

BMJ Open Is body mass index associated with the incidence of endometriosis and the severity of dysmenorrhoea: a case-control study in China?

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ABSTRACT

Objective Endometriosis is considered as a serious gynaecological disease in women at a reproductive age. Lower body mass index (BMI) is thought to be a risk factor. However, recent studies indicated that women with normal BMI were also more likely to develop endometriosis, suggesting the association with BMI is controversial. We therefore investigated the association of BMI and surgically diagnosed endometriosis in a cohort of Chinese women.

Design Retrospective case-control study.

Setting Tertiary hospital.

Patients 709 women with endometriosis and 807 age matched controls between January 2018 and August 2019.

Intervention Age at diagnosis, parity, gravida, BMI and self-reported dysmenorrhoea status were collected and the association of BMI and endometriosis was analysed.

Measurement and main results Overall, the median BMI was not different between patients and controls (21.1 kg/m² vs 20.9 kg/m², $p=0.223$). According to the BMI categories for Asians/Chinese by WHO (underweight: <18.5 kg/m², normal weight: 18.5–22.99 kg/m², overweight: 23–27.49 kg/m², obese: ≥27.50 kg/m²), overall, there was no difference in the association of BMI and endometriosis ($p=0.112$). 60% of patients were of normal weight. However, the OR of obese patients (BMI over 27.50 kg/m²) having endometriosis was 1.979 (95% CI 1.15 to 3.52, $p=0.0185$), compared with women with normal weight. 50.3% patients reported dysmenorrhoea, and the OR of developing severe dysmenorrhoea in obese patients (BMI over 27.50 kg/m²) was 3.64 (95% CI 1.195 to 10.15, $p=0.025$), compared with patients with normal weight.

Conclusion Our data demonstrate that overall there was no association between BMI and the incidence of endometriosis, but there was a significant increase in the incidence of endometriosis in obese women, compared with women with normal weight. Obesity was also a risk factor for severe dysmenorrhoea.

INTRODUCTION

Endometriosis is relatively common and may be considered a serious and chronic gynaecological disease in women of reproductive age. The symptoms usually associated with this

Strengths and limitations of this study

- Endometriosis reported in this study was surgically confirmed, not self-reported.
- Body mass index (BMI) was collected at the time of diagnosis with endometriosis.
- The sample size of this study is relatively large; however, the sample size in subgroup analysis is small.
- Dysmenorrhoea status was self-reported and regional differences may result in a bias as Shanghai has better medical care system.

disease are excessive menstrual bleeding, and dysmenorrhoea (painful during menstrual cycle) and chronic or severe pelvic pain, dyspareunia and an increased infertility rate. Although the presence of endometriosis is increasingly being suggested by pelvic ultrasound or MRI,¹ ultrasound or MRI still have some limitations on diagnosis of endometriotic lesions.² The definitive diagnosis is made at surgery and by histology of tissue excised or biopsied with the presence of endometrial glands and stroma.

The incidence of endometriosis is reported to vary by ethnicity.³ In addition, approximately 25% of women with endometriosis do not have any clinical symptoms,⁴ resulting in a reduced effort to examine the clinical presentation of endometriosis in various ethnicities. Pelvic pain during an individual women's menstrual cycle may also not consider serious enough by the woman to seek medical attention. Access to medical care may also be limited in some circumstances such that the time of diagnosis of endometriosis also becomes associated with the ability to access medical assistance. Studies reported that the average length of delay in diagnosis of endometriosis was 6–10 years, dependent on ethnic group,^{5 6} but the shortest length of delay in diagnosis was reported in a Chinese

population.⁷ In addition, although most diagnoses of endometriosis are in women aged 25–39 years,^{6,8} the age distribution of diagnoses was also dependent on ethnic group, socioeconomic and cultural factors.³

A number of epidemiological studies reported that women with endometriosis normally have a lower body mass index (BMI)^{9,10} or are underweight.^{11,12} However, a recent case–control study done in Australia found that women with a normal BMI were also more likely to experience endometriosis, compared with women with underweight.¹³ That study reported 56% or 25.2% or 14.3% of women with endometriosis at diagnosis were at normal weight or overweight or obese, respectively and only 4.5% of women with endometriosis were underweight.¹³ The differences in the inverse association of BMI and endometriosis between Australia's study and other studies could be explained by differences in the study populations. The diagnosis of endometriosis reported in the study from Australia was surgically confirmed, while endometriosis in most previous population-based studies was self-reported. These differences in reporting the incidence are likely due to how the diagnosis is made and have the potential to introduce a bias in describing demographic associations.¹⁴ A study of young people reported that being overweight in childhood or late adolescence (above 10 years) increased the risk of having endometriosis, suggesting a positive association between BMI and endometriosis.¹⁵ Dysmenorrhoea is one of the main clinical symptoms of endometriosis. Some studies have found a higher rate of severe dysmenorrhoea in obese women.^{13,16} Therefore, it is apparent that the inverse association of lower BMI and endometriosis is unclear.

The WHO classification of BMI for Asians/Chinese is different from other ethnic groups and shows that 10%–12% of Chinese women are underweight (BMI under 18.4 kg/m²), 70% are normal weight (BMI between 18.5 and 22.99 kg/m²), 10%–15% are overweight (BMI between 23 and 27.49 kg/m²) and only 2%–3% are obese (BMI over 27.50 kg/m²).¹⁷ In this retrospective case–control study, we investigated the association between BMI and endometriosis which was surgically diagnosed in a relatively large group of Chinese women. In addition, we also investigated whether BMI is associated with the severity of dysmenorrhoea in women having endometriosis.

METHODS

Patient and public involvement

There was no direct patient and public involvement in this study.

Study population

In this retrospective study, 709 women who were diagnosed with endometriosis by surgery from January 2018 to August 2019 were included from the Yangpu Campus of The Hospital of Obstetrics and Gynaecology, Fudan University of China. In addition, 807 age matched

controls were randomly selected from women who underwent a routine health examination from the same hospital over the same time period. All controls had no history of suggestive of endometriosis (self-reported). Age at diagnosis of endometriosis, parity, gravida, mode of previous delivery (if relevant), BMI and self-reported dysmenorrhoea status by visual analogue scale (VAS) were collected from the hospital electronic-based medical records of the participants. The hospital is the largest tertiary hospital specialising in obstetrics and gynaecology in the region, serving a diverse urban and rural population in Shanghai, the largest and wealthiest city in China with a population of 20 million.

Endometriosis was diagnosed by a physical pelvic examination and transvaginal ultrasound or MRI and was confirmed by histology with the presence of endometrioid glands and stroma. BMI was calculated as the ratio of maternal weight and height (kg/m²) at diagnosis. According to the WHO classification of BMI for Asians/Chinese women, BMI under 18.4 kg/m², or 18.5–22.99 kg/m², or 23–27.49 kg/m², or over 27.50 kg/m², is underweight, or normal weight, or overweight, or obese, respectively.¹⁷ The degree of dysmenorrhoea in last 2 years was scored by VAS using 10 cm line.¹⁸ 10 represented 'unbearable pain', and 0 represented 'no pain at all'. The scores received from the scale were classified into mild dysmenorrhoea if it was between 1 and 3 points moderate between 4 and 7 points, and severe between 8 and 10 points.

Power of sample size

The sample size calculation was based on the estimated incidence of endometriosis (10%–15%).¹⁹ At least 139 cases were need for a statistical power of 90% for each group to detect a significant difference between two group at a level of 0.05. In this study 709 cases included.

Statistical analysis

Age and BMI at diagnosis, and age at menarche were expressed by median and range. The difference in age at diagnosis or age at menarche between patients without a history of pregnancy and controls without a history of pregnancy was assessed by t-test (non-parametric) using the Prism software package. The difference in use of oral contraceptives was assessed by χ^2 . The OR and 95% CIs for the association of obesity and endometriosis or the association of BMI and the severity of dysmenorrhoea or the association of history of surgical termination and endometriosis was assessed by χ^2 using the Prism software package. $P < 0.05$ was considered as statistically significant.

RESULTS

Clinical characteristics of the study population

The clinical characteristics are summarised in table 1. The median age at diagnosis with endometriosis was 33 (range 18–59) years and the median age for controls was

Table 1 Clinical characteristics of women with endometriosis

	Endometriosis (n=709)	Controls (n=807)	P value
Age at diagnosis (years, median/range)	33 (18–59)	32 (17–59)	0.631
BMI (kg/m ² , median/range)	21.1 (15.2–33.5)	20.9 (15.8–33.6)	0.223
Parity (n, %)	351 (49.5%)	327 (40.5%)	0.0004
p=0	358 (50.5%)	481 (59.5%)	
p≥1			
Gravida (n, %)	305 (43.1%)	209 (26%)	<0.0001
G=0	404 (56.9%)	597 (74%)	
G≥1			
Menstrual cycle length	58 (8.2%)	18 (2.5%)	0.258
≤24 days (n, %)	593 (83.6%)	680 (84.3%)	
25–32 days (n, %)	58 (8.2%)	109 (13.5%)	
≥33 days (n, %)			
Age at menarche (years, median/range)	14 (9–17)	14 (10–17)	0.892
Use of oral contraceptives (n, %)	10 (1.4%)	22 (2.7%)	0.105

BMI, body mass index.

32 (17–59) years. There was no difference in age between two groups (p=0.631).

404 (57%) patients had previous pregnancies, which was significantly lower than that in controls (597, 74%) (table 1, p=0.0004). The OR for having a pregnancy in patients was 0.465 (95% CI 0.379 to 0.572, p<0.0001), compared with controls. Because the average age in patients who did not have a history of pregnancy was significantly higher than controls (30.4±6.2 vs 27.6±5.7, p=0.0001), we then calculated the OR adjusted for age. The adjusted OR for having a pregnancy in women with endometriosis was 0.413 (95% CI 0.325 to 0.524, p<0.0001), compared with controls. In addition, 358 (50.5%) patients had previous live births, which was also significantly lower than that in controls (481, 59.5%) (table 1, p<0.0001).

The median BMI in patients was 21.1 (range from 15.2 to 33.5) kg/m² and in the control group it was 20.9 (range from 15.8 to 33.6) kg/m², showing that there was no overall difference between the two groups (p=0.223). There were 357 (50.3%) patients who reported dysmenorrhoea (VAS score ≥1).

BMI was associated with endometriosis

According to the BMI categories for Asians/Chinese women by WHO (the BMI under 18.4kg/m², or

18.5–22.99kg/m², or 23–27.49kg/m², or over 27.50kg/m² is underweight, or normal weight, or overweight, or obese, respectively), 14.2%, or 60.3%, or 20.6% or 4.9% of patients at the time of diagnosis were underweight or normal weight or overweight or obese (table 2). While in controls, 14.1%, or 62.9%, or 20.4% or 2.6% of women were underweight or normal weight or overweight or obese. Although overall, there was no difference in the association between BMI and endometriosis among the four groups (p=0.112), the OR of obese patients (BMI over 27.50kg/m²) having endometriosis was 1.979 (95% CI 1.15 to 3.52, p=0.0185), compared with patients with normal weight.

BMI was associated with the severity of dysmenorrhoea

Overall, there were 357 (50.3%) patients who reported dysmenorrhoea. Of them, 212 (59.3%) patients had mild, 84 (23.5%) patients had moderate and 61 (17.1%) patients had severe dysmenorrhoea. We then analysed whether BMI is associated with the severity of dysmenorrhoea. There were 6 (37.5%) patients with severe dysmenorrhoea among obese patients (BMI over 27.50kg/m²). When we included patients without dysmenorrhoea, there was no association of BMI with the severity of dysmenorrhoea (p=0.171). However, when we focused on analysing the association of BMI with the severity of dysmenorrhoea

Table 2 Association of body mass index and endometriosis

	Endometriosis (n=709)	Controls (n=807)	OR (95% CI)
Normal weight (n, %)	427 (60.3%)	507 (62.9%)	Reference
Underweight (n, %)	101 (14.2%)	114 (14.1%)	1.05 (0.391 to 1.42)
Overweight (n, %)	146 (20.6%)	165 (20.4%)	1.05 (0.406 to 1.36)
Obese (n, %)	35 (4.9%)	21 (2.6%)	1.979 (1.15 to 3.52)*

**p=0.0185.

Table 3 Association of dysmenorrhoea and body mass index in endometriosis

Dysmenorrhoea (n=357)	Mild or moderate (n=296)	Severe (n=61)	OR (95% CI)
Normal weight (n=205)	176 (85.4%)	29 (14.6%)	Reference
Underweight (n=54)	43 (79.6%)	11 (20.4%)	1.55 (0.68 to 3.37)
Overweight (n=82)	67 (81.7%)	15 (18.3%)	1.35 (0.69 to 2.75)
Obese (n=16)	10 (62.5%)	6 (37.5%)	3.64 (1.20 to 10.15)*

**p=0.025.

in patients with dysmenorrhoea, the OR of having severe dysmenorrhoea in obese patients (BMI over 27.50 kg/m²) was 3.64 (95% CI 1.195 to 10.15, p=0.025), compared with patients with normal weight (table 3). However, there was no statistical difference in OR of having severe dysmenorrhoea between patients who are underweight or overweight and patients with a normal weight (p>0.291).

DISCUSSION

Main findings

In this retrospective and case–control study with a large sample size, we found that overall there was no association between BMI and the incidence of endometriosis. However, using the WHO classification of BMI for Asians/Chinese women (BMI >27.5 kg/m² is obese), we found that obesity significantly increased the risk for having endometriosis in Chinese women, compared with women with normal weight. In addition, we also found obesity was associated with the severity of dysmenorrhoea.

Interpretation

Endometriosis affects women during their reproductive age and is one of the leading causes of pelvic pain and/or dysmenorrhoea. Low BMI has been traditionally reported to be associated with the incidence of endometriosis.¹¹ However, a recent case–control study done in Australia highlighted that the association BMI with the incidence of endometriosis may be more complicated than just a simple inverse association.¹³ In that study, authors found that 56% of women with normal weight, or 25.2% of women with overweight, or 14.3% obese women had endometriosis, and only 4.5% of patients were underweight.¹³ Another recent population-based study with a large sample size reported that more than 50% of patients as having a normal BMI, and only 7.8% of patients were underweight in Israeli women.²⁰ In addition, another recent study found that BMI was not associated with the development of endometriosis in Swedish women.²¹ These studies suggested that women with normal BMI were also more likely to experience endometriosis. In our current case–control study, consist with these recent studies, we also found that overall, there was no statistical difference in the association of BMI and the incidence of endometriosis, according to the BMI categories for Asians/Chinese. The difference in the association of BMI and the incidence of endometriosis between these

recent studies including our current study and previous studies could be because of the time in collection of BMI data. In these recent studies, data on BMI were collected at the time of diagnosis (or interview),^{13 20 21} while in previous studies,^{10 15} data on BMI including controls were collected when women were 10–16 years old or at 18 years. Although the average length of delay in diagnosis of endometriosis is 6–10 years dependent on ethnic groups,^{5 6} studies showed that China has a shortest delay in diagnosis of endometriosis (approximately 3 years).⁷ In addition, childbearing is a potential risk factor for weight gain in women with a history of live births.²² This suggests that there was a possibility of higher BMI in women after birth in the non-endometriosis group.

In our current study, however, we found that the OR for having endometriosis in obese patients (BMI over 27.50 kg/m²) was 1.979 (95% CI 1.15 to 3.52), compared with women with normal weight (p=0.0185). Although we only found 5% of obese women having endometriosis, which was significantly lower than other ethnic groups, according to the WHO report, only 2%–3% of Chinese women are obese in the general population.¹⁷ It is well-recognised that BMI in Chinese is smaller than that in Caucasians. Two recent studies have reported that approximately 14.3% of patients were obese, according to the WHO standard BMI category,^{13 20} although the WHO reported that approximately 15% of women aged 18 years and over were obese in 2016 (<https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>). The underlying mechanism of our findings is not clear. The increased levels of oestrogen associated with obesity can affect normal ovulation and result in shorter menstrual cycles, leading to reduced endometriotic lesion formation. However, in our current study we found that there was no statistical difference in the association of BMI and menstrual cycles (p=0.258). In addition, two large follow-up studies also reported the inverse trend association between BMI and the incidence of endometriosis in women with normal menstrual cycles.^{10 23} Therefore, the association of obesity and the increased risk of having endometriosis requires further study to be confirmed.

Endometriosis is the leading cause of secondary dysmenorrhoea. However, the association of dysmenorrhoea and BMI in women with endometriosis has not been well investigated. A recent study reported that BMI was positively associated with the stage of endometriosis.¹³

In our current study, despite there was no association of BMI and the severity of dysmenorrhoea in all cases, but we found in patients with dysmenorrhoea, the OR of developing severe dysmenorrhoea in obese patients (BMI over 27.50 kg/m²) was 3.64 (95% CI 1.195 to 10.15, p=0.025), compared with patients with normal weight. A follow-up study with large sample size suggested a higher risk of dysmenorrhoea in both obese and underweight Australian women,²⁴ although many studies reported an association of lower BMI and dysmenorrhoea.^{25 26} Interestingly in that study,²⁴ authors found that women with lower BMI are increasing in weight by an average of 1.7 kg/year still have a 30% higher risk of getting dysmenorrhoea. The underlying mechanism of obese women with endometriosis likely developing severe dysmenorrhoea is currently unclear. Reduced endometrial stromal cell decidualisation is associated with endometriosis²⁷ and obesity compromises endometrial stromal cell decidualisation.²⁸ It has been speculated that by a direct endometrial effect, compromising endometrial stromal cell decidualisation could result in protection for developing stage 1 endometriosis, but progresses to move severe forms of endometriosis afterwards.¹³ This speculation needs to be further investigated. Taken together, we report that obesity could be a risk factor for developing severe dysmenorrhoea in endometriosis.

Infertility is one of the clinical consequences of endometriosis. In our current case-control study, we found that a lower pregnancy rate in endometriosis and the OR for having a pregnancy in endometriosis was 0.413 (95% CI 0.325 to 0.524, p<0.0001) after adjusting the age, compared with controls. We did not have data on infertility in our study cohort, however, there were still 57% of patients with a history of pregnancy. A recent case-control study of Swedish women reported that 75% of women with endometriosis previously had more than one live birth.²¹ Thus, the association of endometriosis and infertility remains controversial, because it is still not clear whether endometriosis and infertility share a common cause or pathogenesis.²⁹ The association between endometriosis and infertility should be investigated more in the future.

There were some limitations in this study. First, dysmenorrhoea status in patients and a medical history of gynaecological diseases in controls were self-reported, which may cause a bias. The ideal controls would have been confirmed based on a normal laparoscopy or normal examination and imaging. Second, the data included in this study were collected from a single tertiary hospital which is in Shanghai, the wealthiest city in China. This results in a better access to medical care for women who reside in Shanghai, which is important because access to quality medical care can significantly affect the diagnosis of endometriosis.³⁰ In addition, this study was a retrospective study, which may cause a bias on the association between BMI and dysmenorrhoea, as obese women with mild symptoms of endometriosis may not receive the surgical treatment because of the difficulty in surgery.

Our current study did not address the medical comorbidities in our cohort. Finally, due to the small sample size for subanalysis by BMI categories, our findings need to be further investigated with a larger sample size.

In conclusion, in this retrospective and case-control study with a relatively large sample size, we found that BMI is not associated with the incidence of endometriosis, but obesity is a risk factor for having endometriosis in Chinese women. In addition, BMI is associated with the severity of dysmenorrhoea in endometriosis.

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