Endogenous estrogen exposure and chronic kidney disease; A 15-year prospective cohort study

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Research article

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Abstract

Background: Despite strong evidence demonstrating the role of estrogen as a protective factor for kidney function in women, limited data are available regarding the influence of endogenous estrogen exposure (EEE) on chronic kidney disease (CKD). The present study aimed to assess the incidence of CKD in women with various levels of EEE.

Methods: In a prospective population-based study over a 15-year follow-up, a total of 3043 eligible women aged 30-70 years, participating in Tehran-Lipid and Glucose-Study were recruited and divided in two groups(EEE <11 and EEE≥11 years). Cox's proportional hazards model was applied to estimate the hazard ratio of CKD between the study groups, after adjusting for confounders.

Results: The total cumulative incidence rate of CKD at the median follow-up time of approximately 15.6 years was 50.1 per 1000 person years; 95% CI: 47.7–52.6); this was 53.9 per 1000 person years (CI, 50.2–57.8) and 47.1 per 1000 person years (CI, 44.0–50.4) in women with EEE<11 and EEE≥ 11 years, respectively. The multivariate Cox model adjusted for age, BMI, smoking, hypertension and diabetes showed that the HR of developing CKD in women with EEE<11 years was significantly higher than in those with ≥ 11 years (HR: 4.0; 95% CI: 2.5, 6.3).

Conclusion: This study shows a higher hazard ratio of CKD progression in women with low EEE levels in their later life. Our results suggest that the early diagnosis and management of subsequent kidney diseases in these women may potentially prevent the complications of this disease.

Background

The kidney, a powerful endocrine organ, is an important modulator of endocrine function, and a main target for hormonal action[1]. Chronic kidney disease (CKD) can be determined as a persistent injury of the renal parenchyma which causes chronic deterioration of renal function that may progressively worse to end-stage kidney disease (ESKD)[1].

Studies show that slower progression of CKD and lower incidence of ESKD in younger women compared to men, and omitting this gender protectively after menopause, suggests a role for female hormones[2-4]. While the mechanisms responsible for the protection of kidneys by these hormones, mainly estrogen, are not completely understood, it seems to be due to induced vasodilation in the renal vessels, enhancing the production of nitric oxide (NO), attenuation of inflammation and reduction in ischemia mediators[5-7].

It has been shown that estrogen stimulates the release of NO resulting in vasodilation; NO deficiency can be associated with acceleration of kidney injury by reduction of vasodilation and endothelial dysfunction. Estrogen also decreases the synthesis of renin and angiotensin-converting enzyme (ACE), and increases angiotensinogen synthesis[8]. Experimental studies demonstrate that administration of continuous estradiol can prevent glomerulosclerosis and albuminuria[9].

Despite existing strong evidence demonstrating the role of estrogen as a protective factor for kidney function in women, limited data are available regarding the influence of endogenous estrogen exposure (EEE) on chronic kidney disease (CKD); EEE can be calculated based on reproductive factors, including age at menarche, age at menopause, number and duration of pregnancies, lactation, and duration of oral contraceptive use [10]. In this prospective study, we aimed to investigate the incidence and hazard ratio of CKD among women with lower durations of EEE compared to those with higher exposure, after adjustment for known confounders.

Methods

Subjects

Subjects of the present study were recruited from among participants of the Tehran Lipid and Glucose Study(TLGS), , an ongoing prospective study, initiated in 1998, with the purpose of determining the prevalence of non-communicable disease (NCD) risk factors. There were 5226 women, aged 30-70 years selected for our study; after excluding those with CKD at baseline (n=1425), those with missing data of CKD (n=97) and those with missing data on age at menarche (n=1019), 3141women remained; we further excluded those with missing data for calculating EEE (n=98) HRT users (n=87) and those without at least one follow-up(n=92); eventually 3043 women remained for the purpose of the present study.

The study flowchart is presented in Fig. 1.

Study procedure:

A standard questionnaire including information on demographics, smoking behavior, physical activity habits and medical history was completed via face-to-face interviews[11].

Measurements:

Using systolic and diastolic blood pressure (SBP and DBP) was measured twice after a 15 minutes rest in a sitting position on the right arm, and the mean was considered as the participants' blood pressure. Weight was measured with individuals minimally clothed, using digital scales (Seca 707: range 0.1–150 kg) and recorded to the nearest 0.1 kg. Height was measured in a standing position, using a tape meter, while shoulders were in normal alignment.

Blood samples were drawn between 7:00 and 9:00 am after 12 h of overnight fasting. All blood analyses were performed at the TLGS research laboratory on the day of blood collection. All sera were stored at –80°C until the time of testing. Plasma glucose was measured using an enzymatic colorimetric method with glucose oxidase. Serum concentrations of creatinine (Cr) were tested by kinetic colorimetric Jaffe. The sensitivity of the assay was 0.2 mg/dL (range, 18–1330 μmol/L (0.2–15 mg/dL). Reference intervals based on the manufacturer's recommendation was 53–97 μmol/L (0.6–1.1 mg/dL) in men. Intra-assay and inter-assay CVs were less than 3.1% at both baseline and follow-up phases. All biochemical assays

were performed using commercial kits (Pars Azmoon Inc., Tehran, Iran) by a Selectra 2 autoanalyzer (Vital Scientific, Spankeren, The Netherlands).

Definitions:

According to the Kidney Disease Outcome Quality Initiative guidelines (K/DOQI), CKD is defined as either kidney damage or Glomerular Filtration Rate (GFR) <60 mL/min/1.73 m2 for >3 months[12]. In the present study, we estimated GFR using the abbreviated prediction equation, provided by the Modification of Diet in Renal Disease (MDRD) study [13]as follows:

$$GFR = 186 \times (SCr)^{-1.154} \times (Age)^{-0.203} \times 0.742 \times (0.742 \text{ if female}) \times (1.210 \text{ if African-American})$$

In this equation, estimated GFR (eGFR) is expressed as mL/min per 1.73 m2 and serum creatinine (SCr) is expressed as mg/dL; based on the guidelines, we considered CKD as an eGFR > 60 mL/min/1.73 m2, occurring at any time during the follow-up period.

Endogenous estrogen exposure (EEE) was defined as the time interval between age at menarche and menopausal age or age at CKD event or end of follow-up, whichever occurred earlier. To consider only E2 dominant of menstrual cycles, we omitted the cumulative durations of progesterone dominant phases of menstrual as well as those of pregnancies and lactation (assumed 40 weeks for each birth or 20 weeks for each abortion).

Hypertension was defined as systolic blood pressure (SBP)/ diastolic blood pressure (SBP)≥140/90 mmHg or current treatment for diagnosed hypertension[14]. Diabetes was defined as fasting plasma glucose (FPG)≥7.0 mmol/l or 2-h post 75g glucose load ≥11.1 mmol/l or under current treatment for diagnosed diabetes[15]. Smoking status was categorized as ever smoker (current/past) or never smoker[16]. Physical activity was measured as the MET value multiplied by the duration of activity in minutes multiplied by the frequency of activity per week. Each activity was weighted via its relative power, referred to as a MET; one MET shows the energy spent for an individual at rest (1 MET = 3.5 ml/kg.min of oxygen consumption). Energy expending was estimated based on the metabolic equivalent, duration of activity, and body weight. To get the total weekly leisure time energy expending the individual activities values was summed[17].

Statistical Analysis

Results are reported as mean and standard deviation (SD) for numerical variables and number (percentage) for categorical measures. For numerical variables with skewed distribution, median (inter-quartile range) was calculated. Using the Cubic Spline regression, participants were categorized into two groups according to cut-offs of EEE duration, of <11, and ≥11 years. Post hoc analysis was conducted using the cut off of 45 years for age at baseline.

Time to event was specified as a time of censoring or date of incidence of CKD or age at menopause, whichever happened first. Participants were censored as a result of death, loss to follow-up, or the end of the observation duration. For censored subjects, a negative event, the most recent follow-up visit was considered, as leaving the residence area; “time” was considered as the interval between the first and the last follow-up dates. The event date for CKD was defined as midtime between the dates of follow-up visit at which the CKD was recognized for the first time, and the last follow-up visit prior to diagnosis. Incidence rate of CVD was calculated per 1000 person years of follow up between those with EEE <11 and EEE≥ 11 years. Cumulative incidence of CKD was measured via the Kaplan-Meier method and compared between these 2 groups, using the log-rank statistic.

Multivariable Cox proportional hazards regression model was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) between groups (EEE< 11 and EEE≥ 11 years) which was adjusted for age , BMI, smoking, hypertension and diabetes. The proportional hazards assumption of the Cox models was assessed graphically. The Statistical Package for Social Sciences (SPSS version 20; SPSS Inc.) and STATA software (version 13; STATA Inc.) was used for data analysis.

Results

Characteristics of the study subjects according to the EEE cutoff value of 11 years are shown in Table 1. Mean ± SD age and menarcheal age of study subjects were 43.1±10.1, and 13.6 ± 1.5 years, respectively.

The median and 25-75%follow-up time for the current analysis was 15.6 and 12.4, 16.6 years. The overall incidence of CKD was 1598 (50.1 per 1000 person years; CI, 47.7–52.6); it was 769 (53.9 per 1000 person years; CI, 50.2–57.8), and 829 (47.1 per 1000 person years; CI, 44.0–50.4), in women with EEE<11 and EEE≥ 11 years, respectively. As a result of subgrouping the participants into two age groups (<45, and ≥45years), the interaction between age and EEE duration was a statistically significant difference (P<0.001), in those aged < 45, the incidence of CKD were 537 (45.6 per 1000 person years; 95%CI: 41.9, 49.7), and 222 (22.4 per 1000 person years; 95%CI: 19.6, 25.5), in women with EEE<11 and EEE≥ 11, respectively. In those aged ≥ 45, the incidence of CKD was 232 (92.5 per 1000 person years; 95%CI: 81.3, 105.2), and 607 (78.9 per 1000 person years; 95%CI: 72.9, 85.5) in women with EEE<11 and EEE≥ 11, respectively. HRs for CKD events are presented in table2 and figure 2.

In the crude model, HRs of CKD in women with EEE< 11 years in subgroup of women aged<45 was 2.18 (95% CI, 1.9, 2.5); it was 1.18(95% CI, 1.0, 1.4) in those aged ≥45; after adjustment for age, BMI, smoking, hypertension and diabetes; HR of CKD incidence in women with EEE< 11 years in the subgroup of women aged<45 years was 2.66(95% CI, 2.2, 3.2), whereas in the subgroup aged ≥45 years, it was 1.22 (95% CI, 1.04, 1.4).

Discussion

To the best of our knowledge, this is the first study reporting the effects of endogenous estrogen exposure on chronic kidney disease We found that after adjustment for all influencing variables, the hazard ratio of CKD among those women with > 11 years of EEE is four fold (95% CI: 2.5,6.3, P<0.001) that of those with ≥ 11 years of exposure. An adverse effect even stronger among those women aged <45 2.7(95% CI: 2.2, 3.2) vs. 1.22(1.04, 1.4) in women aged≥ 45 y.

There is controversy about the impact of sex hormones on renal function and disease as well as the gender dependency of CKD; the lower susceptibility of women could be due to absence of testosterone or the presence of estrogen[18] via elevated synthase production nitric oxide in kidneys[19-21].

It has been shown that estrogen may affect kidney function through several pathways including improved metabolism, selectivity of Angiotensin Type 2 (AT2) receptor signaling, diminished oxidative stress, and differential renin-angiotensin system (RAS) [22]. There is some evidence that NO deficiency can be associated with acceleration of renal injury, based on receptors that impaired vasodilation and endothelial dysfunction have been reported in CKD [23].

Estradiol may improve kidney function by suppressing the transforming growth factor β -1 (TGF- β -1) that induces mesangial cell apoptosis[24], and enhancing mesangial cell growth[25] by up- regulating NO synthase activity via vascular agents ; furthermore, estrogen receptor α that largely expressed in the kidneys[26], has the opposite effect of apoptosis in podocytes [27] and also acts as a regulator of renal sodium and potassium homeostasis and the renin angiotensin pathway [28]. Several studies have report the anti-apoptotic and anti-fibrotic effects of endogenous estrogens in the kidney [2, 29-31], which may partly explain the protective effect of estrogen on kidney. Estrogen may also have kidney protective effects by reducing renin and angiotensin-converting enzyme (ACE) synthesis and increasing angiotensinogen synthesis [5]. In addition, estrogen acts as a mediator by reducing arterial pressure via signaling the AT2 receptor and ACE2. Animal studies reveal the acceleration of progression of glomerulosclerosis due to estrogen shortage, resulting in diminished glomerular permeability and ischemia-reperfusion damage [2, 39, 41, 44].

Endogenous estrogen has been introduced as an important influential factor in NCDs (such as CKD) for its promotion of angiogenesis and vasodilation and decreasing of reactive oxygen species, oxidative stress, and fibrosis [22]. Shorter durations of EEE have been reported to be associated with increased risk of osteoporosis, total mortality, venous thromboembolism and CVD[10, 16]. However, to the best of our knowledge the association between EEE and CKD has not been reported before.

We found that the impact of the duration of EEE on CKD among younger women is even stronger than in older counterparts, an important finding with high clinical utility given the higher morbidity and mortality of younger women with CKD [32]. However with ageing, this association weakens, possibly due to over expression of other known risk factors of CKD for instance diabetes and hypertension [33]

This study is strengthened by the use of a comprehensive population based data set with a long enough follow-up, large sample size and precise estimation of CKD and influential factors, which enabled us to perform survival analysis, adjusted for the most important potential confounders; however, it does have some limitations. The main one is, as in most epidemiologic studies [1, 34, 35], we have not repeated Cr measurements within 3 months to confirm a chronic reduction in GFR. Second, recall bias for some components that been used for calculation of EEE; however, repeating these measurements every three years may reduce the risk of this bias. Although we tried to adjust our results for major known confounders for which data were available, other potential influencing factors such as diet have not been considered.

Conclusion

Our findings showed that lower duration of endogenous estrogen exposure especially among reproductive age women can be considered as a risk factor for CKD; and the early diagnosis of this susceptible group may improve their short term and long term morbidities.

Declarations

Ethics approval and consent to participate The medical ethics committee of this institute approved the study proposal (IR.SBMU.ENDOCRINE.REC.1397.284) and was in adherence with the Declaration of Helsinki and written informed consent was obtained from all participants.

Consent for publication Informed consent for publication was obtained from all participants.

Availability of data and materials The datasets generated and/or analyzed during the current study are not publicly available due to confidentiality considerations.

Competing interests The authors declare that they have no conflict of interest.

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Authors' contributions MF contributed to the study design and execution, data analysis, manuscript drafting and critical discussion. FRT contributed to the study design and execution, data analysis, manuscript drafting and critical discussion. DK contributed to the study design, and data analysis and manuscript drafting. LC contributed to the data analysis. FA contributed to the study design and execution and manuscript drafting. all authors have read and approved the manuscript.

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Abbreviations

EEE: Endogenous estrogen exposure; CKD: Chronic kidney disease; eGFR: estimated glomerular filtration rate; ESKD: End-stage kidney disease; NO: Nitric oxide; ACE: Angiotensin-converting enzyme; TLGS: Tehran Lipid and Glucose Study; NCD: Non-communicable Disease; CVD: Cardiovascular disease; SCr: Serum creatinine; K/DOQI: Kidney Disease Outcome Quality Initiative guidelines; MDRD: Modification of Diet in Renal Disease; FPG: Fasting plasma glucose; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; SD: Standard deviation; CI: Confidence interval; AT2:Angiotensin Type 2; RAS: renin-angiotensin system; ACE: Angiotensin-converting enzyme.

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Tables

Table 1

Characteristics of subjects in groups by cut-off of exposure durations of endogenous estrogen

Variables	Duration of endogenous estrogen exposure		
	Group 1 <11years	Group 2 ≥11 years	Total
Subjects (no)*	1429 (47.0)	1614(53.0)	3043(100)
Age(years) **	39.2±8.8	46.6±9.8	43.1±10.1
Menarcheal age(years) **	13.7±1.4	13.5±1.5	13.6±1.5
Body mass index (kg/m^2) **	28.1±4.6	28.5±4.8	28.3±4.7
Hypertension (yes)*	195(13.8)	425(26.8)	620(20.6)
Antihypertensive drug use *	60(4.2)	150(9.3)	210(6.9)
Angiotensin-converting-enzyme inhibitor use*	9 (0.6)	19(1.2)	28(0.9)
Diabetes type 2*	110(7.9)	238(15.1)	348(11.7)
Anti-diabetes type 2 drug use*	39(2.7)	92(5.7)	131(4.3)
Ever Smoker (yes) *	82(5.8)	72(4.5)	154(5.1)
eGFR (ml/min per1.73 m^2)	71.9±8.5	70.7±8.0	71.3±8.3
Creatinine (mg/dl)**	0.94±0.08	0.92±0.08	0.93±0.06
Physical activity(MET- min/week)**	1639±2350.5	1577.7±2049.4	1606.7±2195.2
Menopause status (yes)*	345(24.1)	1420(88.0)	1765(58)
Menopausal age(years) **	44.1±6.6	50.0±4.0	48.8±5.2
Total duration of pregnancies (years)**	2.72±1.4	3.09±1.5	2.90±1.5
Total duration of hormonal contraceptive use (years) **	0.55±1.0	0.47±0.5	0.53±0.9
Total duration of breastfeeding (weeks) **	4.35±2.6	2.25±1.6	3.7±2.5
Follow-up time (years)***	15.5(12.2,16.5)	15.6(12.5,16.6)	15.6(12.4,16.6)

Note: ANOVA test, Mann-Whitney test, and Chi-square test were used as appropriate.
* Number and percentage
** Mean± SD
***Median (Interquartile range)
Note: eGFR estimated glomerular filtration rate; Body mass index & age are presented at baseline; Total duration of hormonal contraceptive use was calculated only in contraceptive users. Menopause status was assessed during follow-up or before event or censoring. Menopausal age was calculated among participants who had reached menopause. MET, metabolic equivalent task.

Note: Group1: Endogenous estrogen exposure duration <11 years, group, 2: Endogenous estrogen exposure duration ≥11 years.

Table 2

Unadjusted and multiple adjusted hazard ratios of incident CKD by cut off value of 11 years for duration of EEE and subgroups of age at baseline

Endogenous estrogen exposure duration	Incidence of CKD	Unadjusted		Adjusted*	
	crude number (number per 1000 person years) (95% CI)	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Group1 (<11 years) N=1429	769(53.9) (50.2,57.8)	1.17(1.1,1.3)	0.002	4.0(2.5,6.3)	<0.001
Group 2 (≥11years) N=1614	829(47.1) (44.0,50.4)	Ref	Ref	Ref	Ref
<45 years N=1860					
Group1 (<11 years) N=1120	537(45.6) (41.9,49.7)	2.2(1.9,2.5)	<0.001	2.7(2.2,3.2)	<0.001
Group 2 (≥11years) N=740	222(22.4) (19.6,25.5)	Ref	Ref	Ref	Ref
≥45 years N=1183					
Group1 (<11 years) N=309	232(92.5) (81.3,105.2)	1.17(1.0,1.4)	0.03	1.22(1.04,1.4)	0.01
Group 2 (≥11years) N=874	607 (78.9) (72.9,85.5)	Ref	Ref	Ref	Ref

*Adjusted for baseline age and body mass index, smoking, hypertension, diabetes type 2.

Note: CI, Confidence interval; HR, Hazard ratio

Abbreviations: CKD, Chronic Kidney disease; EEE, Endogenous Estrogen Exposure.

Figures

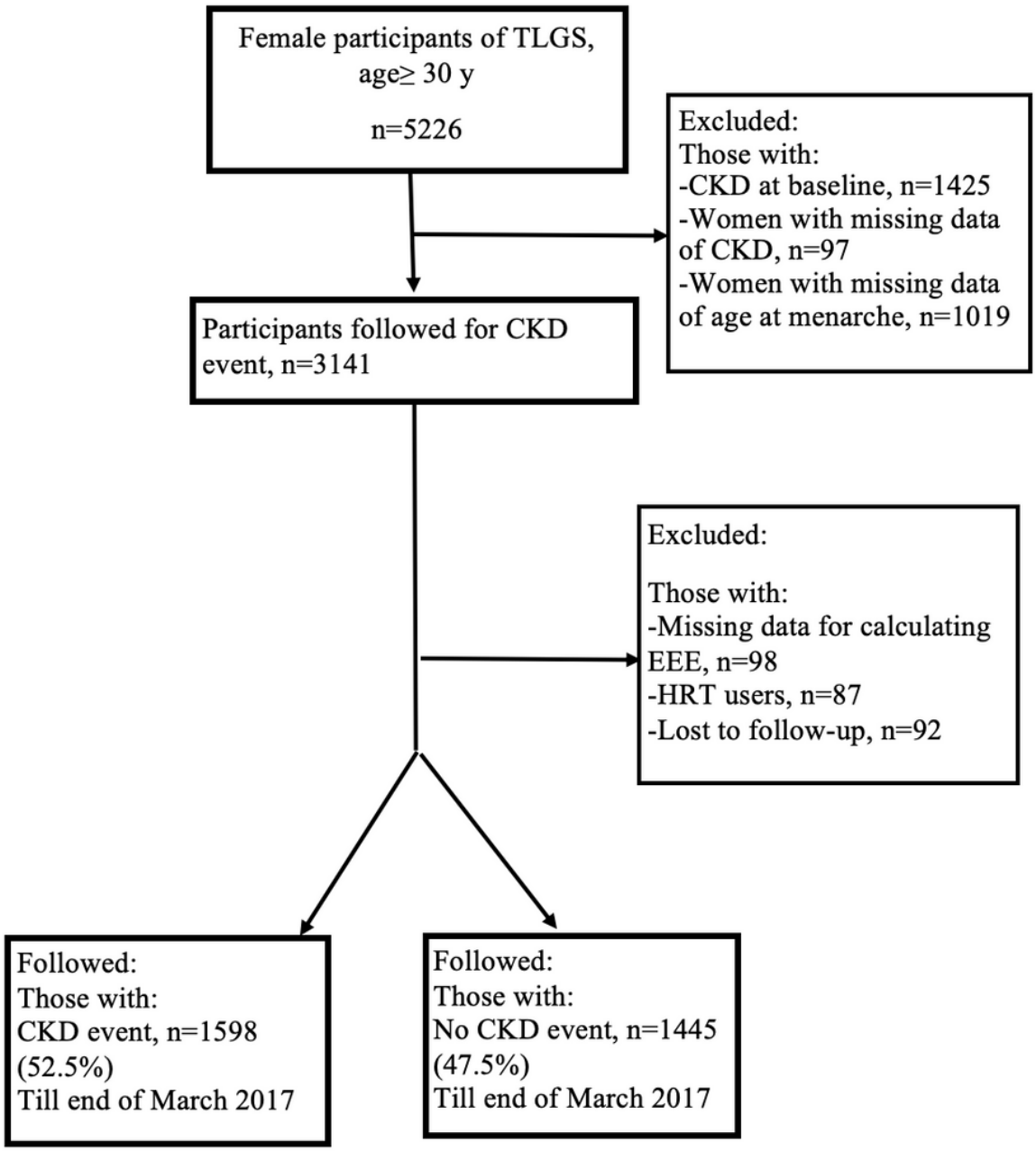

Figure 1

Study flowchart. Abbreviations: TLGS, Tehran Lipid and Glucose Study; CKD, Chronic Kidney Disease; EEE, Endogenous Estrogen Exposure; HRT, Hormone Replacement Therapy.

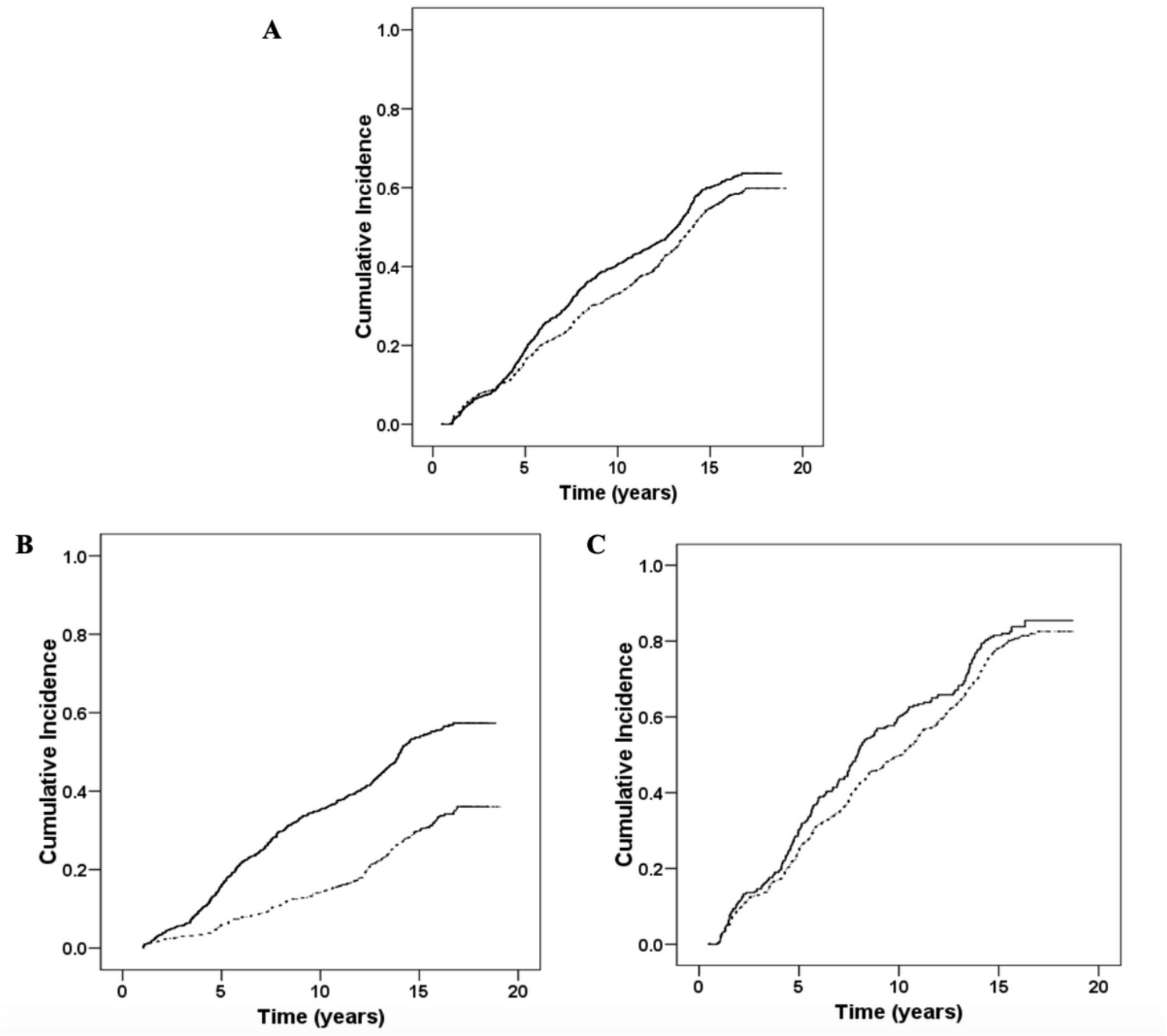

Figure 2

Kaplan-Meier cumulative estimates of incidence rates of CVD in subjects, according to the cutoff of endogenous estrogen exposure duration. A: Total of participants; B: Participants with <45 years; C: Participants with≥45 years. Note: Endogenous estrogen exposure duration<11 years (solid line), and Endogenous estrogen exposure duration≥ 11 years (dotted line).