CJC Open 6 (2024) 347–354

Systematic Review/Meta-analysis

Measurements of Postmenopausal Serum Estradiol Levels and Cardiovascular Events: A Systematic Review

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ABSTRACT

Background: Cardiovascular disease (CVD) is the leading cause of death among female patients and its likelihood increases following menopause. However, whether estradiol levels are related to CVD remains unknown. We aimed to determine the association between serum estradiol levels and cardiovascular (CV) events in postmenopausal females.

Methods: Electronic databases (MEDLINE, Embase) were searched systematically from inception to October 2022. Studies were eligible for inclusion if they included the following: (i) postmenopausal fe-

RÉSUMÉ

Contexte : Les maladies cardiovasculaires (MCV) sont la principale cause de décès chez les femmes et leur probabilité augmente après la ménopause. Cependant, on ne sait pas encore si le taux d'estradiol est lié aux MCV. Nous avons tenté d'établir le lien entre le taux d'estradiol sérique et les événements cardiovasculaires (CV) chez les femmes post-ménopausées.

Méthodologie : Nous avons consulté systématiquement des bases de données électroniques (MEDLINE, Embase) de leur création jusqu'en octobre 2022. Les études admissibles devaient comprendre les

Lay Summary

Cardiovascular (CV) disease is the leading cause of death among women globally. Although CV disease develops because of many factors, serum estradiol levels in menopause have been associated with various CV outcomes. An examination of the association between serum estradiol levels and CV events in postmenopausal women was performed. The results demonstrate that uncertainty remains regarding the association between serum estradiol levels and CV events in postmenopausal women.

Cardiovascular disease (CVD) is the leading cause of death globally.[1] Much of the research conducted to date has not considered female sex (biological attributes) and/or woman gender (socially constructed roles, identity, and expression).[2] Sex-specific CVD risk factors are gaining the attention of clinicians and scientists, and they are being looked at more closely to explain differences in CVD across the lifespan.[3,4] As CVD is the leading cause of death in females,[1] an urgent need exists to identify potentially modifiable risk factors, and ways to prevent and manage CVD in this population.

Globally, 60,000 women become menopausal daily.[5] During menopause, cardiovascular (CV) risk increases, which generally has been attributed to increasing age and a decline in estradiol levels.[6,7] Endogenous estrogens are considered to be cardioprotective against atherosclerosis by increasing vasodilation, enhancing flexibility and pliability of blood vessels, and inhibiting blood-vessel response to tissue injury.[8,9] The use of menopausal hormone therapy (MHT)

Received for publication July 31, 2023. Accepted November 13, 2023.

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See page 353 for disclosure information.

https://doi.org/10.1016/j.cjco.2023.11.010

males; (ii) examination of the association between total serum estradiol levels and CV events (CV mortality, CVD, coronary heart disease, myocardial infarction, stroke, venous thromboembolism, heart failure, and CV hospitalization); (iii) original data (randomized controlled trial, quasi-experimental, cohort, case-control, or cross-sectional study). A narrative synthesis was completed because the data were not amenable to meta-analysis.

Results: Of the 9026 citations retrieved, 8 articles were included, representing a total of 5635 women. The risk-of-bias was fair, and considerable heterogeneity was present. In those not using menopausal hormone therapy, 3 studies demonstrated mixed results between estradiol levels and risk of coronary heart disease, and 1 study showed that higher estradiol levels were associated with an increased risk of myocardial infarction. No significant associations were present between estradiol levels and the remaining events (ie, CV mortality, heart failure, CVD, and stroke).

Conclusions: The association between serum estradiol levels and CV events in postmenopausal females remains unclear. Further studies assessing this association are warranted, given the elevated CVD risk in this population.

éléments suivants : i) femmes post-ménopausées; ii) examen du lien entre le taux total d'estradiol sérique et les événements CV (décès d'origine CV, MCV, coronaropathie, infarctus du myocarde, accident vasculaire cérébral (AVC), thromboembolie veineuse, insuffisance cardiaque et hospitalisation pour une cause CV); iii) données originales (essai contrôlé randomisé; études quasi expérimentales, de cohorte, cas-témoins ou transversales). Une synthèse narrative a été réalisée parce que les données ne se prêtaient pas à une méta-analyse.

Résultats : Parmi les 9 026 citations relevées, 8 articles ont été retenus, représentant un total de 5 635 femmes. Le risque de biais était raisonnable, et une très grande hétérogénéité était présente. Chez les femmes qui ne suivaient pas d'hormonothérapie ménopausique, trois études ont affiché des résultats variables quant au lien entre le taux d'estradiol et le risque de coronaropathie, et une étude a montré que des taux élevés d'estradiol étaient associés à un risque accru d'infarctus du myocarde. Aucun lien notable n'a été observé entre le taux d'estradiol et les autres événements (c.-à-d. décès d'origine CV, insuffisance cardiaque, MCV et AVC).

Conclusions : Le lien entre le taux d'estradiol sérique et les événements CV chez les femmes post-ménopausées n'a pas été élucidé. D'autres études sont nécessaires pour évaluer ce lien en raison du risque élevé de MCV au sein de cette population.

has changed over time. Historically, MHT was prescribed to women, with the intention of providing CV protection, based on observational data.[10] However, later evidence from a randomized controlled trial (RCT) showed a nonsignificant increase in coronary heart disease (CHD) among users taking combined therapy and no differences in those taking estrogen only, while a significant increase in the risk of stroke and deep vein thrombosis was observed for both groups.[11] Moreover, the timing of MHT initiation after menopause may play a role in the observed clinical differences from various studies.[12] This was demonstrated by a follow-up analysis of the Women's Health Initiative, in which starting MHT at a younger age was found to be associated with a decreased risk of CVD, but starting MHT at an older age was found to be associated with an increased CVD risk.[13] Currently, MHT use is not indicated for the primary or secondary prevention of CVD.[14] Additionally, the recommended approach is that MHT be used only for the treatment of moderate-to-severe vasomotor or genitourinary symptoms in females under age 60 years, for whom the onset of menopause is within 10 years and who have no contraindications.[15] Although the development of CVD is a multifactorial process, the role of estradiol levels in contributing to CVD risk in postmenopausal females is unclear. Therefore, the objective of this systematic review was to determine the association between serum estradiol levels and CV events in postmenopausal females. This systematic review aims to address the following question: Are serum estradiol levels associated with CV events in postmenopausal females?

Methods

Reporting standards from the **P**referred **R**eporting **I**tems for **S**ystematic Review and **M**eta-**A**nalyses (PRISMA) 2020 checklist[16] (Supplemental Table S1) and the **S**ynthesis **Wi**thout **M**eta-Analysis (SWiM) guidelines[17] (Supplemental Table S2) were followed for this systematic review. A protocol for this systematic review was registered with the International **Prospe**ctive **R**egister **o**f Systematic Reviews (PROSPERO; CRD42022368235).

This review was guided by a **P**opulation, **E**xposure, **C**omparator, **O**utcome and Study **D**esign (PECOD) framework.[18] The population is postmenopausal females (as defined by study authors). The exposure is total serum estradiol levels. The outcome is CV events defined as CV mortality, CVD, myocardial infarction (MI), ischemic or hemorrhagic stroke, venous thromboembolism (VTE), CHD, heart failure (HF), and CV hospitalization. Lastly, study designs that were of interest for this analysis include RCTs, quasi-RCTs, case-control, cohort, and cross-sectional studies.

Information sources and literature search

MEDLINE (1950 to October 2022) and Excerpta Medica Database (Embase; 1974 to October 2022) were identified as the most relevant databases for this review. A comprehensive search of MEDLINE and Embase was conducted on the Ovid platform, without time, language, or geography restrictions, and the search strategies were developed with the assistance of a medical librarian. The grey literature was hand-searched in our preliminary search, and reference lists of included articles were manually hand-searched and retrieved. Content experts in menopause with expertise in women's health, endocrinology, and internal medicine were consulted to identify additional potential studies. They reviewed findings from the search strategy and were asked to identify any additional studies of which they were aware. Non-English abstracts were translated using Google Translate, and 2 relevant full-text articles were translated from Chinese to English using a translator. Only published, peer-reviewed original articles

were eligible for inclusion; pre-print studies and grey literature were not included.

Our search combined terms from 3 themes using the Boolean operator "AND." Terms within each theme were grouped using the Boolean operator "OR." The first theme used terms that defined the population of interest (eg, menopause, postmenopausal, climacteric). The second theme was related to the exposure (eg, estrogen, estradiol, sex hormone, oestrogen, oestradiol). The third theme pertained to the outcomes of interest (eg, CV mortality, blood pressure, lipid, triglyceride, body mass index, myocardial infarction, hypertension, systole, diastole, thrombosis). Terms were searched as keywords and subject headings (eg, MeSH), as applicable. Search terms for CV events were broader than the outcomes used for the analysis and included CV risk factors to ensure that all relevant literature was captured. A complete MEDLINE and Embase search strategy can be found in Supplemental Tables S3 and S4, respectively.

Study selection

All identified citations from the searches were collated and uploaded using the Covidence platform (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia), which also removed duplicate citations. Two reviewers (N.G. and K.T.M.) independently screened titles and abstracts in duplicate. A calibration exercise to identify discrepancies in abstract classification between the 2 reviewers was completed, using the first 100 abstracts, to mitigate discrepancies in classification of the remaining abstracts. Original studies that included postmenopausal females and reported on any CV events were selected for full-text review. All discrepancies were resolved through discussion and consensus or by the involvement of a third reviewer (S.B.).

Following title and abstract screening, the reviewers completed full-text review independently and in duplicate for articles potentially eligible for inclusion in the study. The inclusion criteria were as follows: (i) inclusion of postmenopausal females; (ii) reporting on total serum estradiol levels; (iii) reporting at least one CV event of interest (CV mortality, CVD, CHD, MI, ischemic or hemorrhagic stroke, VTE, HF, CV hospitalization); and (iv) a study design that was either an RCT, quasi-RCT, cohort, case-control, or cross-sectional study. Articles were deemed ineligible and excluded from the systematic review if the entire cohort had premature menopause (menopause at age < 40 years[19]).

Data extraction

Data extraction was independently completed by the 2 reviewers (N.G. and K.M.T.). The following clinical and methodological variables were extracted: study identifiers (eg, title, author, year of publication, and country); study characteristics (eg, design, sample size, and follow-up period); population characteristics (eg, age, smoking status, family history of CVD, proportion of sample with hypertension and diabetes); if applicable, MHT and menopause characteristics (eg, dose, route of administration, duration of exposure, time since menopause, type of menopause, age at menopause); total serum estradiol levels; and CV events (CV mortality, CVD, MI, ischemic or hemorrhagic stroke, VTE, CHD, HF, CV hospitalization). Measures of association (eg, odds ratios, hazard ratios, risk ratios) and their corresponding 95% confidence intervals were also extracted. For studies that reported multiple estimates or models (eg, crude and adjusted models), the most adjusted estimates were extracted. Extracted data were compared between reviewers, and all discrepancies were resolved by discussion and consensus or by the involvement of a third reviewer (S.B.).

Quality assessment

Study quality was assessed by completing a critical appraisal of eligible studies using the Quality Assessment Tool for Observational Cohort and Cross-sectional Studies,[20] along with the Quality Assessment of Case-Control Studies,[21] both from National Institutes of Health (NIH). Study quality was assessed independently, and in duplicate, by the 2 reviewers (N.G. and K.T.M.), and conflicts were resolved by discussion and consensus or by the involvement of a third reviewer (S.B.). Furthermore, both of the NIH Quality Assessment Tools were modified to include a scale that was used to determine if study quality was poor, fair, or good, to maintain consistency in quality assessment between reviewers. For observational cohort and cross-sectional studies, the following scale was used: yes for 0-4 questions = poor; yes for 5-10 questions = fair; yes for 11-14 questions = good.[22] For case-control studies, the following scale was used: yes for 0-4 questions = poor; yes for 5-8 questions = fair; yes for 9-12 questions = good.

Data synthesis and analysis

A meta-analysis was initially proposed in our study protocol. However, this component was removed because of the large heterogeneity between studies, the lack of consistent reporting for the exposure, the paucity of studies reporting on a common outcome, and the diversity of definitions used for the outcomes of interest (Supplemental Table S5), thereby making a meta-analysis of studies infeasible. Given this context, we chose to present the results as a narrative synthesis using the SWiM guideline.[17] If medians and interquartile ranges were reported, means and standard deviations were obtained using the methodology described by Luo et al.[23] and Wan et al., respectively.[24]

Results

Study selection

The literature search yielded 9026 unique citations (Fig. 1). After removing duplicates, 6628 citations were screened at the title and abstract stage, and of those, 272 underwent full-text screening. A total of 8 studies (3 prospective cohort,[25-27] 4 case-control,[28-31] and 1 cross-sectional[32]) met the inclusion criteria. Interrater reliability was good ($\kappa = 0.65$) at the stage of full-text screening.

Study characteristics

A total of 5635 participants were included from the 8 studies (Table 1). The studies included in this review had significant heterogeneity in the population, reported outcomes, and study design. Study settings were from 3 countries, with the majority being conducted in the United States

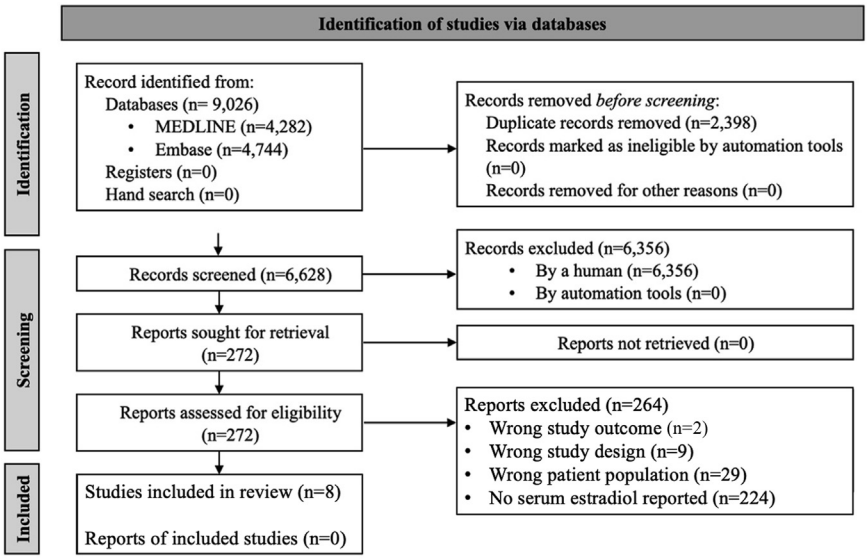

Figure 1. **P**referred **R**eporting **I**tems for **S**ystematic Reviews and **M**eta-**A**nalyses (PRISMA) flow of studies.

(n = 4723) or China (n = 284). Study publication dates ranged from 1989 to 2020. Six studies[26-30,32] reported the age of participants by CV outcome. The mean age range for female patients who experienced a CV outcome was 62.49 ± 4.73 years to 76.60 ± 5.70 years, and for those who did not, the age range was 59.00 ± 5.00 years to 74.3 ± 5.30 years. For the 3 prospective cohort studies, the mean follow-up time was 11.7 years.[25-27]

All included studies[25-32] reported the mean serum estradiol levels according to whether participants had a CV event. The range of mean estradiol levels for women with no CV event was 20.34 ± 12.12 pmol/L to 965.47 ± 906.74 pmol/L. The range of mean estradiol levels in those with a CV event was 24.20 ± 13.24 pmol/L to 939.78 ± 734.20 pmol/L. The reporting of CV events was not uniform. Two studies reported CVD,[27,30] 4 reported CHD,[26,27,31,32] 2 reported on ischemic stroke,[26,29] and only one study reported CVD mortality,[25] HF,[27] and MI.[28]

Study quality

Appraisal of study quality for the cohort and cross-sectional studies[20] demonstrated that all were of fair methodological quality (mean score of 6.8; Supplemental Table S6). No studies assessed the exposure of serum estradiol levels more than once over time or provided a sample size justification, power description, or variance and effect estimate. However, every study clearly stated the objective or research question. Appraisal of study quality for the case-control studies[21] demonstrated fair quality (mean score of 6.3; Supplemental Table S7). No studies justified the study sample size, and blinding did not occur or could not be determined for any of the studies. All case-control studies clearly stated the objective and used concurrent controls.

Outcomes

Figure 2 summarizes the associations observed between serum estradiol levels and each CV event. Four[25,29-31] of the 8 studies demonstrated no significant association of serum estradiol levels with CV events. Four[26-28,32] studies reported a significant association of serum estradiol levels with CV events. Overall, the only CV events that were shown to be associated with serum estradiol levels were MI[28] and CHD,[26,27,32] but with mixed results for CHD. In studies with no MHT use, associations between serum estradiol levels and CHD were inconsistent,[26,31,32] as one study found no association,[31] one reported an inverse association[32] (a lower estradiol level was associated with an increased CHD risk), and one reported a positive association.[26] Additionally, in studies reporting no MHT use, one study reported a significant positive association of estradiol levels with MI risk.[28] Among the studies in which females were using MHT at baseline, one reported on CHD, and it reported an inverse association, with a lower estradiol level being associated with an increased CHD risk.[27]

Discussion

We performed a comprehensive review of studies examining the association between serum estradiol levels and CV events in postmenopausal females. Overall, we found the following: (1) few studies have reported on the associations between serum estradiol levels and CV events in postmenopausal females; (ii) significant heterogeneity is present in the literature examining the associations between serum estradiol levels and CV events in postmenopausal females; and therefore (iii) a possible association between serum estradiol and CV events remains unclear. Our results highlight the paucity of literature on this topic, making it difficult to interpret the data with certainty.

CVD is the leading cause of premature death for women in Canada,[33] and menopause is a time of heighted CVD risk,[34] highlighting the urgent need to identify potential CVD risk factors in postmenopausal females. The aim of this systematic review was to elucidate whether serum estradiol levels are associated with CV events in postmenopausal females. A

Table 1. Study and sample characteristics

Study	Country	Follow-up duration, y	No cardiovascular event				Cardiovascular event				Reported events
			n	Age, mean ± SD, y,	MHT use at baseline, %	Serum estradiol level ± SD, pmol/L	n	Age, y,mean ± SD)	MHT use at baseline, %	Serum estradiol level ± SD, pmol/L	
Prospective cohort studies											
Barrett-Connor and Goodman-Gruen[25] (1995)	USA	19.0	475	NR	0	56.8 ± NR*	176	NR	0	56.20 ± NR*	CVD mortality
Scarabin-Carré et al.[26] (2012)	France	4.0	522	74.3 ± 5.30	0	20.34 ± 12.12	106	76.60 ± 5.70	0	24.20 ± 13.24	CHD, ischemic stroke
Zhao et al.[27] (2018)	USA	12.1	2551	64.4 ± 8.90	33.2	98.21 ± 90.49	283	69.30 ± 8.60	25.7	73.72 ± 49.18	CVD, CHD, HF
Case-control studies											
Dong et al.[28] (2013)	China	NA	60	68.73 ± 8.34	0	57.04 ± 34.66	30	70.20 ± 10.87	0	141.71 ± 91.79	MI
Hu et al.[29] (2020)	USA	NA	419	62.49 ± 4.73	47	37.14 ± 30.96	419	62.49 ± 4.73	47	40.59 ± 31.16	Ischemic stroke
Rexrode et al.[30] (2003)	USA	NA	200	63.13 ± NR	42.5	69.02 ± 44.35	200	63.03 ± NR	42.5	68.94 ± 41.68	CVD
Tan and Yang[31] (1989)	China	NA	25	NR	0	965.47 ± 906.74	25	NR	0	939.78 ± 734.20	CHD
Cross-sectional studies											
Wang et al.[32] (2004)	China	NA	69	59.00 ± 5.00	0	91.70 ± 23.00	75	64.00 ± 7.00	0	67.90 ± 24.40	CHD

CHD, coronary heart disease; CVD, cardiovascular disease; HF, heart failure; MHT, menopausal hormone therapy; MI, myocardial infarction; NA, not applicable; NR, not reported; SD, standard deviation.
* Age-adjusted.

previous systematic review completed by Crandall and colleagues[35] investigated sex hormones and CVD in relation to menopause, with a focus on coronary artery disease. They reported significant heterogeneity in the results and found that serum estrogen levels were not related consistently to coronary artery disease.[35] Similarly, we found the association between serum estradiol levels and CHD to be inconsistent, a finding that may be due to differences in how CHD was defined in each study (Supplemental Table S5). For example, Tan and Yang[31] described CHD as angina pectoris or MI, whereas Scarabin-Carré et al.[26] described CHD as hospitalization for angina pectoris, coronary dilation, artery bypass, MI, or CHD death. Another explanation for the heterogeneity seen in the results may be that different studies adjusted for different covariates. A decline in estradiol levels in postmenopausal women has been found to be associated with CVD,[27,32] but the literature further describes the relationship between other sex hormones and CVD. For example, Sievers et al.[36] demonstrated that women with low testosterone levels had more incident CV events, compared to women with higher testosterone levels, suggesting that testosterone levels may play a contributing role in CVD. More recently, the testosterone-to-estradiol ratio has been studied, and in postmenopausal women, in whom a greater testosterone-to-estradiol ratio was found to be indicative of an elevated CV risk, particularly CHD, CVD, and HF.[27] This finding suggests that sex hormones, beyond estradiol, may play an important role in contributing to CVD.

Up to 80% of postmenopausal women will experience debilitating vasomotor symptoms, such as night sweats and hot flashes,[8] which may be alleviated with the use of MHT, as recommended by current North American guidelines.[37] MHT includes estrogen and progestin, which come in various routes of administration, formulations, and doses. None of the studies included in this review reported the route of administration, the dosage, or the duration and timing of MHT initiation, which are important factors to consider, as emerging evidence indicates that these factors contribute to CVD risk.[38-40] Studies have looked at the route of administration as a potential underlying factor for CVD risk in this population and found that oral estrogen users had higher systolic and diastolic blood pressures, compared to non-oral estrogen users.[38] Further, formulations of exogenous estrogen are postulated to play a role, as the use of conjugated equine estrogens have been shown to be associated with a higher CV risk, compared to estradiol use.[41] Higher doses of exogenous estrogen also have been postulated to increase CV risk.[42] Although the cardioprotective nature of endogenous estradiol has been established in the literature,[9] whether this benefit extends to exogenous estrogen, such as MHT, remains unknown. MHT use has been controversial, as demonstrated by the Nurses' Health Study[10] and the Women's Health Initiative.[11] The results of this review showed that studies that did not utilize MHT had varying associations between estradiol levels and CV events. Studies that did report baseline MHT use showed an inverse association between serum estradiol levels and CHD, suggesting that higher estradiol levels result in fewer CV events. A potential reason for inverse associations being observed with MHT use is that females who undergo MHT have a higher socioeconomic status (eg, higher level of education, greater access to healthcare, and

Study	MHT Use	Events					
		CVD Mortality	CHD	Ischemic Stroke	CVD	HF	MI
Barrett-Connor and Goodman-Gruen, 1995[25]	None	⟺	-	-	-	-	-
Dong et al., 2013[28]		-	-	-	-	-	⇑
Scarabin-Carré et al., 2012[26]		-	⇑	⟺	-	-	-
Tan and Yang, 1989[31]		-	⟺	-	-	-	-
Wang et al., 2004[32]		-	⇓	-	-	-	-
Hu et al., 2020[29]	Baseline	-	-	⟺	-	-	-
Rexrode et al., 2003[30]		-	-	-	⟺	-	-
Zhao et al., 2018[27]		-	⇓	-	⟺	⟺	-

Figure 2. Summary of associations in cardiovascular events categorized by menopausal hormone therapy (MHT) use. Characteristics that were not reported are depicted as **dashes** (−). An **upward arrow** indicates a positive association; a **sideways arrow** indicates no association; and a **downward arrow** indicates an inverse association between serum estradiol level and the cardiovascular event. CHD, coronary heart disease; CVD, cardiovascular disease; HF, heart failure; MI, myocardial infarction.

higher incomes) and are generally healthier, compared to females who do not undergo MHT.[43]

Strengths and limitations

Our study has multiple strengths. First, this study looked at a variety of CV events, allowing for a broad understanding of serum estradiol levels and CV events in postmenopausal females. Next, the studies included were not limited based on MHT use, and therefore, they allowed for a broader variety of postmenopausal females to be captured in this analysis. Our review also has several limitations. First, this review searched 2 databases, which could have led to studies being missed. However, content experts were consulted to identify potential additional studies, and the grey literature was hand-searched, suggesting that lack of inclusion of relevant studies is unlikely. Second, this review did not include any studies that had an entire study population with chronic conditions (eg, chronic kidney disease, inflammatory bowel disease). This approach may make the findings of this study less generalizable, as females with chronic conditions may have different associations between estradiol levels and CV events due to the pathology of their conditions. Currently, estradiol levels are not clinically used to diagnose menopause, and given recognized variability and heterogeneity over a wide range of values, use of a single estradiol measurement is of questionable significance. Thus, this review is comprised of a very limited number of studies of postmenopausal women with variable exposure to exogenous estrogen, in whom an association of single estradiol measurements with CVD events cannot be determined. Many studies included in this review did not specifically state the methodology used to measure estradiol levels, which could have contributed to the wide range in estradiol levels reported. Another point to note is that normal reference ranges for estradiol levels were not reported in these studies. Last, the quality assessment revealed that none of the studies included in this review justified the sample size used, which could have resulted in a lack of power to detect associations that were actually present within individual studies. Furthermore, although many studies adjusted for key confounders, the methodological quality remained low, as certain factors were not accounted for, such as years since menopause, and duration and dose of MHT exposure. However, to mitigate some of the confounding, we examined the association of estradiol level and CV events stratified by MHT use.

Future directions

The quality of included studies highlights the need for future studies to justify their sample size or provide power calculations. Additionally, collecting emerging CVD risk factors such as MHT characteristics (ie, route of administration, formulation, and dose), gravidity, parity, and complications of pregnancy,[44] and accounting for them in the analyses are extremely important. Further research with consistent reporting also is warranted, allowing for a pooled analysis, which would provide additional information regarding the association between serum estradiol and CV events in postmenopausal women. Last, future studies and reviews which examine the association between estradiol levels and CV events in premenopausal and perimenopausal females are needed, as these would further elucidate the relationship between estradiol levels and CV risk.

Conclusions

This systematic review and narrative synthesis demonstrate that serum estradiol levels may be associated with CV events, but the specifics of any association remain unclear. Further prospective studies looking at this association are warranted.

Acknowledgements

The authors thank Yueh Lee, LPN for assisting with the translation of studies included in this systematic review, and acknowledge Heather Ganshorn for assisting with the search strategy.

Ethics Statement

The reported research has adhered to the relevant ethical guidelines.

Patient Consent

The authors confirm that patient consent is not applicable to this article. This is a systematic review; therefore, consent from patients was not required.

Funding Sources

N.G. is supported by a Canadian Graduate Scholarship—Master's, through the Canadian Institutes of Health Research. K.T.M. is supported by an Alberta Strategy for Patient-Oriented Research Graduate Studentship. A.L. is supported by the Heart and Stroke Foundation of Canada's National New Investigator Award. The other authors have no funding sources to declare.

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2023.11.010.