Running title: Meta-analysis of menarche age and EMS risk

Title: Association between early menarche and endometriosis risk: a systematic review and meta-analysis

Mei-Yin Lu [a], Jia-Li Niu [a], Bin Liu [a]

[a] Department of Biobank, Shenzhen Baoan Women's and Children's Hospital, Jinan University 518102, Guangdong, China.

*Correspondence: Bin Liu, Department of Biobank, Shenzhen Baoan Women's and Children's Hospital, Jinan University 518102, Guangdong, China.
Tel. +86-15817327996; Fax: +86-0755-27834718, Email: gz12liubin@163.com (B. Liu)

ABSTRACT

Background Early menarche is reported with the risk of endometriosis (EMS) with varying conclusions.

Objective To assess the association between menarche age and EMS risk.

Search strategy PubMed, Medline and Embase were searched using “endometriosis”, “early menarche” , “EMS”, “menarche age”, and “early menstrual characteristics”.

Selection criteria Articles that reported the EMS risk in early menarche from Jan 2000 to May 2020 were included. Studies without control group, and lack of data of menarche age were excluded.

Data collection and analysis EMS risks in these articles were collected and analysed through in random effects meta-analysis. In addition, subgroup analyses and meta-regressionwere were also performed.

Main results A total of 16 studies (8913 EMS cases and 876477 controls) were included in the meta-analysis. The pooled risk of EMS in early menarche (<12 years) was 1.34 (95% CI: 1.16–1.54), with statistically significant heterogeneity across the studies (I^2=72.0%). Stratified analysis showed that the risks of EMS by earlier menarche was increased in studies started after 2000, and in developing area, which was further confirmed by meta-regression analysis. In addition, higher quality in assessment of the exposure (menarche age) and control of potential confounders can elimenate heterogeneity.

Conclusions The earlier age of menarche is a major risk factor of EMS, and its risk has an increasing trend in recent years and in developing countries. Large-scale studies in different ethnic groups are warranted.

Funding: This research received no external funding.

Keywords: Endometriosis, early menarche, meta-analysis, risk factor

Tweetable abstract: The risk of EMS early menarche increases in recent years and in developing countries.

Introduction

Endometriosis (EMS) is a common gynecological disease that causes infertility[1]: 30% to 50% of women with EMS are infertile[2, 3]. The prevalence of EMS in women of reproductive age is about 10%[4]. EMS can also cause pelvic pain, dysmenorrhea, menorrhagia and difficulty in sexual intercourse[2, 3]. In addition, it increases the risk of pregnancy complications[2,5]. Moreover, EMS is prone to recurrence. After conservative treatment, the recurrence rate of EMS can reach 25 to 50%[6]. Therefore, EMS is an important infertile disease to address.

The pathogenesis of EMS is still unclear. Stem cell transplantation, abnormalities in hormone metabolism and other mechanisms are thought as the causes of EMS[7, 8]. Moreover, many risk factors of EMS have been reported, including age, race, body weight, drinking, smoking, and abnormal menstruation[9-11]. Especially, early menarche (defined as ≤11 years old [12]) is a pivotal factor of EMS risk, which supports the potential role of abnormal hormone secretion and endometrial stem cell transplantation in the pathogenesis of EMS[10]: it increases the hormone exposure in the whole life cycle of a women[13], and longer exposure to estrogens could mediate cellular growth and differentiation in the ectopic endometrial tissue[14]. Moreover, early menarche also plays a pivotal role in the outcome of EMS, such as pregnancy complications[13].

Nnoaham et al have performed a meta-analysis to review 18 case-control studies published from 1980 to 2011 to evaluate early menarche and the risk of EMS, and found that there is a small increased risk of EMS with early menarche[15]. To date, a number of cohort studies have analyzed the association between early menarche and the risk of EMS, with varying conclusions. However, the results of these cohort studies were not systematically reviewed. Moreover, the age at menarche decreased significantly in adolescents born in recent years in some countries, as a result of the improvement of the socioeconomic conditions[15, 16]. Therefore, the association of early menarche and EMS risk in recent years might be a little change to the previous meta-analysis[15]. We hypothesized that the estimated risk of EMS in early menarche are affected by different types of study (ie, cohort study vs. case-control study) and different time. Herein, we conducted a meta-analysis to quantitatively assess the association of early age at menarche (<12 years old) and risk of endometriosis, and combines results by including both cohort studies and case-control studies published after 2000, including all populations.

Materials and Methods

Identification and Selection of Articles

This study is systematic review and meta-analysis of published literatures comparing the menarche age of women with and without EMS. It was conducted in accordance with the reporting guidelines and checklist of criteria set in Preferred Reporting Items for Systematic Review (PRISMA)[17] and Meta-analyses of Observational Studies (MOOSE)[18].

Data Sources

Based on the PubMed, Medline and Embase databases from January 2000 to May 2020 (available data until June 1st 2020), two systematically trained authors (ML and XN) were responsible for extracting data from the eligible articles. (ML and XN) blindedly searched the literatures published in English. Medical Subject Headings (MESH) terms for "endometriosis" and "early menarche" and relevant search keywords, such as "EMS", "menarche age", and "early menstrual characteristics", were used. All published literatures (both case-control and cohort studies) analyzed the relationship between the early menarche age and the risk of EMS were included. In addition, we manually search the references of these published articles for secondary sources.

Inclusion criteria

To analyze the association between the early menarche and EMS risk, the included studies must: 1) cases, at least part of some randomly selected cases, were confirmed by laparoscopy or surgery, 2) included the control group and clearly described the selection criteria of controls, 3) have examined the relationship between the risk of

EMS and menarche. We excluded studies with the following characteristics: 1) Conference abstract and unpublished results, 2)without controls, 3) no enough data of menarche age (even cannot get the data after contacting with the authors), 4) very small population (<50 subjects), 4) duplicate studies.

Data Collection

An investigator (JN) reviewed all the titles. According to the inclusion criteria, two blind investigators (ML and BL), who reviewed and analyzed the quality of abstracts of all the retrieved literatures. The investigators discussed their differences on the retrieved data. All disputes were resolved through discussion with the third investigators (JN).

The following information was extracted and collected: the first author's name, year of study started and publication, type of study, investigated area, number of exposed/unexposed people or cases/controls, statistical methods, adjustment and stratification factors, response rates, the timing of diagnosis of DM relative to that of TB, and the potential duplication of data on the same individuals. Above informations were needed to analyze the estimated risk of EMS by early menarche and its possible bias.

Exposure

Early menarche is usually defined as age at menarche < 12 years old[12]. In this review, only studies with this definition of early menarche were included.

Quality Assessment

The quality of studies was assessed by the Newcastle–Ottawa scale (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp), a validated scale for assessing the quality of observational and non-randomized studies in meta-analyses. The scale graded the study according to participant selection, the comparability of the study group and the exposure assessment. Because the risk of EMS did not significantly vary with quality scores (*P*=0.377, **Figure S1**), all of 16 selected studies were included for further analyses.

Statistical Analysis

The meta-analysis was performed using statistical software STATA 16.0 (StataCorp). All results were expressed as relative risk of EMS with early menarche (odd ratio; OR for case-control studies, or hazard ratio; HR for cohort studies) and 95% confidence intervals (CI). We qualified heterogeneity between studies with the I^2 statistics. Because of high heterogeneity of included studies, the EMS risk was used in random effects meta-analysis by using Stata program. Considering the potential confounding factors such as population and research characteristics, we further conducted subgroup analyses by the study area (Developed vs. Developing), study type (Cohort vs. Case-control), study start years (Before vs. After 2000), and study quality (NOS Score >5 vs. Score≤5).

Furthermore, meta-regression was used to analyze the effect of the confounding factors, such as the study area, type, start years, and quality, on the association between age of menarche and the risk of EMS.

In addition, publication bias was represented by a funnel plot and analyzed by Begg's test and Egger's test. In order to evaluate the stability of the results and the possible bias, we conducted a sensitivity analysis of the literatures. Moreover, statistics of OR/HR and I^2 were performed in those studies with high quality in assessment of the exposure (menarche age) and control of potential confounders, to further specify assessments of risk of bias that may affect the cumulative evidence.

Results

Included Studies

According to the search strategy, 416 studies were selected. **Figure 1** showed the study selection process: 298 duplicate articles were deleted and 71 articles were excluded by systematically checking the title and abstract of the articles. In addition, the reasons for the deletion of the other 34 articles included: 1) no controls (n=4), 2) very small population (<50 subjects) (n=1), 3) duplicate studies (n=8), 4) no enough data (n=21), However, we sent e-mails to the authors of articles which had not enough data for help with raw data on menarche age. Finally, one author answered our questions enthusiastically. But their data had been updated and some of the data were out of line with our inclusion criteria. For the accuracy of this study, we had to leave out the relevant data regretfully. In the database search, 13 studies fulfilled the predefined entry criteria. Other 3 studies were identified from a reference list search. Finally, 16 studies were elected for inclusion in the meta-analysis.

The extracted informations of 16 included studies shown in **Table S1**. The studies published between 2004 and 2019 involved 8913 cases of EMS and 876477 controls. There were 8 studies with the starting year before 2000. These studies were conducted in Germany (n=1)[19], Iran (n=2)[20, 21], France (n=1)[22], Egypt (n=1)[23], Sweden (n=1)[24], Australia (n=1)[25], Canada (n=1)[26], and the USA (n=8)[9, 27-33]. There were 9 case-control studies and 7 cohort studies, with 4 case-control studies ([30],[26],[33],[25]) included in the previous meta-analysis[15].

Quality Assessment

For the 16 studies included, the NOS score ranged from 3 to 7 (5.88 $\pm$ 1.05). The details of the NOS for each study are shown in **Table** S**2**.

In 9 included case-control studies, the selection of subjects varied greatly: We determined the diagnostic accuracy of included studies according to the Quality Assessment of Studies of Diagnostic Accuracy included in Systematic Reviews (QUADAS)[34], most of studies carefully selected cases confirmed by laparoscopy or surgery. However, only 200 randomly selected cases were confirmed in two studies[24],[25]. In three included studies[33],[23],[30], cases were well representative of source populations in a defined catchment area or a defined hospital over a suitable period of time, reducing the risk of selection bias. While in other case-control studies, the catchment area was extensive[26], or time to recruitment was too long[30], or cases were from a twin study[24],[25]. In addition, 4 studies[26],[33],[25],[24] selected the controls from the same community, while others recruited hospital controls who were either healthy[19], or had diverse conditions such as minor unrelated disease[23],[20], gynecological diseases needed surgery[21], and infertility[30]. Apart from three studies[19,23,24], most studies excluded previous EMS from the controls by laparoscopy, surgery or medical history. The overall performance of the included case-control studies on comparability of participants was very good, all of them adequately controlled for potential confounders such as age, thereby enabling the comparability of the study groups. Moreover, 7 of those studies further controlled the confounding effect of adult BMI, and/or the history of menstruation and reproduction, except two studies[26,33]. The overall performance of the included studies on assessment of exposure was very bad. Only Mollazadeh et al[20] reported the ascertainment of exposure questions in questionnaire. In addition, exposure ascertainment was only blinded in three studies: one reported the method of blinding[33], while the other two performed the interview before the laparoscopy or surgery[26,30]. Moreover, only two studies reported the non-respond rate of the subjects[24,25].

In most of 7 cohort studies, the representativeness of exposed individuals was not from a general population, except one study [27]. Therefore, the overall performance of representativeness of these cohort studies was not very good. However, the other 6 studies had a good quality in assessment of the exposure (age at menarche) by a structured questionnaire. Moreover, 6 of these included cohort studies excluded previous EMS at the start of study, except one study including the prevalent EMS [22]. The overall performance of the included cohort studies on comparability of participants was very good: all, except Flores *et al*[27], adequately controlling for potential confounders such as age, and/or BMI, the history of menstruation and reproduction. For performance of the included cohort studies on outcomes of the participants was comparatively good, most of them had a high quality on the assessment of outcome (except Flores *et al*[27]), and a time long enough (>5 years) for follow-up (except two studies[27,9]). However, only two studies[22,31] reported the losses of the follow-up.

Overall meta-analysis

The risk of EMS by early menarche and its 95% CI in each study was also presented in **Table S1**. As shown in **Figure 2**, the overall risk of EMS (OR/HR) derived from the 16 studies indicated a significant association between early menarche and risk of EMS (OR/HR=1.34, 95% CI: 1.16–1.54). However, statistically significant heterogeneity was observed (I^2=72.0%, P<0.001), and thus we further conducted subgroup analyses based on study category, country and area, NOS score, and the beginning year.

Subgroup analyses

As shown in **Figure S2**, stratification of the studies by the study countries showed that the risk of EMS (OR/HR) for Europe and Oceania was 1.40 (I^2=63.6%, 95% CI: 1.16–1.70), for North America was 1.14 (I^2=72.0%, 95% CI: 0.92–1.41), and for Asia and Africa was 2.11 (I^2=0, 95% CI: 1.55–2.87), respectively. Subgroup analysis by the study area showed the risk of EMS in developing countries (I^2=0, OR/HR=2.11, 95% CI: 1.55–2.87) is higher than that in developed countries (I^2=70.6%, OR=1.25, 95% CI: 1.09-1.43) (**Figure S3**).

When stratification analysis was conducted by the type of studies, risk of EMS increased in case-control studies (I^2=81.4%, OR=1.54, 95% CI: 1.14–2.08), compared to cohort studies (I^2=36.5%, HR=1.21, 95% CI: 1.08–1.35) (**Figure S4**).

In studies with NOS score>5, early menarche was correlated with the risk of EMS (I^2=75.2%, OR/HR=1.25, 95% CI: 1.06–1.47); while this risk was increased in those studies with NOS score ≤ 5 (I^2=42.7%, OR/HR=1.61, 95% CI: 1.23–2.11) (**Figure S5**).

Stratified analysis was also conducted by the starting year. For studies began before 2000 and after 2000, OR/HR were 1.13 (95% CI: 0.96–1.35) and 1.62 (95% CI: 1.34–1.97), respectively (**Figure S6**).

Therefore, meta-regression analyses were performed based on the confounding factors, such as categories of studies, country and area of studies, NOS score of studies, and starting year of studies. As shown in **Table 1**, meta-regression analyses suggested that increased risks of EMS with early menarche were seen in studies which performed in developing area (N=3, n=1302, β=1.710±0.446, t = 2.06, P =

0.059), and those studies started after 2000 (N=8, n=32118, β=1.445±0.249, t = 2.14, P=0.051). However, there was no significant association between the either of the study type (Cohort study vs. Case-control study) or NOS score (>5 vs. ≤5) associated with effects on EMS risk by early menarche (both P values ≥ 0.1).

Publication Bias

Funnel plot graphically was used to evaluate the publication bias in meta-analyses[35]. In our study, little evidence for publication bias provided by visual inspection of funnel plots, and Begg's test showed no statistical evidence (**Figure S7**). To avoid the limitations of funnel plot, statistical tests were also analyzed by Egger's test[36-38]. However, Egger's test did not identify statistical evidence for publication bias also (**Supplementary S8**).

Sensitivity Analysis

The stability of the results was evaluated by sensitivity analysis. After removing any study, the pooled risk of EMS (OR/HR) ranged from 1.30 (95% CI: 1.13-1.49) to 1.40 (95% CI: 1.22-1.60), indicating that our results were stable (**Supplementary S9**). However, population characteristics and study designs may affect the stability of the results[15], as shown in the subgroup analyses of study area, types, NOS scores, and the beginning year in this study.

The ascertainment of exposure (age at menarche) varied greatly in 16 included studies in this meta-analyses: only one of 9 included case-control studies validated the exposure questions in the questionnaire; while for 7 included cohort studies, 6 of them used a structured questionnaire to collect information on exposure. The pooled EMS risk of these 7 studies with good quality on exposure ascertaining is close the overall results (OR/HR=1.26, 95% CI: 1.10–1.46), with a decreased heterogeneity (I^2=59.4%); while other studies with poor quality on exposure ascertaining had an increased pooled risk of EMS (OR/HR=1.45, 95% CI: 1.08–1.94), with a higher heterogeneity (I^2=79.3%) (**Figure 3**).

There were 3 of 16 included studies inadequately controlled for potential confounders. After removing these 3 studies, we got an increased pooled EMS risk results (OR/HR=1.45, 95% CI: 1.25–1.62) with a decreased heterogeneity (I^2=62.3%), compared to the overall 16 included studies (**Figure S10**).

Discussion

Main findings

In this meta-analysis, we observed that early menarche (<12 years) was significantly associated with an EMS risk, and this risk increased in recent years and in developing areas. There was a stable combined estimate of EMS risk across sensitivity analyses in this meta-analysis. However, the quality in assessment of the exposure (early menarche) and control of potential confounders can obviously eliminate heterogeneity.

Interpretation

The exact etiology and pathogenesis of EMS are not clear yet. Genetic and environmental factors seem to be involved[39]. However, Sampson's theory of retrograde menstruation is still the most widely accepted[40]. Early menarche may be due to earlier retrograde menstrual flow exposure, leading to increased pelvic endometrial volume, increasing the risk of EMS[41]. Thus, the inverse association between age at menarche and the risk of EMS found in this meta-analysis was biological plausible.

To our knowledge, only one previous meta-analysis of 18 case-control studies published from 1980 to 2011 also reported that early menarche age increases the risk of EMS[15]. The strength of our meta-analysis was that it included the studies published more recently, and also included 7 cohort studies. The pooled estimates of total 8089 cases and 874669 controls indicate that the risk of EMS increased by 1.34 times in earlier menarche in this study. Although the data sources of our meta-analysis are different from the previous published literature[15], we got the similar conclusion which further confirms that early menarche increases the risk of EMS. Moreover, any relevant asymmetry in either of the funnel plot, the Egger's test and Begg's test was not found in this study. Thus, publication bias is unlikely to have appreciably modified the association between early menarche and EMS risk in our meta-analysis. In addition, sensitivity analysis showed a stable combined estimate of EMS risk in this meta-analysis. Together, our results of increased EMS risk by early menarche were reliable.

However, in the stratified analysis based on regions, the risk of EMS in earlier menarche had an increasing trend in developing countries. Studies have shown that among girls in North America, black, Hispanic and low socioeconomic status children mature earlier[42]. The changing trend of menarche age in different countries may be related to the improvement of social conditions, environmental changes, endocrine disruptors and so on[43-45]. Our results implied a higher risk of EMS by early menarche in developing countries, caused by a continuous changing environment. Because the population of developing countries accounts for a large proportion of the whole world, we should pay more attention to prevent the prevalence of infertility by EMS in these countries. It will provide a valuable scientific basis for policy makers and public health doctors.

We also found that the pooled estimate of EMS risk has increased in recent years. The trend of early sexual maturity in girls continues, especially in recent 20 years [15, 16], resulting health problems by early menarche are more serious [46]. In this meta-analysis, the stratification of the starting year revealed that the risk of EMS in earlier menarche started after 2000 was higher than before 2000. Given our findings and above reports, it implied that the incidence of EMS in young females will still increase in the future. Our results attract the attention of policy makers and public health doctors to protect the fertility of young women.

However, above results might be brought by the very few number of included studies in each subgroup, especially in the subgroup of developing coutnries.

Strengths and limitations

In addition to above findings, this study also highlights the effects that inadequacies in ascertainment of exposure can have particular effect to estimate the risk of EMS. In most of 16 included in this meta-analysis, the age at menarche was recalled by participants, thus recall bias is inevitable. However, one included case-control study[20] collected information on exposure through a validated questionnaire, which can eliminate the bias of case-control study[47]. In addition, 6 of 7 included cohort studies in this meta-analysis collected information on exposure through a structured questionnaire predated symptom onset and diseases diagnoses. Therefore, these above 7 included studies with good quality in ascertainment of exposure might decrease the bias. Our results suggested the importance of collecting information on recalling exposure, such as age at menarche. For epidemiologists, our results have reference significance for future studies in this topic.

Additionally, we found that the heterogeneity of our meta-analysis was obviously decreased when removing 3 studies with poor quality on the performance of participants' comparability. Similarly, Nnoaham et al[15] also found controlled more rigorously for potential confounders can eliminate the heterogeneity of meta-analysis. Some important potential confounders, such as age, race, socioeconomic status, adult BMI, drinking, smoking, and abnormal menstruation confounds the relationship between early age at menarche and EMS risk, being inversely related to both early age at menarche and the risk of EMS[9-11,48]. Our findings highlight the need for well-designed studies incorporating collection of other confounder informations in the study of early menarche and EMS risk. It is a useful reference for epidemiological studies on infertile diseases.

Our meta-analysis has several limitations. First, our study did not evaluate the effect of ethnic populations on earlier menarche age and risk of EMS. There may be differences in menarche age[49, 50] and incidence rate of EMS among different races[51, 52]. This is due to the environment in different ethnic populations, which varies with different living standards[53]. However, most of the included studies in this meta-analysis did not have sufficient information on racial classifications. Therefore, we grouped the population according to the countries and areas, and minimize the relevant bias as much as possible. Second, we just identified literature published in English. Some high-quality studies published in other languages may be excluded. In addition, our study lacked geographical diversity, because we did not find any large cohort studies on the relationship between menarche age and EMS in Asia or Africa in the past 20 years. It is necessary to conduct extensive cohort studies in relevant countries and more detailed stratified studies in order to make the results have high confidence. Last, there were 21 studies with no enough data even after contacting the author, which were excluded in this meta-analysis. Therefore, bias of estimated risk of EMS by early menarche is inevitable.

Conclusion

Despite several limitations, earlier menarche age (<12 years) is one of the risk factors of EMS. Furthermore, there were some increasing trends on EMS risk by early menarche in recent years and in developing countries, which suggests more attention should pay in disease prevention in developing countries and in young women. Moreover, we found that higher quality in collecting informations on exposure and potential confounders can eliminate heterogeneity, implying that the methods of collecting exposure information (menarche age) is very pivotal for future study. However, our results might be brought by the very few number of included studies in each subgroup, especially in the subgroup of developing coutnries. Larger population studies with high quality, especially in Asia and Africa, are warranted.

Conflict of Interest

The authors have no conflicts of interest to declare.

Contribution to authorship

M.L.:1) acquisition of data (search the studies included in this meta-analysis), and analysis and interpretation of data, 2) drafting the article, and 3) final approval of the version to be published. J.N: 1) selection of articles, 2) acquisition of data. B.L.:1) study conception and design, acquisition of data (search the studies included in this meta-analysis), and analysis and interpretation of data, 2) revising it critically for important intellectual content, and 3) final approval of the version to be published.

Details of ethics approval

There is no need for ethical approval for a systematic review.

Funding

This research received no external funding.

Data Availability

None.

REFERENCES

1. Farland LV, Missmer SA, Bijon A, Gusto G, Gelot A, Clavel-Chapelon F, et al. Associations among body size across the life course, adult height and endometriosis. Hum Reprod. 2017 Aug 1;32(8):1732-42.
2. Lin YH, Chen YH, Chang HY, Au HK, Tzeng CR, Huang YH. Chronic Niche Inflammation in Endometriosis-Associated Infertility: Current Understanding and Future Therapeutic Strategies. Int J Mol Sci. 2018 Aug 13;19(8).
3. Practice Committee of the American Society for Reproductive M. Endometriosis and infertility: a committee opinion. Fertil Steril. 2012 Sep;98(3):591-8.
4. Holoch KJ, Lessey BA. Endometriosis and infertility. Clin Obstet Gynecol. 2010 Jun;53(2):429-38.
5. Zullo F, Spagnolo E, Saccone G, Acunzo M, Xodo S, Ceccaroni M, et al. Endometriosis and obstetrics complications: a systematic review and meta-analysis. Fertil Steril. 2017 Oct;108(4):667-72 e5.
6. von Theobald P, Cottenet J, Iacobelli S, Quantin C. Epidemiology of Endometriosis in France: A Large, Nation-Wide Study Based on Hospital Discharge Data. Biomed Res Int. 2016;2016:3260952.
7. Burney RO, Giudice LC. Pathogenesis and pathophysiology of endometriosis. Fertil Steril. 2012 Sep;98(3):511-9.
8. Lagana AS, Garzon S, Gotte M, Vigano P, Franchi M, Ghezzi F, et al. The Pathogenesis of Endometriosis: Molecular and Cell Biology Insights. Int J Mol Sci. 2019 Nov 10;20(22).
9. Peterson CM, Johnstone EB, Hammoud AO, Stanford JB, Varner MW, Kennedy A, et al. Risk factors associated with endometriosis: importance of study population for characterizing disease in the ENDO Study. Am J Obstet Gynecol. 2013 Jun;208(6):451 e1-11.
10. Parazzini F, Esposito G, Tozzi L, Noli S, Bianchi S. Epidemiology of endometriosis and its comorbidities. Eur J Obstet Gynecol Reprod Biol. 2017 Feb;209:3-7.
11. Wei M, Cheng Y, Bu H, Zhao Y, Zhao W. Length of Menstrual Cycle and Risk of Endometriosis: A Meta-Analysis of 11 Case-Control Studies. Medicine (Baltimore). 2016 Mar;95(9):e2922.
12. Gaudineau A, Ehlinger V, Vayssiere C, Jouret B, Arnaud C, Godeau E. Factors associated with early menarche: results from the French Health Behaviour in School-aged Children (HBSC) study. BMC Public Health. 2010 Mar 30;10:175.

13. Forman MR, Mangini LD, Thelus-Jean R, Hayward MD. Life-course origins of the ages at menarche and menopause. Adolesc Health Med Ther. 2013;4:1-21.

14. Emons G, Grundker C, Hanf V. [Are estrogens carcinogens?]. Zentralbl Gynakol. 2002 Dec;124(12):559-65.

15. Nnoaham KE, Webster P, Kumbang J, Kennedy SH, Zondervan KT. Is early age at menarche a risk factor for endometriosis? A systematic review and meta-analysis of case-control studies. Fertil Steril. 2012 Sep;98(3):702-12 e6.

16. Papadimitriou A. The Evolution of the Age at Menarche from Prehistorical to Modern Times. J Pediatr Adolesc Gynecol. 2016 Dec;29(6):527-30.

17. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009 Jul 21;6(7):e1000097.

18. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000 Apr 19;283(15):2008-12.

19. Burghaus S, Klingsiek P, Fasching PA, Engel A, Haberle L, Strissel PL, et al. Risk Factors for Endometriosis in a German Case-Control Study. Geburtshilfe Frauenheilkd. 2011 Dec;71(12):1073-9.

20. Mollazadeh S, Sadeghzadeh Oskouei B, Kamalifard M, Mirghafourvand M, Aminisani N, Jafari Shobeiri M. Association between Sexual Activity during Menstruation and Endometriosis: A Case-Control Study. Int J Fertil Steril. 2019 Oct;13(3):230-5.

21. Bouzari Z, Yazdani S, Ahangarkolaee ZH, Zeinalzadeh M, Hajian K. The Comparison of Menstrual Characteristics and BMI in Women with Endometriosis and Without Endometriosis. of. 2016;6:20-2.

22. Kvaskoff M, Bijon A, Clavel-Chapelon F, Mesrine S, Boutron-Ruault MC. Childhood and adolescent exposures and the risk of endometriosis. Epidemiology. 2013 Mar;24(2):261-9.

23. Mamdouh HM, Mortada MM, Kharboush IF, Abd-Elateef HA. Epidemiologic determinants of endometriosis among Egyptian women: a hospital-based case-control study. J Egypt Public Health Assoc. 2011;86(1-2):21-6.

24. Saha R, Kuja-Halkola R, Tornvall P, Marions L. Reproductive and Lifestyle Factors Associated with Endometriosis in a Large Cross-Sectional Population Sample. J Womens Health (Larchmt). 2017 Feb;26(2):152-8.

25. Treloar SA, Bell TA, Nagle CM, Purdie DM, Green AC. Early menstrual characteristics associated with subsequent diagnosis of endometriosis. Am J Obstet Gynecol. 2010 Jun;202(6):534 e1-6.

26. Hemmings R, Rivard M, Olive DL, Poliquin-Fleury J, Gagne D, Hugo P, et al. Evaluation of risk factors associated with endometriosis. Fertil Steril. 2004 Jun;81(6):1513-21.

27. Flores I, Abreu S, Abac S, Fourquet J, Laboy J, Rios-Bedoya C. Self-reported prevalence of endometriosis and its symptoms among Puerto Rican women. Int J Gynaecol Obstet. 2008 Mar;100(3):257-61.

28. Gallagher JS, DiVasta AD, Vitonis AF, Sarda V, Laufer MR, Missmer SA. The Impact of Endometriosis on Quality of Life in Adolescents. J Adolesc Health. 2018 Dec;63(6):766-72.

29. Johnson CY, Grajewski B, Lawson CC, Whelan EA, Bertke SJ, Tseng CY. Occupational risk factors for endometriosis in a cohort of flight attendants. Scand J Work Environ Health. 2016 Jan;42(1):52-60.

30. Matalliotakis IM, Cakmak H, Fragouli YG, Goumenou AG, Mahutte NG, Arici A. Epidemiological characteristics in women with and without endometriosis in the Yale series. Arch Gynecol Obstet. 2008 May;277(5):389-93.

31. Missmer SA, Hankinson SE, Spiegelman D, Barbieri RL, Malspeis S, Willett WC, et al. Reproductive

history and endometriosis among premenopausal women. Obstet Gynecol. 2004 Nov;104(5 Pt 1):965-74.

32. Templeman C, Marshall SF, Ursin G, Horn-Ross PL, Clarke CA, Allen M, et al. Adenomyosis and endometriosis in the California Teachers Study. Fertil Steril. 2008 Aug;90(2):415-24.

33. Buck Louis GM, Hediger ML, Pena JB. Intrauterine exposures and risk of endometriosis. Hum Reprod. 2007 Dec;22(12):3232-6.

34. Deeks JJ. Systematic reviews of evaluations of diagnostic and screening tests. Bmj. 2001;323(7305):157-62.

35. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. J Clin Epidemiol. 2001 Oct;54(10):1046-55.

36. Lin L, Chu H. Quantifying publication bias in meta-analysis. Biometrics. 2018 Sep;74(3):785-94.

37. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994 Dec;50(4):1088-101.

38. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997 Sep 13;315(7109):629-34.

39. Vigano P, Somigliana E, Panina P, Rabellotti E, Vercellini P, Candiani M. Principles of phenomics in endometriosis. Hum Reprod Update. 2012 May-Jun;18(3):248-59.

40. Sampson JA. Metastatic or Embolic Endometriosis, due to the Menstrual Dissemination of Endometrial Tissue into the Venous Circulation. Am J Pathol. 1927 Mar;3(2):93-110 43.

41. Marcellin L, Santulli P, Pinzauti S, Bourdon M, Lamau MC, Borghese B, et al. Age at menarche does not correlate with the endometriosis phenotype. PLoS One. 2019;14(7):e0219497.

42. Piekarski DJ, Johnson CM, Boivin JR, Thomas AW, Lin WC, Delevich K, et al. Does puberty mark a transition in sensitive periods for plasticity in the associative neocortex? Brain Res. 2017 Jan 1;1654(Pt B):123-44.

43. Hiatt RA, Stewart SL, Hoeft KS, Kushi LH, Windham GC, Biro FM, et al. Childhood Socioeconomic Position and Pubertal Onset in a Cohort of Multiethnic Girls: Implications for Breast Cancer. Cancer Epidemiol Biomarkers Prev. 2017 Dec;26(12):1714-21.

44. Toppari J, Juul A. Trends in puberty timing in humans and environmental modifiers. Mol Cell Endocrinol. 2010 Aug 5;324(1-2):39-44.

45. Fisher MM, Eugster EA. What is in our environment that effects puberty? Reprod Toxicol. 2014 Apr;44:7-14.

46. Herman-Giddens ME. Recent data on pubertal milestones in United States children: the secular trend toward earlier development. Int J Androl. 2006 Feb;29(1):241-6; discussion 86-90.

47. Zondervan KT, Cardon LR, Kennedy SH. What makes a good case-control study? Design issues for complex traits such as endometriosis. Hum Reprod. 2002 Jun;17(6):1415-23.

48. Pierce MB, Leon DA. Age at menarche and adult BMI in the Aberdeen children of the 1950s cohort study. Am J Clin Nutr. 2005 Oct;82(4):733-9.

49. Anderson SE, Must A. Interpreting the continued decline in the average age at menarche: results from two nationally representative surveys of U.S. girls studied 10 years apart. J Pediatr. 2005 Dec;147(6):753-60.

50. Deardorff J, Abrams B, Ekwaru JP, Rehkopf DH. Socioeconomic status and age at menarche: an examination of multiple indicators in an ethnically diverse cohort. Ann Epidemiol. 2014 Oct;24(10):727-33.

51. Bougie O, Yap MI, Sikora L, Flaxman T, Singh S. Influence of race/ethnicity on prevalence and

presentation of endometriosis: a systematic review and meta-analysis. BJOG. 2019 Aug;126(9):1104-15.

52. Cramer DW, Missmer SA. The epidemiology of endometriosis. Ann N Y Acad Sci. 2002 Mar;955:11-22; discussion 34-6, 396-406.

53. Parent AS, Teilmann G, Juul A, Skakkebaek NE, Toppari J, Bourguignon JP. The timing of normal puberty and the age limits of sexual precocity: variations around the world, secular trends, and changes after migration. Endocr Rev. 2003 Oct;24(5):668-93.

Figure Captions

Figure 1: Flow diagram of included studies in this meta-analysis according to Systematic Review and Meta-analyses (PRISMA).

Figure 2: Forest plot of 16 included studies evaluating association between early menarche and endometriosis.

Figure 3: Forest plot of the association between early menarche and endometriosis in studies with different quality on the ascertainment of exposure (age at menarche): 2(top), studies with poor quality on the ascertainment of exposure. 1(bottom), and studies with higher quality on the ascertainment of exposure.

Table 1. Meta-analyses of 16 included studies by the confounding factors.

	Exp(β)	Stand Errors	*t*	*P*>|t|	95% CI	I^2 (%)	Adjusted R^2 (%)
Begin year (Before 2000 vs. After 2000)	1.445	0.249	2.14	0.051	0.999-2.090	64.17	45.00
Type of study (Cohort study vs. Case control study)	1.267	0.259	1.16	0.267	0.817-1.966	73.33	-0.54
Area (Developed area vs. Developing area)	1.710	0.446	2.06	0.059	0.977-2.993	65.91	39.97
NOS score (Score>5 vs. Score≤5)	0.922	0.082	-0.91	0.377	0.762-1.116	72.49	-4.34

NOS, Newcastle-Ottawa scale. 95% CI, 95% confidence interval.

Supplementary files:

Figure S1: Linear analysis between NOS score and log(OR) for 16 included studies. NOS, Newcastle-Ottawa scale. Circle size means the reported OR and its 95% CI. Red Line and grey band means the predicted OR and its 95% CI.

Figure S2: Meta-analysis of included studies presented by the subgroups of study countries: Asia & Africa vs. Europe & Oceania vs. North America.**(E),** Starting year: After 2000 vs. Before 2000.

Figure S3: Meta-analysis of included studies presented by the subgroups of study area: Developing vs. Developed.

Figure S4: Meta-analysis of included studies presented by the subgroups of study type: Case-control studies vs. Cohort studies.

Figure S5: Meta-analysis of included studies presented by the subgroups of NOS score: ≤5 vs. >5. NOS, Newcastle-Ottawa scale.

Figure S6: Meta-analysis of included studies presented by the subgroups of starting year: After 2000 vs. Before 2000.

Figure S7: Funnel plot of the publication bias in this meta-analyses. (A)Funnel plot with pseudo 95% CI of 16 included studies. (B), Begg's test for small-study effects.

Figure S8: Egger's test for 16 included studies in this meta-analysis.

Figure S9: Sensitivity analysis of 16 included studies in this meta-analysis.

Figure S10: Forest plot of the association between early menarche and endometriosis in 13 included studies, when removing 3 studies with inadequately controlled for potential confounders.

Table S1: Summary and meta results of included 16 studies.

Table S2: Quality of included studies using Newcastle-Ottawa scale.