Non-malignant gynaecological disease and risk of cardiovascular or cerebrovascular disease: a systematic review and meta-analysis

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ABSTRACT

Background Cardiovascular disease is the leading cause of death globally. Non-malignant gynaecological diseases (NMGD) significantly affect patient health and well-being and may be associated with cardiovascular or cerebrovascular disease (C/CVD).

Methods Seven databases were searched for relevant studies up to 21 April 2024. Observational studies reporting risk estimates and 95% CIs for the association between NMGD and C/CVD were included. Data were extracted by two independent reviewers. Random effects models were used to calculate summary relative risk (SRR) with 95% CI. Composite C/CVD outcome was defined as a combination of ischaemic heart disease, cerebrovascular disease, heart failure, and peripheral vascular disease. The ROBINS-I tool defined study quality and risk of bias.

Results We screened 6639 studies, of which 59 were eligible for full-text review and 28 were included in our analysis, comprising a total of 3 271 242 individuals. The majority (53.5%) of the studies were scored as having a 'serious'/'critical' risk of bias. Overall, individuals with an NMGD had a significantly greater risk of composite C/CVD with low heterogeneity among contributing studies (SRR 1.28, 95% CI 1.20 to 1.37; n=16 studies, I^2=65.3%), ischaemic heart disease (SRR 1.41, 95% CI 1.31 to 1.51; n=21 studies, I^2=73.7%), and cerebrovascular disease (SRR 1.33, 95% CI 1.18 to 1.51; n=16 studies, I^2=91.5%). In NMGD-specific analyses, the risk of C/CVD and its components was greater among those with a history of endometriosis or polycystic ovary syndrome.

Conclusions We found an overall association between NMGD and C/CVD across all studies. However, estimates from individual studies varied substantially.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cardiovascular disease is the leading cause of death globally.
⇒ Non-malignant gynecological diseases (NMGD) significantly affect patient health and wellbeing and may be associated with cardiovascular or cerebrovascular disease (C/CVD)

WHAT THIS STUDY ADDS

⇒ This systematic review and meta-analysis investigates the association between C/CVD and NMGD, providing an overview of the current literature on this topic.
⇒ This review suggests a link between these conditions, although high study heterogeneity and risk of bias prevalence was observed.
⇒ The association between C/CVD and NMGD remains significant when considering subgroups of C/CVD (ischemic heart disease or cerebrovascular disease) and subgroups of NMGD (endometriosis or polycystic ovary syndrome).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Knowledge of an association between C/CVD and NMGD can help inform clinical practice in order to identify C/CVD early and institute prevention programmes.

INTRODUCTION

WHO reports that cardiovascular disease is the leading cause of death globally.[1] Cardiovascular or cerebrovascular disease (C/CVD) comprises conditions including ischaemic heart disease (IHD), cerebrovascular disease, peripheral vascular disease, heart failure and atrial fibrillation.[1] In 2019, there were 10.3 million new cases of C/CVD in patients assigned female at birth (AFAB) across member countries of the European Society of Cardiology compared with 9.6 million new cases of patients assigned male at birth (AMAB) with C/CVD.[2] Patients AFAB remain less likely to receive care despite a higher incidence of C/CVD due to persistent and inaccurate assumptions that C/CVD predominately affects patients AMAB.[3]

Non-malignant gynaecological diseases (NMGD) have emerged as a risk factor contributing to incidence of C/CVD among patients AFAB. Chronic NMGD such as polycystic ovary syndrome (PCOS), endometriosis, adenomyosis, uterine fibroids, primary dysmenorrhea, chronic pelvic pain (CPP), menstrual cycle irregularity, heavy menstrual bleeding (HMB) and abnormal uterine bleeding (AUB) have a significant effect on patients' health and well-being.[4] Given how common some of these NMGD are, with almost three-quarters of those AFAB reporting dysmenorrhea,[5] one in nine having a diagnosis of endometriosis by age 44,[6] and around one in five having PCOS,[7] any association with C/CVD is likely to affect millions of people AFAB worldwide. These chronic NMGD may be

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associated with C/CVD through at least three potential mechanisms[8]: (1) common risk factors or a correlated exposure profile between NMGD and C/CVD (confounding), (2) an underlying association between NMGD treatments and C/CVD (mediation), and (3) a systemic change induced by NMGD that is associated with C/CVD (causality).

The potential link between NMGD and C/CVD has implications for patient care, including the monitoring and follow-up of patients with NMGD, and the knowledge these patients require to manage their own health and well-being, and to dialogue with healthcare professionals to maximise the prevention of C/CVD. There may also be therapeutic opportunities in primary prevention of C/CVD in this undertreated population. We conducted a systematic review and meta-analysis with the aim of synthesising all available epidemiological studies regarding the association between chronic NMGD and C/CVD. This review is the first to investigate the association between NMGD and C/CVD in a meta-analysis, therefore our study provides a novel and comprehensive insight regarding the association between NMGD and C/CVD as a whole, in addition to subgroup populations.

METHODS

This systematic review and meta-analysis is registered with PROSPERO (CRD42020183152) and has been reported according to PRISMA[9] and MOOSE guidelines.[10]

Search strategy and selection criteria

Articles eligible for inclusion were observational studies (cohort, case-control or cross-sectional studies) that reported risk estimates (such as hazard ratios, relative risk or ORs) with 95% CIs for the association between NMGD and a primary C/CVD-related outcome in a population of individuals of the female sex. All relevant studies with or without adjustment for potential confounders were considered in this systematic review. Case reports, case series, experimental or animal studies, and conference abstracts were excluded. NMGD was defined as PCOS, endometriosis, adenomyosis, uterine fibroids, primary dysmenorrhea, CPP, menstrual cycle irregularity, HMB and AUB. C/CVD-related outcomes included cerebrovascular disease (ischaemic stroke, haemorrhagic stroke, transient ischaemic attack), peripheral vascular disease, IHD (myocardial infarction, coronary artery bypass graft intervention, angina), heart failure and atrial fibrillation. All diagnostic methods were accepted with outcome defining method utilised considered in the study's risk of bias (ROB) assessment. NGMD exposure and C/CVD outcome determination methods included medical record or payor database abstraction and self-report with diagnostic methods, including laparoscopy/laparotomy, radiologic imaging, histopathology and biochemistry results.

The following databases were searched from inception until 21 April 2024: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and Embase via OvidSP, and CINAHL. Furthermore, ClinicalTrials.gov, OpenGrey and Google.com were searched for additional studies, trials at any stage of completion, and grey literature. The electronic search algorithm consisted of terms relating to NMGD and C/CVD (online supplemental appendix). No restriction on publication date or language was applied.

Each study identified via the search strategy was independently screened in accordance with the inclusion criteria by two reviewers (GEC and KM or AS); initially by title and abstract, followed by a full-text review. Any conflicts were resolved via discussion with input from a third team member (KM or AS, YMS). In the case of duplicate study populations, only the most recently published data with the largest sample size were included.

Data extraction

Data extraction of the published papers was performed by two independent reviewers (GEC and KM or AS) and compared with identify discrepancies. Categories of data extracted from each study included author names, publication year, country in which the research was conducted, study design, study period, sample size (number of people with NMGD and number of controls), ascertainment method of NMGD and C/CVD, ability to evaluate temporality of the association (ie, ability of the study to ensure that NMGD occurred prior to C/CVD in a time-varying analysis and was not diagnosed concurrently), baseline characteristics of study participants (including mean age, body mass index, ethnicity, cigarette smoking status, co-morbidities, family history of NMGD or C/CVD, parity and infertility history), menopausal status, clinical management of NMGD and C/CVD, risk estimates with 95% CIs, and hypothesised confounding variables adjusted for in the publication-specific analysis. The primary outcome was the association between NMGD and composite C/CVD. Secondary outcomes included the association of NMGD and each of its subtypes, including endometriosis, PCOS, dysmenorrhea and irregular menstrual cycles, with composite C/CVD, ischaemic heart disease, cerebrovascular disease, heart failure, peripheral vascular disease and cardiovascular disease mortality. Data points suitable for aggregation from a clinical perspective were identified by two reviewers (FP and KM).

Data synthesis and quality assessment

The ROBINS-I tool for non-randomised studies[11] was the framework utilised for the assessment of methodological quality and ROB, which was performed by two independent reviewers (GEC and KM or AS), with input from a third (KM or AS, YMS) where required.

All statistical analyses were conducted using Stata software version 15.1 and 17 (Stata Corporation, College Station, TX, USA). Statistical significance was two-sided, and P-values<0.05 were considered statistically significant. Separate meta-analyses were performed for each outcome. Random effects models considering both within-study and between-study variation were utilised to calculate summary relative risk (SRR) for the association between NMGD and C/CVD. The natural logarithm of the SRR was weighted using random effects weights.[12] Statistical heterogeneity between studies was assessed by the Cochrane Q test and the I^2 statistic.[13] I^2 is a measure of how much of the heterogeneity is due to between-study variation. I^2 values of 25%, 50% and 75% indicated low, moderate and high heterogeneity, respectively.

This study was not able to meet all of Hill's criteria for establishing causality,[14] however these criteria were considered in the study design, particularly when determining sensitivity and subgroup analyses. Whenever possible, subgroup analyses were conducted to investigate potential sources of heterogeneity, including study characteristics such as study design (retrospective cohort vs prospective cohort vs cross-sectional), geographical location, definition of NMGD case ascertainment (self-report vs medical records/registries), NMGD preceded CVD (yes vs no), and adjustment for confounding factors (yes vs no). Between-subgroup differences in summary relative risk were examined using meta-regression analysis. For all analyses, the impact of study sample size was accounted for in the statistical modelling

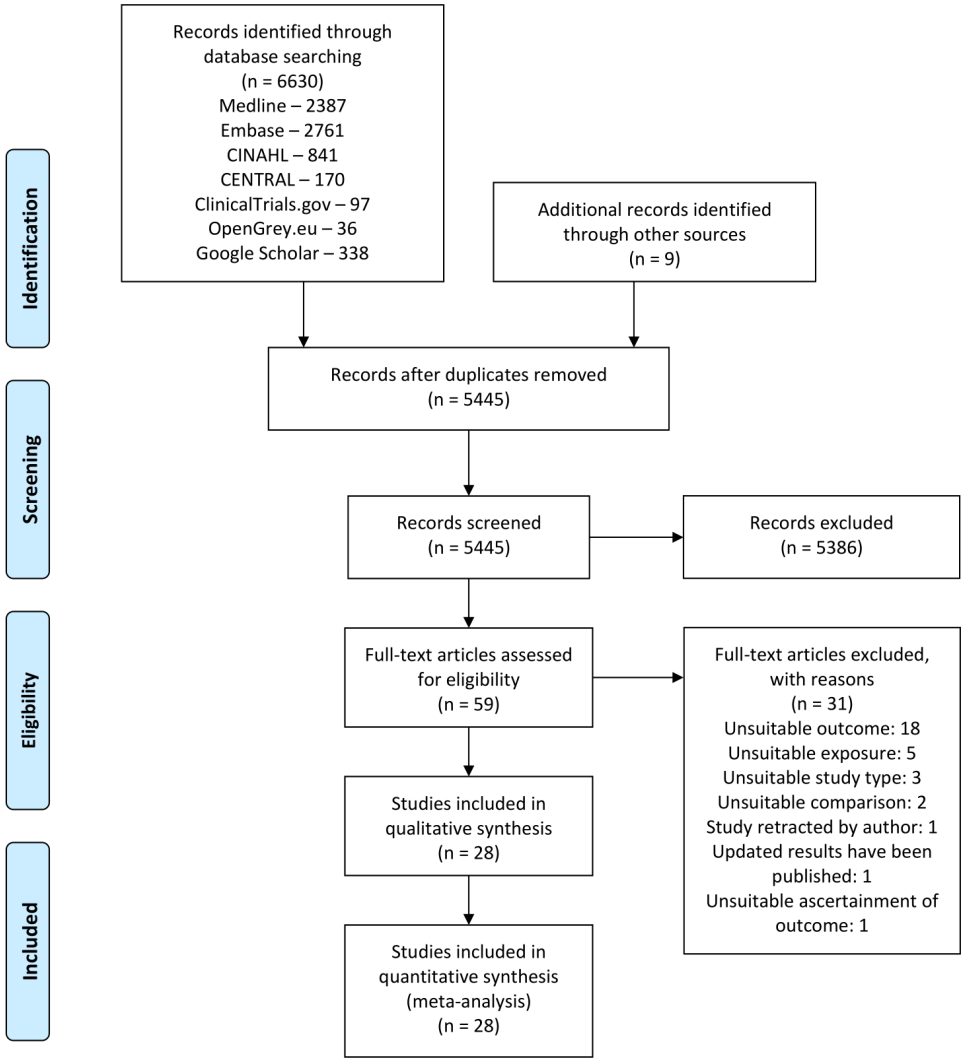

Figure 1 PRISMA flowchart of study selection.

and represented by the width of the CI. In additional sensitivity analyses, we also explored potential differences by quality of the study as per the ROBINS-I risk of bias tool: 'low' or 'moderate' versus 'serious' or 'critical'. Small-study effects, such as publication bias, were visually assessed by examining the funnel plots for asymmetry and applying Egger's test.[15] The results were considered to indicate potential small-study bias when p-values were <0.10. Sensitivity analyses excluding one study at a time were conducted to clarify whether the results were driven by one large study or a study with an extreme result.

Role of the funding source

There was no funding source.

RESULTS

The search strategy identified 6639 records, of which 59 were eligible for full-text review; details regarding the screening process are shown in figure 1. Following the screening process, 28 studies were eligible for inclusion in our systematic review and meta-analysis, comprising a total of 3 271 242 individuals: 992 475 in at least one NMGD exposure group and 2 278 767 in the unexposed groups.[16–43] The baseline characteristics of the included studies are summarised in online supplemental appendix table S1. Studies excluded following full-text review, along with a rationale for the decision, are listed in online supplemental appendix table S2.

No studies included in this review reported atrial fibrillation; therefore, it was not included in the definition of C/CVD for this study. Additionally, NMGD encompasses a range of conditions as described in the Introduction; however, only endometriosis, PCOS, dysmenorrhea and irregular menstrual cycles were examined by the studies included in this review.

ROBINS-I scoring suggested low study quality for the majority of studies, with nine out of the 28 studies (32%) defined to be at critical risk of bias, six (21.5%) at serious ROB, seven (25%) at moderate ROB, and only six studies (21.5%) having high design quality with low ROB. The ROB summary can be visualised in online supplemental figure 9.[44] The domain of bias due to confounding was most often found to be at critical risk, with no or non-rigorous methods applied to address potential confounders. No studies were rated as a critical ROB in more than one domain. Only the study by Merz *et al*[21] was rated as a serious ROB in more than one domain: bias due to selection of participants and misclassification bias, in addition to having a critical ROB due to lack of confounding control.

Meta-analysis revealed a greater risk of composite C/CVD among those with any NMGD compared with those with no NMGD exposure with an SRR of 1.28 (95% CI 1.20 to 1.37;

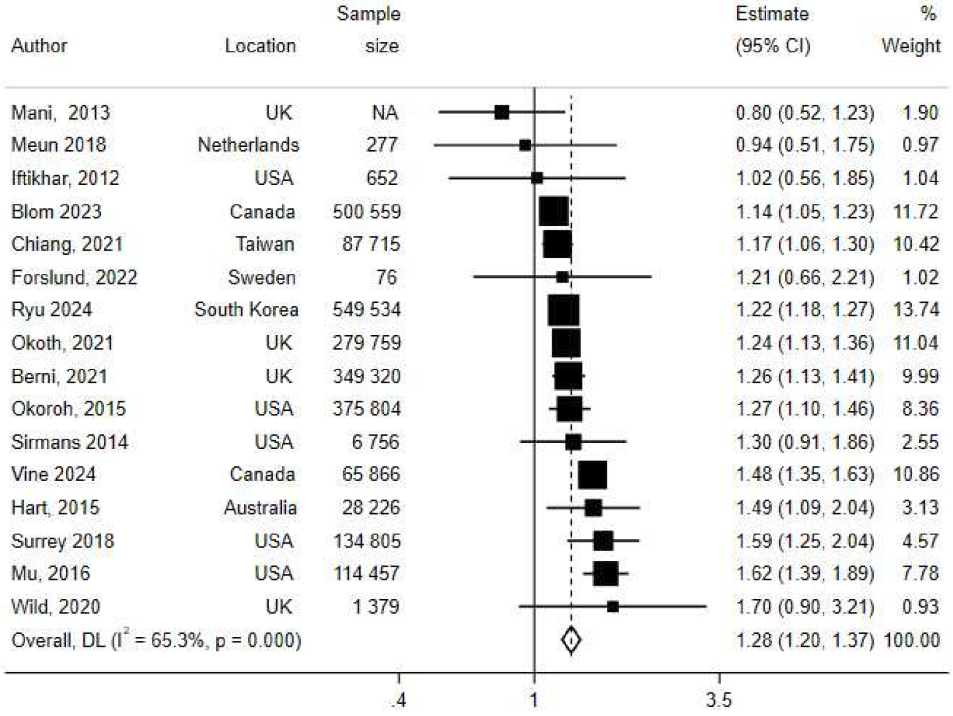

Figure 2 Forest plot for the association between non-malignant gynaecological diseases and composite cardiovascular or cerebrovascular disease.

n=16 studies, I^2=65.3%, Egger's test p=0.46) (figure 2). In NMGD subgroup analyses, the risk of C/CVD for those with PCOS (SRR 1.28, 95% CI 1.18 to 1.39; n=11 studies, I^2=54.0%) and for those with endometriosis (SRR 1.30, 95% CI 1.15 to 1.47; n=5 studies, I^2=81.1%) was similar to NMGD overall (online supplemental figure 1). In C/CVD outcome-specific analyses, NMGD was significantly associated with ischaemic heart disease (SRR 1.41, 95% CI 1.31 to 1.51; n=21 studies, I^2=73.7%, Egger's test p=0.06) (figure 3), with no heterogeneity observed specific to PCOS (SRR 1.42, 95% CI 1.23 to 1.63; n=12 studies, I^2=65.8%) or endometriosis (SRR 1.36, 95% CI 1.22 to 1.51; n=7 studies, I^2=80.2%) exposure.

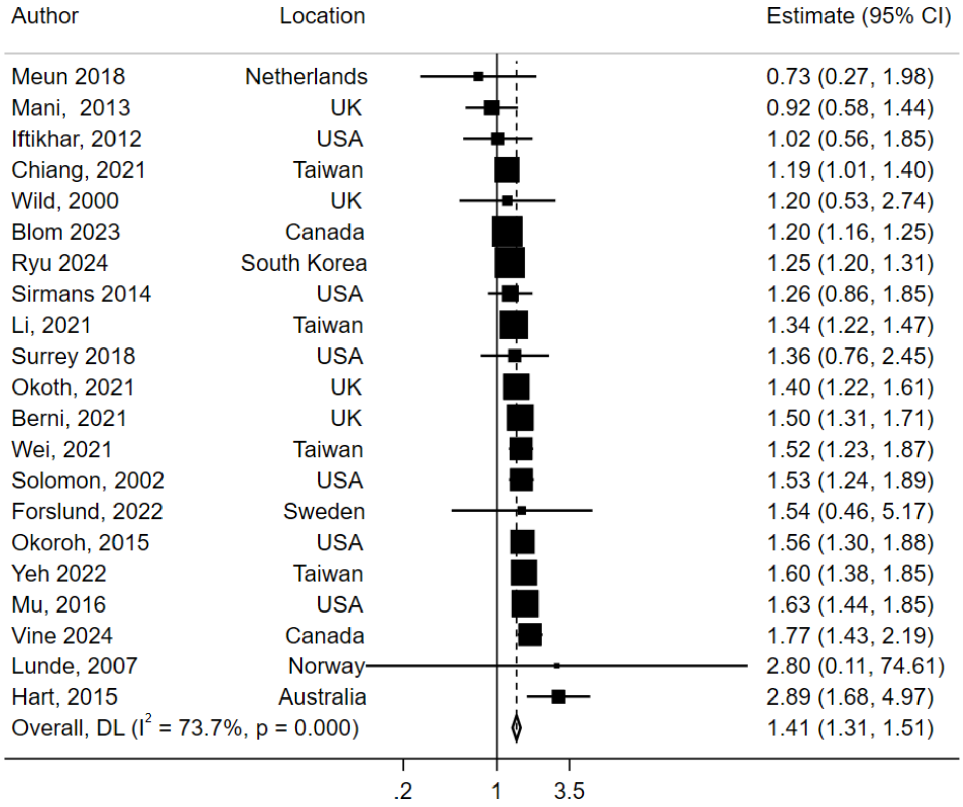

Figure 3 Forest plot for the association between non-malignant gynaecological diseases and ischaemic heart disease

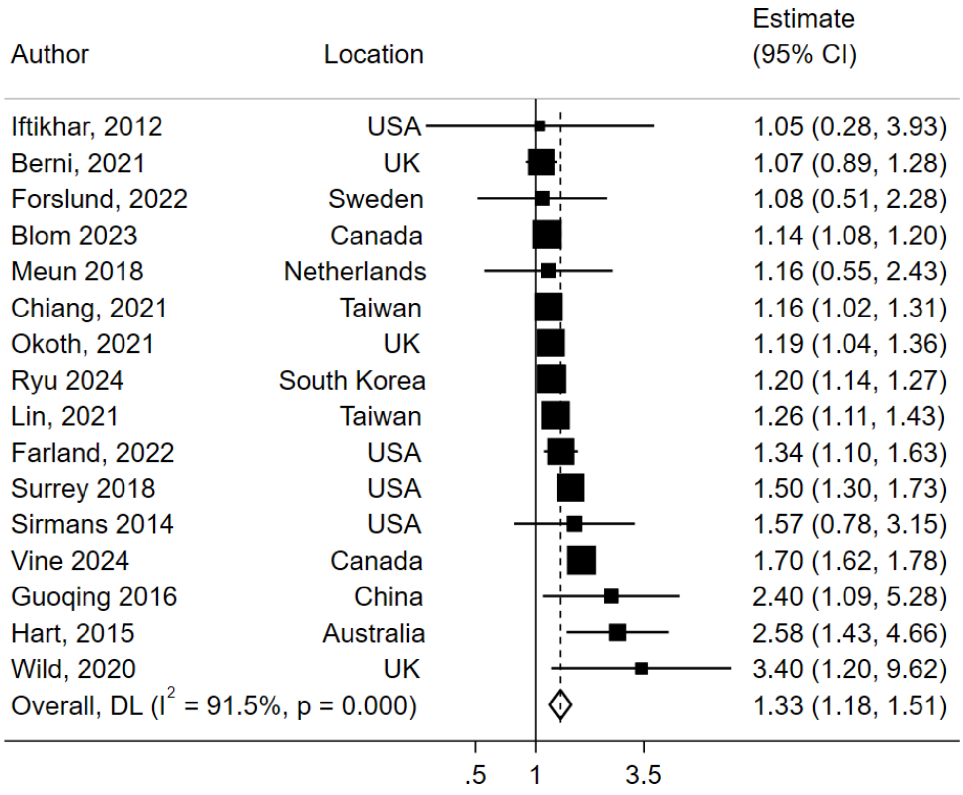

Figure 4 Forest plot for the association between non-malignant gynaecological diseases and cerebrovascular disease.

The meta-analysis also revealed a greater risk of cerebrovascular disease in individuals with NMGD (SRR 1.33, 95% CI 1.18 to 1.51; n=16 studies, I^2=91.5%, Egger's test p=0.99) (figure 4), again with a similarly greater risk for those with PCOS (SRR 1.47, 95% CI 1.18 to 1.82; n=10 studies, I^2=92%) or endometriosis (SRR 1.24, 95% CI 1.12 to 1.38; n=5 studies, I^2=73%).

The influence analysis showed no substantial influence of any of the included studies on the global estimate of NMGD exposure and outcome. For the composite C/CVD risk, the SRR ranged from 1.25 (95% CI 1.18 to 1.33) when excluding Vine *et al*[42] to 1.30 (95% CI 1.21 to 1.39) when excluding Blom *et al*[40] (online supplemental figure 5). In the influence analysis excluding one study at a time from the analysis of cerebrovascular disease risk, the SRR ranged from 1.24 (95% CI 1.16 to 1.33) when excluding Vine *et al*[42] to 1.36 (95% CI 1.19 to 1.54) when excluding Blom *et al*[40] (online supplemental figure 6). We found no substantial influence of any of the included studies on the analysis of ischaemic heart disease (online supplemental figure 7). As five of the included studies were conducted utilising data from the Taiwan National Health Insurance database, we conducted a subgroup analysis including only one study per condition utilising the database. This subgroup analysis showed an SRR of 1.42 (95% CI 1.32 to 1.53) in comparison to an SRR of 1.41 (95% CI 1.31 to 1.51) for all studies reporting the association between NMGD and ischaemic heart disease (online supplemental figure 8).

The meta-analysis suggested a null association between NMGD and C/CVD mortality, although between-study heterogeneity was high (SRR 1.02, 95% CI 0.65 to 1.60; n=8 studies, I^2=89.0%, Egger's test p=0.14). There was the suggestion of an elevated meta-analytic risk of heart failure for those with NMGD compared with those who were unexposed, but there was low precision as evidenced by a wide CI and very high heterogeneity among studies (SRR 1.82, 95% CI 0.98 to 3.39; n=4 studies, I^2=96.3%, Egger's test p=0.78).

The results of these analyses, including further subgroup analyses, are summarised in table 1. The positive association persisted in most subgroup analyses. Our meta-regression analysis showed that the study design, geographical location, assessment of NMGD, risk of bias and adjustment for some confounding factors did not significantly influence the magnitude of the overall association. However, for the composite outcome, heterogeneity between subgroup analyses was observed in analyses stratified by temporality (NMGD preceded CVD, yes vs no) with higher association for studies in which NMGD did not precede CVD compared with those in which NMGD did precede CVD ($P_{heterogeneity} \leq 0.0001$). For the cerebrovascular disease outcome, heterogeneity between subgroup analyses was observed in analyses stratified by ROB, with a greater association in studies with critical or serious ROB compared with those with low or moderate ROB ($P_{heterogeneity} \leq 0.0001$) and when considering adjustment for confounding factors with a greater association for studies without adjustment compared with those that adjusted for multiple factors ($P_{heterogeneity} \leq 0.0001$).

The secondary outcome of the association between NMGD and peripheral vascular disease was reported by five studies[17 24 26 28 42]; however, only two studies[17 17] reported an effect estimate, calculating an HR of 1.81 (95% CI 1.59 to 2.05) for the association between peripheral vascular disease and PCOS. Therefore, a meta-analysis was not conducted for this outcome. Additionally, the only NMGD examined by the studies included in this review were endometriosis, PCOS, dysmenorrhea and irregular menstrual cycles. Most studies adjusted their analysis for age[18 22 23 25 27 29 32–36 38 40 41 43] and three for menopausal status[22 27 29] to account for their potential confounding effects. Several sensitivity analyses outlined in the PROSPERO

Table 1 Subgroup analyses of association between NMGD and C/CVD risk

	NMGD and composite C/CVD outcome					NMGD and ischaemic heart disease					NMGD and cerebrovascular disease				
	n	SRR (95% CI)	I^2 (%)	P_{within}*	$P_{between}$†	n	SRR (95% CI)	I^2 (%)	P_{within}*	$P_{between}$†	n	SRR (95% CI)	I^2 (%)	P_{within}*	$P_{between}$†
All studies	16	1.28 (1.20 to 1.37)	65.3	<0.0001		21	1.41 (1.31 to 1.51)	73.7	<0.001		16	1.33 (1.18 to 1.51)	91.5	<0.001	
Exposure															
PCOS	11	1.28 (1.18 to 1.39)	54.0	0.02	0.83	12	1.42 (1.23 to 1.63)	65.8	<0.001	0.32	10	1.47 (1.18 to 1.82)	91.8	<0.001	0.40
Endometriosis	5	1.30 (1.15 to 1.47)	81.1	<0.0001		7	1.36 (1.22 to 1.51)	80.2	<0.001		5	1.24 (1.12 to 1.38)	72.7	0.006	
Irregular menstrual cycle	—	—	—	—	—	1	1.53 (1.24 to 1.89)	—	—				—	—	
Dysmenorrhea	—	—	—	—	—	1	1.60 (1.38 to 1.85)	—	—	—	1	1.26 (1.11 to 1.43)	—	—	
Study design															
Retrospective	11	1.26 (1.18 to 1.34)	66.4	0.001	0.30	14	1.39 (1.29 to 1.49)	77.1	<0.001	0.10	10	1.30 (1.13 to 1.49)	94.7	<0.001	0.39
Prospective	4	1.49 (1.21 to 1.84)	15.6	0.31		6	1.58 (1.42 to 1.76)	0.0	0.67		4	1.36 (1.04 to 1.78)	15.3	0.32	
Cross-sectional	1	1.30 (0.91 to 1.86)	—	—		1	1.26 (0.86 to 1.85)	—	—		2	1.89 (1.12 to 3.19)	0.0	0.43	
Geographical location															
North America	7	1.37 (1.19 to 1.56)	79.3	<0.0001	0.24	8	1.45 (1.23 to 1.69)	83.1	<0.001	0.05	6	1.41 (1.11 to 1.78)	95.9	<0.001	0.05
Europe	6	1.23 (1.12 to 1.34)	13.1	0.33		7	1.40 (1.27 to 1.56)	4.8	0.39		6	1.20 (1.08 to 1.32)	18.1	0.30	
Asia	2	1.21 (1.17 to 1.26)	0.0	0.45		5	1.35 (1.23 to 1.48)	71.8	<0.001		3	1.20 (1.09 to 1.32)	38.2	0.20	
Australia	1	1.49 (1.09 to 2.04)	—	—		1	2.89 (1.68 to 4.97)	—	—		1	2.58 (1.43 to 4.66)	—	—	
Assessment of NMGD															
Self-reported	1	0.94 (0.51 to 1.75)	—	—	0.32	2	1.25 (0.65 to 2.39)	50.4	0.16	0.73	1	1.16 (0.55 to 2.43)	—	—	0.70
Medical records	15	1.29 (1.21 to 1.37)	67.0	<0.0001		19	1.40 (1.31 to 1.51)	75.0	<0.001		15	1.34 (1.18 to 1.51)	92.0	<0.001	
NMGD preceded CVD															
No	7	1.47 (1.36 to 1.60)	0.0	0.82	0.001	8	1.56 (1.24 to 1.96)	29.0	0.19	0.32	8	1.66 (1.48 to 1.85)	23.0	0.25	<0.001
Yes	9	1.23 (1.16 to 1.31)	63.0	0.006		13	1.38 (1.29 to 1.48)	79.1	<0.001		8	1.18 (1.14 to 1.22)	0.0	0.54	
Risk of bias															
Low	2	1.39 (1.05 to 1.84)	92.0	<0.0001	0.34	4	1.48 (1.29 to 1.70)	83.6	<0.001	0.95	2	1.22 (1.13 to 1.31)	13.7	0.28	<0.001
Moderate	6	1.20 (1.15 to 1.25)	0.0	0.55		7	1.37 (1.22 to 1.55)	80.9	<0.001		5	1.14 (1.09 to 1.20)	0.0	0.92	
Serious	3	1.40 (1.07 to 1.83)	4.6	0.35		4	1.57 (1.00 to 2.47)	60.4	0.06		4	1.70 (1.06 to 2.74)	65.7	0.03	
Critical	5	1.34 (1.11 to 1.62)	54.7	0.06		6	1.38 (1.07 to 1.78)	36.3	0.16		5	1.64 (1.151 to 1.79)	17.0	0.31	
Adjustment for confounders															
No	5	1.34 (1.11 to 1.62)	54.7	0.06	0.48	6	1.38 (1.07 to 1.78)	36.3	0.16	0.90	5	1.64 (1.51 to 1.79)	17.0	0.31	<0.001
Yes	11	1.25 (1.18 to 1.32)	51.9	0.02		15	1.40 (1.31 to 1.51)	78.3	<0.001		11	1.20 (1.13 to 1.26)	40.1	0.08	

I^2 (%) is a measure of the proportion of the heterogeneity attributed to between-study variation rather than due to chance. I^2 values of 25%, 50% and 75% indicate low, moderate and high between-study heterogeneity, respectively.
As there were a limited number of studies reporting heart failure, and only a single study reporting an effect estimate for peripheral vascular disease, the results for these subtypes of C/CVD have been reported narratively.
*P value for heterogeneity within each subgroup.
†P value for heterogeneity between subgroups with meta-regression analysis.
C/CVD, cardiovascular and cerebrovascular disease; NMGD, non-malignant gynaecological disease; SRR, summary relative risk.

protocol were not meta-analysable, including age and menopause status effect modification of, or mediation by hysterectomy/oophorectomy of, the association between NMGD and C/CVD. No study in this review specified the age at diagnosis of NMGD; therefore, it was not possible to conduct a meta-analysis restricted to those with NMGD diagnosed during their reproductive years.

DISCUSSION

This systematic review and meta-analysis suggests an association between NMGD and C/CVD. The meta-analysis comprises a large total sample size allowing exploration of several subtypes of NMGD and C/CVD; the 28 studies yield a total of 3 271 242 individuals. The primary outcome indicates an increased risk of developing composite C/CVD in individuals with at least one NMGD (the exposed population), in comparison to individuals without NMGD (the unexposed population), although high study heterogeneity and risk of bias prevalence were identified. Sub-group analyses correspondingly suggested that the increased risk of C/CVD and its components was observed in individuals with endometriosis or PCOS. Given the importance of temporality for causal inference, we further conducted sensitivity analyses that showed no significant difference in effect estimates when considering only studies that took into account temporality, although the number of studies contributing to this comparative analysis was small. In addition, when excluding the most influential studies, we found no substantial influence of any of the included studies.

Common biological pathways linking NMGD to C/CVD may include systemic inflammation and endogenous estrogenic milieu. The categorisation of atherosclerosis as a chronic low-grade inflammatory condition is now commonly accepted.[45] Inflammation and oxidative stress are important triggers for C/CVD, and various inflammatory markers have been found to be essential contributors to C/CVD.[46 47] When considering endometriosis specifically, the mechanism believed to link this condition to increased cardiovascular risk is systemic inflammation.[48] Similarly, in PCOS, a cross-sectional analysis found a significant association between low-grade inflammation and sympathetic dysfunction and hyperandrogenism.[49] As such, inflammation may be an underlying mechanism for an association between NMGD and C/CVD. However, there is also a possible overlap of gynaecological risk factors and cardiovascular risk factors that may act as confounders. For instance, features of metabolic syndrome, a complex interaction of visceral obesity, dyslipidaemia, hyperglycaemia and hypertension[50] has been consistently shown to be present in individuals with PCOS.[51] Metabolic syndrome is associated with an increased risk of C/CVD events and mortality.[52]

Female steroid hormones are implicated in the development of NMGD and link these to cardiovascular risk factors.[48] Endogenous estrone is related to endothelial function, while estradiol is related to vascular remodelling, suggesting specific roles for different female steroid hormones.[53] The effects on endothelial function seem beneficial, providing cardiovascular protection to individuals AFAB.[54] While some studies adjusted their analysis for menopausal hormone therapy (MHT) use[18 22 27] or oral contraceptive use,[23 27 32 34] only one[35] performed a sub-group analysis, which demonstrated that the risk of subsequent CAD was higher in patients with endometriosis taking hormonal therapy. Similarly, hysterectomy is associated with a greater risk of C/CVD,[55] which could be further exacerbated when bilateral oophorectomy is performed.[56] Although few studies have considered this potential mediation,[23 57] those that have assessed this have found a significant proportion of the causal pathway associating NMGD with C/CVD to be explained by surgical treatments. However, independent variation remained, confirming that other pathways contribute to C/CVD risk among individuals with NMGD.

The results of this review must be interpreted with caution given the limitations. First, most of the findings in the meta-analysis suggest moderate to very high heterogeneity among studies, which may yield imprecise meta-analytic summary estimates. Indeed, there were a few examples of heterogeneous results when comparing single studies. Saavalainen *et al*[25] found that the risk of C/CVD mortality was lower in endometriosis patients compared with controls; the underlying cause of this discrepancy is unclear. Furthermore, Solomon *et al*[27] reported a lower risk of IHD in the irregular menstrual cycle group compared with those reporting regular cycles. The participants were asked to recall and self-reported menstrual cycle irregularity at ages 20–35. This methodology may contribute to inaccurate categorisation, although validation studies conducted within this cohort suggested that the self-reporting of medical conditions was reliable.[58]

The second limitation is the risk of bias in many of the studies. Concerningly, 53.5% of the studies included in this meta-analysis had low design quality with 'serious' or 'critical' risk of bias. The primary driver of poor risk of bias scores was a lack of control for potential confounders. While observational studies require data adequate to quantify and statistical approaches that account for potential confounders to support valid causal inference,[59] we found that a large proportion of the studies published to date did not include any methods for control or assessment of confounding factors at all. It is important to note, however, that the higher quality studies with a low risk of bias (just six studies) that did account for potential confounders observed little evidence of confounding with low magnitudes of confounding effects.[23 25 34 35 39 41] The ROBINS-I risk of bias tool[11] was designed for non-randomised interventional studies; therefore, applying it in this systematic review was potentially less precise.

Furthermore, despite lenient inclusion criteria, the data were sparse for most outcomes. To conduct a robust meta-analysis, outcomes were combined from a clinical perspective, reflecting how these diagnoses are managed in clinical practice. The composite C/CVD outcome reported by the studies was defined within the study, which meant that our primary outcome could not be broken down by C/CVD subtype, although most studies reported a separate outcome for each C/CVD subtype which was reported in our subgroup analyses. No studies reporting the association between atrial fibrillation and NMGD were eligible for inclusion in this review. There was a paucity of studies reporting effect estimates for the association between peripheral vascular disease and NMGD, which meant that this outcome could not be meta-analysed. Including these composite C/CVD subtypes in the meta-analysis would allow for more robust results regarding the association examined. Similarly, the only NMGD subtypes examined by the included studies were endometriosis, PCOS, dysmenorrhea and irregular menstrual cycles.

Additionally, five studies utilised data from the Taiwan National Health Insurance Database,[33–35 38 43] which could potentially inflate the total number of individuals included in this review if an individual appeared in the dataset of more than one study. This limitation was addressed by conducting a subgroup analysis including only one Taiwan National Health Insurance Database study per condition, which was not significantly different from the main outcome. A further limitation

of this review was that a couple of studies split the exposure group into subgroups based on menstrual regularity[27] or PCOS phenotype,[60] which may contribute to misclassification bias. In contrast, multiple studies[17–20 22 28 30 32 33 36 37 39–42] did not differentiate between ischaemic and haemorrhagic stroke subtypes, which have distinct underlying pathophysiological mechanisms.[61] When considering the population included in this study, it is possible that individuals with NMGD were more likely to seek medical attention or to be referred for C/CVD investigations as they had a known health condition than control groups. This may have led to a greater diagnosis of C/CVD in the exposure group and is a limitation to consider when interpreting the results of this review.

Lastly, we pooled different risk estimates, which may overestimate or underestimate the observed association between NMGD and outcomes; therefore, it is important to consider these findings with caution. Ideally, only prospective studies that reported ORs or hazard ratios would be pooled in the meta-analysis; however, as there are few studies available on this topic, our review aims to provide a global view of the association. Despite these limitations, this systematic review and meta-analysis represents the highest level of evidence currently available, with a rigorous methodology and a large patient population for many of the associations explored, and a thorough meta-analysis with multiple subgroups and sensitivity analyses.

The results of this systematic review and meta-analysis may have implications for clinical practice. Although the extent of this association is still to be explored, and causality has not been established, the findings suggest that it is important to raise awareness of the potential association between NMGD and C/CVD both in the general public and healthcare professionals. Awareness of this association would allow healthcare professionals to advise patients regarding risk-reducing behavioural changes and interventions, to potentially prevent or delay the onset of or reduce the severity of C/CVD. Furthermore, healthcare professionals would be aware to monitor their patients with NMGD for early signs and symptoms of C/CVD, and potentially diagnose atypical presentations of C/CVD with the knowledge of the underlying risk for this group of patients. Management strategies for C/CVD in this patient group could be tailored to the hypothesised underlying mechanisms that connect these conditions: systemic inflammation and female steroid hormones.

The association between C/CVD and NMGD requires further exploration with high-quality longitudinal studies adjusted for confounders to establish temporal relationships and causality. Future research should focus on incidence or mortality rates as more studies are published on this topic. It is essential to establish an understanding of the mechanistic pathways linking the conditions, which would allow investigation of the potential modifiers of risk as well as targeted management plans. A larger body of literature with larger sample sizes within each study will afford much more precise estimation and the ability to explore likely variation among all NMGD and C/CVD subtypes. Additionally, it would be beneficial to standardise the reporting of both NMGD conditions and C/CVD outcomes.

In conclusion, our findings suggest an association between NMGD and C/CVD overall and in subgroup populations. Given the limitations of the review, high study heterogeneity and risk of bias prevalence, future research must require study design rigour and improved NMGD and C/CVD harmonisation, and elucidate risk variation among subpopulations. Physicians should be aware of the potential association between NMGD and C/CVD and use this to inform clinical practice in order to mitigate the risk of C/CVD. Our findings reinforce the need for prospective longitudinal lifecourse research evaluating risk of C/CVD outcomes in NMGD overall and in subgroup populations, which may catalyse primary prevention strategies.

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