MR. SHIVA RAJ MISHRA (Orcid ID : 0000-0002-2993-3504)

DR. HSIN-FANG CHUNG (Orcid ID : 0000-0003-3261-5942)

Article type : Systematic review

Duration of oestrogen exposure during reproductive years, age at menarche and age at menopause, and risk of cardiovascular disease events, all-cause and cardiovascular mortality: a systematic review and meta-analysis

Running title: Oestrogen exposure and cardiovascular disease events and mortality

Author's affiliations

Shiva R. Mishra¹, Hsin-Fang Chung¹, Michael Waller¹, Gita D Mishra¹

¹ School of Public Health, The University of Queensland, Brisbane, Australia

Corresponding author:

Shiva R. Mishra, MPH

School of Public Health, University of Queensland, Australia

266 Herston Rd, Herston QLD 4006

Email: shivaraj.mishra@uq.edu.au

ORCID: 0000-0002-2993-3504

Word count:

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/1471-0528.16524](https://doi.org/10.1111/1471-0528.16524)

This article is protected by copyright. All rights reserved

Abstract: 250

Text: 3485

Author Manuscript

ABSTRACT

Background

Little is known about the oestrogen exposure measurement and mutual effect of age at menarche and age at menopause in the risk of cardiovascular disease (CVD) events.

Objectives

To evaluate oestrogen exposure measurement and describe mutual effect of age at menarche and age at menopause in the risk of CVD events.

Search strategy

Systematic review of literature in PubMed, Embase and Web of Science for studies published up to June 28, 2020.

Selection criteria

Observational studies related to oestrogen exposure measurement, including mutual effect of age at menarche and age at menopause and risk of CVD events.

Data collection and analysis

Synthesis of evidence was conducted by reviewing individual estimates, followed by meta-analysis. The study received no external funding.

Main results

A total of 75 studies were included in synthesis of evidence, of which 17 studies were included in meta-analysis. Reproductive lifespan (age at menopause – age at menarche), endogenous oestrogen exposure and total oestrogen exposure were used for oestrogen exposure measurement. By far, reproductive lifespan was the most commonly used method for oestrogen exposure measurement. A shorter reproductive lifespan was associated with a higher risk of CVD events; the pooled relative risk (95% CI) was 1.31 (1.25, 1.36) for stroke events. Further, robust epidemiological studies with measurement of oestrogen exposure and associated health risk would strengthen the evidence.

Conclusions

Reproductive lifespan was the most commonly used method for oestrogen exposure measurement in epidemiological studies. A shorter reproductive lifespan was associated with a higher risk of CVD events particularly stroke.

Funding

GDM is supported by the Australian National Health and Medical Research Council Principal Research Fellowship (APP1121844).

PROSPERO registration: CRD42019126655

Keywords: Menarche, menopause, oestrogen exposure, cardiovascular diseases, mortality

Tweetable abstract: A systematic review and meta-analysis found that women with a shorter reproductive lifespan have a higher risk of stroke events

Introduction

Cardiovascular diseases (CVD) are the leading cause of deaths and disability among women worldwide (1). From 2006 to 2016, the burden of CVDs increased by 14.4% among women (1). Published studies have shown an association between the timing of menarche and menopause and cardiovascular disease events, all-cause and cardiovascular mortality (2, 3). However, there was insufficient evidence to draw conclusions on the role of reproductive lifespan on these health outcomes.

Reproductive lifespan can be described as the difference between age at menarche and age at menopause, which is a simple way to estimate oestrogen exposure (4-7). Some studies further take into account the relevant reproductive processes such as pregnancy (including breastfeeding, stillbirths, and miscarriages) and hormone use (oral contraceptive pills (OCP) and menopausal hormone therapy (MHT)) to estimate endogenous and total oestrogen exposure (8, 9). For instance, it is known that levels of endogenous oestrogen rise during pregnancy, but fall after birth, particularly with breastfeeding. An earlier study found that parous women with four or more children had 20% less concentration of free oestradiol compared to women with one child, while the level of oestrone, another derivative of endogenous oestrogen did not differ by parity (10). Furthermore, breastfeeding (11),

miscarriages, stillbirths and induced abortion (12) causes changes in oestrogen levels in the human body and their effect is likely to extend beyond cardiovascular diseases (8).

If the studies do not calculate the total duration between menarche and menopause, an alternative method is to adjust for both the timing of menarche and menopause in the same analysis, which allows benchmarking these two key reproductive events. These indirect measures of oestrogen exposure are important for population-level study because the direct measures of hormone exposure are difficult to be ascertained. Further, our recent study conducted among 51,450 post-menopausal women from InterLACE consortium found that timing of menarche and menopause are inter-related: women who experienced early menarche were at higher risk of premature (relative risk ratio: 1.80, 95% CI: 1.53, 2.12) and early menopause (1.31, 95%CI: 1.19, 1.44)(13). Therefore, we examined the oestrogen exposure measurements and described mutual effect of age at menarche and age at menopause on the risk of CVD events and mortality accompanied by a meta-analysis.

Methods

A systematic review was conducted following the Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Two independent reviewers (SRM, HFC) conducted the review of literature in PubMed (from inception), Embase (from 1974) and Web of Science (from inception) for studies published up to June 28, 2020, and evaluated the quality of the studies. We used a set of search terms related to oestrogen exposure, menarche, and menopause, which were combined with CVD events, all-cause mortality and CVD mortality (Appendix S1). Search strategy, study selection, statistical analysis and quality evaluation are described in detail in Appendix S2 and Table S1. Patient involvement and core outcome set are not relevant to this study, as we used a systematic review and meta-analysis of published studies. The study received no external funding.

Results

Identification of relevant studies

Our search strategy identified 3908 relevant articles through searches from Pubmed/Medline, Embase and Web of science (Figure 1). After the initial screening, 230 articles were included

for full text review, of which 75 studies met the inclusion criteria: 26 studies examining oestrogen exposure, 34 studies examining age at menarche, and 60 studies examining age at menopause.

<Figure 1>

Definitions of oestrogen exposure

Oestrogen exposure

Table S2 summarizes the key characteristics of the studies. Nearly a third of studies were from Europe and two thirds were prospective in design. Three different definitions of oestrogen exposure were identified: i) Reproductive lifespan (RLS), ii) Endogenous Oestrogen Exposure (EOE), iii) Total Oestrogen Exposure (TOE).

A total of 22 studies calculated the interval between age at menarche and age at menopause, defined as reproductive lifespan. Further, three studies calculated the reproductive lifespan and further subtracted the time spent in pregnancy, breastfeeding, stillbirth/miscarriage, and OCP use (9, 14, 15). Pregnancy is a period marked by sustained rise in both endogenous oestrogen and progesterone whereas breastfeeding and stillbirth/miscarriages are the periods with low endogenous oestrogen. The oral contraceptive pills before 1975 had a very high dose of oestrogen and progesterone that suppresses the normal cycle of endogenous oestrogen (9). Therefore, the calculation of endogenous oestrogen exposure is normally be limited to duration that is unaffected by the opposing effect of progesterone. Those studies justified the subtraction of post-ovulatory period because the period is marked by a rise in progesterone level whilst level of oestrogen is relatively low (9).

The total oestrogen exposure considers both endogenous oestrogen exposure as well as hormone replacement therapy. We found two algorithms to calculate TOE, one that adds OCP and pregnancy [$TOE1: \text{Age at menopause} - \text{age at menarche} + \text{OCP} + \text{pregnancy} + \text{HRT}$], another that subtracts OCP and pregnancy [$TOE2: \text{Age at menopause} - \text{age at menarche} - \text{OCP} - \text{pregnancy} + \text{HRT}$] (16). By inclusion of OCP years and duration of MHT, TOE2 is longer compared to EOE and TOE1.

Menarche adjusting for menopausal age/status

Of 34 studies examining age at menarche, only a third of studies (12 studies) adjusted for age at menopause/status. We only described the results for those adjusting for menopausal age/status (Table S3). A summary of the results for studies without adjusting for menopausal age/status is available in Table S3.

Menopause adjusting for age at menarche

We reviewed 60 studies that examined age at menopause/status, with only a quarter of studies (17 studies) adjusted for age at menarche. We only described the results for studies adjusted for age at menarche, and a summary of the results for studies without adjusting for age at menarche is available in Table S4. Age at menopause was defined as age at last menstruation for natural menopause in nine studies, age at hysterectomy/oophorectomy for surgical menopause in three studies, while for the rest of the studies it was either natural or surgical menopause or undefined.

Association of reproductive lifespan, menarche, and menopause with CVD events

Reproductive lifespan

Studies showed association between RLS and overall CVD (6, 7), coronary heart disease (CHD) (5, 6, 17), and stroke events (4-7). Findings from these studies are summarized in Table 1.

A higher risk of overall CVD event among women who had shorter RLS was reported by the Nurses' Health Study of 83,169 participants and one cross-sectional study of 3,081 participants from the USA (6, 7). The Nurses' Health Study found that the risk of CVD event was 25% higher among those with <30 years of RLS compared to 34-37 years (6). The findings from this and other studies were consistent for CHD (5, 6, 17). However, Jung et al. found a U-shaped association between RLS and ischemic heart disease; the risk of which increased in both RLS <30 years (40% higher) and RLS ≥ 40 years (39% higher) (referent: RLS 36-39 years) (5). Mansoor et al. (2017) showed that for each year increase in RLS was associated with 3% reduction in the risk for overall CVD and stroke events (7). No effect modification was found by body mass index (BMI) (p -interaction=0.14) and smoking variable (p -interaction=0.44)(7). Except thrombotic stroke (p -trend=0.0004) (5) there was no clear evidence of association for other stroke types: haemorrhagic (p -trend=0.2197) (5) and

ischemic stroke ($p\text{-trend} > 0.05$) (18). For other CVD events, such as myocardial infarction, angina, heart failure, and peripheral artery disease, there was not sufficient evidence for an association with reproductive lifespan (Table 1).

<Table 1>

Age at menarche adjusting for age at menopause

Overall, two studies found that earlier menarche was associated with higher risk of stroke after adjustment for age at menopause (4, 28). Of these studies, Alonso de Lecinana et al (2007) found that the odds of stroke were 54% higher among women aged < 12 years at menarche compared to those aged at 13 years (4). Late menarche was not associated with stroke in both studies (4, 28) (Table 1).

For CVD events, a study from China found a lower risk with increasing ages at menarche ($p\text{-trend} = 0.049$) (19). The risk was 29% lower among those aged > 18 years compared to aged 16 years at menarche. Adjusting for BMI and waist circumference (WC) did not attenuate the association (OR: 0.71, 95% CI: 0.57, 0.88 to 0.71, 95% CI: 0.57, 0.89) (19).

Age at menopause adjusting for age at menarche

Overall, there was some evidence to suggest an association between early menopause and a higher risk of CVD events (5, 21, 23, 25, 27) and between late menopause and a lower risk of CVD events (5, 17, 19, 21, 25) after adjustment for age at menarche (Table 1).

A large study comprising 66,104 Korean women found an increasing risk of atherosclerotic cardiovascular disease with decreasing age at menopause ($p\text{-trend} = 0.0176$) (5). The risk was 18% higher in women aged 46-48 years at menopause compared to 49-51 years and the risk was 11% higher in those aged ≤ 45 years compared to 49-51 years at menopause (5). The association for ischemic heart disease followed a similar trend: the risk was 28% higher among women aged ≤ 45 compared to 49-51 years ($p\text{-trend} = 0.0217$) (5). Furthermore, two studies showed that early menopause was associated with a higher risk of heart failure (25, 27).

For stroke, studies showed that early menopause was associated with a higher risk of stroke (5, 28), and similarly late menopause was associated with a reduced risk of stroke (5, 17). Risk of stroke was found to be decreasing across the late menopausal age categories in trend-test ($p\text{-trend} = 0.0013$), though none of the estimates were found to be significant (5). Further, the decreasing risk across age at menopause categories was found for thrombotic stroke ($p\text{-}$

trend=0.0007) but not for haemorrhagic stroke (*p-trend*=0.3234) (5), suggesting inconsistency in finding across stroke sub-types. Stroke subtypes were inconsistently reported across medical insurance databases and hospital records, which could be the reason for the inconsistent findings (5).

Association of reproductive lifespan, menarche, and menopause with CVD and all-cause mortality

Reproductive lifespan

Overall, the association between reproductive lifespan and CVD mortality and all-cause mortality was conflicting. RLS was not significantly associated with CVD-mortality (35-38), while it was significantly associated with 5% higher mortality for every additional year of RLS in one prospective study (*p*=0.03) (14). In this study, adjusting for BMI, WC, and other lifestyle factors only slightly attenuated the findings (14). In contrast, Yang et al. (2017) found that CVD-mortality declined by 1% for every one-year increase in RLS. Further, the risk of CVD-mortality was lower among women in normal weight and pre-obese categories compared to obese women (17) (Table 2).

For stroke mortality, two large prospective studies from Japan showed a decreased risk for longer RLS (36, 39), and adjusting for BMI and type of menopause only slightly attenuated the estimates (36). However, two other prospective studies which only included a low number of stroke cases showed no association (35, 38).

For all-cause mortality, the findings remained conflicting: decreased risk associated with longer RLS was found in one prospective study (40), but an increased risk was found in another prospective study (4,878 participants) that treated RLS as a continuous exposure (14).

<Table 2>

Age at menarche adjusting for age at menopause

There was no clear evidence for the association of early menarche with CVD-mortality (36, 38, 43, 45), CHD-mortality (36, 38, 43), stroke-mortality (36, 38, 43) and all-cause mortality (38, 40, 45, 47, 48) (Table 2). A large prospective study of 423,460 women from Singapore showed the risk of CVD-mortality was lower among non-smokers aged ≥ 17 years at

menarche (hazard ratio: 0.79, 95% CI: 0.68, 0.92) compared to aged 13-14 years at menarche (p -trend <0.001) (43). The estimates remained changed after adjusting for menopausal status/age, oral contraceptives use and MHT use, BMI and other lifestyle factors (43). Additionally adjusting for diabetes and hypertension attenuated the estimates to 0.86 (0.74, 1.01) (43), suggesting a modest effect of these comorbidities on CVD-mortality. The same study found consistent results for CHD mortality, but no association for stroke mortality. In contrast, Wu et al (2014) found that early age at menarche was only associated with stroke-mortality (p -trend=0.03) but not associated with CHD mortality (38).

Further, three studies showed that women who experienced earlier age at menarche had a higher risk of all-cause mortality (38, 45, 48) (Table 2).

Age at menopause adjusting for age at menarche

Overall, there was no sufficient evidence for an association between early menopause and risk of CVD mortality, CHD mortality and stroke mortality, while some evidence was found for the risk of all-cause mortality (38, 41, 42, 45, 46)(Table 2). The risk of CVD-mortality showed either null (38, 42, 44), or positive association: Risk of CVD-mortality was 30% higher among women aged ≥ 55 years compared to 50-54 years at menopause (44). Risk of stroke-mortality, however, showed null association in a large prospective study from the USA(46) and negative association (24% reduced risk) in those with later age at menopause (50-52 vs. 49-50 years) in a larger prospective study from China (38). Further, Hong et al. (2007) showed that risk of stroke mortality varied by the age at entry into the study. For example, the risk was higher among those aged ≥ 80 years at entry (hazard ratio: 2.29, 95% CI: 1.20, 4.36) and remained null among those aged <80 years at entry into the study (hazard ratio: 0.61, 95% CI: 0.18, 2.11) (41). Such differences in the association by age could be due to the uneven distribution of causes of death among women. Particularly, cancer and cardiovascular disease are the leading cause of death in younger and older women, respectively leading to higher incidence of cardiovascular disease related deaths in older compared to younger women (41, 46).

Association of endogenous and total oestrogen exposure with CVD events, and CVD and all-cause mortality

Endogenous Oestrogen Exposure (EOE)

There were only four studies taking pregnancy and use of OCP into account to estimate EOE (9, 14, 15, 49) (Table 3). One prospective study showed that longer duration of EOE was significantly associated with an increased risk of CVD mortality (14), whereas the other prospective study showed an association with a reduced risk of overall CVD mortality but no association with ischemic heart disease (IHD) or stroke mortality (9). No association was seen between EOE and all-cause mortality (14, 15).

De Kleijn et al. (2002) found a lower risk among those who had >18 years of EOE compared to ≤13 years for CVD-mortality (HR: 0.80, 95% CI: 0.67, 0.96), IHD-mortality (0.84, 95%CI: 0.64, 1.10) and stroke-mortality (0.77, 95%CI: 0.52, 1.14) after adjusting for age. While the effect sizes for CVD-mortality was significant, IHD and stroke-mortality yielded no statistical significance. Adjusting for socioeconomic status, BMI and MHT marginally attenuated the association for all CVD subtypes (9). Similarly, in a large study of more than 300,000 participants across 10 countries in Europe, the risk of all-cause mortality was lower in ≥34 years of EOE in the age-adjusted model (HR: 0.89, 95% CI: 0.82, 0.97) compared to 0-22 years of EOE (15). However, the results were attenuated in the fully adjusted model for socio-economic and lifestyle factors (HR:0.98, 95% CI:0.91, 1.06) (15). With a limited number of studies, it remains inconclusive whether longer EOE was cardio protective.

<Table 3>

Total Oestrogen Exposure (TOE)

Studies further took postmenopausal MHT use into account to estimate TOE. Merz et al (2009) used two methods to estimate TOE: (1) adding time of postmenopausal MHT use but subtracting time of premenopausal OCP use and pregnancy from the reproductive lifespan; (2) adding time of MHT use, OCP use, and pregnancy to the reproductive lifespan (Table 3) (16, 50). Under the first definition, there was no significant association with coronary artery disease (CAD) (16). Under the second definition, adding OCP use and pregnancy revealed a decreasing age-adjusted prevalence and severity of CAD with increasing TOE. Further, the study showed that the association of TOE with age-adjusted prevalence and severity of CAD was mainly driven by MHT use (16).

Adjusting for covariates

Most of the studies adjusted for age, education, and lifestyle factors (including BMI and smoking). Six of 26 studies on oestrogen exposure (RLS, EOE, TOE) adjusted for age at menopause/status (4, 6, 7, 14, 24, 47), while only three studies adjusted for age at menarche (4, 38, 40, 50) (Table S6). The correlation coefficient of RLS with age at menopause ranged from 0.7 to 0.9, and with age at menarche was -0.03 to -0.20 (9, 37). Higher percentage of studies adjusted for age at menopause (12 out of 34 studies) than age at menarche (17 out of 60 studies) (Tables S5-S7).

Meta-analysis

Seventeen cohort studies were included in the meta-analysis to compute pooled estimates, with hazard ratio from 14 studies, odds ratio from two studies, and risk ratio from one study. As the outcome measures were incident events, the pooled estimates were equivalent measures of relative risk (RR). Short reproductive lifespan was associated with increased risk of stroke events (RR: 1.31, 95%CI: 1.25, 1.36; heterogeneity $I^2=0\%$, $p=0.331$) (5, 6, 29). There was no evidence for an association of short reproductive lifespan with CVD-mortality (RR: 1.02, 0.89, 1.15; heterogeneity $I^2=0\%$, $p=0.543$) (33-36) and all-cause mortality (RR:1.00, 95%CI: 0.81, 1.19; heterogeneity $I^2=75.3\%$, $p=0.007$) (37-38,40,47)(Figure S1). Similarly, early age at menarche (RR:1.17, 95%CI: 0.20, 2.14; heterogeneity $I^2=69.6\%$, $p=0.070$) (5, 28) and early age at menopause (RR: 1.13, 95%CI: 0.71, 1.56; heterogeneity $I^2=22.9\%$, $p=0.255$) (5, 28) were not significantly associated with moderately higher risk of stroke events. There was no evidence that early age at menarche was associated with CVD-mortality (RR:1.05, 95%CI: 0.95, 1.14; heterogeneity $I^2=0.2\%$, $p=0.391$) (36,38,43,45). For all-cause mortality, the association with age at menarche (RR:1.08, 95%CI: 0.97, 1.19; heterogeneity $I^2=77.4\%$, $p=0.001$) (36-38, 43) and early age at menopause (RR:1.05, 95%CI: 0.95, 1.15; heterogeneity $I^2=79.8\%$, $p=0.000$) (38,40-42,44-46), did not reach statistical significance. Early age at menopause also had no evidence for an association with CVD-mortality (RR:1.08, 95%CI: 0.98, 1.18; heterogeneity $I^2=0\%$, $p=0.431$) (38,41-42,44-45) (Figure S1).

Discussion

Main findings

This study found that a longer RLS was associated with a reduced risk of cardiovascular disease events particularly stroke. Meta-analyses of prospective studies further revealed that women with short reproductive lifespan had 31% increased risk of stroke (RR: 1.31, 95% CI:1.25, 1.36). Further, the role of EOE and TOE was unclear: decreasing risk of all-cause mortality (9) and severity of CAD (16) and increasing risk of all-cause mortality (14).

Strengths and limitations

This is the first comprehensive systematic review and meta-analysis to explore women's reproductive lifespan and risk of CVD events and mortality, including the mutual effect of age at menarche and age at menopause – i.e., the effect of age at menarche adjusted for age at menopause. A small number of studies included in the meta-analysis may limit the interpretation of the pooled relative risks for reproductive lifespan, age at menarche, and age at menopause. However, we have described individual effect estimates in details in the results section for better understanding of true associations. There could be a chance of reporting bias, as only studies with positive results could have been published.

Interpretation

Most studies defined oestrogen exposure as the interval between the timing of menarche and menopause. Also a few studies further accounted for the duration of breastfeeding, pregnancy, stillbirths/miscarriages, OCP and MHT, yielding three indices of OE (51). It was not revealed however, which of these indices were the optimal measure of OE. A previous study of 3,476 Dutch participants, revealed that addition of extra variables such as duration of breastfeeding and duration of use of OCP did not improve the predictive accuracy of model assessing the relationship between endogenous oestrogen exposure (calculated as the interval between age at menarche and menopause) and bone mineral disease disorders (51). Calculating length of oestrogen exposure is dependent on several factors, such as regularity in menstrual cycles, length of non-ovulatory cycling, number of pregnancies, number of miscarriages, and breast-feeding duration, which are prone to recall bias (16). Imprecision in measurement of these factors will lead to measurement bias (9). Therefore, robust

epidemiological studies with measurement of oestrogen exposure and associated health risk would strengthen the evidence.

The underlying mechanism linking a longer reproductive lifespan with reduced risk of CVDs events can be attributed to prolonged exposure to endogenous oestrogen. Oestrogen affect blood vascular system that keeps blood vessels flexible and regulates the level of metabolic markers such as lipids, inflammatory markers and coagulant system (52). Previous epidemiological studies have revealed longer reproductive lifespan is associated with reduced risk of hip fracture mortality (53), bone mineral diseases (53, 54), type 2 diabetes (55) and Parkinson's disease (56). Further, longer endogenous oestrogen exposure is associated with reduced risk of cardiovascular mortality (9). Thus far, no prospective studies have examined the relationship with oestrogen exposure indices in CVD context.

Conclusion

Reproductive lifespan was the most commonly used method for oestrogen exposure measurement. We found evidence of increased risk of CVD events, particularly stroke for those with a shorter reproductive lifespan. Association for endogenous oestrogen exposure and total oestrogen exposure remained unclear due to limited availability of studies.

Author's roles

SRM conducted the literature review, analysed and drafted the article. SRM and HFC performed the searches and screening of articles. SRM, HFC, MW and GDM contributed to the conceptualization of study. All authors contributed to the interpretation of results and critical revision of the article. All the authors approved the final version of article.

Acknowledgements

None.

Funding

The study received no external funding. GDM is supported by the Australian National Health and Medical Research Council Principal Research Fellowship (APP1121844).

This article is protected by copyright. All rights reserved

Conflicts of interest

None. Completed disclosure of interest forms are available to view online as supporting information.

References

1. Naghavi M, Abajobir AA, Abbafati C, Abbas KM, Abd-Allah F, Abera SF, et al. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet*. 2017;390(10100):1151-210.
2. Charalampopoulos D, McLoughlin A, Elks CE, Ong KK. Age at menarche and risks of all-cause and cardiovascular death: a systematic review and meta-analysis. *American journal of epidemiology*. 2014;180(1):29-40.
3. Muka T, Oliver-Williams C, Kunutsor S, Laven JS, Fauser BC, Chowdhury R, et al. Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis. *JAMA cardiology*. 2016;1(7):767-76.
4. Alonso de Lecinana M, Egido JA, Fernandez C, Martinez-Vila E, Santos S, Morales A, et al. Risk of ischemic stroke and lifetime estrogen exposure. *Neurology*. 2007;68(1):33-8.
5. Jung KJ, Kim M-R, Yun YD, Kim HC, Jee SH. Duration of ovarian hormone exposure and atherosclerotic cardiovascular disease in Korean women: the Korean Heart Study. *Menopause*. 2016;23(1):60-6.
6. Ley SH, Li Y, Tobias DK, Manson JE, Rosner B, Hu FB, et al. Duration of reproductive life span, age at menarche, and age at menopause are associated with risk of cardiovascular disease in women. *Journal of the American Heart Association*. 2017 6(11):e006713.
7. Mansoor H, Elgendy IY, Segal R, Hartzema A. Duration of Reproductive Years and the Risk of Cardiovascular and Cerebrovascular Events in Older Women: Insights from the National Health and Nutrition Examination Survey. *Journal of Women's Health*. 2017 Oct 1;26(10):1047-52.
8. Shufelt CL, Merz CNB. Contraceptive hormone use and cardiovascular disease. *Journal of the American College of Cardiology*. 2009;53(3):221-31.

9. de Kleijn MJ, van der Schouw YT, Verbeek AL, Peeters PH, Banga JD, van der Graaf Y. Endogenous estrogen exposure and cardiovascular mortality risk in postmenopausal women. 2002;155(4):339-45.
10. Chubak J, Tworoger SS, Yasui Y, Ulrich CM, Stanczyk FZ, McTiernan A. Associations between reproductive and menstrual factors and postmenopausal androgen concentrations. *Journal of women's health*. 2005;14(8):704-12.
11. Peters SA, Yang L, Guo Y, Chen Y, Bian Z, Du J, et al. Breastfeeding and the Risk of Maternal Cardiovascular Disease: A Prospective Study of 300 000 Chinese Women. *Journal of the American Heart Association*. 2017;6(6):e006081.
12. Peters SA, Yang L, Guo Y, Chen Y, Bian Z, Tian X, et al. Pregnancy, pregnancy loss, and the risk of cardiovascular disease in Chinese women: findings from the China Kadoorie Biobank. *BMC medicine*. 2017;15(1):148.
13. Mishra GD, Pandeya N, Dobson AJ, Chung H-F, Anderson D, Kuh D, et al. Early menarche, nulliparity and the risk for premature and early natural menopause. *Human Reproduction*. 2017;32(3):679-86.
14. Jaspers L, Kavousi M, Erler NS, Hofman A, Laven JS, Franco OH. Fertile lifespan characteristics and all-cause and cause-specific mortality among postmenopausal women: the Rotterdam Study. *Fertil Steril*. 2017;107(2):448-56 e1.
15. Merritt MA, Riboli E, Murphy N, Kadi M, Tjønneland A, Olsen A, et al. Reproductive factors and risk of mortality in the European Prospective Investigation into Cancer and Nutrition; a cohort study. *BMC medicine*. 2015;13(1):252.
16. Merz CNB, Johnson BD, Berga SL, Braunstein GD, Azziz R, Yang Y, et al. Total estrogen time and obstructive coronary disease in women: insights from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE). *Journal of Women's Health*. 2009;18(9):1315-22.
17. Yang L, Lin L, Kartsonaki C, Guo Y, Chen Y, Bian Z, et al. Menopause Characteristics, Total Reproductive Years, and Risk of Cardiovascular Disease Among Chinese Women. *Circ Cardiovasc Qual Outcomes*. 2017;10(11).(pii):CIRCOUTCOMES.117.004235. doi: 10.1161/CIRCOUTCOMES.117..
18. Hsieh Y-C, Hwang L-C, Hsieh F-I, Lien L-M, Lin H-J, Hu C-J, et al. Early menarche and ischemic stroke risk among postmenopausal women. *International Journal of Gerontology*. 2010;4(1):16-22.

19. Qiu C, Chen H, Wen J, Zhu P, Lin F, Huang B, et al. Associations between age at menarche and menopause with cardiovascular disease, diabetes, and osteoporosis in Chinese women. *The Journal of Clinical Endocrinology & Metabolism*. 2013;98(4):1612-21.
20. Kim H-L, Kim M-A, Shim W-J, Park SM, Kim YH, Na JO, et al. Reproductive factors predicting angiographic obstructive coronary artery disease: The KoRean wOmen'S Chest Pain rEgistry (KoROSE). *Journal of Women's Health*. 2016;25(5):443-8.
21. Dam V, Van Der Schouw YT, Onland-Moret NC, Groenwold RH, Peters SA, Burgess S, et al. Association of menopausal characteristics and risk of coronary heart disease: a pan-European case-cohort analysis. 2019 Aug 1;48(4):1275-85..
22. Bertuccio P, Tavani A, Gallus S, Negri E, La Vecchia C. Menstrual and reproductive factors and risk of non-fatal acute myocardial infarction in Italy. *Eur J Obstet Gynecol Reprod Biol*. 2007;134(1):67-72.
23. Palmer JR, Rosenberg L, Shapiro S. Reproductive factors and risk of myocardial infarction. *American journal of epidemiology*. 1992;136(4):408-16.
24. Saltiki K, Doukas C, Kanakakis J, Anastasiou E, Mantzou E, Alevizaki M. Severity of cardiovascular disease in women: relation with exposure to endogenous estrogen. *Maturitas*. 2006;55(1):51-7.
25. Appiah D, Schreiner PJ, Demerath EW, Loehr LR, Chang PP, Folsom AR. Association of Age at Menopause With Incident Heart Failure: A Prospective Cohort Study and Meta-Analysis. *Journal of the American Heart Association*. 2016;5(8):e003769.
26. Hall PS, Nah G, Howard BV, Lewis CE, Allison MA, Sarto GE, et al. Reproductive Factors and Incidence of Heart Failure Hospitalization in the Women's Health Initiative. *Journal of the American College of Cardiology*. 2017;69(20):2517-26.
27. Rahman I, Åkesson A, Wolk A. Relationship between age at natural menopause and risk of heart failure. *Menopause*. 2015;22(1):12-6.
28. Murakami K, Metoki H, Satoh M, Asayama K, Hosaka M, Matsuda A, et al. Menstrual Factors and Stroke Incidence in Japanese Postmenopausal Women: The Ohasama Study. *Neuroepidemiology*. 2016;47(2):109-16.
29. Yang S, Kwak S, Kwon S, Lee H-J, Lee H, Park J-B, et al. Association of Total Reproductive Years With Incident Atrial Fibrillation, and Subsequent Ischemic Stroke in Women With Natural Menopause. 2019;12(11):e007428.

30. Wong JA, Rexrode KM, Sandhu RK, Moorthy MV, Conen D, Albert CM. Age of menopause, postmenopausal hormone therapy and incident atrial fibrillation. *Heart*. 2017 Dec 1;103(24):1954-61.
31. Stöckl D, Peters A, Thorand B, Heier M, Koenig W, Seissler J, et al. Reproductive factors, intima media thickness and carotid plaques in a cross-sectional study of postmenopausal women enrolled in the population-based KORA F4 study. *BMC women's health*. 2014;14(1):17.
32. Cortés YI, Parikh N, Allison MA, Criqui MH, Suder N, Barinas-Mitchell E, et al. Women's Reproductive History and Pre-Clinical Peripheral Arterial Disease in Late Life: The San Diego Population Study. *Journal of Women's Health*. 2018.
33. Holzer G, Koschat MA, Kicking W, Clementi W, Holzer LA, Metka MM. Reproductive factors and lower extremity arterial occlusive disease in women. *European journal of epidemiology*. 2007;22(8):505-11.
34. Stöckl D, Döring A, Thorand B, Heier M, Peters A, Lamina C, et al. Reproductive factors and its association with peripheral arterial disease in women aged 52–81 years: the KORA F4 study. *Atherosclerosis*. 2013;228(1):224-9.
35. Chang HS, Odongua N, Ohrr H, Sull JW, Nam CM. Reproductive risk factors for cardiovascular disease mortality among postmenopausal women in Korea: the Kangwha Cohort Study, 1985-2005. *Menopause*. 2011;18(11):1205-12.
36. Cui R, Iso H, Toyoshima H, Date C, Yamamoto A, Kikuchi S, et al. Relationships of age at menarche and menopause, and reproductive year with mortality from cardiovascular disease in Japanese postmenopausal women: the JACC study. *Journal of epidemiology*. 2006;16(5):177-84.
37. Jansen SC, Temme EH, Schouten EG. Lifetime estrogen exposure versus age at menopause as mortality predictor. *Maturitas*. 2002;43(2):105-12.
38. Wu X, Cai H, Kallianpur A, Gao Y-T, Yang G, Chow W-H, et al. Age at menarche and natural menopause and number of reproductive years in association with mortality: results from a median follow-up of 11.2 years among 31,955 naturally menopausal Chinese women. *PLoS One*. 2014;9(8):e103673.
39. Otsuki S, Saito E, Sawada N, Abe SK, Hidaka A, Yamaji T, et al. Female reproductive factors and risk of all-cause and cause-specific mortality among women: The Japan Public Health Center-based Prospective Study (JPHC Study). *Annals of Epidemiology*. 2018 Sep 1;28(9):597-604.

40. Shadyab AH, Macera CA, Shaffer RA, Jain S, Gallo LC, Gass MLS, et al. Ages at menarche and menopause and reproductive lifespan as predictors of exceptional longevity in women: the Women's Health Initiative. *Menopause-the Journal of the North American Menopause Society*. 2017;24(1):35-44.
41. Hong JS, Yi S-W, Kang HC, Jee SH, Kang HG, Bayasgalan G, et al. Age at menopause and cause-specific mortality in South Korean women: Kangwha Cohort Study. *Maturitas*. 2007;56(4):411-9.
42. Li S, Rosenberg L, Wise LA, Boggs DA, LaValley M, Palmer JR. Age at natural menopause in relation to all-cause and cause-specific mortality in a follow-up study of US black women. *Maturitas*. 2013;75(3):246-52.
43. Mueller NT, Odegaard AO, Gross MD, Koh WP, Yuan J-M, Pereira MA. Age at menarche and cardiovascular disease mortality in Singaporean Chinese women: the Singapore Chinese Health Study. *Annals of epidemiology*. 2012;22(10):717-22.
44. Tom SE, Cooper R, Wallace RB, Guralnik JM. Type and timing of menopause and later life mortality among women in the Iowa Established Populations for the Epidemiological Study of the Elderly (EPESE) cohort. *Journal of Women's Health*. 2012;21(1):10-6.
45. Zhang X, Liu L, Song F, Song Y, Dai HJM. Ages at menarche and menopause, and mortality among postmenopausal women. 2019;130:50-6.
46. Mondul AM, Rodriguez C, Jacobs EJ, Calle EE. Age at natural menopause and cause-specific mortality. *American journal of epidemiology*. 2005;162(11):1089-97.
47. Giles LC, Glonek GF, Moore VM, Davies MJ, Luszcz MA. Lower age at menarche affects survival in older Australian women: results from the Australian Longitudinal Study of Ageing. *BMC public health*. 2010;10(1):341.
48. Tamakoshi K, Yatsuya H, Tamakoshi A, Group JS. Early age at menarche associated with increased all-cause mortality. *European journal of epidemiology*. 2011;26(10):771-8.
49. Farahmand M, Tehrani FR, Khalili D, Cheraghi L, Khomami MB, Azizi FJLs. Association between duration of endogenous estrogen exposure and cardiovascular outcomes: A population-based cohort study. 2019;221:335-40.
50. Lee JJ, Cook-Wiens G, Johnson BD, Braunstein GD, Berga SL, Stanczyk FZ, et al. Age at Menarche and Risk of Cardiovascular Disease Outcomes: Findings From the National Heart Lung and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation. 2019;8(12):e012406.

51. Hagemans ML, Van Der Schouw YT, De Kleijn MJ, van Staveren WA, Pop VJ, Leusink GL, et al. Indicators for the total duration of premenopausal endogenous estrogen exposure in relation to BMD. *Human Reproduction*. 2004;19(9):2163-9.
52. Maas A, Appelman Y. Gender differences in coronary heart disease. *Netherlands Heart Journal*. 2010;18(12):598-603.
53. Jacobsen BK, Nilssen S, Heuch I, Kvåle G. Reproductive factors and fatal hip fractures. A Norwegian prospective study of 63,000 women. *Journal of Epidemiology & Community Health*. 1998;52(10):645-50.
54. DeCherney A. Bone-sparing properties of oral contraceptives. *American journal of obstetrics and gynecology*. 1996;174(1):15-20.
55. Brand JS, Van Der Schouw YT, Onland-Moret NC, Sharp SJ, Ong KK, Khaw K-T, et al. Age at menopause, reproductive life span, and type 2 diabetes risk: results from the EPIC-InterAct study. *Diabetes care*. 2013;36(4):1012-9.
56. Frentzel D, Judanin G, Borozdina O, Klucken J, Winkler J, Schlachetzki J. Increase of Reproductive Life Span Delays Age of Onset of Parkinson's Disease. *Frontiers in neurology*. 2017;8:397.

FIGURE LEGENDS

Figure 1. Flow chart of study process.

Table 1. Summary of studies examining associations between reproductive lifespan, age at menarche and age at menopause with CVD events

Outcomes	Short reproductive lifespan	Long reproductive lifespan	Early menarche	Late menarche	Early menopause	Late menopause
CVD (n=3 studies)						
Ley(2017)(6)	↑ (<30 vs 34-37 yrs)	↓ (≥42 vs 34-37 yrs)*				
Mansoor(2017)(7)	↑ (≤30 vs 36-40 yrs)	↔ (>45 vs 36-40 yrs)				↔ (per year)
Qiu(2013)(19)			↔ (9-14 vs 16 yrs)	↓ (≥18 vs 16 yrs)	↔ (≤46 vs 50 yrs)	↓ (≥53 vs 50 yrs)*

CHD (n=5 studies)						
Jung(2016) ^a (5)	↑ (<30 vs 36-39 yrs)	↑ (≥40 vs 36-39 yrs)	↔ (≤12 vs 13-14 yrs)	↔ (≥17 vs 13-14 yrs)	↑ (≤45 vs 49-51 yrs)*	↓ (≥52 vs 49-51 yrs)*
Kim(2016)(20)		↔ (mean diff.)				
Ley(2017)(6)	↑ (<30 vs 34-37 yrs)	↓ (≥42 vs 34-37 yrs)*				
Yang(2017)(17)		↓ (per year)				↓ (per year)
Dam(2019)(21)					↑ (<40 vs ≥55 y)	↓ (per year)
Myocardial infarction (n=5 studies)						
Bertuccio(2007)(22)			↔ (<12 vs 13 yrs)	↔ (≥15 vs 13 yrs)		
Jung(2016) (5)	↑ (<30 vs 36-39 yrs)	↔ (≥40 vs 36-39 yrs)	↔ (≤12 vs 13-14 yrs)	↑ (≥17 vs 13-14 yrs)	↔ (≤45 vs 49-51 yrs)	↔ (≥52 vs 49-51 yrs)
Mansoor(2017)(7)		↔ (>30 vs ≤30 yrs)				
Palmer(1992) ^b (23)			↔ (≤11 vs 12-14 yrs)	↔ (≥15 vs 12-14 yrs)	↑ (<45 vs ≥50 yrs)	
Saltiki(2006)(24)		↓ (per year)				
Angina (n=2 studies)						
Mansoor(2017)(7)		↓ (>30 vs ≤30 yrs)				
Saltiki(2006)(24)		↔ (per year)				
Heart failure (n=3 studies)						
Appiah(2016)(25)					↑ (<45 vs 50-54 yrs)	↓ (≥55 vs 50-54 yrs)*
Halls(2017) (26)		↓ (per year)				
Rahman(2015)(27)					↑ (40-45 vs 50-54 yrs)	↔ (≥55 vs 50-54 yrs)
Stroke (n=8 studies)						
Alonso(2007)(4)	↔ (<34 vs 34-36 yrs)	↓ (>40 vs 34-36 yrs)	↑ (<12 vs 13 yrs)	↔ (≥14 vs 13 yrs)	↔ (<47 vs 51-53 yrs)	↔ (>53 vs 51-53 yrs)
Hsieh(2010) ^c (18)	↔ (≤32 vs 33-36 yrs)	↔ (≥37 vs 33-36 yrs)				
Jung(2016) ^d (5)	↑ (<30 vs 36-39 yrs)*	↓ (≥40 vs 36-39 yrs)*	↓ (≤12 vs 13-14 yrs)*	↑ (≥17 vs 13-14 yrs)	↑ (≤45 vs 49-51 yrs)*	↓ (≥52 vs 49-51 yrs)*
Ley(2017)(6)	↑ (<30 vs 34-37 yrs)	↔ (≥42 vs 34-37 yrs)				
Murakami(2016)(28)			↑ (≤13 vs 15 yrs)	↔ (≥16 vs 15 yrs)	↑ (46-49 vs 50 yrs)	↔ (≥51 vs 50 yrs)
Mansoor(2017) (7)		↓ (>30 vs ≤30 yrs)				
Yang(2017)(17)		↔ (per year)				↓ (per year)
Yang(2019) ^e (29)	↑ (<30 vs 35-39 yrs)*	↑ (≥40 vs 35-39 yrs)*				
Other CVDs (n=6 studies)						
Arterial fibrillation						
Wong(2017)(30)					↔ (<45 vs 45-49 yrs)	↔ (>54 vs 45-49 yrs)
Yang(2019)(29)	↑ (<30 vs ≥30 yrs)				↑ (<45 vs ≥45 yrs)	
Carotid Plaques						
Stockl(2014)(31)		↔ (>35 vs ≤35 yrs)				
Peripheral artery disease						
Corte(2018)(32)		↔ (per year)				
Holzer(2007)(33)		↓ (per year)				
Stockl(2013)(34)	↔ (<34 vs >39 yrs)					

Abbreviations: CVD: Cardiovascular diseases, CHD: Coronary heart disease.

*Trend of ordered exposure levels based on statistical significance at $p < 0.05$

↑ Indicates the risk of outcome increased, ↓ indicates the risk of outcome decreased, ↔ indicates no evidence of association based on statistical significance at $p < 0.05$.

a: ischemic heart disease, b: natural menopause, c: ischemic stroke, d: all stroke, e: among women without arterial fibrillation

Table 2. Summary of studies examining associations between reproductive lifespan, age at menarche and age at menopause with CVD mortality and all-cause mortality

Outcomes	Short reproductive lifespan	Long reproductive lifespan	Early menarche	Late menarche	Early menopause	Late menopause
CVD mortality (n=11 studies)						
Chang(2011)(35)	↔ (2-25 vs 26-32 yrs)	↔ (≥33 vs 26-32 yrs)				
Cui(2006)(36)	↔ (≤27 vs 31-33 yrs)	↔ (≥37 vs 31-33 yrs)	↔ (≤13 vs 14 yrs)	↔ (≥17 vs 14 yrs)		
Hong(2007)(41)					↑ (<40 vs 45-49 yrs)	↔ (≥50 vs 45-49 yrs)
Jansen(2002)(37)	↔ (≤33 vs 36-37 yrs)	↔ (≥40 vs 36-37 yrs)				
Jaspers(2017)(14)		↑ (per year)				
Li(2013) ^a (42)					↔ (<40 vs 50-54 yrs)	↔ (≥55 vs 50-54 yrs)
Li(2013) ^b (42)					↔ (<40 vs 50-54 yrs)	↔ (≥55 vs 50-54 yrs)
Muller(2012) ^b (43)			↑ (≤12 vs 13-14 yrs)*	↓ (≥17 vs 13-14 yrs)*		
Tom(2012) ^c (44)					↔ <45 vs 50-54 yrs)	↑ (≥55 vs <50-54 yrs)
Wu(2014)(38)	↔ (<27 vs 30-33 yrs)	↔ (≥35 vs <30-33 yrs)	↔ (<14 vs 15 yrs)	↔ (≥17 vs 15 yrs)	↔ (<47 vs 49-50 yrs)	↔ (≥52 vs 49-50 yrs)
Yang(2017)(17)		↓ (per year)				↓ (per year)
Zhang (2019)(45)			↔ (≤11 vs 12-13 yrs)	↔ (≥14 vs 12-13 yrs)	↑ (≤44 vs 45-54 yrs)	↓ (≥55 vs 45-54 yrs)*
CHD mortality (n=7 studies)						
Chang(2011)(35)	↔ (2-25 vs 26-32 yrs)	↔ (≥33 vs 26-32 yrs)				
Cui(2006)(36)	↔ (≤27 vs 31-33 yrs)	↔ (≥37 vs 31-33 yrs)	↔ (≤13 vs 14 yrs)	↔ (≥17 vs 14 yrs)		
Hong(2007)(41)					↑ (<40 vs 45-49 yrs)	
Mondul(2005)(46)					↔ (40-44 vs 45-49 yrs)	↓ (50-54 vs 45-49 yrs)*
Muller(2012) ^b (43)			↑ (≤12 vs 13-14 yrs)*	↓ (≥17 vs 13-14 yrs)*		
Otuski(2018)(39)		↓ (≥35 vs ≤28 yrs)*				
Wu(2014)(38)	↔ (<27 vs 30-33 yrs)	↔ (≥35 vs 30-33 yrs)	↔ (<14 vs 15 yrs)	↔ (≥17 vs 15 yrs)	↔ (<47 vs 49-50 yrs)	↔ (≥52 vs 49-50 yrs)
Stroke mortality (n=7 studies)						
Chang(2011)(35)	↔ (2-25 vs 26-32 yrs)	↔ (≥33 vs 26-32 yrs)				
Cui(2006)(36)	↔ (≤27 vs 34-36 yrs)	↓ (≥37 vs 31-33 yrs)	↔ (≤13 vs 14 yrs)	↔ (≥17 vs 14 yrs)		
Hong(2007)(41)					↑ (<40 vs 45-49 yrs)	
Mondul(2005)(46)					↔ (40-44 vs 45-49 yrs)	
Muller(2012) ^b (43)			↔ (≤12 vs 13-14 yrs)	↔ (≥17 vs 13-14 yrs)		
Wu(2014)(38)	↔ (<27 vs <30-33 yrs)	↔ (≥35 vs <30-33 yrs)	↑ (<14 vs 15 yrs)*	↓ (≥17 vs 15 yrs)*	↔ (<47 vs 49-50 yrs)	↓ (50-52 vs 49-50 yrs)

Otuski(2018)(39)	↓ (≥35 vs ≤28 yrs)*					
All-cause mortality (n=11 studies)						
Giles(2010)(47)	↔ (≤30 vs 31-39 yrs)	↔ (≥40 vs 31-39 yrs)	↔ (<12 vs ≥12 yrs)			
Hong(2007)(41)					↑ (<40 vs 45-49 yrs)	↔ (≥50 vs 45-49 yrs)
Jansen(2002)(37)	↔ (≤33 vs 36-37 yrs)	↔ (≥40 vs 36-37 yrs)				
Jaspers(2017)(14)		↑ (per year)				
Li(2013) ^a (42)					↑ (<40 vs 50-54 yrs)	↓ (≥55 vs 50-54 yrs)*
Li(2013) ^b (42)					↔ (<40 vs 50-54 yrs)	↔ (≥55 vs 50-54 yrs)
Mondul(2005)(46)					↑ (40-44 vs 45-49 yrs)*	↓ (50-54 vs 45-49 yrs)*
Shadyab(2017) ^d (40)	↓ (<33 vs 38-40 yrs)	↓ (>40 vs 38-40 yrs)	↔ (<12 vs ≥12 yrs)		↓ (<40 vs 50-54 yrs)*	↓ (≥55 vs 50-54 yrs)*
Tamakoshi(2011)(48)			↑ (9-12 vs 14 yrs)	↑ (18-20 vs 14 yrs)*		
Tom(2012) ^c (44)					↓ (<45 vs 50-54 yrs)*	↑ (≥55 vs 50-54 yrs)*
Wu(2014)(38)	↔ (<27 vs 30-33 yrs)	↔ (≥35 vs <30-33 yrs)	↑ (<14 vs 15 yrs)*	↓ (≥17 vs 15 yrs)*	↑ (<47 vs 49-50 yrs)	↓ (52 vs 49-50 yrs)*
Zhang(2019)(45)			↑ (≤11 vs 12-13 yrs)	↓ (≥14 vs 12-13 yrs)	↑ (≤44 vs 45-54 yrs)	↓ (≥55 vs 45-54 yrs)*

Abbreviations: CVD: Cardiovascular diseases, CHD: Coronary heart disease.

*Trend of ordered exposure levels based on statistical significance at $p < 0.05$

↑ Indicates the risk of outcome increased, ↓ indicates the risk of outcome decreased, ↔ indicates no evidence of association based on statistical significance at $p < 0.05$.

a: not receiving hormone replacement therapy, b: no smoker, c: natural menopause, d: all women

Table 3. Summary of studies examining associations between endogenous oestrogen exposure (EOE) and total oestrogen exposure (TOE) and CVD events, CVD mortality and all-cause mortality

Author (year)	Sample size	Formula of OE	CVD	CVD mortality	All-cause mortality
Endogenous oestrogen exposure (n=4 studies)					
Farahmand(2019)(49)	3,656	Age at menopause – age at menarche – pregnancy – OCP – breastfeeding – pregnancy-termination – post-ovulatory period ^a	↑ (T ₁ vs T ₃)		
Merritt(2015)(15)	322,972	Age at recruitment/age at menopause – age at menarche – pregnancy – OCP ^b			↔ (≥34 vs 0-22 yrs)
Jaspers(2017)(14)	1,736	Age at menopause – age at menarche – pregnancy – OCP – breastfeeding – post-ovulatory period ^c		↑ (per year)	↔ (per year)
De Kleijn(2002) (9)	9,450	Age at menopause – age at menarche – pregnancy – OCP – breastfeeding – miscarriage/stillborn – post-ovulatory period ^d		All CVDs ↓ (>18 vs ≥13 yrs) IHD ↔ (>18 vs ≥13 yrs) Stroke ↔ (>18 vs ≥13 yrs)	
Total oestrogen exposure (n=2 studies)					
Lee (2019)(50)	648	Age at menopause – age at menarche – OCP – pregnancy + HRT ^e	↔ (per year)		↔ (per year)

Lee (2019)(50)	648	Age at menopause – age at menarche + OCP + pregnancy + HRT ^f	↔ _(per year)	↔ _(per year)
Merz(2009)(16)	646	Age at menopause – age at menarche – OCP – pregnancy + HRT ^e	70 carotid artery stenosis ↔ 50 carotid artery stenosis ↔	
Merz(2009)(16)	646	Age at menopause – age at menarche + OCP + pregnancy + HRT ^f	70 carotid artery stenosis ↓ 50 carotid artery stenosis ↓	

Abbreviations: CHD: coronary heart disease, CVD: cardiovascular diseases, IHD: ischemic heart disease, HRT: hormone replacement therapy, OCP: oral contraceptive pills, OE: oestrogen exposure, T: tertiles

Notes: ↑ indicates the risk of outcome increased significantly with OE; ↓ indicates the risk of outcome significantly decreased with OE; ↔ indicates no evidence of a significant association.

^a calculated as the difference between the participant's age at menopause or age at CVD event or end of follow up – based on their first occurrence, and age at menarche. Further, pregnancy (40 weeks/per pregnancy), OCP, breastfeeding (duration of breastfeeding in months/per live birth), pregnancy-termination (20 weeks/per termination), and post ovulatory period (2 weeks/per cycle) were subtracted to yield endogenous oestrogen exposure.

^a The endogenous oestrogen exposure was calculated as the difference between the participant's age at menopause (post-menopausal) and age at recruitment (either pre, peri or of unknown menopause status) and age at menarche, minus the length of time that a woman was pregnant or using OCPs.

^b The total postovulatory period in months ($\{\text{lifetime number of menstrual cycles} \times 2\} / 4$), subtracted from the cumulative endogenous oestrogen exposure in months (age at menopause-age at menarche-pregnancy-breastfeeding-OCP), and finally expressed in years.

^c calculated by subtracting age at menopause (in months) by age at menarche (in months). For each live birth, 9 months was subtracted additionally. Further, for each miscarriage or stillborn child, three months was subtracted. And for each child, four months (the average duration of breastfeeding) was subtracted. Furthermore, the total duration of oral contraceptive use was subtracted. Finally, the total duration of all postovulatory period was subtracted to obtain the total duration of endogenous oestrogen exposure.

^d [age at last cycle – age at menarche] – (premenopausal oral contraceptive time) – (pregnancy time) + (postmenopausal HT time), the study called it as a total oestrogen exposure.

^e [age at last cycle – age at menarche] + (premenopausal oral contraceptive use time) + (pregnancy time) + (postmenopausal HT time), the study called it as a supra-total oestrogen exposure.

Figure 1: Flow chart of study process.

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Mishra, SR;Chung, H-F;Waller, M;Mishra, GD

Title:

Duration of estrogen exposure during reproductive years, age at menarche and age at menopause, and risk of cardiovascular disease events, all-cause and cardiovascular mortality: a systematic review and meta-analysis

Date:

2020-11-05

Citation:

Mishra, S. R., Chung, H. -F., Waller, M. & Mishra, G. D. (2020). Duration of estrogen exposure during reproductive years, age at menarche and age at menopause, and risk of cardiovascular disease events, all-cause and cardiovascular mortality: a systematic review and meta-analysis. BJOG-AN INTERNATIONAL JOURNAL OF OBSTETRICS AND GYNAECOLOGY, 128 (5), pp.809-821. <https://doi.org/10.1111/1471-0528.16524>.

Persistent Link:

<http://hdl.handle.net/11343/276575>