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

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1 **Non-malignant gynecological disease and risk of cardiovascular or cerebrovascular**  
2 **disease: a systematic review and meta-analysis**

3 *Short title:* Gynecological disease and C/CVD: a meta-analysis

4  
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41

42 *Keywords*

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44 Preventative medicine; Endometriosis; Polycystic ovary syndrome; Meta-analyses.

45

46 *Word count*

47 3,074 words

48 **Abstract**

49

50 *Background*

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

54

55 *Methods*

56 Seven databases were searched for relevant studies up to 21/04/2024. Observational studies  
57 reporting risk estimates and 95% confidence intervals (CI) for the association between NMGD  
58 and C/CVD were included. Data were extracted by two independent reviewers. Random effects  
59 models were used to calculate summary relative risks (SRR) with CI. Composite C/CVD  
60 outcome was defined as a combination of ischemic heart disease, cerebrovascular disease, heart  
61 failure, and peripheral vascular disease. The ROBINS-I tool defined study quality and risk of  
62 bias.

63

64 *Results*

65 We screened 6639 studies, of which 59 were eligible for full-text review and 28 were included in  
66 our analysis, comprising a total of 3,271,242 individuals. The majority (53.5%) of the studies  
67 were scored as having a ‘serious’/‘critical’ risk of bias. Overall, those with an NMGD had a  
68 significantly greater risk of composite C/CVD with low heterogeneity among contributing  
69 studies (summary risk ratio (SRR)=1.28, 95% confidence interval (CI)=1.20–1.37; n=16 studies,  
70  $I^2=65.3%$ ), ischemic heart disease (SRR=1.41, 95% CI=1.31–1.51; n=21 studies,  $I^2=73.7%$ ), and

71 cerebrovascular disease (SRR=1.33, 95%CI=1.18–1.51; n=16 studies,  $I^2=91.5\%$ ). In NMGD-  
72 specific analyses, the risk of C/CVD and its components was greater among those with a history  
73 of endometriosis or polycystic ovary disease.

74

#### 75 *Conclusions*

76 Meta-analysis suggests a robust association between NMGD and C/CVD. Given study  
77 heterogeneity and risk of bias prevalence, future research must require study design rigor and  
78 elucidate risk variation among subpopulations.

79 **1. Introduction**

80

81 The World Health Organization (WHO) reports that cardiovascular disease is the leading cause  
82 of death globally [1]. Cardio- or cerebrovascular disease (C/CVD) S fibrillation [1]. In 2019,  
83 there were 10.3 million new cases of C/CVD in patients assigned female at birth (AFAB) across  
84 member countries of the European Society of Cardiology, compared with 9.6 million new cases  
85 of patients assigned male at birth (AMAB) with C/CVD [2]. AFAB patients remain less likely to  
86 receive care despite a higher incidence of C/CVD due to persistent and inaccurate assumptions  
87 that C/CVD predominately affects AMAB patients [3].

88

89 Non-malignant gynecological diseases (NMGD) have emerged as a risk factor contributing to  
90 incidence of C/CVD among patients AFAB. Chronic NMGD such as polycystic ovary syndrome  
91 (PCOS), endometriosis, adenomyosis, uterine fibroids, primary dysmenorrhea, chronic pelvic  
92 pain (CPP), menstrual cycle irregularity, heavy menstrual bleeding (HMB), and abnormal uterine  
93 bleeding (AUB) have a significant effect on patients' health and well-being [4]. Given how  
94 common some of these NMGD are, with almost three quarters of those AFAB reporting  
95 dysmenorrhea [5], one in nine having a diagnosis of endometriosis by age 44 [6], and around one  
96 in five having PCOS [7], any association with C/CVD is likely to affect millions of people  
97 AFAB worldwide. These chronic NMGD may be associated with C/CVD through at least three  
98 potential mechanisms [8]: 1) common risk factors or a correlated exposure profile between  
99 NMGD and C/CVD (confounding), 2) an underlying association between NMGD treatments and  
100 C/CVD (mediation), and 3) a systemic change induced by NMGD that is associated with C/CVD  
101 (causality).

102

103 The potential link between NMGD and C/CVD has implications for patient care, including the  
104 monitoring and follow-up of patients with NMGDs, and the knowledge these patients require to  
105 manage their own health and well-being and to dialogue with their clinicians to maximize the  
106 prevention of C/CVD. There may also be therapeutic opportunities in primary prevention of  
107 C/CVD in this undertreated population. We conducted a systematic review and meta-analysis  
108 with the aim of synthesizing all available epidemiological studies regarding the association  
109 between chronic NMGD and C/CVD. Our study provides a novel and comprehensive insight  
110 regarding the association between NMGD and C/CVD as a whole, in addition to subgroup  
111 populations.

112

113 **2. Methods**

114

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

117

118 *Search strategy and selection criteria*

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

134

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

141  
142 Each study identified via the search strategy was independently screened in accordance with the  
143 inclusion criteria by two reviewers (GEC and KM or AS); initially by title and abstract, followed  
144 by a full-text review. Any conflicts were resolved via discussion with input from a third team  
145 member (KM or AS, YMS). In the case of duplicate study populations, only the most recently  
146 published data with the largest sample size were included.

147  
148 *Data analysis*

149 Data extraction of the published papers was performed by two independent reviewers (GEC and  
150 KM or AS) and compared to identify discrepancies. Categories of data extracted from each study  
151 included: author names, publication year, country in which the research was conducted, study  
152 design, study period, sample size (number of NMGD cases and number of controls),  
153 ascertainment method of NMGD and C/CVD, ability to evaluate temporality of the association  
154 (i.e. ability of the study to ensure that NMGD occurred prior to C/CVD in a time-varying  
155 analysis and was not diagnosed concurrently), baseline characteristics of study participants  
156 (including mean age, body mass index, ethnicity, cigarette smoking status, co-morbidities, family  
157 history of NMGD or C/CVD, parity, and infertility history), menopausal status, clinical

158 management of NMGD and C/CVD, risk estimates with 95% confidence intervals (CI), and  
159 hypothesized confounding variables adjusted for in the publication-specific analysis. Data points  
160 suitable for aggregation from a clinical perspective were identified by two reviewers (FP and  
161 KM). Composite C/CVD was defined as a combination of ischemic heart disease,  
162 cerebrovascular disease, heart failure, and peripheral vascular disease.

163  
164 The ROBINS-I tool for non-randomized studies [11] was the framework utilized for the  
165 assessment of methodological quality and risk of bias, which was performed by two independent  
166 reviewers (GEC and KM or AS), with input from a third (KM or AS, YMS) where required.

167  
168 All statistical analyses were conducted using Stata software version 15.1 and 17 (Stata  
169 Corporation, College Station, TX, USA), and a P-value <0.05 was considered statistically  
170 significant. Separate meta-analyses were performed for each outcome. Random effects models  
171 considering both within-study and between-study variation were utilized to calculate summary  
172 relative risks (SRR) for the association between NMGD and C/CVD. The natural logarithm of  
173 the RR was weighted using random effects weights [12]. Statistical heterogeneity between  
174 studies was assessed by the Cochrane Q test and the  $I^2$  statistic [13].  $I^2$  is a measure of how  
175 much of the heterogeneity is due to between-study variation.  $I^2$  values of 25%, 50%, and 75%  
176 indicated low, moderate, and high heterogeneity, respectively.

177  
178 Whenever possible, subgroup analyses were conducted to investigate potential sources of  
179 heterogeneity, including study characteristics such as study design (retrospective cohort versus  
180 prospective cohort versus cross-sectional), geographic location, definition of NMGD case

181 ascertainment (self-report versus medical records/registries), NMGD preceded CVD (yes versus  
182 no), and adjustment for confounding factors (yes versus no). Between-subgroup differences in  
183 summary risk estimates were examined using meta-regression analysis. For all analyses, the  
184 impact of study sample size was accounted for in the statistical modelling and represented by the  
185 width of CI. In additional sensitivity analyses, we also explored potential differences by quality  
186 of the study as per the ROBINS-I risk of bias tool: ‘low’ or ‘moderate’ versus ‘serious’ or  
187 ‘critical’. Small-study effects, such as publication bias, were visually assessed by examining the  
188 funnel plots for asymmetry and applying Egger’s test [14]. The results were considered to  
189 indicate potential small-study bias when p-values were <0.10. Sensitivity analyses excluding  
190 one study at a time were conducted to clarify whether the results were driven by one large study  
191 or a study with an extreme result.

192

#### 193 *Role of the funding source*

194 There was no funding source.

195 **3. Results**

196

197 The search strategy identified 6,639 records, of which 59 were eligible for full-text review;  
198 details regarding the screening process are shown in Figure 1. Following the screening process,  
199 28 studies were eligible for inclusion in our systematic review and meta-analysis, comprising a  
200 total of 3,271,242 individuals: 992,475 in at least one NMGD exposure group and 2,278,767 in  
201 the unexposed groups [15,16,25–34,17,35–42,18–24]. The baseline characteristics of the  
202 included studies are summarized in Table 1. Studies excluded following full-text review, along  
203 with a rationale for the decision, are listed in Table S1 in the Supplementary Appendix.

204

205 ROBINS-I scoring suggested low study quality for the majority of studies, with 9 out of the 28  
206 studies (32%) defined to be at critical risk of bias, six (21.5%) at serious ROB, seven (25%) at  
207 moderate ROB, and only six studies (21.5%) having high design quality with low ROB. The  
208 ROB summary can be visualized in Figure 2 [43]. The domain of bias due to confounding was  
209 most often found to be at critical risk, with no or non-rigorous methods applied to address  
210 potential confounders. No studies were rated as a critical ROB in more than one domain. Only  
211 Merz *et al.* 2016 [20] was rated as a serious ROB in more than one domain: bias due to selection  
212 of participants and misclassification bias, in addition to having a critical ROB due to lack of  
213 confounding control.

214

215 Meta-analysis revealed a greater risk of composite C/CVD among those with any NMGD  
216 compared to those with no NMGD exposure with a summary risk ratio (SRR) of 1.28  
217 (95%CI=1.20–1.37; n=16 studies,  $I^2=65.3%$ , Egger's test  $p=0.46$ ) (Figure 3). In NMGD

218 subgroup analyses, the risk of C/CVD for those with PCOS (SRR=1.28, 95%CI=1.18–1.39;  
219 n=11 studies,  $I^2=54.0\%$ ) and for those with endometriosis (SRR=1.30, 95%CI=1.15–1.47; n=5  
220 studies,  $I^2=81.1\%$ ) was similar to NMGD overall. In C/CVD outcome-specific analyses, NMGD  
221 was significantly associated with ischemic heart disease (SRR=1.41, 95%CI=1.31–1.51; n=21  
222 studies,  $I^2=73.7\%$ , Egger's test  $p=0.06$ ), with no heterogeneity observed specific to PCOS  
223 (SRR=1.42, 95%CI=1.23–1.63; n=12 studies,  $I^2=65.8\%$ ) or endometriosis (SRR=1.36,  
224 95%CI=1.22–1.51; n=7 studies,  $I^2=80.2\%$ ) exposure. The meta-analysis also revealed a greater  
225 risk of cerebrovascular disease in individuals with NMGD (SRR=1.33, 95%CI=1.18–1.51; n=16  
226 studies,  $I^2=91.5\%$ , Egger's test  $p=0.99$ ), again with a similarly greater risk for those with PCOS  
227 (SRR=1.47, 95%CI=1.18–1.82; n=10 studies,  $I^2=92\%$ ) or endometriosis (SRR=1.24,  
228 95%CI=1.12–1.38; n=5 studies,  $I^2=73\%$ ). The results of these analyses, including further  
229 subgroup analyses, are summarized in Table 2.

230  
231 The meta-analysis suggested a null association between NMGD and C/CVD mortality, although  
232 between-study heterogeneity was high (SRR=1.02, CI=0.65-1.60; n=8 studies,  $I^2=89.0\%$ ,  
233 Egger's test  $p=0.14$ ). There was the suggestion of an elevated meta-analytic risk of heart failure  
234 for those with NMGD compared to unexposed, but there was low precision as evidenced by a  
235 wide confidence interval and very high heterogeneity among studies (SRR=1.82, CI=0.98-3.39;  
236 n=4 studies,  $I^2=96.3\%$ , Egger's test  $p=0.78$ ).

237  
238 ADD ROB SENSITIVITY ANALYSIS

239

240 Most studies adjusted their analysis for age [17,21,22,24,26,28,31–35,37,39,40,42] and three for  
241 menopausal status [21,26,28] to account for their potential confounding effects. Several  
242 sensitivity analyses outlined in the PROSPERO protocol were not meta-analyzable, including  
243 age and menopause status effect modification of, or mediation by hysterectomy/oophorectomy  
244 of, the association between NMGD and C/CVD. No study in this review specified the age at  
245 diagnosis of NMGD; therefore, it was not possible conduct a meta-analysis restricted to those  
246 with NMGD diagnosed during their reproductive years.

247 **4. Discussion**

248

249 This systematic review and meta-analysis confirms the association between NMGD and C/CVD.  
250 The meta-analysis comprises a large total sample size allowing exploration of several subtypes  
251 of NMGD and C/CVD; the 28 studies yield a total of 3,271,242 individuals. The primary  
252 outcome demonstrates an increased risk of developing composite C/CVD in individuals with at  
253 least one NMGD (the exposed population), in comparison to individuals without NMGD (the  
254 unexposed population). Sub-group analyses correspondingly revealed that the increased risk of  
255 C/CVD and its components was observed in individuals with endometriosis or PCOS. Given the  
256 importance of temporality for causal inference, we further conducted sensitivity analyses that  
257 showed no significant difference in effect estimates when considering only studies that took into  
258 account temporality, although the number of studies contributing to this comparative analysis  
259 was small.

260

261 Common biologic pathways linking NMGD to C/CVD may include systemic inflammation and  
262 endogenous estrogenic milieu. The categorization of atherosclerosis as a chronic low-grade  
263 inflammatory condition is now commonly accepted [49]. Inflammation and oxidative stress are  
264 important triggers for C/CVD, and various inflammatory markers have been found to be essential  
265 contributors to C/CVD [50,51]. When considering endometriosis specifically, the mechanism  
266 believed to link this condition to increased cardiovascular risk is systemic inflammation [52].  
267 Similarly, in PCOS, a cross-sectional analysis found a significant association between low-grade  
268 inflammation and sympathetic dysfunction and hyperandrogenism [53]. As such, inflammation  
269 may be an underlying mechanism for an association between NMGD and C/CVD. However,

270 there is also a possible overlap of gynecological risk factors and cardiovascular risk factors that  
271 may act as confounders. For instance, features of metabolic syndrome, a complex interaction of  
272 visceral obesity, dyslipidemia, hyperglycemia, and hypertension [54], have been consistently  
273 shown to be present in individuals with PCOS [55]. Metabolic syndrome is associated with an  
274 increased risk of C/CVD events and mortality [56].

275

276 Female steroid hormones are implicated in the development of NMGD and link these to  
277 cardiovascular risk factors [52]. Endogenous estrone is related to endothelial function, while  
278 estradiol is related to vascular remodeling, suggesting specific roles for different female steroid  
279 hormones [57]. The effects on endothelial function seem beneficial, providing cardiovascular  
280 protection to individuals AFAB [58]. While some studies adjusted their analysis for MHT use  
281 [17,21,26] or oral contraceptive use [22,26,31,33], only one [34] performed a sub-group analysis,  
282 which demonstrated that the risk of subsequent CAD was higher in endometriosis patients taking  
283 hormonal therapy. Similarly, hysterectomy is associated with a greater risk of C/CVD [59],  
284 which could be further exacerbated when bilateral oophorectomy is performed [60]. Although  
285 few studies have considered this potential mediation [22,61], those that have assessed this have  
286 found a significant proportion of the causal pathway associating NMGD with C/CVD to be  
287 explained by surgical treatments. However, independent variation remained – confirming that  
288 other pathways contribute to C/CVD risk among individuals with NMGD.

289

290 Although the results of outcomes in our study that were meta-analyzable consistently indicated a  
291 higher risk of C/CVD among those with NMGD, these results must be interpreted with caution  
292 given that we quantified strong evidence for three primary limitations. First, most of the findings

293 in the meta-analysis suggest moderate to very high heterogeneity among studies, which may  
294 yield imprecise meta-analytic summary estimates. Indeed, there were a few examples of  
295 heterogeneous results when comparing single studies. Saavalainen *et al.* 2019 [24] found that the  
296 risk of C/CVD mortality was lower in endometriosis patients compared with controls; the  
297 underlying cause of this discrepancy is unclear. Furthermore, Solomon *et al.* 2002 [26] reported  
298 a lower risk of IHD in the irregular menstrual cycle group compared to those reporting regular  
299 cycles. The participants were asked to recall and self-reported menstrual cycle irregularity at  
300 ages 20-35. This methodology may contribute to inaccurate categorization, although validation  
301 studies conducted within this cohort suggested that the self-reporting of medical conditions was  
302 reliable [62].

303

304 The second limitation is the risk of bias in many of the studies. Concerningly, 53.5% of the  
305 studies included in this meta-analysis had low design quality with “serious” or “critical” risk of  
306 bias. The primary driver of poor risk of bias scores was a lack of control for potential  
307 confounders. While observational studies require data adequate to quantify and statistical  
308 approaches that account for potential confounders to support valid causal inference [63], we  
309 found that a large proportion of the studies published to date did not include any methods for  
310 control or assessment of confounding factors at all. It is important to note, however, that the  
311 higher quality studies with a low risk of bias (just six studies) that did account for potential  
312 confounders observed little evidence of confounding with low magnitudes of confounding  
313 effects [22,24,33,34,38,40]. The ROBINS-I risk of bias tool [11] was designed for non-  
314 randomized interventional studies; therefore, applying it in this systematic review was potentially  
315 less precise.

316

317 Third, despite lenient inclusion criteria, the data were sparse for most outcomes. To conduct a  
318 robust meta-analysis, outcomes were combined from a clinical perspective, reflecting how these  
319 diagnoses are managed in clinical practice. A larger body of literature with larger sample sizes  
320 within each study will afford much more precise estimation and the ability to explore likely  
321 variation among NMGD and C/CVD subtypes. Additionally, it would be beneficial to  
322 standardize the reporting of both NMGD conditions and C/CVD outcomes. For instance, a  
323 limited number of studies included in this review split the exposure group into subgroups based  
324 on menstrual regularity [26] or PCOS phenotype [64], which may contribute to misclassification  
325 bias. In contrast, multiple studies [16–19,21,27,29,31,32,35,36,38–41] did not differentiate  
326 between ischemic and hemorrhagic stroke subtypes, which have distinct underlying  
327 pathophysiological mechanisms [65].

328

329 Despite these limitations, this systematic review and meta-analysis represents the highest level of  
330 evidence currently available, with a rigorous methodology, a large, combined patient population  
331 for many of the associations explored, and a thorough meta-analysis with multiple subgroups and  
332 sensitivity analyses.

333

334 In conclusion, our findings indicate an association between NMGD and C/CVD overall and in  
335 subgroup populations. Given high study heterogeneity and risk of bias prevalence, future  
336 research must require study design rigor, improved NMGD and C/CVD harmonization, and  
337 elucidate risk variation among subpopulations. Physicians should be aware of the association  
338 between NMGD and C/CVD and use this to inform clinical practice in order to mitigate the risk

339 of C/CVD. Awareness of these risks allows clinicians to advise patients regarding risk reducing  
340 behavioral changes and interventions, monitor their NMGD patients for early signs and  
341 symptoms of C/CVD, and potentially diagnose atypical presentations of C/CVD with the  
342 knowledge of the underlying risk for this group of patients. Our findings reinforce the need for  
343 prospective longitudinal lifecourse research evaluating risk of C/CVD outcomes in NMGD  
344 overall and in subgroup populations, which may catalyze primary prevention strategies.  
345

346 *Contributors*

347 GEC was involved in study design, search strategy, study selection, data extraction, data  
348 interpretation, risk of bias and study quality assessment, and drafting of the manuscript. YMS  
349 was involved in study design, statistical analysis, data interpretation, risk of bias assessment, and  
350 editing of the manuscript. MA was involved in study design, statistical analysis, data  
351 interpretation, and editing of the manuscript. KM was involved in study design, search strategy,  
352 study selection, data extraction, risk of bias assessment, and editing of the manuscript. AS was  
353 involved in study design, search strategy, study selection, data extraction, risk of bias  
354 assessment, and editing of the manuscript. MK was involved in study design, data interpretation,  
355 and editing of the manuscript. SM was involved in study design, data interpretation, and editing  
356 of the manuscript. GC was involved in study design and editing of the manuscript. FP was  
357 involved in study design, search strategy, data interpretation, and editing of the manuscript. ML  
358 was involved in study design, search strategy, data interpretation, and drafting of the manuscript.

359

360 *Declaration of interests*

361 A/Prof Armour reports a leadership position in the advisory board of Endometriosis Australia.  
362 Prof Missmer reports participation on a past advisory board of AbbVie and Roche, roundtable  
363 participation for Abbott, a position as Field Chief Editor for *Frontiers in Reproductive Health*;  
364 conference travel or honoraria from WES and Mayo Clinic; board or committee membership for  
365 current - SWHR, WERF, and WES, and past - ASRM and ESHRE; and grants from AbbVie,  
366 National Institutes of Health, Department of Defense, Marriot Family Foundations outside the  
367 submitted work.

368 Prof Condous reports honoraria from Samsung and GE healthcare; participation on the board for  
369 International Deep Endometriosis Analysis (IDEA), Clinical Data Miner (CDM) Steering  
370 Committee, and IMAGENDO Steering Committee; the following leadership positions: WFUMB  
371 President Elect, ISUOG Co-Chair Scientific Committee, Head of Discipline OBGYN Sydney  
372 Medical School Nepean, Head of Department Gynaecology Nepean Hospital, World  
373 Endometriosis Society Ambassador, Australasian Society of Ultrasound in Medicine DDU  
374 Board; receipt of a Samsung ultrasound machine and GE Healthcare ultrasound machine; and  
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383 outside the submitted work. The remaining authors report no conflict of interest.

384

385 *IARC disclaimer*

386 Where authors are identified as personnel of the International Agency for Research on Cancer /  
387 World Health Organization, the authors alone are responsible for the views expressed in this  
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390

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393

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**Table 1:** Baseline characteristics of the included 35 studies (1966-2024) examining the association between NMGD and C/CVD

Author, year, location	Design	Study period	NMGD: #cases, type	NMGD: ascertainment	C/CVD: #cases, type	C/CVD: ascertainment	Unexposed: number, source population	Temporality	RR (95% CI)	Adjustment factors
<i>Atiomo et al., 2003 UK</i>	Cross-sectional	NR	41, PCOS	Medical records (Infertility clinic)	0, <u>MI</u>	Self-reported, confirmed with medical records	66, patients with infertility	<b>Cross-sectional:</b> no information on years of dx	NR	N/A
<i>Hart et al., 2015 Australia</i>	Retrospective cohort	1997-2011	2,566, PCOS	Medical records (hospital admission coding)	21, <u>hospitalisation for IHD</u> 15, <u>hospitalisation for C/CVD</u> 44, <u>hospitalisation for other heart disease</u> 275, <u>hospitalisation for arterial/venous disease</u>	Medical records (hospital admission coding)	25,660, patients without PCOS	<b>NMGD dx did not necessarily precede C/CVD dx:</b> patients with hospital admission coded for PCOS, however all hospital admissions from age 15 considered, not only after PCOS diagnosis	<u>IHD:</u> HR 2.89 (1.68-4.97) <u>C/CVD:</u> HR 2.58 (1.43-4.67) <u>Other:</u> HR 1.49 (1.09-2.05) <u>Arterial/venous:</u> HR 1.81 (1.59-2.05)	Admission with diagnosis of obesity
<i>Iftikhar et al., 2012 USA</i>	Retrospective cohort	1966-1988	309, PCOS	Medical records	15, <u>MI</u> 10, <u>unstable angina</u> 6, <u>stroke</u> 7, <u>CABG</u> 4, <u>C/CVD deaths</u>	Self-reported, confirmed with medical records	343, patients receiving medical care in Olmsted County without PCOS	<b>NMGD dx did not necessarily precede C/CVD dx:</b> PCOS cases identified, then postal survey sent out but does not state PCOS had to occur first	<u>MI:</u> HR 0.74 (0.32-1.72) <u>Unstable angina:</u> HR 1.32 (0.42-4.13) <u>Stroke:</u> HR 1.05 (0.28-3.92) <u>CABG:</u> 1.52 (0.42-5.48) <u>C/CVD deaths:</u> HR 5.67 (0.51-63.7)	Age at last follow-up, BMI, infertility treatment, postmenopausal hormone therapy, and family history of hypertension
<i>Lunde et al., 2007 Norway</i>	Prospective cohort	1970-1995	131, PCOS	Medical records	2, <u>MI</u> 0, <u>cerebral infarct</u>	Self-reported, confirmed with medical records	723, age-adjusted patients from Norwegian Health Survey	<b>NMGD dx did not necessarily precede C/CVD dx:</b> PCOS cases identified, then postal survey sent out but does not state PCOS had to occur first	<u>MI:</u> RR 2.8 (0.10-71) <u>Cerebral infarct:</u> RR 0 (0-11)	None
<i>Mani et al., 2013 UK</i>	Retrospective cohort	1988-2009	2,301, PCOS	Medical records (endocrinology clinic)	10, <u>MI</u> 12, <u>angina</u> 3, <u>HF</u> 0, <u>CVA</u> 5, <u>CV death</u>	Medical records (hospital admissions)	Comparison to local and national population	<b>NMGD dx preceded C/CVD dx:</b> PCOS cases identified then they were followed-up until they had the event of interest, died, migrated out of the Leicestershire area or reached the end of observation	<u>MI:</u> OR 0.97 (0.59-1.58) <u>Angina:</u> OR 0.42 (0.27-0.64) <u>Composite C/CVD:</u> OR 0.33 (0.24-0.45)	None
<i>Merz et al., 2016 USA</i>	Case-control	1997-2001	25, PCOS	Self-reported Hx irregular cycles, measurement of serum androgens	6, <u>MI or C/CVD death</u>	Self-reported and medical records (National Death Index)	270, participants in WISE study without Hx of irregular menses and high serum androgens	<b>NMGD dx did not necessarily precede C/CVD dx:</b> all participants had suspected myocardial ischaemia, then asked to re-call Hx irregular menses and serum	NR	N/A

## Gynecological disease and C/CVD: a meta-analysis

Author, year, location	Design	Study period	NMGD: #cases, type	NMGD: ascertainment	C/CVD: #cases, type	C/CVD: ascertainment	Unexposed: number, source population	Temporality	RR (95% CI)	Adjustment factors
								androgens measured at time of study		
<i>Meun et al., 2018 Netherlands</i>	Prospective cohort	1997-2001	106, PCOS	Self-reported Hx irregular cycles, measurement of serum androgens	NR	Medical records (GP, specialists, and hospital admissions)	171, post-menopausal patients without Hx irregular cycles and normal serum androgens	<b>NMGD dx preceded C/CVD dx:</b> patients with prevalent C/CVD at baseline were excluded from analysis of incident C/CVD	<u>Incidence CHD:</u> HR 0.73 (0.27-1.99) <u>Incidence stroke:</u> HR 1.16 (0.55-2.42) <u>Incidence C/CVD:</u> HR 0.94 (0.51-1.76)	Age, years since menopause, cohort, waist/hip ratio, total and HDL cholesterol, smoking, systolic blood pressure, treatment of hypertension, DM, and use of hormones
<i>Mu et al., 2016 USA</i>	Prospective cohort	1989-2009	5,296, endometriosis	Self-reported, confirmed with medical records (laparoscopy)	69, <u>incidence MI</u> 149, <u>incidence angina</u> 91, <u>incidence CABG/Angio/Stent</u>	Medical records (hospital records, National Death Index, autopsy report)	109,161, registered female nurses aged 25-42 at enrollment without laparoscopically confirmed endometriosis	<b>NMGD dx preceded C/CVD dx:</b> patients with C/CVD prior to enrollment in study were excluded, incident C/CVD was recorded	<u>Incidence MI:</u> RR 1.52 (1.17-1.98) <u>Incidence angina:</u> RR 1.91 (1.59-2.29) <u>Incidence CABG/Angio/Stent:</u> RR 1.35 (1.08-1.69) <u>Combined CHD:</u> RR 1.62 (1.39-1.89)	Age in months and questionnaire cycle and adjusted for race, age at menarche, birth weight, maternal or paternal history of myocardial infarction <60 years old, body mass index at age 18, and time-varying risk factors: current body mass index, parity, total months of breast feeding, oral contraceptive use, smoking history, alcohol consumption, alternate healthy eating index quintile 2010, physical activity, multivitamin use, and health care utilization rate
<i>Okoroh et al., 2015 USA</i>	Retrospective cohort	2004-2011	125,268, PCOS	Medical records (ICD codes for insurance claims)	268, <u>ischaemic stroke</u> 137, <u>MI</u> 56, <u>PVD</u>	Medical records (ICD codes for insurance claims)	250,536, age matched participants	<b>NMGD dx preceded C/CVD dx:</b> diagnosis of PCOS was index date and participants were tracked longitudinally	NR	N/A
<i>Saavalien et al., 2019 Finland</i>	Retrospective cohort	1987-2012	49,956, endometriosis	Medical records (Finnish Hospital Discharge Register)	205, <u>C/CVD death</u> 115, <u>MI death</u> 90, <u>cerebrovascular death</u> 20, <u>cerebral infarct death</u>	Medical record (Finnish Hospital Discharge Register & Statistics Finland)	98,824, randomly drawn from Finnish population information system	<b>NMGD dx preceded C/CVD dx:</b> diagnosis of endometriosis was index date	<u>C/CVD deaths:</u> crude MRR 0.58 (0.50-0.68) <u>IHD deaths:</u> MRR 0.52 (0.42-0.64) <u>Cerebrovascular disease deaths:</u> MRR 0.6 (0.47-0.76) <u>Cerebral infarct deaths:</u> crude mRR 0.58 (0.35-0.95)	Age and time since the index day as modeled by spline functions, the highest educational level and baseline calendar time, parity as assessed in a time- dependent manner

## Gynecological disease and C/CVD: a meta-analysis

Author, year, location	Design	Study period	NMGD: #cases, type	NMGD: ascertainment	C/CVD: #cases, type	C/CVD: ascertainment	Unexposed: number, source population	Temporality	RR (95% CI)	Adjustment factors
<i>Schmidt et al., 2011 Sweden</i>	Prospective cohort	1987-2008	32, PCOS	Medical records (Hospital Discharge Register)	3, <u>MI hospitalisation</u> 1, <u>MI death</u> 6, <u>stroke hospitalisation</u>	Medical records (Hospital Discharge Registry, National Board of Health and Welfare Registry)	95, population of the MONICA study	<b>NMGD dx did not necessarily precede C/CVD dx:</b> data on MI, stroke, and C/CVD death is during the follow-up period of the study however prevalence of C/CVD at baseline not stated	NR	N/A
<i>Sirmans et al., 2014 USA</i>	Cross-sectional	2009-2010	1,689, PCOS	Medical records (Medicaid claims)	1, <u>MI</u> 14, <u>angina</u> 5, <u>chronic HF</u> 0, <u>CABG</u> 21, <u>CHD</u> 8, <u>ischaemic stroke</u> 4, <u>TIA</u> 1, <u>PCI</u> 4, <u>PVD</u>	Medical records (Medicaid claims)	5,067, female patients under Medicaid aged 15-45 who were not pregnant and did not have confounding conditions	<b>Cross-sectional:</b> comparison of C/CVD in patients with NMGD and without, no information of years of dx	NR	N/A
<i>Solomon et al., 2002 USA</i>	Prospective cohort	1976-1996	3,545, very irregular menstrual cycles	Self-reported	96, <u>total CHD</u> 36, <u>fatal CHD</u>	Self-reported, confirmed with medical records	51,030, participants in Nurses Health Study with very regular cycles	<b>NMGD dx preceded C/CVD dx:</b> participants with C/CVD at baseline were excluded	<u>Total CHD:</u> RR 1.53 (1.24-1.9) <u>Fatal CHD:</u> RR 1.88 (1.32-2.67)	Age, body mass index, cigarette smoking, menopausal status/postmenopausal hormone use, parental history of MI before age 60 yr, parity, alcohol intake, aspirin use, multivitamin use, vitamin E supplement use, physical activity level, and history of oral contraceptive use
<i>Surrey et al., 2018 USA</i>	Retrospective cohort	2006-2015	26,961, endometriosis	Medical records (Commercial insurance claims)	15, <u>MI</u> 75, <u>congestive HF</u> 22, <u>PVD</u> 264, <u>cerebrovascular disease</u>	Medical records (Commercial insurance claims)	107,844, patients without insurance claims for endometriosis	<b>NMGD dx did not necessarily precede C/CVD dx:</b> data on C/CVD from participants' baseline characteristics, comorbidities studied following index date did not include C/CVD	NR	N/A
<i>Wang et al., 2020 USA</i>	Prospective cohort	1993-2017	2,685, irregular menstrual cycle	Self-reported	30, <u>C/CVD deaths</u>	Medical records (state vital statistics records, National Death Index) and reports from next of kin or the postal authorities	43,695, participants in Nurses' Health Study II	<b>NMGD dx preceded C/CVD dx:</b> participants with C/CVD at baseline were excluded	<u>C/CVD deaths:</u> HR 1.59 (1.04-2.45)	Age, menopausal status, age at menarche, race, family history of myocardial infarction, stroke, or diabetes, baseline hypertension or high blood cholesterol level, parity, alcohol consumption, BMI, physical activity, smoking status, and fifths of alternative healthy eating index 2010 score

## Gynecological disease and C/CVD: a meta-analysis

Author, year, location	Design	Study period	NMGD: #cases, type	NMGD: ascertainment	C/CVD: #cases, type	C/CVD: ascertainment	Unexposed: number, source population	Temporality	RR (95% CI)	Adjustment factors
Wild <i>et al.</i> , 2000 UK	Retrospective cohort	1979-1999	319, PCOS	Medical records	15, CHD 10, <u>cerebrovascular disease</u>	Medical records (NHSCR)	1,060, patients adjacent to participants on age-sex register at the same general practice	<b>NMGD dx did not necessarily precede C/CVD dx:</b> patients diagnosed with PCOS were traced via NHSCR and medical records studied to identify CHD, no specification of timeline	<u>CHD</u> : OR 1.2 (0.5-2.6) <u>Cerebrovascular disease</u> : OR 3.4 (1.2-9.6) <u>CHD and/or cerebrovascular disease</u> : OR 1.7 (0.9-3.2)	BMI
Guoqing <i>et al.</i> , 2017 China	Cross-sectional	2012-2014	70, PCOS	Diagnosis retrospectively made by gynaecologist	12, <u>SCIs</u>	MRI report	140, healthy post-menopausal patients seen for gynaecological examination	<b>Cross-sectional:</b> patients with PCOS identified then MRI performed	NR	N/A
Okoth <i>et al.</i> , 2021 UK	Retrospective cohort	1995–2018	56,090, endometriosis	Medical records (The Health Improvement Network)	574, <u>composite C/CVD</u> 279, <u>IHD</u> 294, <u>cerebrovascular disease</u> 41, <u>HF</u>	Medical records (The Health Improvement Network)	223,669, matched from general population	<b>NMGD dx preceded C/CVD dx:</b> diagnosis of endometriosis was index date	<u>Composite C/CVD</u> : HR 1.24 (1.14-1.37) <u>IHD</u> : HR 1.40 (1.22-1.61) <u>Cerebrovascular disease</u> : HR 1.19 (1.04-1.36) <u>HF</u> : HR 0.76 (0.54-1.07)	Age, Townsend deprivation quintiles, BMI, smoking status, lipid-lowering medication, alcohol use, diabetes mellitus, hypertension, connective tissue disorders, migraine, contraceptive use, parity status, PCOS
Chiang <i>et al.</i> , 2021 Taiwan	Retrospective cohort	1997-2013	17,543, endometriosis	Medical records (Taiwan National Health Insurance Database)	201, <u>major C/CVD</u> 485, <u>MACCE</u> 315, <u>CVA</u>	Medical records (Taiwan National Health Insurance Database)	70,172, population dataset	<b>NMGD dx preceded C/CVD dx:</b> participants with C/CVD diagnosis prior to endometriosis diagnosis were excluded	<u>Major C/CVD</u> : HR 1.19 (1.01-1.40) <u>MACCE</u> : HR 1.17 (1.05-1.29) <u>CVA</u> : HR 1.16 (1.02-1.31)	Adjusting for age, urbanization/ income, and associated comorbidities
Li <i>et al.</i> , 2021 Taiwan	Retrospective cohort	2000–2012	19,454, endometriosis	Medical records (Taiwan National Health Insurance Database)	853, <u>CAD event</u>	Medical records (Taiwan National Health Insurance Database)	77,816, randomly selected from Taiwan National Health Insurance Database	<b>NMGD dx preceded C/CVD dx:</b> participants with CAD diagnosis prior to index date were excluded	<u>CAD event</u> : HR 1.34 (1.22-1.47)	Age, comorbidities (obesity, CKD, hypertension, hyperlipidemia, DM, hysterectomy, oophorectomy), and medication [hormonal (estradiol, premarin), statin, aspirin, antihypertensive, antihyperglycemic, insulin)
Wei <i>et al.</i> , 2021 Taiwan	Retrospective cohort	2000–2012	13,998, endometriosis	Medical records (Longitudinal Health Insurance Database 2000)	199, <u>CAD event</u>	Medical records (Longitudinal Health Insurance Database 2000)	13,998, selected from Longitudinal Health Insurance Database 2000 using propensity scores	<b>NMGD dx preceded C/CVD dx:</b> participants with CAD diagnosis prior to index date were excluded	<u>CAD event</u> : HR 1.52 (1.23–1.88)	Age, hypertension, hyperlipidemia, diabetes, cancer, COPD, autoimmune disease, hysterectomy/oophorectomy, stroke, outpatient visits, corticosteroids, NSAIDs, aspirin, and statin
Berni <i>et al.</i> , 2021 UK	Retrospective cohort	1998-2017	174,660, PCOS	Medical records (CPRD Aurum database linked)	804, <u>composite C/CVD</u> 221, <u>MI</u> 319, <u>angina</u>	Medical records (CPRD Aurum database linked with HES &	174,660, matched from primary care practice	<b>NMGD dx preceded C/CVD dx:</b> participants with MACE diagnosis prior to index date were	<u>Composite C/CVD</u> : HR 1.26 (1.13- 1.41) <u>MI</u> : HR 1.38 (1.11-1.72)	Age, BMI category, smoking status, alcohol status, T2DM, baseline morbidity represented by the Charlson

## Gynecological disease and C/CVD: a meta-analysis

Author, year, location	Design	Study period	NMGD: #cases, type	NMGD: ascertainment	C/CVD: #cases, type	C/CVD: ascertainment	Unexposed: number, source population	Temporality	RR (95% CI)	Adjustment factors
				with HES & ONS)	102, <u>revascularization</u> 68, <u>CV mortality</u> 267, <u>stroke</u>	ONS)		excluded	<u>Angina</u> : HR 1.60 (1.32- 1.94) <u>Revascularization</u> : HR 1.50 (1.08- 2.07) <u>CV mortality</u> : RR 0.90 (0.64- 1.27) <u>Stroke</u> : RR 1.07 (0.92- 1.32)	index, systolic blood pressure (BP) and diastolic BP, and relative deprivation based on quintiles of Index of Multiple Deprivation
<i>Forslund et al., 2022 Sweden</i>	Prospective cohort	1987-2019	21, PCOS	Histopathology & Rotterdam criteria	8, <u>C/CVD event</u> 2, <u>MI</u> 3, <u>angina</u> 2, <u>stroke</u> 1, <u>TIA</u>	Medical records (National Board of Health and Welfare)	55, randomly selected from MONICA study population	<b>NMGD dx did not necessarily precede C/CVD dx</b> : data on MI, stroke, and C/CVD death is during the follow-up period of the study however prevalence of C/CVD at baseline not stated	<u>C/CVD event</u> : HR 1.21 (0.66–2.20) <u>MI</u> : HR 1.54 (0.44–4.95) <u>Stroke</u> : HR 0.99 (0.44–2.42) <u>TIA</u> : HR 1.43 (0.33–7.48) <u>C/CVD mortality</u> : HR 1.65 (0.66–4.29)	N/A
<i>Lin et al., 2021 Taiwan</i>	Retrospective cohort	1996-2013	66,048, Dysmenorrhea	Medical records (Taiwan National Health Research Institutes)	116, <u>stroke</u> 183, <u>TIA</u>	Medical records (Taiwan National Health Research Institutes)	66,048, randomly selected from the Health and Welfare Data Science Center of the Ministry of Health and Welfare	<b>NMGD dx preceded C/CVD dx</b> : participants with stroke diagnosis prior to index date were excluded	<u>Stroke</u> : HR 1.24 (0.94–1.63) <u>TIA</u> : HR 1.64 (1.29–2.08)	Age
<i>Farland et al., 2022 USA</i>	Prospective cohort	1989-2017	5,244, Endometriosis	Laparoscopically confirmed endometriosis	893, <u>incident stroke</u>	Medical records where available or corroborated by nurse participant information	106,812, female registered nurses without endometriosis	<b>NMGD dx preceded C/CVD dx</b> : participants with C/CVD diagnosis prior to index date were excluded	<u>Stroke incidence</u> : HR 1.34 (1.10–1.62)	Age, calendar time, alcohol intake, BMI at age 18 y, current BMI, age at menarche, menstrual cycle pattern in adolescence, current menstrual cycle pattern in adulthood, parity, oral contraceptive use history, smoking history, diet score in quintiles, physical activity, race, income, family history of MI, family history of stroke, aspirin use, and NSAID use
<i>Blom et al., 2023 Canada</i>	Retrospective cohort	1993-2015	166,853, Endometriosis	Medical records Ontario Health Insurance Plan (OHIP)	4652, <u>hospital admission for CVD</u> 3150, <u>hospital admission for IHD</u> 1317, <u>hospital admission for cerebrovascular disease</u>	Medical records Ontario Health Insurance Plan (OHIP)	333,706, matched by age and geographical location of residence	<b>NMGD dx preceded CVD dx</b> : participants with CVD diagnosis prior to index date were excluded	<u>Hospital admission for CVD</u> : aHR 1.14 (1.10–1.29) <u>Hospital admission for IHD</u> : IRR 1.23 (1.17–1.28) <u>Hospital admission for cerebrovascular disease</u> : IRR 1.16 (1.08–1.24)	Age, parity, hypertension, diabetes, obesity and immigration status

## Gynecological disease and C/CVD: a meta-analysis

Author, year, location	Design	Study period	NMGD: #cases, type	NMGD: ascertainment	C/CVD: #cases, type	C/CVD: ascertainment	Unexposed: number, source population	Temporality	RR (95% CI)	Adjustment factors
Ryu <i>et al.</i> , 2024 South Korea	Retrospective cohort	2002-2019	137,416, PCOS	Medical records (K-NHIS)	6.6/1000 PY, C/CVD 4/1000 PY, IHD 2.9/1000 PY, cerebrovascular disease	Medical records (K-NHIS)	412,118, matched for age, income, and region of residence	<b>NMGD dx preceded CVD dx:</b> participants with CVD diagnosis prior to index date were excluded	C/CVD: aHR 1.22 (1.18–1.27) IHD: aHR 1.25 (1.20–1.31) Cerebrovascular disease: aHR 1.20 (1.14–1.27)	Age, BMI, diabetes mellitus, hypertension, dyslipidemia, systolic BP, diastolic BP, total cholesterol, triglyceride levels, history of alcohol consumption, current smoking, and physical exercise level
Vine <i>et al.</i> , 2024 Canada	Retrospective cohort	2002-2018	16,531, PCOS	Medical records (Alberta Health Services database)	614, <u>lifetime prevalence CVD</u> 134, <u>lifetime prevalence MI</u> 2332, <u>lifetime prevalence cerebrovascular disease</u> 233, <u>lifetime prevalence HF</u>	Medical records (Alberta Health Services database)	49,335, matched for age	<b>NMGD dx did not necessarily precede CVD dx:</b> prevalence of C/CVD reported without specifying temporality	N/A	None
Yeh <i>et al.</i> , 2022 Taiwan	Retrospective cohort	2000-2008	18,455, dysmenorrhea	Medical records Longitudinal Health Insurance Database (LHID)	338, <u>incidence IHD</u>	Medical records Longitudinal Health Insurance Database (LHID)	36,910, matched by age and index-year	<b>NMGD dx preceded CVD dx:</b> participants with CVD diagnosis prior to index date were excluded	IHD: aHR 1.60 (1.38–1.85)	Dysmenorrhea, age, all comorbidities (diabetes, hypertension, hyperlipidemia, arrhythmias, thyroid disease, migraine), and NSAID use

**Footnote:** RR summary relative risk; CI confidence interval; C/CVD cerebro- and cardiovascular disease; NMGD non-malignant gynecological disease; PCOS polycystic ovary syndrome; NSAID non-steroidal anti-inflammatory drugs; MI myocardial infarction; BMI body mass index; TIA transient ischemic attack; CAD coronary artery disease; CVD cardiovascular disease; CHD coronary heart disease; IHD ischemic heart disease; MACCE major adverse cardiovascular and cerebrovascular events; HF heart failure; LVEF left ventricular ejection fraction; GLS global longitudinal strain; CVA cerebrovascular accident; COPD chronic obstructive pulmonary disease; T2DM type 2 diabetes mellitus; CABG coronary artery bypass graft; PCI percutaneous coronary intervention; PVD peripheral vascular disease; PY person-years; ICD International Classification of Diseases; N/A not applicable

**Table 2: Subgroup analyses of association between NMGD and cardiovascular disease risk**

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

**Footnote:** RR summary relative risk; CI confidence interval; CVD cardiovascular disease; NMGD non-malignant gynecological disease

I<sup>2</sup> (%) is a measure of the proportion of the heterogeneity attributed to between study variation rather than due to chance. I<sup>2</sup> values of 25%, 50% and 75% indicate low, moderate and high between study heterogeneity, respectively.

\*P value for heterogeneity within each subgroup

†P value for heterogeneity between subgroups with meta-regression analysis

***Figure Legend***

**Figure 1:** PRISMA flowchart of study selection

**Figure 2:** ROBINS-I risk of bias assessment summary

**Figure 3:** Forest plot for the association between NMGD and composite C/CVD