narra j

Review Article

Examining the interplay between endometriosis and later-life cerebro-cardiovascular diseases: A systematic review, meta-analysis, and trial sequential analysis

I GS. Winata[1,2*], Surya S. Immanuel[3], Leonardo Leonardo[1,2,3], Fransiskus X. Rinaldi[3], Gabriel Tandecxi[3] and Richard Wijaya[3]

[1]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Udayana, Denpasar, Indonesia; [2]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Prof. Dr. I.G.N.G. Ngoerah General Hospital, Denpasar, Indonesia; [3]School of Medicine and Health Sciences, Universitas Katolik Indonesia Atma Jaya, Jakarta, Indonesia

*Corresponding author: sastra@unud.ac.id

Abstract

Beyond gynecological issues, women with endometriosis have a significant risk of cardiac outcomes. Despite this evidence, the extent and mechanisms of the association remain unclear. The aim of this study was to evaluate the association between endometriosis and the incidence of cerebro-cardiovascular disorders. Using preferred reporting items for systematic review and meta-analyses (PRISMA) guidelines, seven databases were searched as of October 14, 2024, for observational studies assessing the association between endometriosis and cerebro-cardiovascular disorders. The main outcome was major adverse cardiovascular and cerebrovascular event (MACCE) while the secondary outcomes included all-cause mortality, cerebrovascular accident (CVA), ischemic heart disease (IHD), myocardial infarction (MI), arrhythmia, and heart failure (HF). Bias was assessed with the risk of bias in non-randomized studies of exposures (ROBINS-E) tool. Odds ratios with 95% confidence interval (CI) were calculated using random-effects meta-analysis. Evidence certainty was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. Robustness was assessed via sensitivity analyses and trial sequential analysis (TSA). Out of 3,141 studies, nine cohort studies encompassing 1,670,589 women (follow-up 7–28 years) were included. Endometriosis was associated with 24% higher odds of MACCE incidence (95%CI: 1.18–1.31, moderate certainty). In addition, having endometriosis increased the odds of CVA by 49% (95%CI: 1.20–1.85, high certainty), IHD by 64% (95%CI: 1.31–2.05, low certainty), MI by 53% (95%CI: 1.18–1.98, high certainty), arrhythmias by 24% (95%CI: 1.12–1.37, high certainty), and HF by 13% (95%CI: 1.03–1.25, high certainty). Endometriosis did not significantly associate with all-cause mortality. Sensitivity analyses and TSA reinforced all of these findings. In conclusion, endometriosis was significantly associated with increased odds of cerebro-cardiovascular disorders. Future research should clarify the underlying mechanisms and develop targeted prevention strategies.

Keywords: Epidemiology, endometriosis, cerebrovascular disorder, cardiovascular disease, risk factor

Copyright: © 2025 by the authors. This is an open access article distributed under the terms and conditions of the CC BY-NC 4.0.

https://narraj.org/

Introduction

Endometriosis is a non-malignant and chronic inflammatory condition characterized by the proliferation of endometrial glands and stroma beyond the uterine cavity [1,2]. This disease is a

Received: December 17, 2024 - Accepted: February 13, 2025 - Published online: February 18, 2025

significant global burden because it occurs in 10–15% of women of reproductive age and causes approximately 30–50% infertility [3]. Data from the World Health Organization (WHO) in 2023 shows that the prevalence of endometriosis worldwide was estimated at roughly 190 million million [4]. Endometriosis is associated with cardiovascular disease (CVD), one of the leading causes of premature mortality in females worldwide. This is due to its mechanism in altering the lipid profile, which will increase the risk of atherosclerosis. A study found that patients presenting with endometriosis had a higher risk of hospital admission for CVD [5,6]. However, the risk of death associated with CVD caused by endometriosis is still poorly studied.

Cerebrovascular diseases such as stroke are also associated with endometriosis. A previous study in the United Kingdom found that women with endometriosis had a 19% higher risk of developing cerebrovascular disease [7]. Another investigation reported that 10.7% of women with laparoscopic diagnosis of endometriosis developed a higher risk of hypercholesterolemia and 11% had a higher risk for hypertension. Several factors have also been implicated in promoting CVD [8-10], including hysterectomy and postmenopausal hormone therapy, both of which can contribute to atherosclerosis. These findings underscore the potential association between endometriosis and cerebrovascular and CVD. Nevertheless, the evidence on the role of endometriosis in increasing the risk of incidence of CVD and cerebrovascular diseases remains scarce. The aim of this study was to synthesize current evidence on the association between endometriosis and the risk of CVD and cerebrovascular disease. Additionally, this study sought to identify gaps in literature to guide future research efforts addressing this significant public health concern.

Methods

Study design and registration

This systematic review and meta-analysis were conducted in accordance with the 2020 preferred reporting items for systematic review and meta-analyses (PRISMA) standards [11], and the protocol has been registered in PROSPERO (an international prospective register of systematic reviews) under the identifier CRD42024603074.

Database and literature search

A comprehensive literature search was conducted on October 9, 2024, across various electronic databases (PubMed, ProQuest, SAGE Journals, EBSCOhost, Wiley Online Library, Google Scholar, and the Cochrane Library). The search utilized a combination of keywords with their synonyms and Medical Subject Headings (MeSH) terms of “endometriosis” OR “endometrioma” OR “endometrioses” AND “cerebrovascular disease” OR “cardiovascular disease” OR “CVD” OR “cardiac event(s)” OR “coronary artery disease” OR “CAD” OR “ischemic heart disease” OR “IHD”. Filters were implemented to encompass research published in English from inception until the search date. The relevant review and article reference lists were systematically analyzed to identify additional pertinent studies. Duplicate entries were identified and removed using the duplicate detection tool in EndNote X9 (Clarivate Analytics, Philadelphia, USA).

Eligibility criteria

Studies eligible for inclusion were observational studies, encompassing cohort, case-control, and cross-sectional designs that was focused on women diagnosed with endometriosis. Although all observational designs were eligible, only cohort studies fulfilled the inclusion criteria after full screening. Inclusion criteria required studies to assess the association between endometriosis and subsequent cerebrovascular and CVD in later life. Exclusion criteria included studies where endometriosis was not the primary exposure of interest, lacked specific diagnostic criteria for endometriosis, or did not include a comparator group of women without endometriosis.

Study selection and data extraction

Three independent reviewers (SSI, FXR, and RW) thoroughly examined the titles, abstracts, and full text of the studies for clarity. Discrepancies were resolved through discussion with a senior author (IGSW). Extracted data included study design, data sources, sample sizes of the endometriosis and control groups, baseline characteristics including age and race, follow-up

duration, nulliparity rates, oral contraceptive pill use, smoking status, rates of hysterectomy and/or oophorectomy, infertility rates, hypertension, dyslipidemia, diabetes, and outcomes of interest such as major adverse cardiac and cerebrovascular event (MACCE), cerebrovascular accident (CVA), ischemic heart disease (IHD), myocardial infarction (MI), heart failure (HF), arrhythmia, and all-cause mortality. Outcome measures were documented for both the endometriosis and non-endometriosis groups.

Risk of bias assessment

The risk of bias of the included studies was independently evaluated by three investigators (SSI, LL, and GT) using the risk of bias in non-randomized studies of exposures (ROBINS-E) tool, as recommended by the Cochrane Handbook [12]. This assessment addressed seven domains: (1) confounding bias, (2) measurement bias of exposures, (3) selection bias of participants, (4) bias from post-exposure interventions, (5) bias due to missing data, (6) measurement bias of outcomes, and (7) selection bias of reported results. Each domain was rated as "low risk," "moderate risk," "serious risk," or "critical risk" of bias. Disagreements were resolved through consultation with the senior author (IGSW).

Data synthesis and statistical analysis

The statistical analyses were conducted utilizing a random-effects model with the Mantel-Haenszel method for dichotomous outcomes. Pooled odds ratio (OR) with 95% confidence interval (CI) were calculated, considering a $p<0.05$ as statistically significant. Heterogeneity among studies was assessed using the I^2 statistic, with values exceeding 50% or a $p<0.10$, indicating substantial heterogeneity. The certainty of evidence for each outcome was graded using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, categorizing as high, moderate, low, or very low certainty [13]. Sensitivity analyses were performed by sequentially excluding individual studies or those with a high risk of bias to evaluate the robustness of the pooled results. All statistical computations were performed using Review Manager (RevMan) version 5.4 (Cochrane, London, UK). A trial sequential analysis (TSA) was performed using TSA software version 0.9.5.10 Beta (Copenhagen Trial Unit, Copenhagen, Denmark) to address potential random errors arising from small sample sizes and multiple significance tests [14]. The TSA calculated the cumulative Z-curve and established trial sequential monitoring boundaries (TSMB), allowing firm conclusions when the Z-curve crossed the thresholds. The analysis utilized a two-sided alpha (α) of 0.05 and a power (1–β) of 90%, adjusted using the O'Brien-Fleming spending function for stringent control of type I errors [15]. The relative risk reduction was based on a low-bias estimate, and heterogeneity was adjusted using model variance. This methodology enhanced the reliability of the findings by reducing the risk of random errors.

Results

Study selection

Our comprehensive literature search identified a total of 3,141 studies (PubMed = 710, EBSCOhost = 241, ProQuest = 55, SAGE Journals = 403, Wiley Online Library = 8, ScienceDirect = 1,701, and Google Scholar = 23). Following the removal of duplicates and the screening of titles and abstracts, 12 studies were selected for full-text evaluation [16-27]. Three studies were excluded for failing to meet the inclusion criteria [16-18]. Additionally, two studies were identified through manual searches of reference lists. However, both studies were excluded: the first was abstract-only study [28] and the second had data reflected a priori baseline values rather than being observational [29]. Nine papers fulfilled all inclusion requirements and were included in the quantitative meta-analysis [19-27]. The detailed of study selection process are presented in **Figure 1**.

Characteristics of the studies

Nine included studies comprising seven retrospective studies and two prospective cohort studies published between 2016 and 2024 [19-27]. They encompassed 1,670,589 participants with follow-up durations ranging from 7 to 28 years. The mean age at baseline was 36.3±7.9 years, and

the largest proportion of the participants were Caucasian (68.3%), followed by Asian (23.9%) and other ethnicities (7.8%). Detailed characteristics of the included studies are presented in **Table 1**.

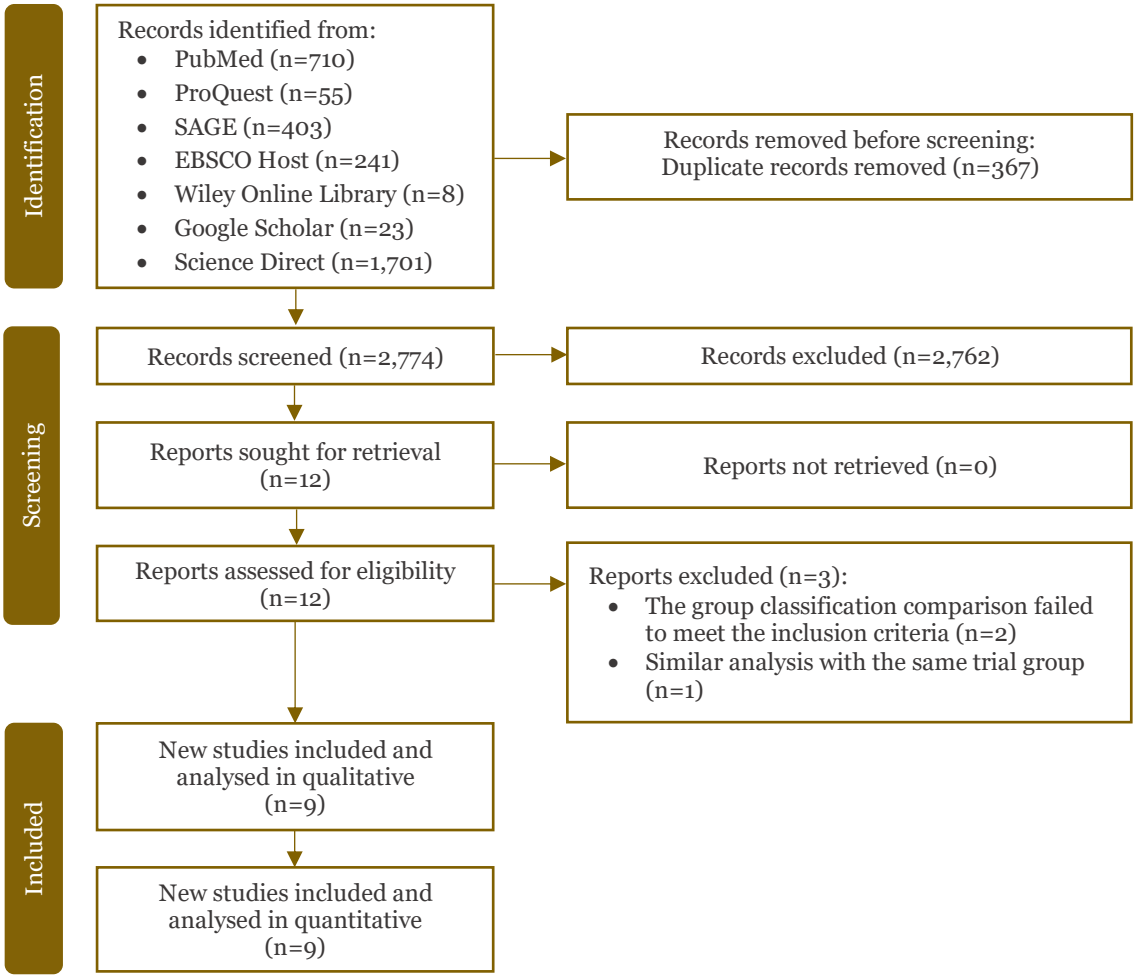

Figure 1. PRISMA flow diagram depicting study selection.

Quality of the studies

The included studies were evaluated for their quality using the ROBINS-E tool, and the detailed risk of bias assessment is presented in **Figure 2**. Among the nine studies, one was classified as having a low risk of bias [22], while the remaining eight were deemed to have "some concerns" [19-21,23-27]. Six studies [20,21,23,24,26,27] exhibited concerns about confounding factors, as they did not adequately adjust for lifestyle variables such as smoking, physical activity, or dietary habits, which could influence the outcomes. Wei *et al.* [23] did not consider systemic inflammatory factors as potential confounders. Four studies raised concerns in the participant selection domain [19,20,25,26]. Saavalainen *et al.* [20] restricted their cohort to women with surgically confirmed endometriosis, potentially introducing selection bias. Blom *et al.* [26] used diagnostic criteria based on an outdated WHO classification. Mu *et al.* [19] and Farland *et al.* [25] included the Nurses' Health Study participants, which may introduce selection bias due to higher health awareness among nurses.

Regarding post-exposure interventions, three studies [21,23,24] had concerns about the influence of exposure severity on subsequent interventions, particularly in cases of severe endometriosis. Additionally, four studies [20,23,25,27] exhibited concerns due to missing data, as they needed more information on management strategies. Wei *et al.* [23] did not report the status of participants lost to follow-up, further contributing to potential bias. All studies demonstrated a low risk of bias in exposure measurement, outcome measurement, and selection of reported results.

Figure 2. Risk of bias assessment using the risk of bias in non-randomized studies of exposures (ROBINS-E) tool.

Meta-analysis assessing the association of endometriosis and incidence of major adverse cardiac and cerebrovascular event (MACCE)

Nine studies [19-27] examining the association between endometriosis and cerebrovascular and CVD were included in meta-analysis. Reported outcomes included MACCE, CVA, IHD, MI, HF, arrhythmias, and all-cause mortality.

The meta-analysis revealed a significantly higher risk of MACCE in women with endometriosis relative to those without OR of 1.24 (95%CI: 1.18–1.31; p<0.00001; I^2=78%) (**Figure 3A**). Sensitivity analysis, conducted by methodically excluding individual studies to assess the robustness of the results, validated this association and diminished heterogeneity OR of 1.28 (95%CI: 1.20–1.36; p<0.00001; I^2=52%). The GRADE methodology evaluated the evidence certainty and was categorized as moderate (**Table 2**). The TSA further validated the sufficiency of the evidence, as the cumulative Z-score surpassed the TSMB, thereby confirming the association (**Figure 3B**).

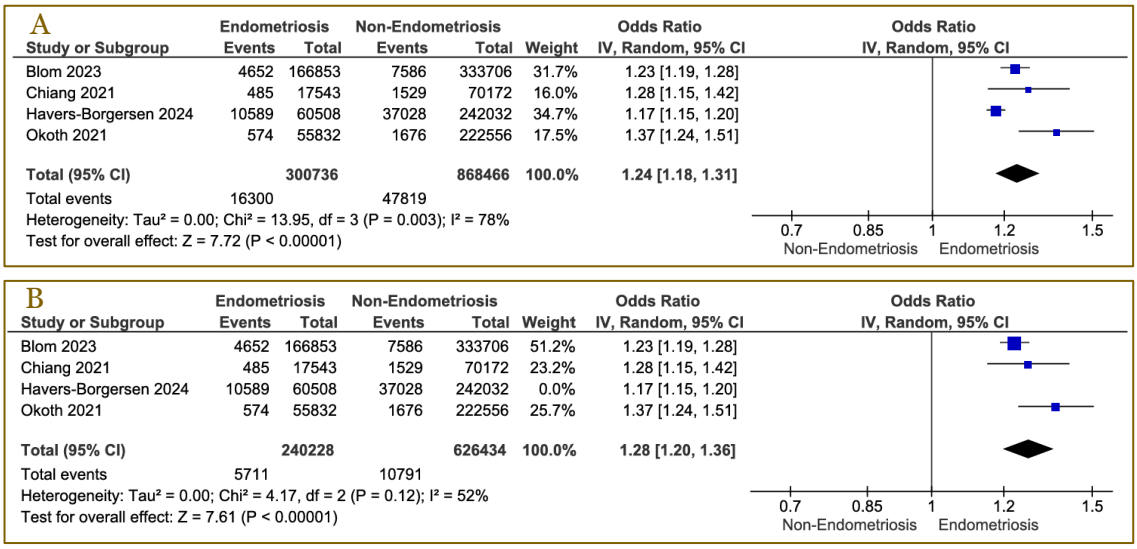

Figure 3. Forest plot showing the association of endometriosis and incidence of major adverse cardiac and cerebrovascular events (MACCE) before (A) and after sensitivity analysis using trial sequential analysis (TSA) (B).

Table 1. Baseline characteristics of included studies

Study	Design	Database	Groups (n)		Age at baseline (years)	Follow-up (years)	Race (%)	Nulliparity (%)	OCP use (%)	Smoker (%)	Histerectomy/ oophorectomy (%)	Infertility (%)	HT (%)	DLD (%)	DM (%)
					Mean±SD	Mean±SD									
Mu *et al.*, 2016 [19]	Prospective cohort	The Nurses' Health Study II, United States	EM	5,296	36.0±4.2	20.0±0.0	White (94.0) Other (6.0)	42.0	89.0	36.0	21.0	NA	7.0	14.0	1.0
			Non-EM	109,161	34.7±4.7		White (92.0) Other (8.0)	30.0	83.0	35.0	4.0		5.0	11.0	1.0
Saavalainen *et al.*, 2019 [20]	Retrospective cohort	Finnish Hospital Discharge Register, Finland	EM	49,956	36.4±9.0	16.8±7.3	Finnish (100.0)	NA	NA	NA	18.2	NA	NA	NA	NA
			Non-EM	98,824							2.0				
Chiang *et al.*, 2021 [21]	Retrospective cohort	Taiwan National Health Insurance Research Database, Taiwan	EM	17,543	38 (31–44)	9.3±0.0	Taiwanese (100.0)	NA	NA	NA	NA	13.1	16.5	15.5	7.9
			Non-EM	70,172	38 (31–44)							3.5	12.5	10.7	5.9
Okoth *et al.*, 2021 [22]	Retrospective cohort	The Health Improvement Network, United Kingdom	EM	56,074	36.7±8.6	23.0±0.0	NA	NA	NA	23.8	15.1	NA	3.2	NA	1.0
			Non-EM	223,576	36.6±8.6					23.0	3.2		3.1		1.3
Wei *et al.*, 2021 [23]	Retrospective cohort	Taiwan National Health Insurance Research Database, Taiwan	EM	13,988	37.8±8.4	13.0±0.0	Taiwanese (100.0)	NA	NA	NA	10.5	NA	3.2	1.3	1.5
			Non-EM	13,988	37.9±8.5						10.4		3.2	1.4	1.3
Li *et al.*, 2021 [24]	Retrospective cohort	Taiwan National Health Insurance Research Database, Taiwan	EM	19,454	37.4±8.9	7.4±3.8	Taiwanese (100.0)	NA	58.3	NA	25.0	NA	7.6	6.5	5.0
			Non-EM	77,816	37.3±9.0	7.0±3.9			36.5		2.3		6.3	5.0	3.9
Farland *et al.*, 2022 [25]	Prospective cohort	The Nurses' Health Study II, United States	EM	5,244	36.0±4.2	28.0±0.0	White (94.0) Other (6.0)	NA	89.3	14.2	NA	54.0	NA	NA	NA
			Non-EM	106,812	34.7±4.7		White (92.5) Other (7.5)		83	13.2		16.5			
Blom *et al.*, 2023 [26]	Retrospective cohort	Ontario Health Insurance Plan, Canada	EM	166,853	36.4±8.0	20.0±0.0	NA	65.3	NA	NA	28.0	24.4	7.8	NA	2.7
			Non-EM	333,706	36.4±8.0			59.6			2.3	8.7	5.6		2.3
Havers-Borgersen *et al.*, 2024 [27]	Retrospective cohort	Danish National Patient Registry, Denmark	EM	60,508	37.3 (29.9–44.6)	16.1 (7.8–26.2)	Danish (90.4) Other (9.6)	NA	NA	NA	NA	NA	4.1	NA	1.7
			Non-EM	242,032	37.3 (29.9–44.6)		Danish (80.8) Other (19.2)						2.6		1.2
Summary[†]			1,670,589		36.3±7.9	19.7±6.5	Asian (23.9) Caucasian (68.3) Other (7.8)	55.7	70.5	23.7	11.5	13.5	4.9	8.7	2.2

DLD: dyslipidemia; DM: diabetes mellitus; EM: endometriosis; HT: hypertension; NA: not available; OCP: oral contraceptive pills; SD: standard deviation
[†]Accounting for only the available data

Table 2. GRADE approach on endometriosis compared to non-endometriosis for the development of cerebro-cardiovascular disorders

Outcome	Certainty assessment							Summary of findings				
	Participants (studies) follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95%CI)	Anticipated absolute effects	
								With non-endometriosis	With endometriosis		Risk with non-endometriosis	Risk difference with endometriosis
Major adverse cardiovascular and cerebrovascular events	1,169,202 (4 non-randomised studies) [20,21,25,26]	Not serious	Serious*	Not serious	Not serious	None	⊕⊕⊕◯ Moderate*	47,819/868,466 (5.5%)	16,300/300,736 (5.4%)	OR 1.24 (1.18–1.31)	47,819/868,466 (5.5%)	12,324 more per 1,000,000 (from 9,273 more to 15,859 more)
Cerebrovascular accidents	1,281,850 (5 non-randomised studies) [20,21,24-26]	Not serious	Not serious†	Not serious	Not serious	None	⊕⊕⊕⊕ High†	29,761/975,772 (3.0%)	9,209/306,078 (3.0%)	OR 1.49 (1.20–1.85)	29,761/975,772 (3.0%)	14,276 more per 1,000,000 (from 5,878 more to 24,499 more)
Ischemic heart disease	1,107,213 (6 non-randomised studies) [18,20-23,25]	Not serious	Very serious‡	Not serious	Not serious	None	⊕⊕◯◯ Low‡	12,189/828,080 (1.5%)	5,728/279,133 (2.1%)	OR 1.64 (1.31–2.05)	12,189/828,080 (1.5%)	9,195 more per 1,000,000 (from 4,475 more to 14,996 more)
Myocardial infarction	917,556 (3 non-randomised studies) [18,25,26]	Not serious	Not serious†	Not serious	Not serious	None	⊕⊕⊕⊕ High†	17,559/684,899 (2.6%)	5,553/232,657 (2.4%)	OR 1.53 (1.18 to 1.98)	17,559/684,899 (2.6%)	13,062 more per 1,000,000 (from 4,476 more to 23,880 more)
Heart failure	1,082,749 (3 non-randomised studies) [21,25,26]	Not serious	Not serious§	Not serious	Not serious	None	⊕⊕⊕⊕ High§	21,425/799,314 (2.7%)	6,546/283,435 (2.3%)	OR 1.13 (1.03–1.25)	21,425/799,314 (2.7%)	3,379 more per 1,000,000 (from 782 more to 6,478 more)
Arrhythmias	1,169,161 (4 non-randomised studies) [20,21,25,26]	Not serious	Not serious†	Not serious	Not serious	None	⊕⊕⊕⊕ High†	56,089/868,545 (6.5%)	16,530/300,616 (5.5%)	OR 1.24 (1.12–1.37)	56,089/868,545 (6.5%)	14,277 more per 1,000,000 (from 7,193 more to 21,829 more)
All-cause mortality	1,003,322 (4 non-randomised studies) [19-21,25]	Not serious	Very serious‡	Not serious	Serious‖	None	⊕◯◯◯ Very low‡‖	14,888/715,640 (2.1%)	6,275/287,682 (2.2%)	OR 0.88 (0.72–1.08)	14,888/715,640 (2.1%)	2,451 fewer per 1,000,000 (from 5,737 fewer to 1,627 more)

CI: confidence interval; OR: odds ratio
*Downgraded by one level due to considerable heterogeneity, which could be reduced by sensitivity analysis
†Not downgraded due to considerable heterogeneity, which was reduced by sensitivity analysis
‡Downgraded by two levels due to considerable heterogeneity, which could not be reduced by sensitivity analysis
§Not downgraded due to substantial heterogeneity, which was reduced by sensitivity analysis
‖Downgraded by one level due to wide confidence interval

Meta-analysis assessing the association of endometriosis and incidence of cerebrovascular accident (CVA)

Endometriosis was significantly associated with an elevated risk of CVA (OR: 1.49; 95%CI: 1.20–1.85; p=0.0003; I^2=97%) (**Figure 4A**). The GRADE assessment suggested the confidence in evidence as high (**Table 2**). Sensitivity analysis using TSA reduced heterogeneity and maintained statistical significance with an OR of 1.21 (95%CI: 1.15–1.27; p<0.00001; I^2=39%). The cumulative Z-curve intersected the TSMB, as indicated by the TSA (**Figure 4B**), thereby confirming the reliability and sufficiency of the evidence.

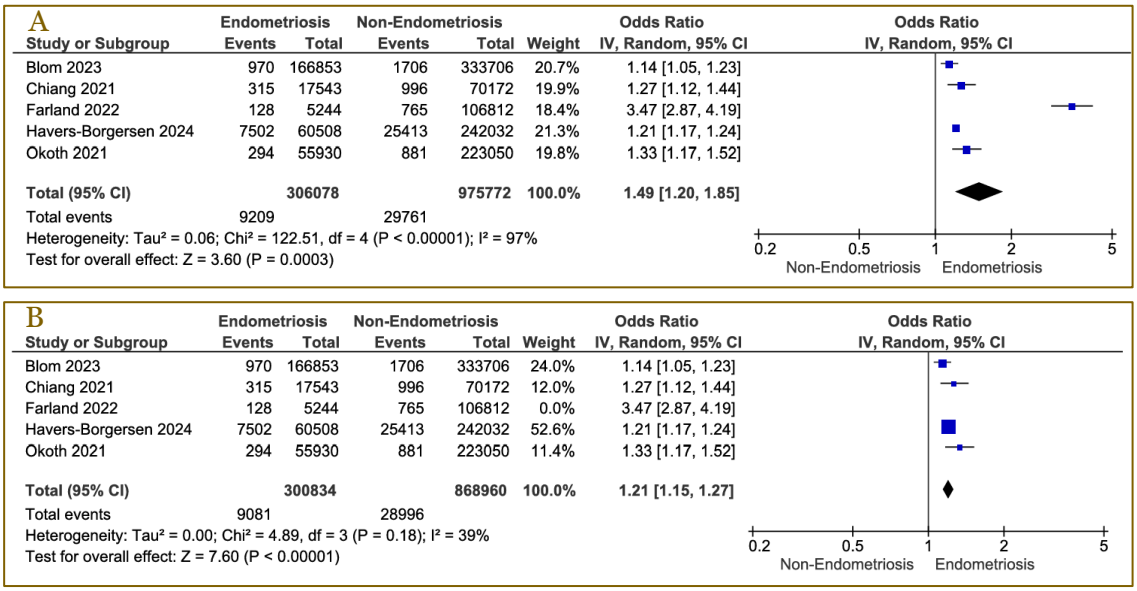

Figure 4. Forest plot showing the association of endometriosis and cerebrovascular accidents (CVA) before (A) and after sensitivity analysis using trial sequential analysis (TSA) (B).

Meta-analysis assessing the association of endometriosis and incidence of ischemic heart disease (IHD)

The analysis demonstrated a substantial correlation between endometriosis and increased risk of IHD (OR: 1.64; 95%CI: 1.31–2.05; p<0.0001; I^2=97%) (**Figure 5A**). The sensitivity analysis validated the correlation with a marginal decrease in heterogeneity (OR: 1.41; 95%CI: 1.26–1.58; p<0.0001; I^2=88%). The GRADE assessment indicated a poor certainty of evidence owing to significant heterogeneity and possible confounding variables (**Table 2**). The cumulative Z-curve from TSA intersected the TSMB, confirming that sufficient evidence supports the association (**Figure 5B**).

Meta-analysis assessing the association of endometriosis and incidence of myocardial infarction (MI)

Endometriosis was notably linked to an increased risk of MI (OR: 1.53; 95%CI: 1.18–1.98; p=0.001; I^2=97%) (**Figure 6A**). The sensitivity analysis reaffirmed the connection with negligible heterogeneity (OR: 1.13; 95%CI: 1.10–1.17; p<0.00001; I^2=0%). The GRADE assessed the certainty of evidence as high (**Table 2**). The cumulative Z-curve intersected the TSMB, as demonstrated by the TSA (**Figure 6B**), indicating that the evidence was both robust and sufficient.

Meta-analysis assessing the association of endometriosis and incidence of heart failure (HF)

The meta-analysis indicated that endometriosis was linked to a markedly elevated risk of HF (OR: 1.13; 95%CI: 1.03–1.25; p=0.01; I^2=63%) (**Figure 7A**). Sensitivity analysis corroborated this result with diminished heterogeneity (OR: 1.17; 95%CI: 1.11–1.23; p<0.00001; I^2=30%). The evidence certainty was assessed as high based on the GRADE methodology (**Table 2**). The TSA

validated the adequacy of the evidence by demonstrating that the cumulative Z-curve intersected the TSMB (**Figure 7B**).

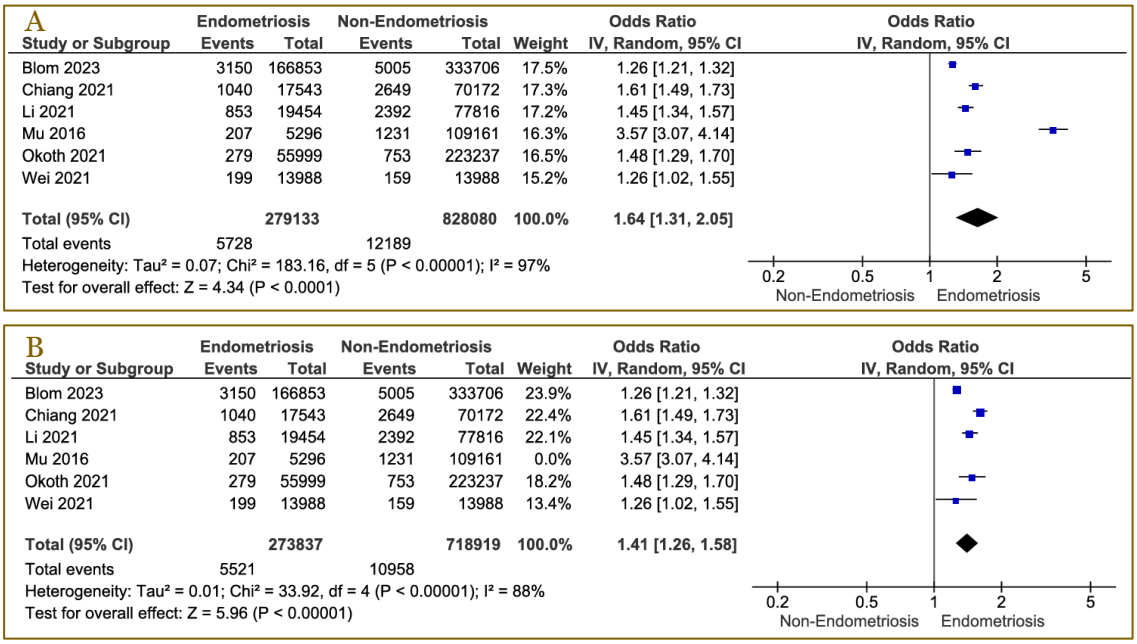

Figure 5. Forest plot showing the association of endometriosis and ischemic heart disease (IHD) before (A) and after sensitivity analysis using trial sequential analysis (TSA) (B).

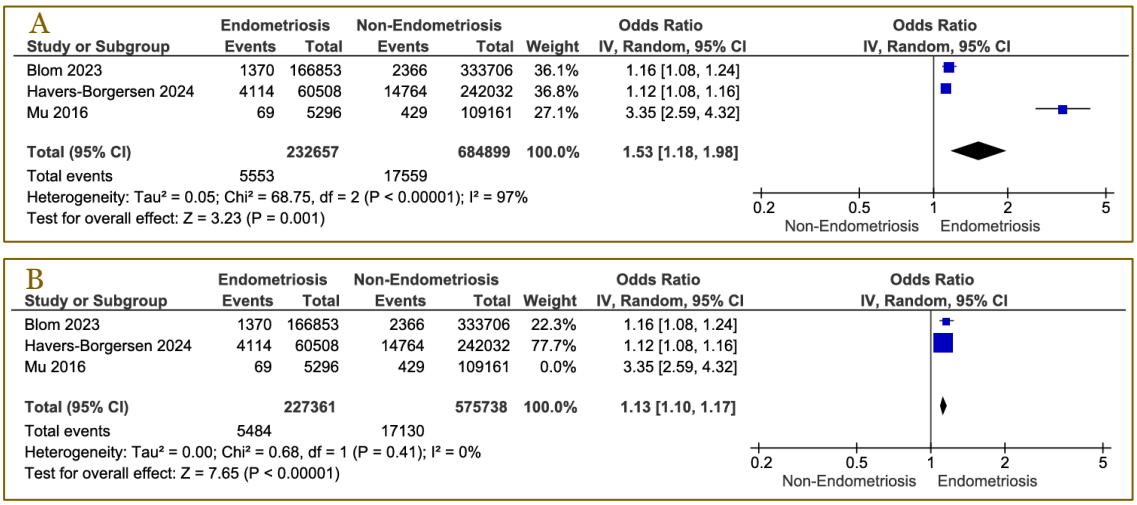

Figure 6. Forest plot showing the association of endometriosis and myocardial infarction (MI) before (A) and after sensitivity analysis using trial sequential analysis (TSA) (B).

Meta-analysis assessing the association of endometriosis and incidence of arrhythmia

Endometriosis demonstrated a significant association with an increased risk of arrhythmias (OR: 1.24; 95%CI: 1.12–1.37; p<0.0001; I^2=75%) (**Figure 8A**). Sensitivity analysis preserved the significance of the connection and diminished heterogeneity (OR: 1.19; 95%CI: 1.17–1.22; p<0.00001; I^2=0%). The GRADE assessed the certainty of evidence as high (**Table 2**). TSA analysis found a cumulative Z-curve intersecting TSMB, confirming evidence as sufficient and trustworthy (**Figure 8B**).

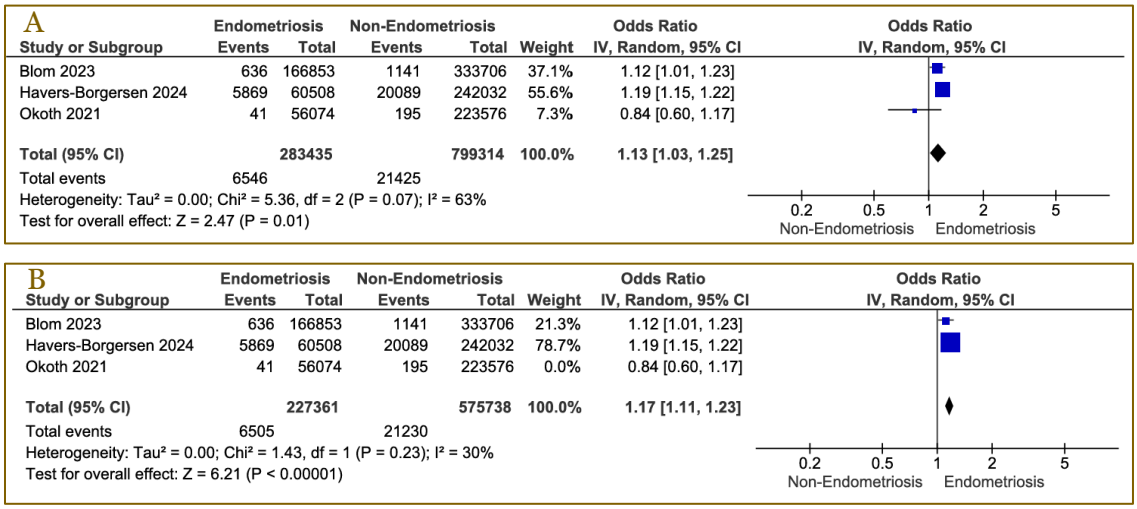

Figure 7. Forest plot showing the association of endometriosis and heart failure (HF) before (A) and after sensitivity analysis using trial sequential analysis (TSA) (B).

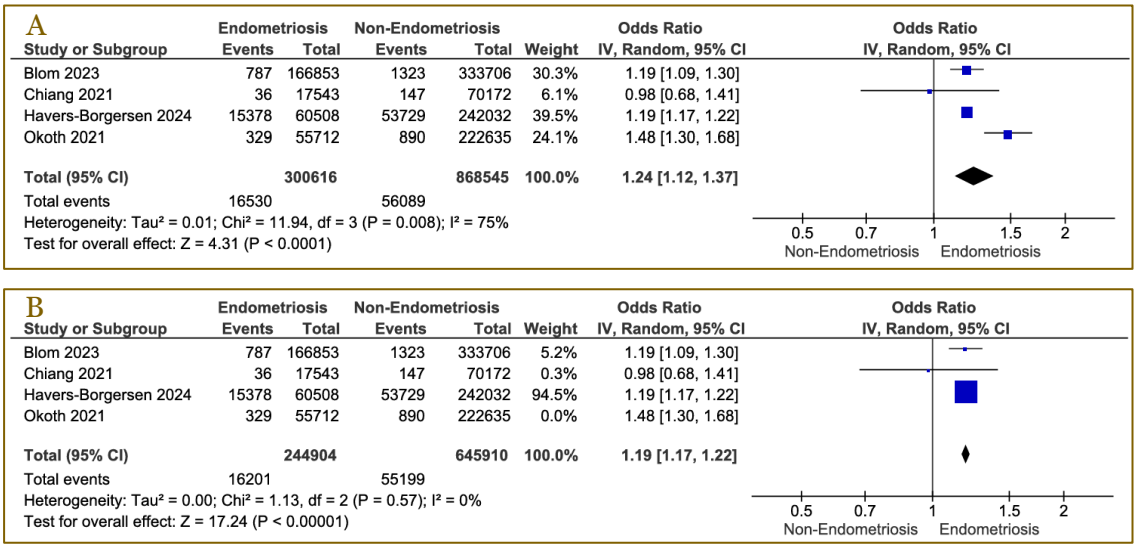

Figure 8. Forest plot showing the association of endometriosis and arrhythmia before (A) and after sensitivity analysis using trial sequential analysis (TSA) (B).

Meta-analysis assessing the association of endometriosis and incidence of all-cause mortality

Analysis indicated no meaningful association between endometriosis with all-cause mortality (OR: 0.88; 95%CI: 0.72–1.08; p=0.22; I^2=97%) (**Figure 9A**). Sensitivity assessment produced similar results of lacking statistical importance (OR: 0.84 95%CI: 0.68–1.05; p=0.13; I^2=92%). GRADE assessment categorized evidence certainty as very low, primarily due to notable heterogeneity and imprecision (**Table 2**). TSA analysis showed its cumulative Z-curve did not intersect TSMB, suggesting existing evidence cannot yield definitive determination regarding this outcome (**Figure 9B**).

Discussion

This study demonstrated that endometriosis is associated with a significantly increased risk of MACCE. Specifically, endometriosis was linked to 24% higher odds of MACCE (95%CI: 1.18–1.31, moderate certainty). The condition significantly elevated the odds of CVA by 49% (95%CI: 1.20–1.85, high certainty), IHD by 64% (95%CI: 1.31–2.05, low certainty), MI by 53% (95%CI: 1.18–1.98, high certainty), arrhythmias by 24% (95%CI: 1.12–1.37, high certainty), and HF by 13% (95%CI: 1.03–1.25, high certainty). Sensitivity analyses and TSA reinforced these findings, underscoring the robustness of the observed associations.

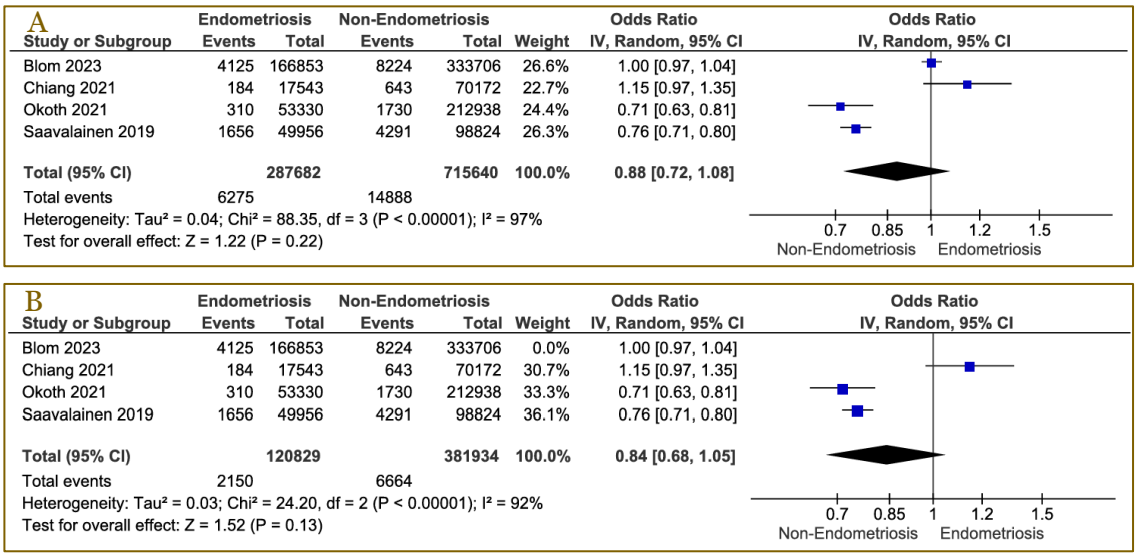

Figure 9. Forest plot showing the association of endometriosis and all-cause mortality before (A) and after sensitivity analysis using trial sequential analysis (TSA) (B).

In line with previous meta-analyses [30,31], our findings indicated that women with endometriosis face a heightened risk of both cerebrovascular and CVD, likely driven by overlapping mechanisms such as chronic inflammation, oxidative stress, and dysregulated lipid metabolism. Beyond reinforcing existing data, a novelty was introduced by assessing a broader range of endpoints (e.g., HF, arrhythmias, and all-cause mortality), utilizing standardized Cochrane risk-of-bias (ROBINS-E) and evidence-certainty (GRADE) tools, and incorporating TSA for enhanced conclusiveness. The present study also addressed the limitations of earlier meta-analyses—while Poeta do Couto *et al.* included only five studies [19,21-23,25], we incorporated four more [20,24,26,27]. Although Okoli *et al.* used nine studies [19,21-25,28,29,32], one was abstract-only (high risk of bias) [28], and another employed priori data rather than observational findings [29]. Since those publications, two additional studies have emerged, contributing 803,099 new participants and further bolstering our analysis's power and generalizability.

The pathophysiological mechanisms underlying the association between endometriosis and adverse events are complex and multifactorial. A recent study proposed a mechanism involving chronic systemic inflammation induced by retrograde menstruation, where endometrial cells flow back into the fallopian tubes and pelvic cavity [33]. This process introduces inducers of oxidative stress, such as apoptotic endometrial tissue, enhancing systemic subclinical inflammation. Furthermore, this condition leads to coelmic metaplasia which worsen the inflammation process associated with endometriosis [2]. Chronic inflammation can lead to alterations in lipid metabolism, promoting atherogenesis. Atherosclerosis, characterized by endothelial dysfunction and low-density lipoprotein retention in the arterial wall, progresses through stages of fatty streak formation, plaque development, and eventual plaque rupture, leading to ischemic events like MI and stroke [34,35]. Moreover, this condition can affect both structure and function of the brain, resulting in neurological symptoms [36].

Endometriosis, which is a chronic estrogen-dependent disorder, is associated with systemic inflammation, oxidative stress, and an atherogenic lipid profile. These factors promote vascular damage, atheromatous plaque formation, and coronary artery atherosclerosis, increasing the risk of coronary heart disease, which may lead to HF. These underlying mechanisms may explain the significantly increased odds of IHD and HF in patients with endometriosis [19].

Furthermore, oxidative stress and reactive oxygen species (ROS) production in endometriosis may contribute to arrhythmogenesis and disrupt the balance of oxidation and reduction in cells, leading to oxidative stress. This imbalance affects ion channels like potassium, calcium, sodium, and ryanodine receptors, impairing physiological cardiac electrical activity and triggering arrhythmias [37]. Oxidative stress may also alter cardiac electrophysiology, increasing susceptibility to arrhythmias. Chronic inflammation and endothelial dysfunction caused by

prolonged oxidative stress and ROS may promote pro-arrhythmic substrates within the myocardium. Genetic factors may also play a role; endometriosis and CVD might share genetic polymorphisms predisposing individuals to both conditions, warranting further genetic studies to explore this potential link [38,39]. All-cause mortality may also not be significantly reduced because of the presence of confounding factors such as age, accident, and smoking which may cause circulatory problems.

This study offers several notable strengths. First, it employed a rigorous, comprehensive literature search across multiple databases, reducing the risk of missing relevant studies. Second, it included a large sample size (1.67 million women), enhancing the findings' power and generalizability. Third, it used standardized risk-of-bias tool (ROBINS-E) and the GRADE framework to assess the certainty of evidence bolsters methodological integrity. Fourth, incorporating TSA and extensive sensitivity analyses further strengthened the reliability of our results by mitigating the influence of random error and testing the robustness of pooled estimates. Nonetheless, important limitations remain. The observational nature of included studies did not permit definitive causal inferences, and residual confounders—particularly unmeasured lifestyle, genetic, and metabolic factors—may persist. Moreover, diagnostic criteria for endometriosis and cardiovascular outcomes varied across studies, introducing heterogeneity. Finally, some studies' incomplete reporting of key exposures and outcomes could have influenced our overall effect estimates. Future prospective trials with standardized definitions, extended follow-up, and attention to potential confounders are needed to clarify the mechanisms underlying the observed association between endometriosis and cerebro-cardiovascular diseases.

Conclusion

This study found that a significant association between endometriosis and the incidence of cardiovascular and cerebrovascular disorders, including MACCE, IHD, CVA, MI, HF, and arrhythmias. Sensitivity analysis and TSA repeatedly corroborated these data, demonstrating strong evidence for these associations. Chronic inflammation, oxidative stress, and disrupted lipid metabolism are hypothesized pathways connecting endometriosis to these detrimental effects, potentially facilitating atherogenesis and endothelial dysfunction. Despite these findings, no significant association was seen between endometriosis and all-cause mortality, necessitating more investigation to elucidate this outcome.

Ethics approval

No formal ethical approval was necessary.

Competing interests

All authors confirm that they have no relevant conflicts of interest to disclose.

Funding

This investigation did not receive any financial support from external sources.

Underlying data

Any secondary data that informed the conclusions of this research are accessible from the corresponding author upon reasonable request.

Declaration of artificial intelligence use

We hereby confirm that no artificial intelligence (AI) tools or methodologies were utilized at any stage of this study, including during data collection, analysis, visualization, or manuscript preparation. All work presented in this study was conducted manually by the authors without the assistance of AI-based tools or systems.

How to cite

Winata IGS, Immanuel SS, Leonardo L, *et al*. Examining the interplay between endometriosis and later-life cerebro-cardiovascular diseases: A systematic review, meta-analysis, and trial sequential analysis. Narra J 2025; 5 (1): e1935 - http://doi.org/10.5225/narra.v5i1.1935.

References

1. Parasar P, Ozcan P, Terry KL. Endometriosis: Epidemiology, diagnosis and clinical management. Curr Obstet Gynecol Rep 2017;6(1):34-41.
2. Patel BG, Lenk EE, Lebovic DI, *et al*. Pathogenesis of endometriosis: Interaction between endocrine and inflammatory pathways. Best Pract Res Clin Obstet Gynaecol 2018;50:50-60.
3. Smolarz B, Szyłło K, Romanowicz H. Endometriosis: Epidemiology, classification, pathogenesis, treatment and genetics (review of literature). Int J Mol Sci 2021;22(19):10554.
4. Ellis K, Munro D, Clarke J. Endometriosis is undervalued: A call to action. Front Glob Womens Health 2022;3:902371.
5. Rossi HR, Uimari O, Terho A, *et al*. Increased overall morbidity in women with endometriosis: A population-based follow-up study until age 50. Fertil Steril 2023;119(1):89-98.
6. Starodubtseva N, Chagovets V, Tokareva A, *et al*. Diagnostic value of menstrual blood lipidomics in endometriosis: A pilot study. Biomolecules 2024;14(8):899.
7. Zheng M, Zheng S. Endometriosis increases the risk of stroke: A Mendelian randomization study. Stroke 2023;54(2):e30-e33.
8. Webb TR, Erdmann J, Stirrups KE, *et al*. Systematic evaluation of pleiotropy identifies 6 further loci associated with coronary artery disease. J Am Coll Cardiol 2017;69(7):823-836.
9. Widyaning PPF. Endometriosis and cardiovascular disease: A systematic review. Asian J Heal Res 2024;3(2):183-189.
10. Elefante C, Brancati GE, Oragvelidze E, *et al*. Psychiatric symptoms in patients with cerebral endometriosis: A case report and literature review. J Clin Med 2022;11(23):7212.
11. Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
12. Higgins JPT, Morgan RL, Rooney AA, *et al*. A tool to assess risk of bias in non-randomized follow-up studies of exposure effects (ROBINS-E). Environ Int 2024;186:108602.
13. Kirmayr M, Quilodrán C, Valente B, *et al*. The GRADE approach, part 1: How to assess the certainty of the evidence. Medwave 2021;21(2):e8109.
14. Claire R, Gluud C, Berlin I, *et al*. Using trial sequential analysis for estimating the sample sizes of further trials: Example using smoking cessation intervention. BMC Med Res Methodol 2020;20(1):284.
15. Wetterslev J, Jakobsen JC, Gluud C. Trial sequential analysis in systematic reviews with meta-analysis. BMC Med Res Methodol 2017;17(1):39.
16. Chiang HJ, Lan KC, Yang YH, *et al*. Effects of medical and surgical treatment on the risk of major adverse cardiovascular and cerebrovascular events in Asian women with endometriosis. Research Square. 201916.
17. Farland LV, Wang Y, Gaskins AJ, *et al*. Infertility and risk of cardiovascular disease: A prospective cohort study. J Am Heart Assoc 2023;12(5):e027755.
18. Mu F, Rich-Edwards J, Rimm EB, *et al*. Association between endometriosis and hypercholesterolemia or hypertension. Hypertension 2017;70(1):59-65.
19. Mu F, Rich-Edwards J, Rimm EB, *et al*. Endometriosis and risk of coronary heart disease. Circ Cardiovasc Qual Outcomes 2016;9(3):257-264.
20. Saavalainen L, But A, Tiitinen A, *et al*. Mortality of midlife women with surgically verified endometriosis-a cohort study including 2.5 million person-years of observation. Hum Reprod 2019;34(8):1576-1586.
21. Chiang HJ, Lan KC, Yang YH, *et al*. Risk of major adverse cardiovascular and cerebrovascular events in Taiwanese women with endometriosis. J Formos Med Assoc 2021;120:327-336.
22. Okoth K, Wang J, Zemedikun D, *et al*. Risk of cardiovascular outcomes among women with endometriosis in the United Kingdom: A retrospective matched cohort study. BJOG 2021;128(10):1598-1609.
23. Wei CH, Chang R, Wan YH, *et al*. Endometriosis and new-onset coronary artery disease in Taiwan: A nationwide population-based study. Front Med 2021;8:619664.
24. Li PC, Yang YC, Wang JH, *et al*. Endometriosis is associated with an increased risk of coronary artery disease in Asian women. J Clin Med 2021;10(18):4173.
25. Farland LV, Degnan WJ, Bell ML, *et al*. Laparoscopically confirmed endometriosis and risk of incident stroke: A prospective cohort study. Stroke 2022;53(10):3116-3122.
26. Blom JN, Velez MP, McClintock C, *et al*. Endometriosis and cardiovascular disease: A population-based cohort study. CMAJ Open 2023;11(2):E227-E236.

27. Havers-Borgersen E, Hartwell D, Ekelund C, *et al*. Endometriosis and long-term cardiovascular risk: A nationwide Danish study. Eur Heart J 2024;45(44):4734-4743.
28. Akinjero A, Adegbala O, Akinyemiju T. Abstract P320: Is co-occurring endometriosis among women with myocardial infarction associated with worse in-hospital outcomes? Findings from the nationwide inpatient sample. Circulation 2017;135 Suppl 1:AP320-AP320.
29. Surrey ES, Soliman AM, Johnson SJ, *et al*. Risk of developing comorbidities among women with endometriosis: A retrospective matched cohort study. J Womens Health 2018;27(9):1114-1123.
30. Poeta do Couto CP, Policiano C, Pinto FJ, *et al*. Endometriosis and cardiovascular disease: A systematic review and meta-analysis. Maturitas 2023;171:45-52.
31. Okoli U, Charoenngam N, Ponvilawan B, *et al*. Endometriosis and risk of cardiovascular disease: Systematic review and meta-analysis. J Womens Health 2023;32(12):1328-1339.
32. Chao YH, Liu CH, Pan YA, Yen FS, Chiou JY, Wei JCC. Association Between Endometriosis and Subsequent Risk of Sjögren's Syndrome: A Nationwide Population-Based Cohort Study. Front Immunol. 2022;13.
33. Lamceva J, Uljanovs R, Strumfa I. The main theories on the pathogenesis of endometriosis. Int J Mol Sci 2023;24(5):4254.
34. Taskin O, Rikhraj K, Tan J, *et al*. Link between endometriosis, atherosclerotic cardiovascular disease, and the health of women midlife. J Minim Invasive Gynecol 2019;26(5):781-784.
35. Marchandot B, Curtiaud A, Matsushita K, *et al*. Endometriosis and cardiovascular disease. Eur Heart J Open 2022;2(1):oeac001.
36. Taylor HS, Kotlyar AM, Flores VA. Endometriosis is a chronic systemic disease: Clinical challenges and novel innovations. Lancet 2021;397(10276):839-852.
37. Adameova A, Shah AK, Dhalla NS. Role of oxidative stress in the genesis of ventricular arrhythmias. Int J Mol Sci 2020;21(12):4200
38. Jebari-Benslaiman S, Galicia-García U, Larrea-Sebal A, *et al*. Pathophysiology of atherosclerosis. Int J Mol Sci 2022;23(6):3346.
39. Severino P, D'Amato A, Pucci M, *et al*. Ischemic heart disease pathophysiology paradigms overview: From plaque activation to microvascular dysfunction. Int J Mol Sci 2020;21(21):8118.