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Association of Reproductive Lifespan Duration and Chronic Kidney Disease in Postmenopausal Women

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Abstract

Objective: To investigate the relationship between endogenous estrogen exposure and renal function, the association of female reproductive life span duration (RLD) and chronic kidney disease (CKD) was analyzed in postmenopausal women.

Patients and Methods: Data were retrieved from the Korean Genome and Epidemiology Study, which was constructed from May 1, 2001, through December 25, 2017. A total of 50,338 and 3155 postmenopausal women were each included in the cross-sectional and longitudinal analyses. The RLD was determined by subtracting the age at menarche from the age at menopause. Participants were grouped into RLD quartiles. Participants with estimated glomerular filtration rates less than 60 mL/min/1.73 m^2 were regarded to have CKD.

Results: In the cross-sectional analysis, mean ± SD age and estimated glomerular filtration rate were 56.3±4.9 years and 93.1±13.6 mL/min/1.73 m^2, respectively. Mean ± SD RLD was 34.2±4.0 years. A total of 765 of 50,338 (1.52%) women were found to have CKD. Logistic regression analysis revealed that the odds ratio for CKD was lower in groups with longer RLDs as compared with the shortest RLD group. In longitudinal analysis, postmenopausal women with normal kidney function were followed up for 9.7 years and incident CKD occurred in 221 of 3155 (7.00%) participants. Cox analysis revealed that the risk for CKD development was significantly lower in longer RLD groups. This finding was significant even after adjustments for confounding factors.

Conclusion: The risk for CKD was lower in women with longer RLDs. The amount of endogenous estrogen exposure could be a determining factor for renal function in postmenopausal women.

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Accumulating evidence has shown that female sex is associated with better renal prognosis in patients with chronic kidney disease (CKD).[1-3] Animal models of various renal diseases have shown the progression of renal injury to be more indolent in female animals than in their male counterparts.[4-6] In the general population, physiologic renal function decline is significantly slower in women than in men.[7] In addition, renal outcome has been found to be more favorable in female patients with CKD of diverse disease entities, including polycystic kidney disease and glomerulonephritis, than in male patients.[8-10] Despite these repeatedly observed sex differences in renal outcomes, the underlying mechanism has not yet been fully elucidated.

Several factors, including lifestyle, comorbid conditions, and estrogen exposure, have been proposed as potential mechanisms that could be responsible for this sex difference effect.[3] Estrogen-administered rats were found to be significantly resistant to proteinuria and glomerulosclerosis development, suggesting

For editorial comment, see page 2582

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that estrogen per se rather than the genetic difference between the sexes may yield a protective effect against progressive renal injury.[11,12] However, this possibility has rarely been demonstrated in humans.

The female reproductive life span duration (RLD), commonly regarded as the period between menarche and menopause, has been considered to correlate with the amount of endogenous estrogen exposure in several clinical investigations.[13-20] Furthermore, this length of time between menarche and menopause has been shown to be significantly related to cardiovascular risks.[13-16] Several malignancies, including breast and ovarian cancers, were also found to be associated with age at menarche and at menopause, respectively.[17,18] Recently, the development of metabolic diseases such as type 2 diabetes mellitus and osteoporosis was reported to be affected by RLD.[19,20]

Understanding the mechanism of rapid renal disease progression and identifying risk factors may lead to more effective prevention and management of kidney diseases. Therefore, to investigate whether female endogenous estrogen exposure amount is associated with decreased renal function, the relationship between RLD and CKD was analyzed in postmenopausal women using a population-based cohort.

PATIENTS AND METHODS

The present study obtained data from the Korean Genome and Epidemiology Study (KoGES), a population-based cohort study constructed from May 1, 2001, through December 25, 2017. The detailed profile and methods concerning the development of KoGES have been described previously.[21] KoGES is composed of 2 geographically distinctive cohorts, the KoGES_health examinee (HEXA) cohort and the KoGES_Ansan-Ansung cohort. The KoGES_HEXA cohort consists of participants residing in 14 metropolitan cities in Korea. The KoGES_Ansan-Ansung cohort includes participants from a medium-sized city (Ansan) and a rural area (Ansung) in Korea. Baseline data from the KoGES_HEXA cohort were used for the cross-sectional analysis. For the longitudinal analysis, the KoGES_Ansan-Ansung cohort was used. A total of 173,343 participants from the KoGES_HEXA cohort and 10,030 participants from the KoGES_Ansan-Ansung cohort were initially screened.

For this study, males, those older than 65 years, and those who were premenopausal or did not offer information about their menarche and menopausal ages were excluded. Additionally, women who had premature menopause, defined as those in whom menopause occurred at younger than than 40 years, were also excluded because these cases were more likely to involve a recall error or nonphysiologic condition such as an underlying endocrinologic problem. A total of 50,338 women from the KoGES_HEXA cohort were included in the final cross-sectional analyses (Figure 1). Participants in the KoGES_Ansan-Ansung study went through a series of health checks and surveys biannually from 2001 to 2014. Excluding participants with a baseline estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2 and without follow-up creatinine data, 3155 women were analyzed for the longitudinal analysis.

All participants were enrolled in the study voluntarily, and informed consent was obtained from all patients. This study was conducted in accordance with the Declaration of Helsinki principles and was approved by the Institutional Review Board of Yonsei University Health System Clinical Trial Center (4-2019-0858).

Anthropometric and Laboratory Data

All participants underwent a comprehensive health examination with laboratory tests and completed surveys concerning their lifestyle and health status at study entry. Menstrual status, age at menarche, and age at menopause were also surveyed. Biochemical data were determined using fasting blood samples. Proteinuria was present if results of the urine dipstick test were higher than the 1+ level. Serum creatinine level was measured using the Jaffé assay. Creatinine levels were reduced by a calibration factor of 5% for standardization to isotope-dilution mass spectrometry reference

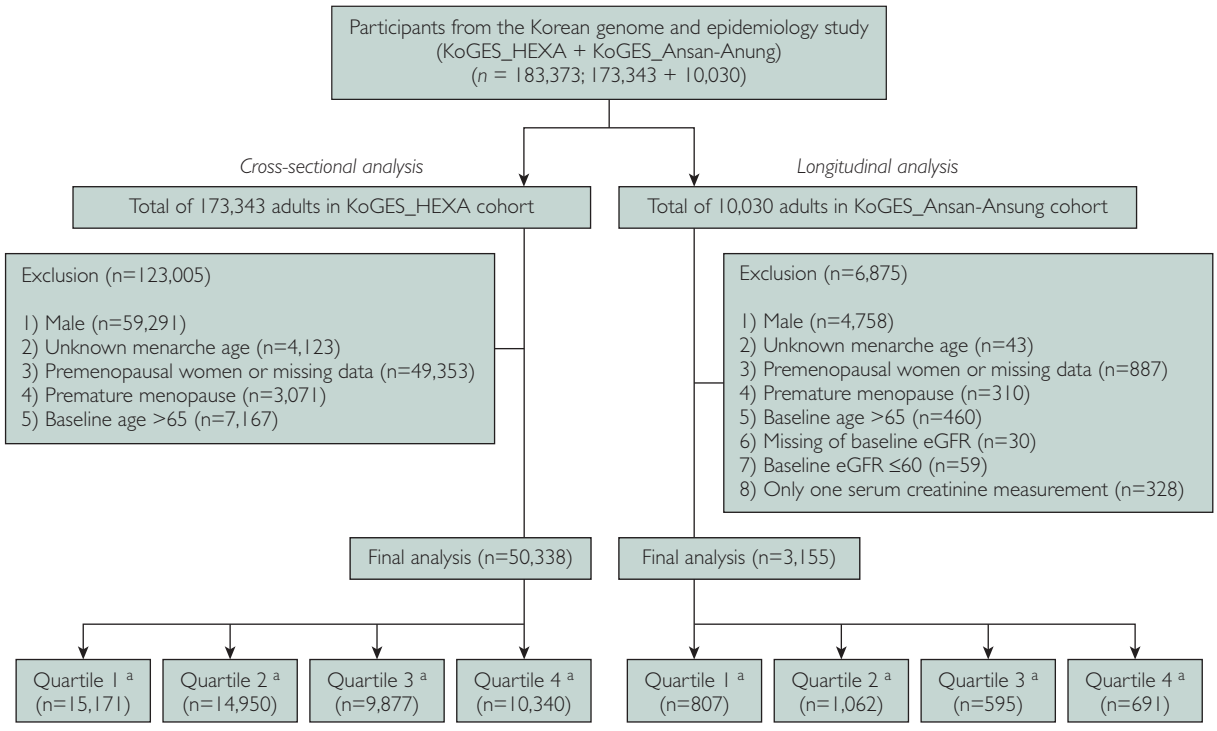

FIGURE 1. Flow diagram of the study. [a]Participants were categorized into 4 groups according to reproductive life span duration quartile. eGFR, estimated glomerular filtration rate; KoGES = Korean Genome and Epidemiology Study; KoGES_Ansan-Ansung = Korean Genome and Epidemiology Study with participants from a medium-sized city (Ansan) and a rural area (Ansung) in Korea; KoGES_HEXA = Korean Genome and Epidemiology Study_Health Examinee.

method values.[22,23] The eGFR was calculated using the Korean version of the CKD Epidemiology Collaboration equation.[24] For detailed methods, see Supplemental Methods (available online at http://www.mayoclinicproceedings.org).

Measurement of the RLD

Participants were regarded as postmenopausal when menstrual bleeding was not noted for at least 12 months, and age at menopause was defined as the age at the time of the last menstrual period. The RLD was calculated by subtracting the age at menarche from the age at menopause. Study participants were stratified into quartiles according to their RLD for analysis.

Definition of CKD

The presence of CKD was determined by definitions using eGFR only, as well as criteria considering both eGFR and proteinuria. CKD based on eGFR only was defined as eGFR less than 60 mL/min/1.73 m^2. CKD based on eGFR and proteinuria was defined as eGFR less than 60 mL/min/1.73 m^2 and/or the presence of proteinuria with protein excretion of 1+ or higher according to the urine dipstick test. For the cross-sectional analysis, only 1 measurement of eGFR and proteinuria was used. The longitudinal analysis used at least 2 consecutive results to define CKD. The CKD development time point was defined as the time when the second consecutive assessment met the CKD definition criteria.

Statistical Analyses

All statistical analyses were performed using the Stata, version 15.1 for Windows, software program (StataCorp LLC). Continuous variables are expressed as mean ± SD, and categorical variables, as absolute numbers with percentages, respectively. Comparisons

TABLE 1. Baseline Characteristics of Postmenopausal Participants Included in the Cross-Sectional Analysis Cohort[a,b]

Variables	Total (N=50,338)	Quartiles of Reproductive Lifespan Duration (y) Q1; 15-32 (n=15,171)	Q2; 33-35 (n=14,950)	Q3; 36-37 (n=9877)	Q4; 38-50 (n=10,340)	*P*
Demographic data						
Reproductive life span duration (y), mean ± SD	34.2±4.0	29.5±2.4	34.1±0.8	36.5±0.5	39.4±1.5	
Reason of menopause, no. (%)						<.001
Aging	41,779 (83.0)	9614 (63.4)	13,097 (87.6)	9228 (93.4)	9840 (95.2)	
Surgery	7802 (15.5)	5066 (33.4)	1705 (11.4)	585 (5.9)	446 (4.3)	
Radiation therapy	110 (0.2)	64 (0.4)	29 (0.2)	12 (0.1)	5 (0)	
Chemotherapy	263 (0.5)	176 (1.2)	42 (0.3)	21 (0.2)	24 (0.2)	
Age at menarche (y), mean ± SD	15.6±1.8	16.3±1.9	15.7±1.6	15.2±1.6	14.6±1.6	
Age at menopause (y), mean ± SD	49.8±3.7	45.7±2.9	49.8±1.7	51.7±1.6	54.0±2.0	
Postmenopausal period (y), mean ± SD	6.5±5.0	9.3±5.8	6.1±4.5	4.9±3.8	4.2±3.2	
Age (y), mean ± SD	56.3±4.9	55.1±5.8	55.9±4.7	56.6±4.1	58.3±3.7	<.001
Body mass index, (kg/m^2), mean ± SD	24.0±2.9	23.9±3.0	23.8±2.9	24.0±2.9	24.3±2.9	<.001
Systolic blood pressure (mm Hg), mean ± SD	123.1±15.4	122.4±15.4	122.5±15.2	123.5±15.5	124.8±15.4	<.001
Diastolic blood pressure (mm Hg), mean ± SD	76.1±9.7	75.7±9.7	75.8±9.7	76.3±9.7	76.9±9.5	<.001
Educational level, no. (%)						<.001
Low	13,907 (27.6)	4700 (31.0)	4067 (27.2)	2532 (25.6)	2608 (25.2)	
Intermediate	28,508 (56.6)	8391 (55.3)	8669 (58.0)	5752 (58.2)	5696 (55.1)	
High	7336 (14.6)	1884 (12.4)	2037 (13.6)	1487 (15.1)	1928 (18.6)	
Income level, no. (%)						<.001
Low	13,035 (25.9)	4054 (26.7)	3785 (25.3)	2456 (24.9)	2740 (26.5)	
Intermediate	15,711 (31.2)	4597 (30.3)	4806 (32.1)	3064 (31.0)	3244 (31.4)	
High	14,869 (29.5)	4300 (28.3)	4394 (29.4)	3101 (31.4)	3074 (29.7)	
Marriage, ever, no. (%)	49,546 (98.4)	14,921 (98.4)	14,707 (98.4)	9734 (98.6)	10,184 (98.5)	.66
No. of children, mean ± SD	2.4±1.0	2.4±1.0	2.4±0.9	2.4±0.9	2.5±1.0	<.001
Drinking history, ever, no. (%)	13,832 (27.5)	4364 (28.8)	4192 (28.0)	2711 (27.4)	2565 (24.8)	<.001
Smoking history, ever, no. (%)	923 (1.8)	334 (2.2)	277 (1.9)	157 (1.6)	155 (1.5)	<.001
Comorbid conditions, no. (%)						
Hypertension	11,701 (23.2)	3270 (21.6)	3241 (21.7)	2286 (23.1)	2904 (28.1)	<.001
Diabetes mellitus	4762 (9.5)	1428 (9.4)	1329 (8.9)	909 (9.2)	1096 (10.6)	<.001
Cardiovascular disease[c]	1758 (3.5)	550 (3.6)	469 (3.1)	337 (3.4)	402 (3.9)	.01
Laboratory parameters, mean ± SD						
Serum urea nitrogen (mg/dL)	14.7±3.9	14.6±4.0	14.7±3.9	14.7±3.7	14.9±3.9	<.001
Creatinine (mg/dL)	0.7±0.2	0.7±0.2	0.7±0.2	0.7±0.2	0.7±0.2	.03
eGFR (mL/min/1.73 m^2)	93.1±13.6	93.7±14.1	93.5±13.6	93.1±13.1	91.8±13.3	<.001
Glycated hemoglobin (%)	5.8±0.7	5.8±0.7	5.8±0.7	5.8±0.7	5.9±0.7	<.001
Total cholesterol (mg/dL)	206.5±36.3	204.7±36.6	206.5±35.8	207.3±36.4	208.3±36.6	<.001
High-density lipoprotein cholesterol (mg/dL)	55.5±12.8	55.5±12.8	55.6±12.9	55.7±12.9	55.1±12.8	.004
Triglycerides (mg/dL)	123.6±78.6	122.6±78.9	123.1±77.8	122.6±78.5	126.8±79.3	<.001
Hemoglobin (g/dL)	13.3±0.9	13.3±1.0	13.3±0.9	13.3±0.9	13.4±1.0	.14
Albumin (g/dL)	4.6±0.3	4.6±0.3	4.6±0.3	4.6±0.3	4.6±0.3	.52
High-sensitivity C-reactive protein (mg/dL)	0.1±0.4	0.1±0.4	0.1±0.4	0.1±0.5	0.1±0.3	.87

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TABLE 1. Continued

Variables	Total (N=50,338)	Quartiles of Reproductive Lifespan Duration (y) Q1; 15-32 (n=15,171)	Q2; 33-35 (n=14,950)	Q3; 36-37 (n=9877)	Q4; 38-50 (n=10,340)	*P*
Medication history, no. (%)						
Oral contraceptives, ever	10,257 (20.4)	3068 (20.2)	2989 (20.0)	2036 (20.6)	2164 (20.9)	.27
Postmenopausal hormone therapy						<.001
Past	9761 (19.4)	3341 (22.0)	2962 (19.8)	1744 (17.7)	1669 (16.1)	
Current	3317 (6.6)	1233 (8.1)	1038 (6.9)	568 (5.8)	478 (4.6)	

[a]eGFR = estimated glomerular filtration rate; Q = quartile.
[b]SI conversion factors: To convert cholesterol values to mmol/L, multiply by 0.0259; to convert triglyceride values to mmol/L, multiply by 0.0113; to convert albumin values to g/L, multiply by 10.
[c]History of cardiovascular accident was defined as the composite of coronary artery disease and/or cerebrovascular accident.

between groups were performed using Student *t* test or analysis of variance for continuous variables and χ^2 test or Fisher exact test for categorical variables. The Kolmogorov-Smirnov test was performed to determine the normality of the distribution of the parameters. If the resulting data did not show a normal distribution, median and interquartile range were reported; Mann-Whitney *U* test or Kruskal-Wallis test was used for comparing the groups.

Logistic regression analyses were performed to determine the independent relationship of RLD with CKD in the cross-sectional analysis. Restricted cubic spline curves were depicted for logistic regression models. Each of the 5 knots was placed at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles of RLD, according to the recommended percentiles of Harrell.[25] The reference point of RLD was 30 years, which was the median RLD of quartile 1. Each 1 percentile of upper and lower RLD was eliminated to reduce distortion. Cox proportional hazard analyses were performed to determine the independent relationship of RLD with incident CKD development. Cumulative kidney survival rates were estimated using Kaplan-Meier analysis. Multivariable models were constructed for adjusting confounding factors. Variables that showed statistical significance ($P<.05$) in univariate analysis or have clinical significance were included in multivariable models. For all analyses, $P<.05$ was considered to be statistically significant.

RESULTS

Baseline Characteristics

Baseline characteristics of the postmenopausal women included in the cross-sectional analysis are described in Table 1. Mean ± SD age and RLD of participants were 56.3±4.9 and 34.2±4.0 years, respectively. Additionally, mean ± SD eGFR was 93.1±13.6 mL/min/1.73 m^2.

Stratification into quartiles was performed according to RLD. Mean age tended to be increased in women with longer RLDs ($P<.001$). In the shortest RLD quartile, more participants experienced menopause due to causes other than aging, including especially due to surgery ($P<.001$). Comorbid conditions such as hypertension ($P<.001$) and diabetes mellitus ($P<.001$) were more frequent in the longest RLD quartile. Mean eGFR ($P<.001$), mean glycated hemoglobin ($P<0.001$), total cholesterol ($P<.001$), high-density lipoprotein cholesterol ($P=.004$), and triglyceride levels ($P<.001$) were statistically significantly different among the quartiles, but differences were not large. Both past and current use of postmenopausal hormone therapy were more frequent in quartiles with shorter RLDs ($P<.001$). The pairwise comparison results between the groups are

TABLE 2. Logistic Regression Analysis of the Association Between RLD and Prevalent CKD[a,b]

	Model 1		Model 2		Model 3		Model 4	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
CKD based on eGFR only								
Linear[c]	0.90 (0.84-0.96)	.002	0.90 (0.84-0.97)	.003	0.90 (0.84-0.96)	.003	0.89 (0.82-0.97)	.01
Q1	Reference		Reference		Reference		Reference	
Q2	0.81 (0.68-0.97)	.02	0.83 (0.69-1.00)	.05	0.84 (0.70-1.01)	.07	0.83 (0.67-1.03)	.10
Q3	0.63 (0.51-0.78)	<.001	0.64 (0.51-0.80)	<.001	0.64 (0.51-0.80)	<.001	0.63 (0.49-0.82)	<.001
Q4	0.72 (0.59-0.88)	.001	0.73 (0.60-0.89)	.002	0.72 (0.59-0.88)	.001	0.67 (0.53-0.84)	.001
CKD based on eGFR and proteinuria								
Linear[c]	0.91 (0.87-0.95)	<.001	0.91 (0.87-0.96)	<.001	0.91 (0.87-0.96)	<.001	0.94 (0.88-0.99)	.02
Q1	Reference		Reference		Reference		Reference	
Q2	0.86 (0.76-0.97)	.01	0.87 (0.77-0.98)	.02	0.89 (0.78-1.00)	.06	0.92 (0.80-1.06)	.26
Q3	0.80 (0.70-0.92)	.002	0.81 (0.70-0.93)	.003	0.82 (0.71-0.95)	.01	0.87 (0.74-1.03)	.11
Q4	0.76 (0.67-0.88)	<.001	0.77 (0.67-0.89)	<.001	0.77 (0.66-0.88)	<.001	0.77 (0.65-0.91)	.003

[a]CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; OR = odds ratio; Q = quartile; RLD = reproductive life span duration.
[b]N=50,338. Model 1 adjusted for age; model 2, model 1 plus number of children; model 3, model 2 plus history of hypertension and diabetes mellitus; and model 4, model 3 plus body mass index, high-density lipoprotein cholesterol level, triglyceride level, high-sensitivity C-reactive protein level, levels of education and income, and history of smoking.
[c]ORs for linear variable is per 1-SD change in RLD.

presented in Supplemental Table 1 (available online at http://www.mayoclinicproceedings.org).

Prevalence of CKD

With respect to each RLD quartile, CKD based on eGFR only was found in 263 of 15,171 (1.73%), 218 of 14,950 (1.46%), 118 of 9877 (1.19%), and 166 of 10,340 (1.60%) participants , respectively. Women with CKD based on the eGFR and proteinuria definition numbered 574 of 15,171 (3.78%), 500 of 14,950 (3.34%), 319 of 9877 (3.23%), and 342 of 10,340 (3.31%), respectively. The adjusted rate of CKD prevalence tended to decrease in quartiles with longer RLDs (*P* for trend <.001; Supplemental Figure, available online at http://www.mayoclinicproceedings.org).

Association of RLD With CKD Prevalence

Logistic regression models revealed that the odds ratios (ORs) of CKD based on eGFR only were lower in the third (OR, 0.63; 95% CI, 0.49-0.82) and fourth (OR, 0.67; 95% CI, 0.53-0.84) RLD quartiles vs the quartile with the shortest RLD after adjustments were made for confounding factors. In addition, when RLD was considered as a continuous variable, the OR of CKD was significantly decreased with longer RLD values (OR, 0.89; 95% CI, 0.82-0.97). A similar finding was also observed when CKD was defined based on eGFR and proteinuria criteria (Table 2). When the adjusted ORs for prevalent CKD according to RLD were depicted as cubic spline curves, the OR of CKD gradually decreased with the increase of RLD (Figure 2).

The relationship between RLD and prevalent CKD was further explored in a series of sensitivity analyses that yielded results consistent with those of the main analyses (Supplemental Tables 2-4, available online at http://www.mayoclinicproceedings.org).

Association of RLD With Incident CKD Development

To further validate the association between kidney function and RLD, the risk of RLD on incident CKD development was evaluated in a longitudinal analysis. Baseline characteristics of the longitudinal analysis cohort are shown in Supplemental Table 5 (available online at http://www.mayoclinicproceedings.org).

During a mean follow-up of 9.7 years, incident CKD based on eGFR only and eGFR and proteinuria occurred in 221

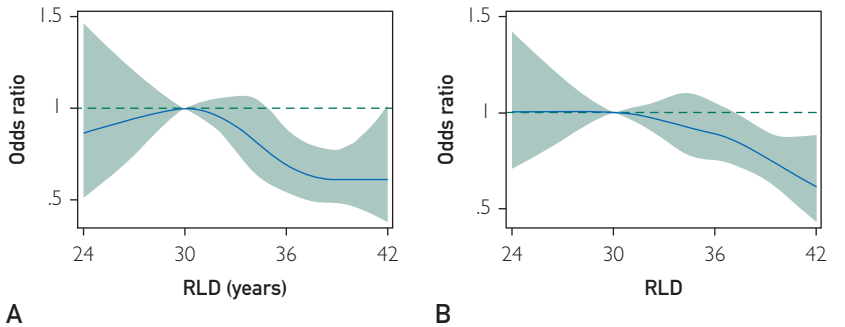

FIGURE 2. Cubic spline curves for chronic kidney disease prevalence according to reproductive life span duration (RLD). Plots for decreased renal function based on (A) estimated glomerular filtration rate (eGFR) only and (B) eGFR and proteinuria. Shaded area represents 95% CIs. Adjustments were made for age, number of children, history of hypertension, history of diabetes mellitus, body mass index, high-density lipoprotein cholesterol level, triglyceride level, high-sensitivity C-reactive protein level, levels of education and income, and history of smoking. A reference point was created at 30 years of RLD, which was the median RLD of the shortest RLD quartile.

(7.00%) and 234 (7.42%) of 3155 participants, respectively. The corresponding incident rates of CKD for each RLD quartile were 9.5, 7.6, 5.2, and 4.9 per 1000 person-years, based on the eGFR only definition. According to the eGFR and proteinuria definition, incident rates of CKD for the RLD quartiles were 10.3, 7.9, 5.2, and 5.5 per 1000 person-years, respectively.

When Cox proportional hazard regression analysis was performed, the risk for incident CKD development was significantly lower in those in the third (hazard ratio [HR], 0.62; 95% CI, 0.40 to 0.96) and fourth (HR, 0.47; 95% CI, 0.30 to 0.74) RLD quartiles compared with those in the shortest RLD quartile. Similar findings were also observed when CKD was defined based on eGFR and proteinuria criteria (Table 3). Kaplan-Meier curves showed that time to development of incident CKD was significantly longer in those with longer RLDs compared with the group with the shortest RLD (Figure 3). The association between RLD and incident CKD development was further evaluated in a series of sensitivity analyses that showed results consistent with those of the main analyses (Supplemental Tables 6 and 7, available online at http://www.mayoclinicproceedings.org).

DISCUSSION

In this study, the relationship between RLD and CKD was investigated in a population-based cohort of postmenopausal women. The odds for prevalent CKD and risk for incident CKD development were lower in women with longer RLDs than in those with the shortest RLDs. These relationships were significant even after adjustments for confounding factors, including lifestyle factors and comorbid conditions that affect renal function. These findings suggest that longer exposure to endogenous estrogen, which would correlate with a shorter duration of estrogen deficiency, may be associated with a lower possibility of kidney damage.

Previous investigations have shown that iatrogenic changes made to estrogen exposure amounts could affect kidney function. A recent cohort study of women who underwent bilateral oophorectomy before the onset of menopause revealed that the risk for incident CKD was higher vs in an age-matched group that did not undergo oophorectomy, suggesting that the premature depletion of endogenous estrogen due to surgical procedures could accelerate the deterioration in kidney function.[26] However, observational studies evaluating the effect of

TABLE 3. Cox Proportional Hazard Model of the Association Between RLD and Incident CKD Development[a,b]

	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
CKD based on eGFR only								
Linear[c]	0.87 (0.77-0.92)	.02	0.87 (0.77-0.98)	.02	0.86 (0.76-0.97)	.01	0.83 (0.74-0.94)	.004
Q1	Reference		Reference		Reference		Reference	
Q2	0.96 (0.70-1.30)	.78	0.96 (0.71-1.31)	.80	0.95 (0.70-1.29)	.74	0.93 (0.68-1.27)	.63
Q3	0.66 (0.43-1.02)	.06	0.66 (0.43-1.03)	.07	0.65 (0.42-1.00)	.05	0.62 (0.40-0.96)	.03
Q4	0.53 (0.35-0.82)	.01	0.54 (0.35-0.83)	.01	0.52 (0.33-0.80)	.003	0.47 (0.30-0.74)	.001
CKD based on eGFR and proteinuria								
Linear[c]	0.87 (0.77-0.97)	.02	0.87 (0.77-0.98)	.02	0.85 (0.76-0.96)	.01	0.83 (0.74-0.94)	.002
Q1	Reference		Reference		Reference		Reference	
Q2	0.90 (0.67-1.21)	.49	0.90 (0.67-1.22)	.50	0.89 (0.66-1.19)	.43	0.87 (0.64-1.18)	.38
Q3	0.60 (0.39-0.92)	.02	0.60 (0.39-0.92)	.02	0.58 (0.38-0.90)	.02	0.56 (0.36-0.87)	.01
Q4	0.54 (0.36-0.81)	.003	0.54 (0.36-0.82)	.004	0.52 (0.34-0.78)	.002	0.47 (0.31-0.72)	.001

[a]CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HR = hazard ratio; KoGES = Korean Genome and Epidemiology Study; Q = quartile; RLD = reproductive life span duration.

[b]N=3,155. Model 1 adjusted for age; model 2, model 1 plus history of pregnancy (data regarding number of children were not available in the longitudinal KoGES_Ansan-Ansung cohort); model 3, model 2 plus history of hypertension and diabetes mellitus; and model 4, model 3 plus body mass index, high-density lipoprotein cholesterol level, triglyceride level, high-sensitivity C-reactive protein level, levels of education and income, and history of smoking.

[c]HRs for linear variable is per 1-SD change in RLD.

hormone therapy on kidney function have shown conflicting results. A 5-year follow-up of postmenopausal women reported that those who received hormone therapy were at lower risk for developing albuminuria.[27] However, a different study of 5845 women indicated that hormone therapy was associated with a greater decline in eGFR during a 2-year study period.[28] These inconsistent results could be because these previous studies did not take into account the amount of endogenous estrogen exposure. In addition, estrogen may have different effects depending on its types (endogenous/exogenous) and the consequence of estrogen exposure may also vary regarding to the site of action in the kidney.[29] The results of the present study propose that lifetime endogenous estrogen exposure amount, represented by RLD, may be a significant factor affecting kidney function. Evaluations excluding the possibilities of external factors

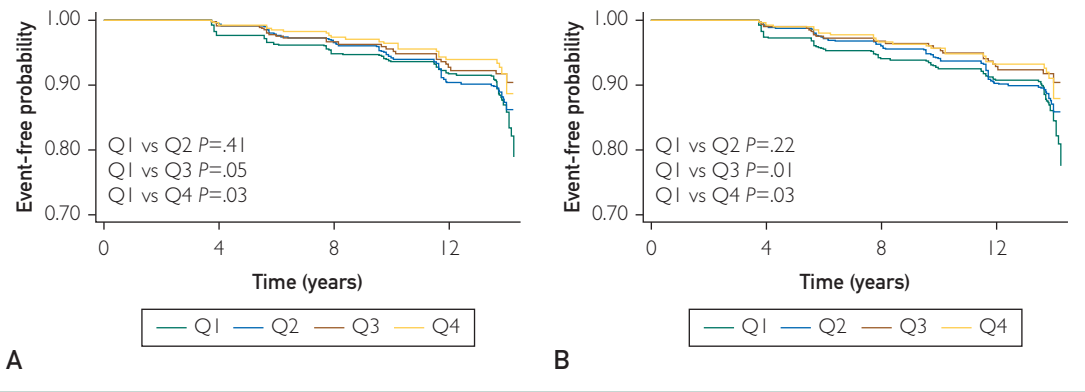

FIGURE 3. Kaplan-Meier curves of incident chronic kidney disease (CKD) development according to reproductive life span duration. Plots for CKD based on (A) estimated glomerular filtration rate (eGFR) only and (B) eGFR and proteinuria. *P* values were derived from pairwise log-rank tests. Q = quartile.

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that could affect estrogen exposure amount, such as surgery-related menopause and hormone therapy history, also revealed a clear association, further suggesting a significant role of endogenous estrogen exposure amount on kidney function.

Although the contribution of sex to disease progression has been repeatedly observed in various types of renal diseases, the precise mechanisms have not been fully understood. Although some studies have suspected direct effects of sex hormones, others have proposed factors associated with sex differences, such as lifestyle.[3,18,30,31] Previous clinical studies comparing renal outcomes between men and women could not fully dissect the effects of these sex-related lifestyle factors from hormonal effects. This is because most potential lifestyle factors that could affect renal function vary widely between sexes. Commonly, the amounts of calories and protein consumed differ between men and women.[32] In addition, smoking is more common among men than among women in certain cultural regions.[33]

In this study, by evaluating the effect of lifetime endogenous estrogen exposure in women, the influence of sex-related lifestyle factors could be somewhat excluded. In addition, extensive adjustments, which included lifestyle factors such as smoking history and socioeconomic factors, further support the possibility of estrogen playing a protective role against renal disease development. Some animal studies investigating the mechanism of sex differences in renal disease development have also suggested the presence of testosterone rather than the absence of estrogen to be the main cause of this sex dimorphism.[34,35] The results of this study propose that even without the effects of testosterone, less lifetime estrogen exposure could have an influence on renal function.

Several molecular mechanisms could be considered as explanations for the reduction in the prevalent CKD risk found in women with longer RLDs. Recent investigations have reported that the receptors for estrogen are found not only in reproductive organs but also in other solid organs, such as the brain, liver, and kidneys, suggesting a direct effect of estrogen acting as a ligand.[36] Activation of the estrogen receptor α in the renal vasculature was found to activate nitric oxide synthase through a phosphoinositide 3 kinase—Akt—dependent pathway.[37,38] In addition, activation of the estrogen receptor β was found to attenuate the inflammatory responses induced by tumor necrosis factor α in vascular smooth muscle cells.[39] Direct effects on glomerular cells have also been suggested. In an animal experiment with cultured rat mesangial cells, treatment with 17 β-estradiol inhibited mesangial cell proliferation and collagen synthesis.[40] In addition, in podocytes, treatment with 17 β-estradiol decreased transforming growth factor β expression and increased the estrogen receptor subtype β, suggesting that estrogen may provide protective effects by directly acting on renal cells.[41] Another possibility is the possible contribution of estrogen-induced epigenetic changes. A recent study showed that 17 β-estradiol attenuates angiotensin II—induced H3 acetylation in the aorta and investigations proving the involvement of microRNAs in estrogen-related vascular biology support the probability of epigenetic changes playing a role.[42-44] Moreover, because shorter RLDs are linked with longer durations of estrogen deficiency, the findings of the study may suggest a harmful effect of estrogen deficiency rather than a protective role of estrogen. Further evaluations would be needed to elucidate clearly whether these possibilities have significant biomolecular applications.

This study has several limitations. First, because ages at menarche and menopause relied on self-reporting, there is a possibility that the ages given for these events could be inaccurate. However, studies have shown that the recall of menarche is generally well reported, showing that 80% to 90% of women accurately recall their age at menarche, with an error range within a year.[45] In addition, previous studies have reported self-reporting of menopause to be in satisfactory agreement with gynecology medical reports.[46-49] Nonetheless, the possibility of recall bias should be recognized.

Second, an inverse causal-effect relationship between RLD and CKD could be probable in the cross-sectional analysis. As suggested by Cheung et al,[30] even slight decreases in eGFR may be capable of inducing early menopause. However, results of the longitudinal analysis showing that RLD has an effect on incident CKD development among women with normal kidney function strengthens the probability of a causal association.

Third, using only single measurements of eGFR and proteinuria in the cross-sectional analyses to define CKD would also be a limitation. Further evaluations more accurately discerning CKD would be necessary. Last, medication histories that could affect renal function, such as renin-angiotensin-aldosterone system blockage, diuretics, or nonsteroidal anti-inflammatory drug use, were unobtainable. Investigations taking these factors into consideration would be needed.

CONCLUSION

The CKD prevalence and incidence were significantly associated with RLD. Assuming that RLD is closely correlated with the total amount of endogenous estrogen exposure, the results indicate that the amount of endogenous estrogen exposure is closely associated with CKD risk in postmenopausal women. Further investigations are needed to understand the pathophysiologic mechanism of this phenomenon fully.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **CKD** = chronic kidney disease; **eGFR** = estimated glomerular filtration rate; **HR** = hazard ratio; **KoGES** = Korean Genome and Epidemiology Study; **KoGES_Ansan-Ansung** = participants in Korean Genome and Epidemiology Study from a medium-sized city (Ansan) and a rural area (Ansung) in Korea; **KoGES_HEXA** = Korean Genome and Epidemiology Study_Health Examinee; **OR** = odds ratio; **Q** = quartile; **RLD** = reproductive life span duration

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REFERENCES

1. Grams ME, Yang W, Rebholz CM, et al; on behalf of the CRIC Study Investigators. Risks of adverse events in advanced CKD: the Chronic Renal Insufficiency Cohort (CRIC) Study. *Am J Kidney Dis*. 2017;70(3):337-346.
2. Cobo G, Hecking M, Port FK, et al. Sex and gender differences in chronic kidney disease: progression to end-stage renal disease and haemodialysis. *Clin Sci (Lond)*. 2016;130(14):1147-1163.
3. Neugarten J, Golestaneh L. Gender and the prevalence and progression of renal disease. *Adv Chronic Kidney Dis*. 2013;20(5):390-395.
4. Elema JD, Arends A. Focal and segmental glomerular hyalinosis and sclerosis in the rat. *Lab Invest*. 1975;33(5):554-561.
5. Lemos CC, Mandarim-de-Lacerda CA, Dorigo D, Coimbra TM, Bregman R. Chronic renal failure in male and female rats. *J Nephrol*. 2005;18(4):368-373.
6. Kang KP, Lee JE, Lee AS, et al. Effect of gender differences on the regulation of renal ischemia-reperfusion-induced inflammation in mice. *Mol Med Rep*. 2014;9(6):2061-2068.
7. Berg UB. Differences in decline in GFR with age between males and females. Reference data on clearances of inulin and PAH in potential kidney donors. *Nephrol Dial Transplant*. 2006;21(9):2577-2582.
8. Neugarten J, Acharya A, Silbiger SR. Effect of gender on the progression of nondiabetic renal disease: a meta-analysis. *J Am Soc Nephrol*. 2000;11(2):319-329.

9. Iseki K, Iseki C, Ikemiya Y, Fukiyama K. Risk of developing end-stage renal disease in a cohort of mass screening. *Kidney Int*. 1996;49(3):800-805.
10. Su S-L, Lin C, Kao S, et al. Risk factors and their interaction on chronic kidney disease: a multi-centre case control study in Taiwan. *BMC Nephrol*. 2015;16(1):83.
11. Maric C, Sandberg K, Hinojosa-Laborde C. Glomerulosclerosis and tubulointerstitial fibrosis are attenuated with 17beta-estradiol in the aging Dahl salt sensitive rat. *J Am Soc Nephrol*. 2004;15(6):1546-1556.
12. Antus B, Hamar P, Kokeny G, et al. Estradiol is nephroprotective in the rat remnant kidney. *Nephrol Dial Transplant*. 2003;18(1):54-61.
13. Cui R, Iso H, Toyoshima H, et al; JACC Study Group. Relationships of age at menarche and menopause, and reproductive year with mortality from cardiovascular disease in Japanese postmenopausal women: the JACC study. *J Epidemiol*. 2006;16(5):177-184.
14. Feng Y, Hong X, Wilker E, et al. Effects of age at menarche, reproductive years, and menopause on metabolic risk factors for cardiovascular diseases. *Atherosclerosis*. 2008;196(2):590-597.
15. Qiu C, Chen H, Wen J, et al. Associations between age at menarche and menopause with cardiovascular disease, diabetes, and osteoporosis in Chinese women. *J Clin Endocrinol Metab*. 2013;98(4):1612-1621.
16. Jacobsen BK, Knutsen SF, Fraser GE. Age at natural menopause and total mortality and mortality from ischemic heart disease: the Adventist Health Study. *J Clin Epidemiol*. 1999;52(4):303-307.
17. Jung KJ, Park C, Yun YD, Jee SH. Duration of ovarian hormone exposure and gynecological cancer risk in Korean women: the Korean Heart Study. *Cancer Epidemiol*. 2016;41:1-7.
18. Kummer S, von Gersdorff G, Kemper MJ, Oh J. The influence of gender and sexual hormones on incidence and outcome of chronic kidney disease. *Pediatr Nephrol*. 2012;27(8):1213-1219.
19. Brand JS, van der Schouw YT, Onland-Moret NC, et al; InterAct Consortium. Age at menopause, reproductive life span, and type 2 diabetes risk: results from the EPIC-InterAct study. *Diabetes Care*. 2013;36(4):1012-1019.
20. Kim SH, Sim MY, Park SB. Association between duration of reproductive lifespan and Framingham risk score in postmenopausal women. *Maturitas*. 2015;82(4):431-435.
21. Kim Y, Han BG; KoGES group. Cohort profile: the Korean Genome and Epidemiology Study (KoGES) Consortium [published erratum for Cohort Profile: The Korean Genome and Epidemiology Study (KoGES) Consortium. *Int J Epidemiol*. 2017]. *Int J Epidemiol*. 2017;46(4):1350.
22. Matsushita K, Mahmoodi BK, Woodward M, et al; Chronic Kidney Disease Prognosis Consortium. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. *JAMA*. 2012;307(18):1941-1951.
23. Levey AS, Coresh J, Greene T, et al; Chronic Kidney Disease Epidemiology Collaboration. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem*. 2007;53(4):766-772.
24. Jeong TD, Lee W, Yun YM, Chun S, Song J, Min WK. Development and validation of the Korean version of CKD-EPI equation to estimate glomerular filtration rate. *Clin Biochem*. 2016;49(9):713-719.
25. Harrell FE Jr. *Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis*. Cham, Switzerland: Springer; 2015.
26. Kattah AG, Smith CY, Gazzuola Rocca L, Grossardt BR, Garovic VD, Rocca WA. CKD in patients with bilateral oophorectomy. *Clin J Am Soc Nephrol*. 2018;13(11):1649-1658.
27. Agarwal M, Selvan V, Freedman BI, Liu Y, Wagenknecht LE. The relationship between albuminuria and hormone therapy in postmenopausal women. *Am J Kidney Dis*. 2005;45(6):1019-1025.
28. Ahmed SB, Culleton BF, Tonelli M, et al; Alberta Kidney Disease Network. Oral estrogen therapy in postmenopausal women is associated with loss of kidney function. *Kidney Int*. 2008;74(3):370-376.
29. Ahmed SB, Ramesh S. Sex hormones in women with kidney disease. *Nephrol Dial Transplant*. 2016;31(11):1787-1795.
30. Gluhovschi G, Gluhovschi A, Anastasiu D, Petrica L, Gluhovschi C, Velciov S. Chronic kidney disease and the involvement of estrogen hormones in its pathogenesis and progression. *Rom J Intern Med*. 2012;50(2):135-144.
31. Brown LJ, Clark PC, Armstrong KA, Liping Z, Dunbar SB. Identification of modifiable chronic kidney disease risk factors by gender in an African-American metabolic syndrome cohort. *Nephrol Nurs J*. 2010;37(2):133-141. 148; quiz 142.
32. Berryman CE, Lieberman HR, Fulgoni VL 3rd, Pasiakos SM. Protein intake trends and conformity with the Dietary Reference Intakes in the United States: analysis of the National Health and Nutrition Examination Survey, 2001-2014. *Am J Clin Nutr*. 2018;108(2):405-413.
33. Jarvis MJ, Giovino GA, O'Connor RJ, Kozlowski LT, Bernert JT. Variation in nicotine intake among U.S. cigarette smokers during the past 25 years: evidence from NHANES surveys. *Nicotine Tob Res*. 2014;16(12):1620-1628.
34. Elliot SJ, Berho M, Korach K, et al. Gender-specific effects of endogenous testosterone: female alpha-estrogen receptor-deficient C57Bl/6J mice develop glomerulosclerosis. *Kidney Int*. 2007;72(4):464-472.
35. Metcalfe PD, Leslie JA, Campbell MT, Meldrum DR, Hile KL, Meldrum KK. Testosterone exacerbates obstructive renal injury by stimulating TNF-alpha production and increasing proapoptotic and profibrotic signaling. *Am J Physiol Endocrinol Metab*. 2008;294(2):E435-E443.
36. Eyster KM. The estrogen receptors: an overview from different perspectives. *Methods Mol Biol*. 2016;1366:1-10.
37. Nevzati E, Shafighi M, Bakhtian KD, Treiber H, Fandino J, Fathi AR. Estrogen induces nitric oxide production via nitric oxide synthase activation in endothelial cells. *Acta Neurochir Suppl*. 2015;120:141-145.
38. Haynes MP, Sinha D, Russell KS, et al. Membrane estrogen receptor engagement activates endothelial nitric oxide synthase via the PI3-kinase-Akt pathway in human endothelial cells. *Circ Res*. 2000;87(8):677-682.
39. Xing D, Feng W, Miller AP, et al. Estrogen modulates TNF-alpha-induced inflammatory responses in rat aortic smooth muscle cells through estrogen receptor-beta activation. *Am J Physiol Heart Circ Physiol*. 2007;292(6):H2607-H2612.
40. Kwan G, Neugarten J, Sherman M, et al. Effects of sex hormones on mesangial cell proliferation and collagen synthesis. *Kidney Int*. 1996;50(4):1173-1179.
41. Catanuto P, Doublier S, Lupia E, et al. 17 Beta-estradiol and tamoxifen upregulate estrogen receptor beta expression and control podocyte signaling pathways in a model of type 2 diabetes. *Kidney Int*. 2009;75(11):1194-1201.
42. Bendale DS, Karpe PA, Chhabra R, Shete SP, Shah H, Tikoo K. 17-β Oestradiol prevents cardiovascular dysfunction in post-menopausal metabolic syndrome by affecting SIRT1/AMPK/H3 acetylation. *Br J Pharmacol*. 2013;170(4):779-795.
43. Zhao J, Imbrie GA, Baur WE, et al. Estrogen receptor-mediated regulation of microRNA inhibits proliferation of vascular smooth muscle cells. *Arterioscler Thromb Vasc Biol*. 2013;33(2):257-265.
44. Pérez-Cremades D, Mompeón A, Vidal-Gómez X, Hermenegildo C, Novella S. miRNA as a new regulatory mechanism of estrogen vascular action. *Int J Mol Sci*. 2018;19(2):473.

45. Lundblad MW, Jacobsen BK. The reproducibility of self-reported age at menarche: the Tromso Study. *BMC Womens Health*. 2017;17(1):62.
46. Clavel-Chapelon F, Dormoy-Mortier N. A validation study on status and age of natural menopause reported in the E3N cohort. *Maturitas*. 1998;29(2):99-103.
47. Den Tonkelaar I. Validity and reproducibility of self-reported age at menopause in women participating in the DOM-project. *Maturitas*. 1997;27(2):117-123.
48. Colditz GA, Stampfer MJ, Willett WC, et al. Reproducibility and validity of self-reported menopausal status in a prospective cohort study. *Am J Epidemiol*. 1987;126(2):319-325.
49. Cho GJ, Park HT, Shin JH, et al. Age at menarche in a Korean population: secular trends and influencing factors. *Eur J Pediatr*. 2010;169(1):89-94.
50. Cheung KL, Stefanick ML, Allison MA, et al. Menopausal symptoms in women with chronic kidney disease. *Menopause*. 2015;22(9):1006-1011.