

# Effects of medical and surgical treatment on the risk of major adverse cardiovascular and cerebrovascular events in Asian women with endometriosis

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## Research article

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# Abstract

**Background:** Endometriosis (EM) is linked to cardiovascular disease (CVD). However, whether this finding can be applied to the Asian population remained unanswered. Results are still conflicting in terms of therapeutic effect on the risk of CVD in patients with EM. Therefore, we investigated the association between EM and major adverse cardiovascular and cerebrovascular events (MACCE) and the therapeutic effect on the risk of MACCE in Asian women with EM.

**Methods:** The Taiwan National Health Insurance Research Database was used for this retrospective population-based cohort study from 1997 to 2013. A total of 17 543 patients with EM aged between 18 and 50 years were identified from a general population of 1 million after excluding diagnoses of major CVD and cerebrovascular accident (CVA) prior to EM. The comparison group (n = 70 172) without EM was selected by matching the study cohort with age, sex, and income and urbanization levels in a 4:1 ratio. Demographic data and the frequency of comorbidities between groups were compared using the independent t test and chi-square test. The incidence and risk of MACCE were analyzed using the log-rank test and a multivariate Cox proportional hazards model.

**Results:** During a median follow-up period of 9.2 years, Asian women with EM had a significantly higher frequency of comorbidities, medical and surgical treatment, and MACCE than did their non-EM counterparts (2.76% vs 2.18%,  $P < .0001$ ). After adjustment for comorbidities, patients with EM had an approximately 1.2-fold increased risk of MACCE (95% CI 1.05-1.29;  $P = .0053$ ) and a higher cumulative incidence of MACCE compared with the normal population. Among women with EM, neither medical nor surgical treatment increased the risk of MACCE, including major CVD and CVA. Furthermore, medical treatment for EM appeared to be protective against MACCE.

**Conclusion:** Asian women with EM not only had a substantially higher frequency of comorbidities but also an increased risk of MACCE compared with the general population. In terms of medical or surgical treatment of EM, the safety concern regarding MACCE was not evident.

## Background

Endometriosis (EM), characterized by extrauterine endometrial lesions, is a worldwide concern affecting many women of childbearing age. Approximately 10% of the general female population has EM, and nearly 50% of women with infertility are affected by it [1,2]. EM is strongly associated with systemic inflammation, neovascularization, and tissue remodeling [3]. Additionally, a recent study reported that endothelial dysfunction (ED) plays a crucial role in one of the pathological mechanisms underlying EM [4].

The development of atherosclerotic cerebrovascular or cardiovascular disease (CVD), such as vascular dementia, coronary artery disease (CAD), and peripheral vascular disease, is closely related to systemic inflammation and ED [5,6]. Therefore, considering the common pathological pathways of inflammation and ED, the hypothesis that women with EM have a higher risk of CVD has been supported directly or

indirectly by several studies [7,8]. Recently, data from the US Health Study II registry indicated that the risk of CAD is not only linked to EM but also higher in patients with EM who underwent hysterectomy or oophorectomy [9]. The unfavorable effect of surgical treatment for EM on the risk of CVD raised clinical safety concerns among operators, health care providers, and patients. Furthermore, hormonal treatment strategies for EM [10,11], including gonadotropin-releasing hormone (GnRH) analogs, oral contraceptives, progesterone, and danazol, potentially or controversially increase the cardiovascular risk and yield inconsistent results [7,8,12]. However, whether the aforementioned findings derived from Western countries can be generally applied to the Asian population and whether women with EM receiving medical, surgical, or combined treatment have increased risks of major adverse cardiovascular and cerebrovascular events (MACCE) remain unanswered. Using the Taiwan National Health Insurance Research Database (NHIRD), we studied (1) the risk of MACCE and (2) the therapeutic effect on MACCE in Asian women with EM.

## Methods

### Introduction of the Taiwan NHIRD

The Taiwan National Health Insurance program provides health care to 99% of the population of 24 million and is linked to 97% of hospitals and clinics in Taiwan (<http://nhird.nhri.org.tw/en/>) [13]. The NHIRD is a considerable source of information on medical facilities, inpatient and outpatient order details, dental services, drug prescriptions, patient care, and other paramedical registration files (eg, payment, regions, and catastrophic illness), but it does not include laboratory data. Diagnoses are entered based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD–9-CM). The NHIRD longitudinal data collection started in 2000, and 1 000 000 beneficiaries were randomly sampled. The database contains the entire original claims data from 1997 to 2013. The study design and protocol were approved by the Institutional Review Board of Chang Gung Memorial Hospital (No. 201800664B1).

### Study population

We selected female patients with EM (ICD–9-CM code 617) from 1 million individuals in the NHIRD between January 1997 and December 2013 to conduct a retrospective nationwide population-based cohort study. Women aged between 18 and 50 with a record of at least 3 medical visits or 1 admission for EM were included in the study. To confirm the diagnosis of EM, we linked the relevant clinical information with the corresponding vaginal ultrasound, laparoscope, medications, and operations. Those patients with clinically suspected EM but without image- or procedure-proven EM were not included. We excluded patients aged <18 or >50 years, male patients, patients experiencing menopause (627), patients with missing or incomplete baseline characteristics data, and patients with a follow-up duration of less than 1 year. For the first purpose of the study, that is, the incidental MACCE in women with EM, patients with diagnoses of acute myocardial infarction (AMI; 410–411), heart failure (HF; 428), or cerebrovascular accident (CVA; 430–436) in the beginning or prior to EM were excluded. Thus, we identified a total of 17

543 women with EM at the beginning of the study. A comparison cohort of 70 172 non-EM women was selected after matching the study cohort at a 4:1 ratio with age and socioeconomic background, including income and urbanization level (Fig. 1). Urbanization was categorized into 4 levels, from level 1 indicating the least urbanized level (country) to level 4 indicating the most urbanized level (city). The insurance taxable income level was stratified into 4 categories based on the monthly insurance payment of each insured participant (ie, level 1: none; level 2: 1–15 840; level 3: 15 841–25 000; and level 4: > 25 000 New Taiwan dollars per month).

## Definition

The MACCE were divided into 2 disease entities, namely CVD and CVA. Major CVD involved AMI or HF. CVA encompassed acute ischemic (433–436) or hemorrhagic stroke (430–432). Moreover, information on medications was acquired based on the World Health Organization Anatomical Therapeutic Chemical classification system. Medical treatment for EM comprised danazol, gestrinone, oral contraceptives, and GnRH agonists. Patients with prescriptions exceeding a month were considered medication users. By contrast, we considered patients with a regimen duration of less than a month as nonusers, because drugs might have been prescribed temporarily for symptomatic relief, diagnostic test, or purposes other than standard treatment for EM. Surgical treatment for EM mainly consisted of therapeutic laparotomy and laparoscopy (ICD–9-CM procedure codes 541 and 542).

## Identification of symptoms, comorbidities, location, and outcomes

We conducted a retrospective longitudinal study. The date of initial diagnosis of EM was defined as the index date. To clarify the association between MACCE and EM, potential risk factors for MACCE and possible confounders were retrieved for further analysis. We assessed gynecological presentations and relevant comorbidities for each patient during the follow-up period, including dysmenorrhea (ICD–9-CM code 625.3), amenorrhea (ICD–9-CM code 626.0), infertility (ICD–9-CM code 628), ovarian cancer (ICD–9-CM code 183), hypertension (ICD–9-CM codes 401–405), diabetes (ICD–9-CM code 250), dyslipidemia (ICD–9-CM code 272), gout (ICD–9-CM code 274), chronic ischemic heart disease (ICD–9-CM codes 412–414 and 429.2), peripheral vascular disease (ICD–9-CM codes 440, 443.9, 444.0, 444.2, 444.8, 444.9, 447.8, 447.9, 445.0, and 445.02), atrial fibrillation (ICD–9-CM code 427.31), and chronic kidney disease (ICD–9-CM code 585). EM was further divided into ovarian and extraovarian groups according to its occurrence location.

With respect to study outcomes, the day of the first event occurrence was defined as the event date. The diagnosis of MACCE, including AMI, HF, and CVA, was confirmed by 3 consecutive records of outpatient visits or a one-time diagnosis on admission with the corresponding standard treatment during the whole study period. Endpoints between the 2 groups were censored, whereas clinical events were identified by

ICD–9-CM codes and the event date. We investigated the frequency and incidence of MACCE in both EM and non-EM Asian groups. Additionally, we analyzed whether the risk of MACCE was higher in the EM group than in the normal population in Asian women. Furthermore, we studied changes in risk according to surgical or medical treatment for EM.

## Statistical analysis

The ratios of demographic data and comorbidities between the study cohort (EM) and the matched control cohort (non-EM) were compared using the independent *t* test and chi-square test, as appropriate. The incidence rates and 95% CIs of MACCE were calculated for the entire follow-up period. We also examined the outcomes of MACCE and stratified them by subgroups according to age, amenorrhea diagnosis, and comorbidities. Additionally, the Kaplan–Meier method was used to estimate the cumulative incidences, and a log-rank test was performed to examine differences between disease and nondisease groups. Using Cox proportional hazards regression models, we analyzed hazard ratios (HRs) and corresponding 95% CIs after adjusting for age, medications, surgery types, and associated comorbidities. To further understand the effect of surgical or medical treatment for EM, a multivariate Cox regression model was used to examine the adjusted HRs of EM for the occurrence of MACCE in the subgroups. A two-tailed *P* value of <.05 was considered statistically significant. All analyses were conducted using the SAS statistical software program (Version 9.4; SAS Institute, Cary, NC, USA).

## Results

### Demographic data and outcomes in women with and without EM (Table 1)

Over the 17-year dataset period, there were a total of 17 543 and 70 172 eligible patients in the EM and non-EM group, respectively. More than 60% of women with EM were aged between 35 and 50 years with a median age of 38 years. The frequencies of irregular menstruation, infertility, and ovarian cancer were higher in the EM group than in the non-EM group. Approximately 13% of EM cases were detected in the ovaries alone. A majority of women with EM had EM in both ovarian and extraovarian locations. Approximately 1 in 5 patients with EM received regular medical or standard surgical treatment for EM. The EM group had a significantly higher prevalence of comorbidities compared with its non-EM counterpart, except for atrial fibrillation and chronic kidney disease.

The mean follow-up duration was 9.3 years. At the end of the study, the frequency of MACCE in patients with EM and without EM was 2.76% and 2.18%, respectively. Therefore, the frequency of MACCE, including major CVD and CVA, was significantly higher in the EM group than in the non-EM group (all *P* values <.002). However, the all-cause mortality rate was approximately 1% and did not significantly differ between groups.

## Incidence and risk of MACCE in women with EM and without EM (Table 2 and Fig. 2)

The incidence rate of MACCE in patients with and without EM was 300.0 and 235.5 per 100,000 person-years, respectively, amounting to an incidence rate ratio of major CVD in the EM group to major CVD in the non-EM group of 1.27 (95% CI 1.15–1.41;  $P < .0001$ ). After adjustment for age, socioeconomic background, and associated comorbidities, women with EM had a 1.17-fold increased risk of MACCE compared with women without EM (95% CI = 1.05–1.29;  $P = .005$ ). Moreover, the Kaplan–Meier curve demonstrated that the EM group had a significantly higher cumulative incidence of MACCE compared with the non-EM group ( $P < .001$  in the log-rank test). The cumulative incidence of major CVD and CVA between groups displayed a similar pattern to that of MACCE (Fig. 2).

The findings of the stratified analysis revealed that the adjusted HRs of MACCE in the EM cohort to the non-EM cohort were significantly higher in the subgroups of patients aged 35 to 50 years and without conventional atherosclerotic risk factors (ie, hypertension, diabetes, dyslipidemia, and gout). Nevertheless, the adjusted HRs did not change significantly for patients with amenorrhea and those experiencing premature menopause, which suggested that the risk of MACCE might be higher for those relatively healthy middle-aged Asian women with EM, regardless of their menstrual presentation.

## Association between MACCE and EM (Table 3)

Using a multivariate Cox regression model with adjustment for age, urbanization/income, and conventional atherosclerotic risk factors, we observed that apart from EM, age between 35 and 50 years, higher urbanization and income levels, hypertension, and diabetes were significantly associated with MACCE. Moreover, EM was identified to be related to both major CVD and CVA.

## Effects of medical and surgical treatment on clinical outcomes (Table 4 and Fig. 3)

Approximately 20% of patients with EM received medical or surgical therapy. To clarify the effect of various EM treatment strategies on the occurrence of MACCE, we divided the EM group into 4 subgroups according to whether they received surgical or medical treatment. Fig. 3 indicates that the cumulative incidence of MACCE was the highest in the EM subgroup without any treatment and significantly lower in the subgroups of patients who received medical, surgical, or combined treatment ( $P < .001$  in the log-rank test). However, there was no significant difference in MACCE among the aforementioned 3 subgroups.

We further adjusted for procedures and medications apart from the aforementioned potential confounders in a multivariate analysis of these women with EM. Findings indicated that women who were aged  $\geq 35$  years and had a higher urbanization level, hypertension, and diabetes were closely

associated with MACCE in EM as expected. In addition, there was no safety concern regarding the increase of the risk of MACCE in surgical treatment of EM. Medical treatment alone appeared to be associated with a significantly decreased MACCE risk. The occurrence of MACCE in combined medical and surgical treatment for EM did not further increase compared with that in conservative therapy.

## Discussion

The present study that used the Taiwan NHIRD to investigate the association between EM and MACCE and the effect of EM treatment on the risk of MACCE in the Asian population yielded several relevant clinical findings. First, the risk of MACCE, including AMI, HF, and CVA, was substantially higher in the Asian women with EM than in those without. Women with EM had an approximately 1.2-time increased risk of MACCE throughout their early life, especially those aged between 35 and 50 years but without atherosclerotic risk factors. Second, in addition to the aforementioned age range, hypertension, and diabetes, EM was notably associated with MACCE after multivariate adjustment. Third, based on the findings of this Asian population-based study, surgical and medical treatment for EM did not present a safety risk of increased MACCE incidence. Furthermore, Asian women with EM treated only with medication had a significantly lower risk of MACCE compared with those who received surgical or combined treatment.

This large-scale nationwide population-based cohort study identified the association between EM and MACCE as well as the therapeutic effect on cardiovascular events in the Asian population. The increased risk of MACCE after surgical treatment of EM reported in a previous publication [9] was not observed in our study. Asian women with EM could be treated with medication first and receive surgical intervention either subsequently or simultaneously because there was no concern of a further increase in the MACCE risk. Our findings, therefore, highlighted a safe and effective management strategy that should be taken into consideration not only for EM per se but also for preventing future occurrence of MACCE in these relatively young and healthy women.

The link between systemic inflammation and ED has been well documented for several decades [4,14]. Furthermore, abundant evidence has supported the relationship among ED, arterial atherosclerosis, and acute arterial occlusive diseases (eg, acute stroke, AMI, and critical limb ischemia) [15–18]. Although the causal relationship between ED and CVD is complex, they are undoubtedly linked with an unfavorable prognostic outcome [5]. Similarly, the underlying mechanisms of EM have been proposed to be multifactorial and multifaceted and to include genetic and environmental factors, stem cell theory, vasculogenesis, neurohormonal dysregulation, and autoimmune dysfunction [19–21]. Recently, increasing data have demonstrated that the strong association between EM and ED can be attributed to abnormal vasculogenesis from endothelial progenitor cells to the microvascular endothelium of ectopic endometrial tissue rather than to the normal angiogenesis process [20]. Additionally, EM is recognized as a disabling disease owing to chronic pelvic pain, dysmenorrhea, dyspareunia, and dysuria, thus severely affecting quality of life [22]. Patients with intractable EM experience painful symptoms or psychological and emotional stress, which further increases the risk of future CVD [7]. Therefore, these findings [15–21]

raised the hypothesis that EM and MACCE share a common pathological pathway and disease mechanism of inflammation, ED, and emotional or physical stress from frequent dysmenorrhea. In the present study, not only were the frequency and incidence of MACCE higher in Asian women with EM than in those without, but EM also appeared to be independently associated with major CVD and CVA. The aforementioned hypotheses were verified by the present real-world analytic results. In addition to age between 35 and 50 years and conventional atherosclerotic (or CAD) risk factors, EM might be considered as another risk factor for MACCE.

Santoro et al addressed a similar issue regarding the relationship between EM and atherosclerosis [23]. Verit et al also reported that the risk of CVD may increase in women with unexplained infertility [24]. Furthermore, the causes of female infertility include polycystic ovarian syndrome, obesity, thyroid function, and EM [25,26], and all these factors strongly influence CVD outcomes [27–29]. Therefore, our finding regarding MACCE in EM is not only consistent with previous clinical observations but also compatible with their pathological hypotheses. However, the causal relationship between EM and CVD through the possible mechanism of inflammation and ED as well as associated mediators deserves further investigation.

de Kat et al [8] demonstrated the negative correlation of the anti-Müllerian hormone (AMH) level with an increased CVD risk. The level of AMH, an indicator of ovarian preservation, remarkably decreased after surgical or laparoscopic treatment for EM [30,31]. Therefore, the aforementioned phenomena could, at least in part, explain why the CVD risk notably increased after surgery for EM in a recent observational study [3]. Unfortunately, the level of AMH was unavailable in the present study; therefore, we could not analyze the association among AMH, EM surgery, and CVD risk. Data from the present study based on the Asian population revealed that patients with EM treated with surgery or combined therapy did not have a higher risk of MACCE than those who did not receive treatment. Therefore, the effect of EM surgery on the risk of MACCE might not be a cause for concern. Our finding was supported by results reported by Santoro et al [32] according to which surgical treatment of EM can lead to the regression of ED, and an improved cardiovascular outcome from surgery is predictable. Taken together, the results of the current study suggested that surgical intervention for EM might adversely affect the ovarian function but may not be considered as a risk factor for MACCE. Based on the results of the current study, which demonstrated lower MACCE risks in patients with EM receiving medical treatment only, we recommend medical treatment followed by surgical management for refractory EM.

## Limitations

Our study has several limitations. First, the detailed personal history and lifestyle of patients, such as smoking or alcohol abuse, body mass index, and functional capacity, were not provided in the Taiwan NHIRD. This weakness was overcome by matching the socioeconomic level at baseline. Second, all diagnoses in the present study were retrieved according to registered ICD–9-CM codes; therefore, the staging or severity of EM are lacking. Third, laboratory data including the AMH level or other inflammatory biomarkers are not available in the NHIRD. Fourth, compared with the therapeutic rate of

over 50% for EM in a UK-based population [33], data from the current study Asian cohort revealed a surgical or medical treatment rate for EM of 20% only. Therefore, we are unsure whether the results of this Asian population-based study can be applied to the clinical practice worldwide and vice versa. Thus, the effect of EM treatment on the incidence of MACCE deserves further investigation through a well-designed prospective study. Finally, the type of medication used for cardiovascular protection (eg, antihypertensive medicine and antidiabetic or lipid-lowering agents) could not be obtained from the NHIRD. Therefore, the effect of medications beyond standard treatment for EM on the occurrence of MACCE was not fully investigated. Exploring the medications with potential benefit to reduce CVD risks paves the way for future studies.

## **Conclusions**

Asian women with EM had a higher prevalence of comorbidities and risk of MACCE than the matched general population, especially those aged between 35 and 50 years and relatively healthy. Medical therapy should be considered as the first step in the management of EM because the risk of MACCE was significantly lower than that in case of no treatment. Furthermore, EM can be safely treated with surgery alone or a combined medical and surgical therapy because no safety concern was raised regarding a further increase in the MACCE risk.

## **Abbreviations**

EM: endometriosis; MACCE: major adverse cardiovascular and cerebrovascular events; CVD: cardiovascular disease; CAD: coronary artery disease; CVA: cerebrovascular accident; AMI: acute myocardial infarction; HF: heart failure; NHIRD: National Health Insurance Research Database.

## **Declarations**

## **Acknowledgments**

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## **Authors' contributions**

PHS and HJC participated in the study design, data acquisition and analysis, as well as manuscript drafting. FTK, FJH, YJL, and YTS were responsible for the data acquisition and troubleshooting. YHY and JYC participated in the data analysis and interpretation. KCL conceived the study and coordinated all research efforts. All authors read and approved the final manuscript.

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none.

## **Availability of data and materials**

The datasets used and/or analyzed during the current study are provided by the corresponding author on a reasonable request.

## **Ethics approval and informed consent**

The study design and protocol were approved by the Institutional Review Board of Chang Gung Memorial Hospital (No. 201800664B1). The informed consent was waived due to delinked database.

## **Consent for publication**

Not applicable

## **Competing interests**

All authors report no conflict of interest.

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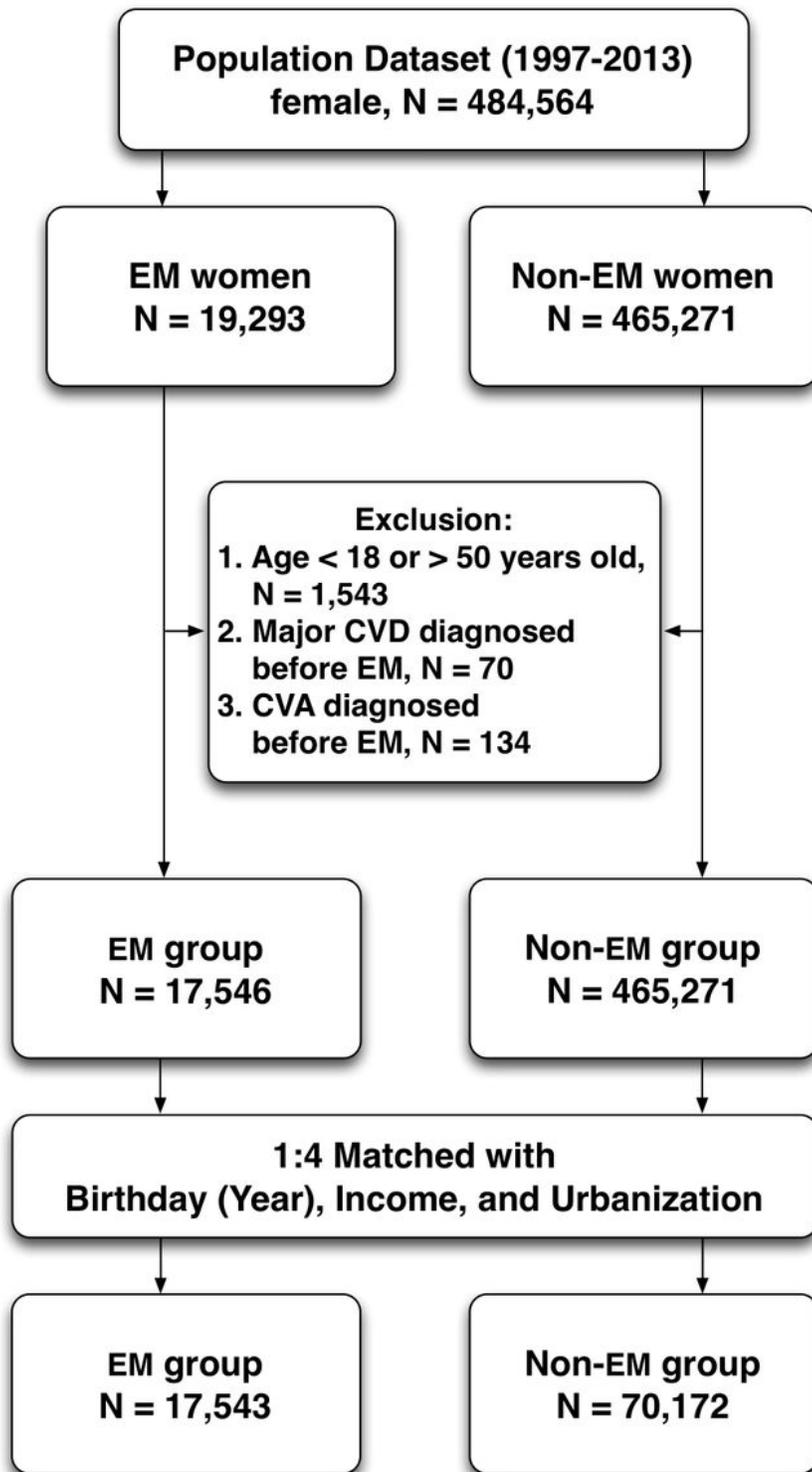
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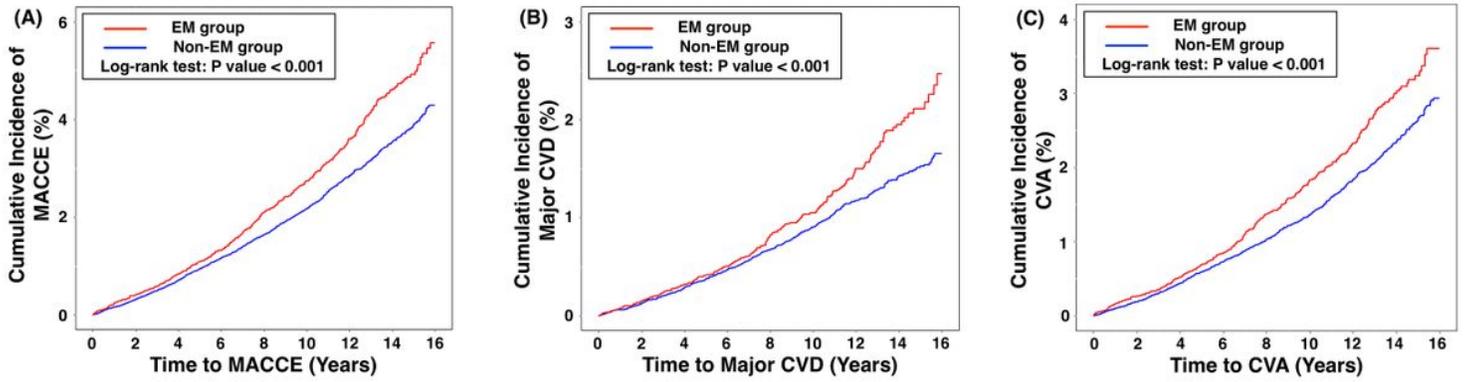
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## Figures



**Figure 1**

Flowchart of patient screening, enrollment, and assignment for the EM and matched non-EM groups. The non-EM group was selected by matching the EM group with age and socioeconomic background in a 4:1 ratio after excluding major CVD and CVA before the diagnosis of EM and patients aged < 18 or > 50. Abbreviations: EM, endometriosis; CVD, cardiovascular disease; CVA, cerebrovascular accident.



**Figure 2**

Cumulative incidence of MACCE (2A), major CVD (2B), and CVA (2C) in the EM versus non-EM groups. Abbreviations: EM, endometriosis; MACCE, major adverse cardiovascular and cerebrovascular events; CVD, cardiovascular disease; CVA, cerebrovascular accident.

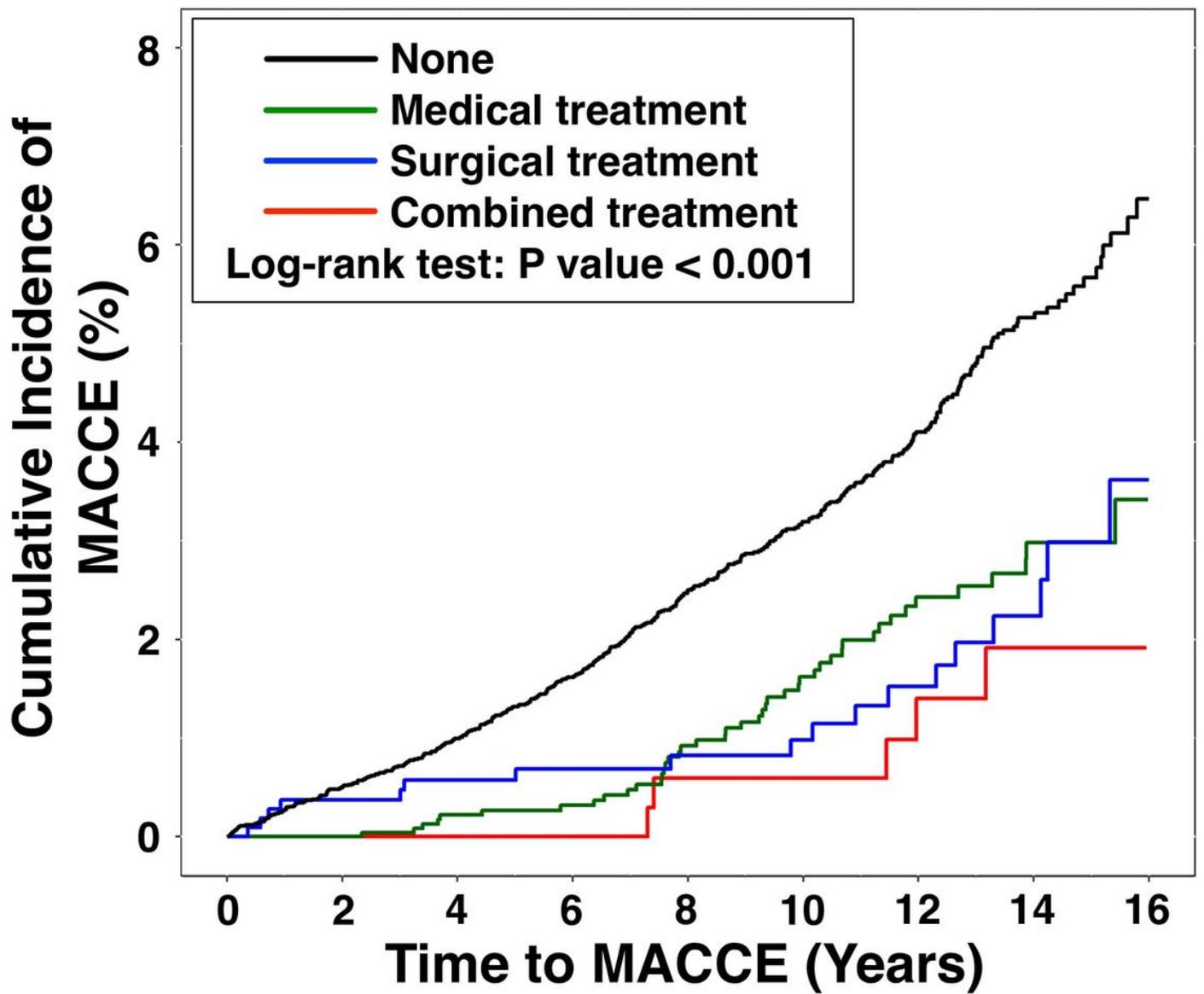


Figure 3

Cumulative incidence of MACCE in the EM subgroups, namely the no treatment, medical treatment, surgical treatment, or combined treatment groups. Abbreviations: EM, endometriosis; MACCE, major adverse cardiovascular and cerebrovascular events.