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Association between duration of endogenous estrogen exposure and cardiovascular outcomes: A population – based cohort study

Maryam Farahmand[a], Fahimeh Ramezani Tehrani[a,*], Davood Khalili[b,c], Leila Cheraghi[c], Mahnaz Bahri Khomami[d], Fereidoun Azizi[e]

[a] Reproductive Endocrinology Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[b] Prevention of Metabolic Disorders Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[c] Department of Epidemiology and Biostatistics, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[d] Monash Centre for Health Research and Implementation, School of Public Health and Preventive Medicine, Monash University, Clayton, Vic, Australia
[e] Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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ABSTRACT

Aims: Duration of endogenous estrogen exposure is apparently associated with risk of cardiovascular disease, the longer durations being more cardiovascular disease protective in women. We aimed to investigate the association of cumulative duration of endogenous estrogen exposure over women's reproductive lifespans with cardiovascular disease outcomes.

Main methods: For the purpose of the present study, of 10,192 female participants, after excluding those using HRT (n = 84), 3656 women, aged ≥30 years, who met eligibility criteria were selected and divided into three groups based on tertiles (T1, T2, T3) of exposure durations to endogenous estrogen. Cox proportional hazards regression model was used to estimate associations between exposure durations and cardiovascular disease outcomes.

Key findings: Cardiovascular events occurred in 352 participants over a median follow-up of 14.2 (13.5, 14.6) years (7.7 per 1000 person years; 95% CI: 6.9–8.5). Incidence of outcome was 10.9 per 1000 person years (CI, 9.4–12.8) in T_1, 7.2 per 1000 person years (CI, 6.0–8.7) in T_2, and 5.1 per 1000 person years (CI, 4.1–6.4) in T_3. The hazard ratio of cardiovascular events in T_1 was significantly higher than that inT_3, before and after adjustment for confounding variables. Before adjustment, women in T_2 had a 40% higher risk of CVD, compared to T_3; after adjustment however the risk was similar to that of women in T_3.

Significance: Shorter durations of exposure to endogenous estrogen may increase the risk of cardiovascular diseases among these women later in life. Future studies should target women with short duration of exposure for timely screening and implementation of preventative interventions.

1. Introduction

Cardiovascular disease (CVD) is one of the main rising causes of mortality and morbidity in both the developed and developing countries [1]. Despite literature available on the role of CVD in women's mortality, the risk perceptions levels of these women are relatively poor [2]. Results from a community based study in Iran showed that modifiable risk factors can explain approximately 50% of coronary heart disease, as one of CVD burden, in women [3]. Recently, it has been reported that clinical presentations, pathophysiology of CVD and its response to therapy, differs by gender. This suggests that cardiovascular risk factors are probably sex-specified and should be investigated in characteristics specified to each sex such as hormonal variations and chromosomal composition [4].

Reproductive-age women are at lower risk for CVD, compared to postmenopausal women and men of similar age [5–7], a finding reported to be related to the endogenous estrogen production in reproductive-aged women. The guidelines of the American Heart Association for prevention of CVD in women strongly recommend that future researches should be focused on the role of reproductive factors including menarche, pregnancy, and menopause to target high risk subgroups for timely prevention. Various biologically mechanisms have been hypothesized to explain the effect of estrogens on the etiology of CVD including either directly (by influencing on vascular wall) or

* Corresponding author at: Reproductive Endocrinology Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, 24 Parvaneh St., Yaman St., Velenjak, PO Box 19395-4763, Tehran, Iran.
E-mail addresses: ramezani@endocrine.ac.ir, framezan@post.harvard.edu (F. Ramezani Tehrani).

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indirectly (by modifying other risk factors for CVD). It is not clear to what extent durations of endogenous estrogen exposure (EEE) may influence the CVDs. Duration of EEE is specified by a range of factors including menarcheal age, number and duration of pregnancies, duration of breastfeeding, oral contraceptive use and menopausal age [8]. Exposure to progestogen in the second phase of the menstrual cycle, pregnancy, breastfeeding and/or progestogen containing contraceptives may ameliorate the protective CVD effect of estrogen (E2). All these factors should be taken into account in an optimal definition of the duration of EEE [9].

We therefore aimed to explore the longitudinal association of EEE duration with CVDs, considering factors which have the most impact in EEE, including menopausal age, menarcheal age, and duration of pregnancies, breastfeeding, and oral durations of contraceptive use in women in a well-known population based study, the Tehran Lipid and Glucose Study (TLGS).

2. Materials and methods

2.1. Subjects

For the purpose of the present study, we used data from the TLGS, an ongoing prospective study, initiated in 1998, with the aim of determining the prevalence of non-communicable disease risk factors. In this study 15,005 people, aged ≥3 years, were selected from a geographically defined population, using a multistage cluster sampling method [9]. There were 5226 women, aged ≥30 years in the TLGS, of whom 3656 met the eligibility criteria; of these, 2434 women were post-menopausal and for each of them information on anthropometrics, demographics, lifestyle variables, various risk factors for non-communicable diseases and medical and reproductive histories were collected by trained interviewers, during face-to-face interviews; details of the measurement methods have been published elsewhere [10]. For the purpose of the present study, we excluded those with CVD history at baseline (n = 188), missing data of menarcheal age (n = 1019), hormone replacement therapy (HRT) (n = 87), missing data for calculating EEE (n = 233) and no follow-up information (n = 43), leaving us with data of 3656 women for the analysis. The study flowchart is presented in Fig. 1.

2.2. CVD outcomes

Details of CVD outcome measurements have been explained elsewhere [11,12]. Data on cardiovascular outcomes was collected for each participant of TLGS annually. For this study, first diagnosed CVD events, including definite Myocardial Infarction (MI), probable MI, unstable angina, angiographic-proven Coronary heart disease (CHD), and stroke were considered as CVD events [13]. To validate the diagnoses, an outcome committee (Cohort Outcome Panel), including a principal investigator, an internist, an endocrinologist, a cardiologist, an epidemiologist and a physician re-assessed the symptoms documented in patients' medical records. Other experts were invited if required. The final diagnosis was via consensus of the majority of committee members, (i.e. by ≥3 members of the committee) [13].

2.3. Exposures

Duration of EEE was initially defined as the time interval between age at menarche and menopausal age or age at CVD event or end of follow-up, whichever occurred earlier. The cumulative duration of progesterone dominant (luteal) phases of menstrual cycles (2 weeks for each menstrual cycle), pregnancies (40 weeks for each birth or 20 weeks for each abortion), progestogen containing contraception use and breastfeeding (i.e. number of months for each child) were deducted from the initial EEE variable to consider only E_2 dominant (follicular) phases of menstrual cycles. It should be noted that none of the participants used the combination of progesterone 4 as oral contraceptive pills.

An ever smoker was defined as a person who has used any tobacco products at some time/any time including cigarettes, pipe, and water pipe. Women were asked about family history of CVD, i.e. if any of their first-degree family members had had MI, stroke or sudden cardiac arrest, prior to the ages of 55 years in males and 65 years in females [14].

2.4. Data analysis

Comparisons of quantified and categorical variables were conducted using ANOVA and Chi-square test, as appropriate.

Study subjects were divided into 3 groups based on tertiles of EEE duration (T_1–T_3). The event date for CVD was defined as the date of the follow-up visit at which the outcome was first diagnosed. For those with a negative event, the most recent follow-up visit was considered, leaving the residence area out (censored subjects); “time” was considered as the interval between the first and the last follow up dates. Incidence rate of CVD was calculated per 1000 person years of follow up among the 3 groups, and cumulative incidence of CVD was assessed by the Kaplan-Meier method and compared between the 3 groups using the log-rank statistic.

Cox proportional hazards regression model was performed to estimate the adjusted hazard ratio (HR) for CVD in association with EEE duration. The proportional hazards assumption of the Cox models was assessed by the Schoenfeld residual test and proportionality was appropriated (Fig. 2). The most common reported confounder variables were selected [8,15,16]. As a result we adjusted the Cox model for baseline age and BMI, family history of CVD, smoking status and educational level, with $P < 0.05$ was considered as statistically significant. Data was analyzed using the Statistical Package for Social Sciences (SPSS version 20; SPSS Inc.) and STATA software (version 12; STATA Inc.).

2.5. Ethics approval

The ethics committee of the Research Institute for Endocrine Sciences approved the study proposal and written informed consent was obtained from all subjects.

3. Results

Characteristics of the participants according to the EEE tertiles are presented in Table 1. Mean age ± SD of participants at baseline and menarche were 45.7 ± 11.0, and 13.6 ± 1.4 years, respectively. There were no significant differences in mean BMI and menarcheal age in three study groups. Mean BMI was 29.0 ± 4.7, 28.3 ± 4.6, 28.7 ± 4.5 kg/m^2 in T_1, T2, T3, respectively (P = 0.4), and mean menarcheal age was 14.0 ± 1.4, 13.7 ± 1.4, 13.3 ± 1.4 years in T_1,T_2,T_3, respectively (P = 0.1). The remaining variables differed significantly between the three groups ($P < 0.05$).

The median follow-up time for the current analysis was 14.2(13.5, 14.6) years. At the end of the follow up, among 3656 women, the overall incidence of CVD was 160 in T_1 (10.9 per 1000 person years; CI, 9.4–12.8), 111 in T_2 (7.2 per 1000 person years; CI, 6.0–8.7), 81 in T_3 (5.1 per 1000 person years; CI, 4.1–6.4) and in total 352 (7.7 per 1000 person years; 95% CI: 6.9–8.5). Before end of follow-up, 3304 of participants were censored. It is worth mentioning that information from both censored and uncensored observations incorporated in estimating model parameters.

Table 2 shows the characteristics of CVD events. According to this table there is no significant statistical difference in age between all groups at first CVD event and duration of menarche to the first CVD event. Among all those participants who experienced menopause (with or without CVD event), the mean (SD) of time duration of menarche to menopause in T1, T2 and T3 were 32.1 (5.3), 36.0 (3.1) and 39.4 (2.8),

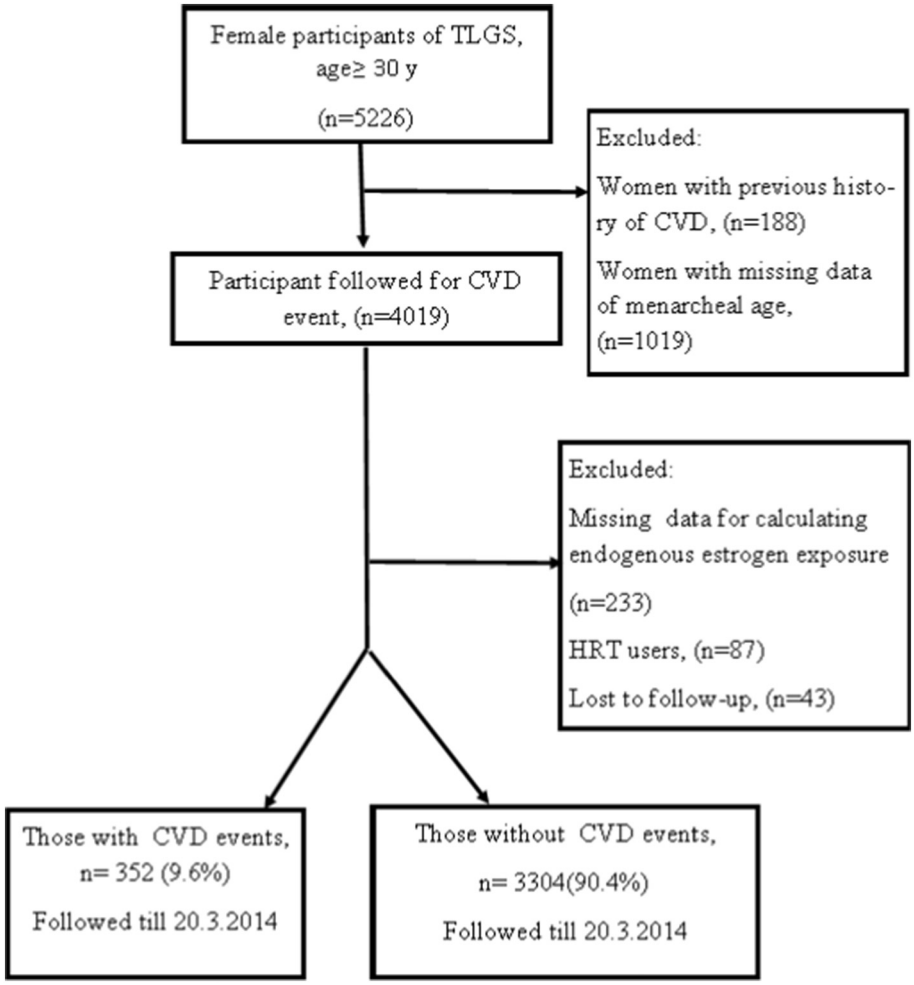

Fig. 1. Study flowchart. Abbreviations: TLGS, Tehran Lipid and Glucose Study; CVD, cardio-vascular disease; HRT, hormone replacement therapy.

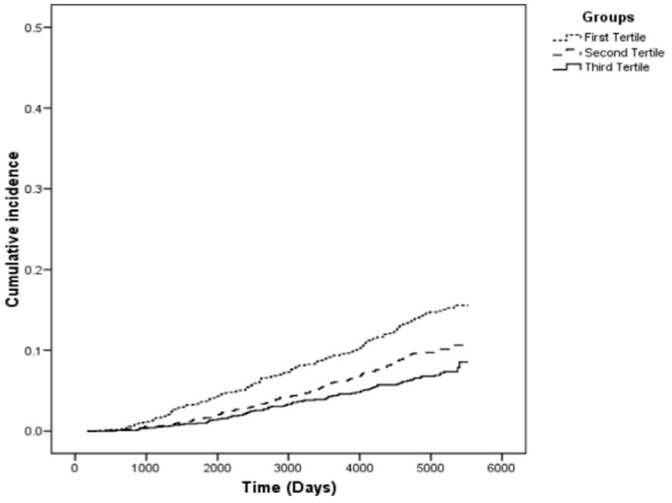

Fig. 2. Kaplan-Meier cumulative estimates of incidence rates of CVD in subjects, according to the tertiles of endogenous estrogen exposure duration. T1: endogenous estrogen exposure duration < 667 weeks. T2: endogenous estrogen exposure duration between 667 and 795 weeks. T3: endogenous estrogen exposure duration ≥795 weeks.

respectively (P < 0.001).

At the end of follow-up, there were 2434 women who had reached menopause, of whom 2111 had not experienced CVD events. Among all the remaining 1222 participants that were still having menstrual cycles at the end of follow up, 29 women had experienced their first CVD event (Supplementary Table 1).

The unadjusted and adjusted HRs, for CVD events are shown in Table 3. Crudely, women in T_1 had a higher risk for CVD, compared to T_3 (HR 2.2; 95% CI, 1.6–2.8; P < 0.001), a risk which remained significant after adjustment for potential confounders (HR = 1.5; 95% CI, 1.1–2.0; P = 0.004). Before adjustment, the HR for CVDs was higher in women of T_2, compared to those of T_3 (HR =1.4; 95% CI, 1.1–1.9; P = 0.021). After adjustments for potential confounders HRs were similar between T_2 and T_3 (HR 1.3; 95% CI, 1.0–1.7; P = 0.086).

4. Discussion

In this large prospective cohort study, we found that CVD was more prevalent in women in the first and second tertiles of duration of EEE, compared to women in the third tertile. After adjustment for known risk factors, the increased risk remained significant for the first tertile but this was not so for the second tertile. To the best of our knowledge, this is the first study assessing the incidence of CVDs over the EEE duration, as a predictor, over a 15-year follow up cohort study, taking into account all eligible women, regardless of their menopausal status.

Reproductive-aged women are less likely to develop CVD, compared to their male counterparts of the same age, a finding which is most likely multifactorial and is affected by both sexual hormones and potentially sex chromosomal composition [17–19]. Previous studies report estrogen (E2) as a CVD protective factor, which acts as a mediator in CVD protection by promoting angiogenesis and vasodilation and

Table 1
Characteristics of subjects in groups by tertiles of exposure durations to endogenous estrogen.

Variables	Duration of endogenous estrogen exposure			
	T1	T2	T3	Total
Subjects (no)[a]	1219 (33.3)	1218 (33.3)	1219 (33.3)	3656 (100)
Age (years)[b]	47.6 ± 12.0	44.2 ± 11.4	45.2 ± 9.2	45.7 ± 11.0
Menarcheal age (years)[b]	14.0 ± 1.4	13.7 ± 1.4	13.3 ± 1.4	13.6 ± 1.4
Body mass index (kg/m^2)[b]	29.0 ± 4.7	28.3 ± 4.6	28.7 ± 4.5	28.7 ± 4.6
Ever smoker (yes)[a]	64 (5.3)	63 (5.3)	74 (6.1)	201 (5.6)
Family history of CVD (yes)[a]	201 (16.5)	209 (17.2)	248 (20.3)	658 (18.0)
Educational level[a]				
Illiterate	252 (20.7)	151 (12.4)	100 (8.2)	503 (13.8)
< 12 years	661 (54.3)	632 (52.1)	598 (49.2)	1891 (51.9)
12 years	243 (20.0)	354 (29.2)	413 (34.0)	1010 (27.7)
> 12 years	61 (5.0)	77 (6.3)	105 (8.6)	243 (6.7)
Menopause status (yes)[a]	946 (77.7)	742 (60.9)	745 (61.1)	2434 (66.6)
Menopausal age (years)[b]	46.1 ± 5.4	49.7 ± 3.1	52.7 ± 2.9	49.2 ± 4.9
Total duration of pregnancies (weeks)[b]	197.2 ± 96.8	158.3 ± 73.8	131.6 ± 56.8	162.4 ± 82.1
Total duration of hormonal contraceptive use (weeks)[b]	49.2 ± 77.1	21.8 ± 26.7	15.8 ± 12.4	28.7 ± 48.8
Total duration of breastfeeding (weeks)[b]	266.1 ± 135.0	110.8 ± 71.8	56.8 ± 40.0	208.2 ± 142.3

Note: ANOVA test, and Chi-square test were used as appropriate. Body mass index & age are presented at baseline, Total duration of hormonal contraceptive use was calculated only in contraceptive users. Menopause status was during follow-up or before event or censoring. Menopausal age was calculated among participants who had reached menopause. T1: Endogenous estrogen exposure duration < 667 weeks, T2: endogenous estrogen exposure duration 667-795 weeks, T3: endogenous estrogen exposure duration ≥ 795 weeks.
[a] Number and percentage.
[b] Mean ± SD.

decreasing reactive oxygen species, oxidative stress, and fibrosis [20]. Given that serum levels of estrogen (E2) and the expression of its receptors differ between genders, the lower prevalence of CVD in women may be partly explained by higher serum levels of E2 [20].

Contradictory results from several previous studies show that age at menarche, and menopause, parity and gravidity, breast-feeding and menstrual cycle may be considered as influential factors impacting CVD [4,8,15,16,21–26]. However it remains unclear how women's reproductive histories affect cumulative endogenous estrogen levels during their life span [27]; hence it has been suggested that the overall impact of all reproductive factors on CVD risk be investigated in women [15]. Given that progestin may reduce the protective effect of estrogen on CVD, E2 dominant (follicular) phases of menstrual cycles may need to be considered for precise estimation of EEE. Additionally it assumed that pregnancy period of women need to be excluded, as this period is progesterone dominant; despite well-known attenuating effect of synthetic progesterone (except P4), on cardio-protective behavior of estrogens, data on natural progesterone are lacking and controversial [28–31]. For the first time Kleijn et al. introduced a composite variable (EEE), including menopause and menarcheal age, duration of pregnancies, contraception use and breastfeeding and assessed its relationship with CVD mortality [8]. Since then this composite variable has been used in several researches, however using various definitions. The method we use for calculation of each EEE component however varied in previous studies [23–27]. Furthermore the majority of these publications were cross sectional studies and hence were not potentially suitable for precise evaluation of the dynamic changes in estrogens [27,32–34].

Shorter durations of EEE have been reported to be associated with increased risk of osteoporosis, total mortality, venous thromboembolism and CVD [8,16,21,35–38]. A population-based cohort study in the Netherlands of 9450 postmenopausal women, aged 35–65 years, assessed the association of EEE with CVD mortality; EEE duration was defined based on reproductive factors including menopausal and menarcheal age, number and duration of oral contraceptive use, the average duration of pregnancies and breastfeeding. In this study the duration of EEE was inversely associated with CVD mortality [8]. Some previous studies also report duration of lactation, and the number and duration of parities to be inversely associated with CVD [23,24] and also that history of miscarriage has been associated with increased risk of CVD [25]. The association of reproductive factors with both the known risk factors for CVD and CVD endpoints have been investigated

Table 2
Characteristics of CVD event in groups by tertiles of exposure durations to endogenous estrogen.

Variables	Duration of endogenous estrogen exposure			P_{value}
	T1	T2	T3	
	Mean ± SD	Mean ± SD	Mean ± SD	
Number of subject with CVD event[a]	160	111	81	
Age at first CVD event[a] (years)	65.3 ± 9.4	63.7 ± 9.9	63.5 ± 8.1	0.23
Time of menarche to first CVD event[a] (years)	51.4 ± 9.5	50.0 ± 10.1	50.2 ± 8.2	0.4
Number of subject with CVD event[b]	153	99	71	
Time of menarche to menopause in those with CVD event[b] (years)	32.9 ± 5.2	37.0 ± 2.9	40.7 ± 3.3	< 0.001
Number of subjects without CVD event[b]	794	643	674	
Time of menarche to menopause in those without CVD event[b] (years)	31.9 ± 5.4	35.9 ± 3.1	39.3 ± 2.7	< 0.001

Note: T1: endogenous estrogen exposure duration < 667 weeks, T2: endogenous estrogen exposure duration 667–795 weeks, T3: endogenous estrogen exposure duration ≥ 795 weeks. Abbreviation: CVD, cardio-vascular disease.
[a] Among all participants.
[b] Among those participants who reached menopause during the study.

Table 3
Unadjusted and multiple adjusted hazard ratios of incident CVD by tertiles of endogenous estrogen exposure duration.

Endogenous estrogen exposure duration	Incidence of CVD	Unadjusted		Adjusted[a]	
	Crude number (number per 1000 person years)	HR (95% CI)	P value	HR (95% CI)	P value
T1 (< 667 weeks)	160 (13.1)	2.2 (1.6, 2.8)	< 0.001	1.5 (1.1, 2.0)	0.004
T2 (667–795 weeks)	111 (9.1)	1.4 (1.1, 1.9)	0.021	1.3 (1.0, 1.7)	0.082
T3 (≥795 weeks)	81 (6.6)	Ref	Ref	Ref	Ref

Note: CI, confidence interval; HR, hazard ratio. Abbreviations: CVD, cardio-vascular disease; BMI, body mass index.
[a] Adjusted for age and BMI are presented at baseline, smoking, education, family history of CVD.

using heterogeneous methodologies on different outcomes and different risk factors [39,40] which make the results inconclusive.

In the present study we found that the shortest EEE duration is associated with increased CVDs, results in agreement with those of other studies that report shorter durations and levels of endogenous estrogen to be associated with a higher incidence of CVD [8,41,42] although one study showed estradiol level was not associated with CVD risk [43]. These finding most likely suggest that longer EEE duration does not protect women from CVD although insufficient duration is a risk factor in these women. Our model duration of EEE enabled us to combine all endogenous estrogen-related information into a composite variable to explore the association of EEE duration and with CVDs.

This study is strengthened by the ongoing community-based cohort data of over a decade long follow-up, its large sample size and an accurate estimation of CVD which enabled us to perform survival analysis, adjusted for the most important potential confounders. Duration of breastfeeding was documented as the cumulative number of months that each child was breastfed. Our criteria also enabled us to include all women regardless of their menopausal status. We included all women, aged ≥30 years. Information on important risk factors of CVDs including age, BMI at entry, smoking, education and family history of CVD were available for adjustment in the Cox model. The main limitation of present study is recall bias; age at menarche and menopause, time of breast feeding and duration of hormonal contraceptive use were self-reported. However, in the TLGS cohort, all this information was documented every three years and showed a good consistency. Additionally using a unique time for estimating the follicular phase of all participants may be considered as a limitation for the present study; and also given the lack of knowledge on cardiac effect of natural progesterone, excluding the progesterone dominant phase of menstrual cycles and pregnancy for calculation of EEE may be questionable. Moreover our results might be confounded by not considering other lifestyle factors, such a diet and physical activity. Lack of validation of method for calculation of EEE may also be considered a potential limitation.

5. Conclusion

In this longitudinal cohort community-based study, we found that shorter durations of EEE are associated with increased incidence of CVDs, which needs to be confirmed by further researches. These results add to the current knowledge regarding the impact of the duration of endogenous estrogen on CVDs, information which should help healthcare providers screen and provide appropriate management policies for women with shorter EEE duration.

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Conflict of interest

The authors have declared no conflicts of interests.

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