in women. Darrow SL et al. [10] found no significant differences in the BMI among women with endometriosis and control subjects. Similar results were reported by other authors [11-13]. These studies are in contrast with those of Grodstein, F., Vouk, K. and Signorello, L. B. who found that the risk of endometriosis is inversely associated with BMI [14-16]. Based on the lack of conclusive information on BMI and endometriosis, this systematic review and meta-analysis focu-

sed on the evaluation of the possible association of BMI with endometriosis.

Methods

Data sources and searches

We performed a systematic search for publications using Medline (1966-2014), Embase (from 1988) and the Cochrane Library. Search strategies used subject headings and key words ("endometriosis" AND ("body mass index" OR "BMI")). Further information was retrieved through a manual search of references from recent reviews and relevant published original studies. The latest search was performed on 30 August 2014.

Selection criteria

First, two reviewers primarily examined the titles and abstracts of all the literatures. Then, the full text articles were screened separately by two reviewers to determine whether they met the inclusion criteria. We contacted the corresponding authors when the crucial data were not reported in the original papers. Articles

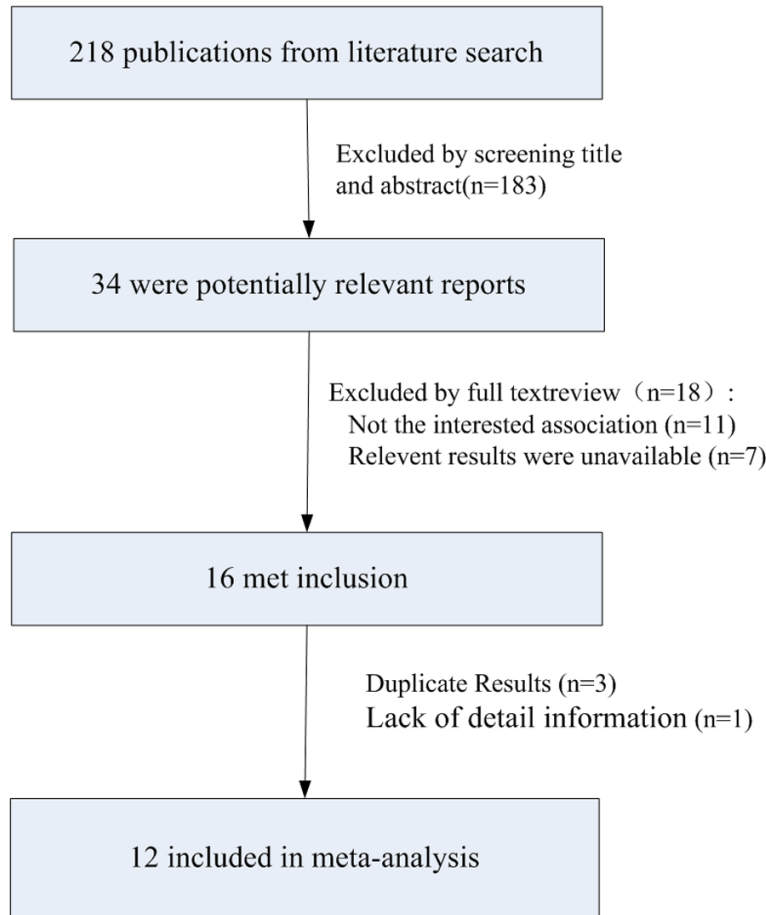


Figure 1. Flow chart for selecting article.

were independently read and selected according to the inclusion criteria. Disagreements were resolved through the consensus with a third reviewer.

Inclusion criteria

① An original article published from January 1966 to August 2014; ② A case-control or cohort or cross-sectional population study; ③ Determine the relationship between BMI and endometriosis; ④ Including OR (odds ratio) or HR (hazard ratio), 95% CIs (confidence intervals), or relevant data that could be used to calculate the OR or HR and 95% CI.

Exclusion criteria: ① Non-English; ② Letters, reviews, case reports, conference abstracts, editorials, expert opinion, non-English.

Data extraction

From the identified studies and respective populations, we recorded first author's names, year

of publication, study design, number of case and control patients, effect sizes (95% CI) and BMI category. The adjusted results were extracted when adjusted results and non-adjusted results were showed in same article.

Meta-analysis

All pooled outcome measures were determined using a random effects model as described by DerSimonian and Laird [17] and the OR was estimated with its variance and 95% CI. The random effects analysis weighted the natural logarithm of each study's OR by the inverse of its variance plus an estimate of the between-study variance in the presence of between study heterogeneity. Heterogeneity between ORs for the same outcome between different studies was assessed. This was through the use of the I^2 inconsistency test and Chi-square-based Cochran's Q statistic test [18] in which $P < 0.05$ is taken to indicate

the presence of significant heterogeneity. In the subgroup analysis in studies considering BMI as a category variable, Cutoff 1 represented the cutoff value of BMI is 21/22/23, Cutoff 2 represented the cutoff value of BMI is 25. Analyses were conducted using Stata 12.0 (Stata Corporation, TX, USA).

Results

Description of the included studies

Our systematic literature search identified 218 publications for eligibility, 34 of which were potentially relevant reports for further review by title and abstract. After excluding 18 papers, a total of 16 articles met the inclusion criteria. Two articles [19, 20] reported the same study, thus one data was used in final meta-analysis. Three articles [12, 21, 22] reported the same study (Nurse's Health Study), one article was used in final analysis. One study [23] excluded by lack of detail information. Thus, 12 articles included in the final meta-analysis (**Figure 1**).

BMI and risk of endometriosis

Table 1. The characteristic of included studies (continuous)

ID	Year	Study	Sample size	OR/RR	LL	UU	Adjusted	Effect size	Location	Outcome/Case	Quality score*
Signorello (fertile) [16]	1997	Case-control	149	0.7	0.4	1.1	Yes	OR	USA	Endometriosis	7
Signorello (infertile) [16]	1997	Case-control	97	0.8	0.5	1.2	Yes	OR	USA	Endometriosis	7
Hediger, M. L. [25]	2005	Cohort	83	0.88	0.79	0.99	Yes	OR	USA	Endometriosis	8
Peterson (O) [27]	2013	Case-control	473	0.95	0.93	0.98	Yes	OR	USA	Endometriosis	8
Peterson (P) [27]	2013	Cohort	127	1.01	0.93	1.09	Yes	OR	USA	Endometriosis	8
Andolf, E. [26]	2013	Cohort	709090	0.98	0.97	0.99	Yes	HR	Sweden	Endometriosis	8
Moini, A. [28]	2013	Case-control	520	0.897	0.844	0.953	Yes	OR	Tehran	Pelvic endometriosis	7

*: The quality was assessed using NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE.

Table 2. The characteristic of included studies (category)

ID	Year	Study	Sample size	Case _high	Control _high	Case _low	Control _low	Case	Location	Cutoff value	Quality score
Vercellini, P. (RE) [13]	2013	Case-control	200	34	39	66	61	Deep endometriosis	Italy	22	7
Vercellini, P. (PE) [13]	2013	Case-control	200	31	39	69	61	Peritoneal and/or ovarian endometriosis	Italy	22	7
Shah, D. K. [12]	2013	Case-control	1040	162	284	186	408	Endometriosis	USA	25	8
Vouk, K. [15]	2012	Case-control	91	3	28	37	23	Ovarian endometriosis	Slovenia	25	7
Louis, G. M. (O) [19]	2012	Case-control	465	81	181	105	98	Endometriosis	USA	25	8
Louis, G. M. (P) [19]	2012	Case-control	123	7	57	7	52	Endometriosis	USA	25	8
Ferrero, S. [11]	2005	Case-control	602	39	34	327	202	Endometriosis	Italy	25	6
Grodstein, F. [14]	1993	Case-control	4013	23	900	157	2933	Endometriosis	USA	23	6
Parazzini, F. (D) [24]	2008	Case-control	507	82	197	98	130	Deep endometriosis	Italy	21	6
Parazzini, F. (O) [24]	2008	Case-control	489	81	197	81	130	Ovarian endometriosis	Italy	21	6

*: The quality was assessed using NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE.

The characteristic of included studies were shown in **Tables 1, 2**. 7 studies [11-15, 19, 24] (including 7730 subjects) investigated the association between BMI and endometriosis, considering BMI as a category variable; 5 studies [16, 25-28] (including 710539 subjects) investigated the association considering BMI as a continuous variable. 9 of including studies were case-control design [11-16, 19, 24, 28], the rest 3 studies were cohort design [25-27]. All the including studies were conducted in Europe and USA, no one was conducted in Asia.

The association between BMI and endometriosis (continuous)

6 studies investigated the association of endometriosis with BMI, considering BMI as a continuous variable (**Figure 2A**). The overall meta-analysis results indicated that the risk of endometriosis was inversely associated with BMI (OR=0.95, 95% CI: 0.92-0.98), but showed significant heterogeneity ($I^2=67.1\%$, $P=0.006$). When excluded one study with HR [26], the heterogeneity of pooled OR decreased for the association (OR=0.93, 95% CI: 0.89-0.98; $I^2=45.1\%$, $P=0.105$) (**Figure 2B**).

The association between BMI and endometriosis (category)

When considering BMI as a category variable, the pooled analysis presented an OR of 0.61 (95% CI 0.44 to 0.85) with significant heterogeneity ($I^2=79.5\%$, $P<0.001$) (**Figure 3A**). After stratified by different BMI cutoff values, in Cutoff 1 subgroup (BMI cutoff value from 21 to 23), the pooled OR was 0.61 (95% CI 0.50 to 0.74), without significant heterogeneity ($I^2=0.0\%$, $P=0.603$). But the significant association was not observed among Cutoff 2 group (BMI cutoff value is 25) (**Figure 3B**).

Publication bias

No publication bias was observed in studies assessed the association between BMI and endometriosis (continuous: Begg's $P=0.881$, Egger's $P=0.075$; category: Begg's $P=0.858$, Egger's $P=0.108$).

Discussion

Our meta-analysis investigated the association of BMI with endometriosis. Results of 11 studies with OR indicated that the risk of endometriosis was inversely associated with BMI.

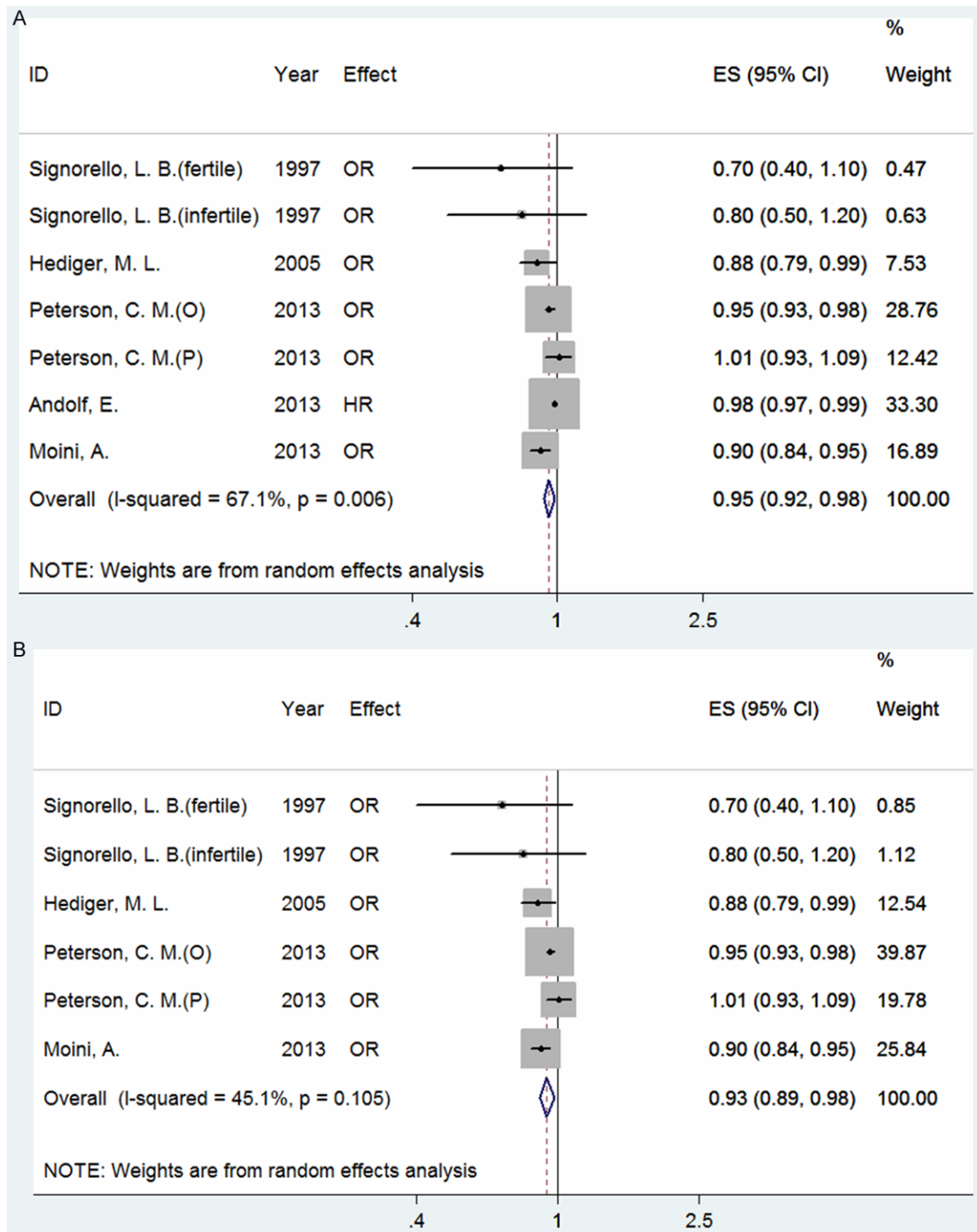


Figure 2. A: The association between BMI and endometriosis. BMI was considered as a continuous variable; overall analysis of ORs and HRs. B: The association between BMI and endometriosis. BMI was considered as a continuous variable; overall analysis of ORs.

The reason for the inverse association between BMI and endometriosis is still unclear and has not found generally agreed scientific explanation. One possible reason may be the important

role of leptin in both obesity and endometriosis. It has been showed that patients with endometriosis have significantly higher peritoneal fluid leptin concentrations, a difference that

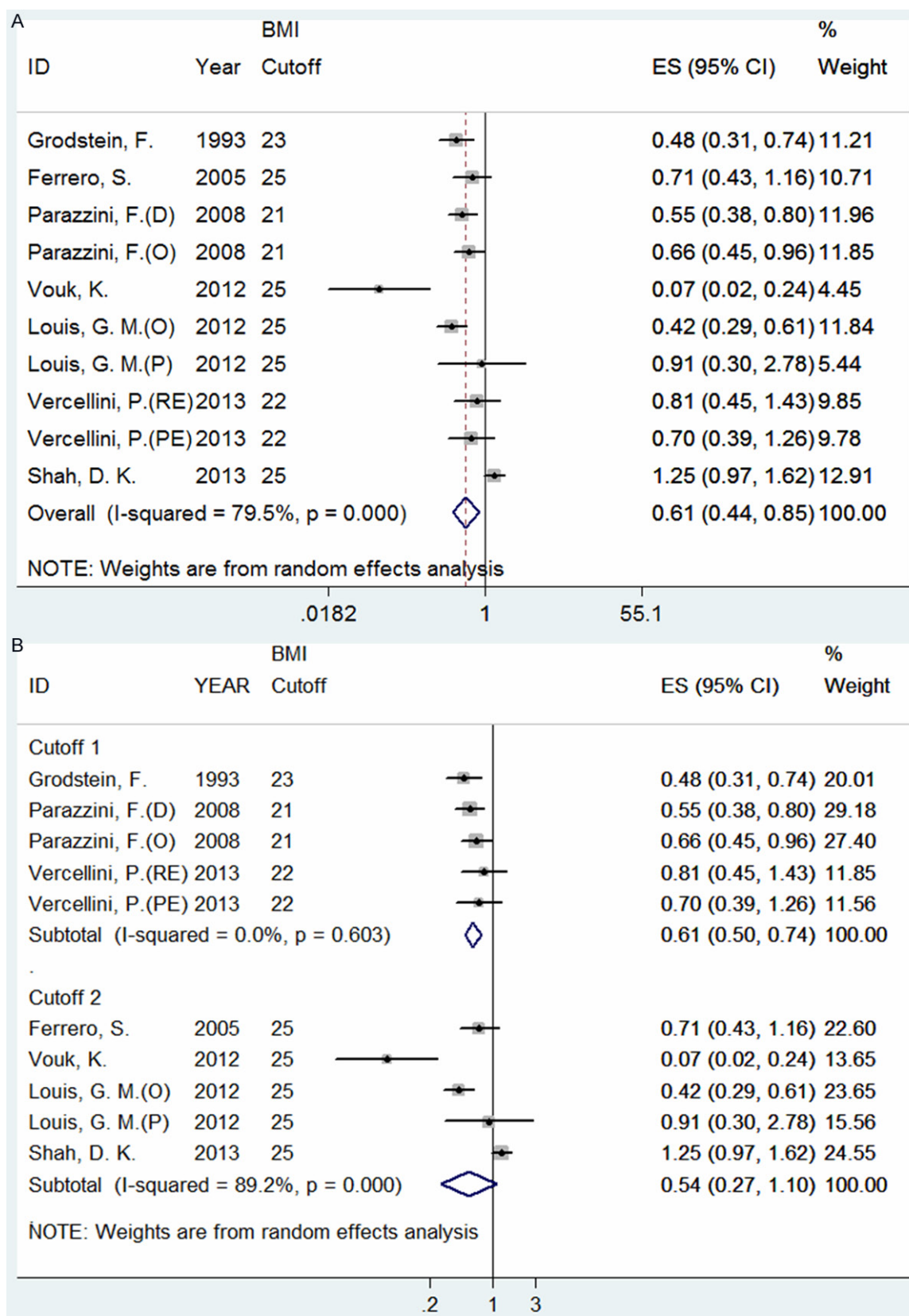


Figure 3. A: The association between BMI and endometriosis. BMI was considered as a category variable; overall analysis of all BMI cut-off values. B: The subgroup analysis of association between BMI and endometriosis. BMI was considered as a category variable; Cutoff 1 subgroup: BMI cutoff value range from 21 to 23; Cutoff 2 subgroup: BMI cutoff value is 25.

remained significant when corrected for BMI [29-32]. Further, leptin has been shown to influence the formation of endometriosis by different pathways [33, 34]. Another potential explanation may be the fact that an anovulatory and irregular menstrual cycle secondary to high estrogen level in obese women can lead to a reduction in retrograde bleeding [28]. Additionally, genetic factors that are linked to endometriosis could also affect the metabolic determinant of weight [35]. It can be hypothesized that genetic factors determining endometriosis could also impact on, or be associated with those impacting on, BMI [23].

The results of studies considering BMI as a continuous variable were homogenous, but those of studies considering BMI as a category variable were heterogeneous. The source of heterogeneity was due to the different cutoff values of BMI. In subgroup with a BMI cutoff value from 21 to 23, the heterogeneity decreased to 0.0%. However, the significant association was not observed among subgroup with a BMI cutoff value of 25. This may be due to the high heterogeneity between articles.

Our analysis pooled 12 articles including large number of samples, and indicated a inverse correlation between BMI and endometriosis. This may be important for risk assessment of endometriosis in prevention; however, the current analysis is restricted by several limitations. First, we could not assess the effect of confounding variables, such as detail types of endometriosis, infertility or not. Second, the strategy of selection of published studies in English only could bring about possible publication bias. Third, our search was restricted to published articles, which could also cause potential bias to affect our findings. Fourth, the available studies involved in the current analysis were mostly observational studies, which are vulnerable to selection bias, information bias and confounding. Thus, inadequate control of the confounders might lead to exaggeration or underestimation of the association.

Conclusion

We conducted a detailed meta-analysis for summarized HR or OR estimates from researches focused on the association between BMI and endometriosis risk. Our subgroup results indicated that the risk of endometriosis was

inversely associated with BMI. The exact relationship needs further verification research in the future.

Disclosure of conflict of interest

I certify that all my affiliations with or financial involvement in, within the past 5 years and foreseeable future, any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript are completely disclosed (e.g. employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, royalties).

Abbreviations

BMI, Body mass index; HR, Hazard Ratio; OR, Odds Ratio; 95% CI, 95% confidence interval.

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