The risk of chronic kidney disease among women with polycystic ovary syndrome: A long-term population-based cohort study

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Title Page

The risk of chronic kidney disease among women with polycystic ovary syndrome: A long-term population-based cohort study

Short running title: CKD risk in PCOS

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SBG: Project development, Data analysis, Manuscript writing

MA: Data collection, Critical discussion, Manuscript writing

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Summary

Background and Objective: Results of studies focusing on chronic kidney disease (CKD) among women with polycystic ovary syndrome (PCOS) are insufficient and controversial. This study aimed to evaluate the incidence rate of CKD in women with PCOS, compared to a control group of healthy women.

Methods: This study was a population-based cohort study conducted from among 1460 reproductive-age women including 156 women with PCOS and 1304 controls. Incidence rates per 1000 person-years of follow-up were calculated for PCOS and control groups. Cox proportional hazards regression with age as the time scale was used to estimate hazard ratios (HR) and 95% confidence intervals for developing CKD in relation to PCOS in both univariable and multivariable models.

Results: During a median follow-up of 12.9 years, 330 new cases of CKD were identified, including 25 PCOS women (14.8 per 1,000 person-years; 95% CI, 10-22) and 305 healthy controls (21.5 per 1,000 person-years; 95% CI, 19.2-24.1). The results of the Cox model showed that the risk of CKD among women with PCOS and healthy women is comparable and women with PCOS did not have a higher risk of developing CKD compared to healthy women (unadjusted HR: 0.883; 95% CI: 0.587-1.328; P = 0.551). The results remained unchanged after adjustment for

potential confounders of smoking status, BMI, hypertension and diabetes at baseline and follow-up of study (multiple adjusted HR: 0.911; 95% CI: 0.600-1.383; P = 0.661).

Conclusion: Our population-based study with a long-term follow-up period showed that the risk of CKD in PCOS patients was similar to the general female population. Large studies, with long term follow-up and more diverse phenotypes are needed to confirm the findings.

Key words: chronic kidney disease, incidence, PCOS, population-based cohort study

1. INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies among premenopausal women, with a prevalence of 5%-20% based on diagnostic criteria, reported by recent studies. [1, 2] Heterogeneous by nature, PCOS is characterized by the androgen excess in the absence of specific etiology, ovarian dysfunction with the main manifestations of menstrual irregularity and polycystic ovary morphology. [3, 4] The exact underlying etiology of the syndrome remains largely unclear, but emerging evidence suggests that multigenic abnormalities, epigenetic and environmental factors play a role in the pathophysiology of PCOS (5). It is well documented that PCOS is strongly associated with hyperandrogenemia, insulin resistance (IR) and compensatory hyperinsulinemia, [4, 6-8] as well as increased prevalence of traditional cardiovascular and metabolic risk factors particularly diabetes, obesity and central obesity, dyslipidemia, metabolic syndrome, and hypertension competed to age-matched women without PCOS. [9]

Chronic kidney disease (CKD) is a common disorder that refers to the long-term damage of renal function, eventually may progress into end-stage renal disease with a significantly increased rate of mortality. [10] It tends to be diagnosed in the presence of other cardiovascular and metabolic comorbidities including diabetes, hypertension and adiposity obesity that arises from many heterogeneous disorders which could irreversibly impair the renal function and structure, over months or years. [11, 12] In this respect, given the higher prevalence of cardio-metabolic risk factors in PCOS, an increased incidence of CKD in later life in these patients might be expected. However, the results of studies focusing on kidney dysfunction in PCOS are limited. Few studies have shown that some important markers for renal risk including pre/over microalbuminuria and decreased glomerular filtration rate (GFR) are more prevalent among women with PCOS. [13-16] In the in-vitro study, a higher risk of age-dependent chronic kidney injury was reported among the female PCOS rate. [17] However, the incidence of CKD in this population has not been addressed. Therefore, the aim of this study was to assess the incidence rate and risk of CKD among women with PCOS compared with healthy controls in a long-term population-based study.

2. METHODS

This study was approved by the ethics committee of the Research Institute for Endocrine Sciences and written informed consent was signed by all participants, after an explanation of the purpose of the study to them.

This study was a population-based cohort study conducted from among reproductive aged women who participate from Tehran Lipid and Glucose Study (TLGS). In brief, the TLGS is an ongoing long-term community-based longitudinal study conducted on a representative sample of Tehran, the capital of Iran. TLGS was initiated from 1998, designed to continue for at least 20 years, to explore the prevalence and risk factors of noncommunicable diseases

mainly cardiovascular diseases including diabetes, heart attacks, and stroke, cancers, chronic respiratory and kidney diseases. A total of 15005 people aged ≥ 3 years were recruited. Data on different risk factors for noncommunicable diseases, demographic variables, and reproductive and obstetrics characteristics were collected during face-to-face interviews conducted every 3 years by trained staff. Every follow-up visit included a comprehensive questionnaire, information on general anthropometrics, a physical examination, and blood samples collection. Detailed descriptions of the TLGS have been published elsewhere. [18]

2.1. Study Population

For the present study, all reproductive-aged women who participate in the first phase of the TLGS (1998–2001) and attended at least one follow-up visit until March 31, 2017, were recruited. Women who were pregnant, were surgical /natural menopause, had undergone the hysterectomy or oophorectomy, who had a history of endocrine disorders including Cushing's syndrome, congenital adrenal hyperplasia or androgen secreting neoplasm, hyperprolactinemia, thyroid disease or any corticosteroid and nephroprotectant medication including metformin usage (n = 138). We also excluded women if they had isolated menstrual irregularity or hyperandrogenism (n = 244). The remaining participants (n = 1702) fulfilled the eligibility criteria for the study and were classified as follows: women with PCOS (n = 178) and healthy eumenorrheic, non-hirsute control women (n = 1524). For detecting the new cases of CKD among these populations, women who suffered from CKD at the baseline (n = 81) and had missing data on CKD (n = 30), were lost to follow up (n = 131) were excluded from the final analysis. Analyses were conducted on a total of 1460 women (156 PCOS and 1304 healthy controls) to identify the incidence and risk of CKD incidence over a median of 12.9 years of follow-up (Figure 1).

2.2. Measurements

Data about the PCOS in TLGS female population were specifically collected at the first phase of TLGS (1998-2001) and were updated at 4th, 5th, sixth and 7th follow-up visits. A comprehensive questionnaire on reproductive lifespan including menarche, menopause, menstrual regularity, parity, abortion, type and duration of contraception usage, infertility, and lactation were collected through face to face interviews by trained staff. Androgen excess manifestations were evaluated using valid tools. The hirsutism scores were evaluated using the modified Ferriman-Gallwey (mFG) scoring scale. Acne was assessed based on its type, number, and distribution. For hormonal assessments, fasting venous blood sampling were collected on the third day of spontaneous or progesterone withdrawal menstrual period. Another serum was obtained on any one day between days 22-24 of the cycle for the measurement of progesterone (P4) to confirm ovulatory function (P4 level < 4 ng/ml, indicating anovulation) among those with the predictable and regular menstrual cycle. This data was specifically collected. In addition, the general anthropometric and physical examinations including hirsutism using the modified Ferriman-Gallwey scoring method, [19] has been performed by a general practitioner. Body weight was measured with the least clothes using a digital scale and rounded to the nearest 100 grams. Likewise, height was measured without shoes in the standing position and normal posture of shoulders with a tape measure. Body mass index (BMI) was calculated using the formula [weight in kilograms (kg) divided by height squared (m^2)]. Waist circumference (WC) was measured with an unstretched tape measure at the level of the umbilicus, without any pressure to the body surface. Hip circumference (HC) was measured at the level of the anterior superior iliac spine without any pressure on the body surface. We also measured

systolic blood pressure (SBP) and diastolic blood pressure (DBP) twice on the right arm in a seated position using a standard mercury sphygmomanometer after 15 mines of rest and the mean of these measurements was recorded. A baseline overnight fasting venous blood sample was obtained on the second or third day of the participant's' spontaneous or progesterone-induced menstrual cycles, and overnight fasting blood samples were obtained at every follow-up visit for biochemical assessments. All blood analyses were performed at the TLGS research laboratory on the day of blood collection. Triglyceride (TG) levels were assayed using glycerol phosphate. Total cholesterol (TC) was assayed using the enzymatic colorimetric method with cholesterol esterase and cholesterol oxidase. The level of high-density lipoprotein cholesterol (HDL-C) was measured after precipitation of the apolipoprotein B (apo B)-containing lipoproteins with phosphotungstic acid. We used a modified Friedewald to calculate LDL-C. All metabolic analyses were performed using related kits (Pars Azmon Inc., Tehran, Iran) and a Selecta 2 autoanalyzer (Vital Scientific, Spankeren, Netherlands). Intra-assay and inter-assay coefficients of variations for TG, TC, HDL-C, and LDL-C were less than 2.1, 1.9, 3, and 3%, respectively. Dehydroepiandrosterone sulfate (DHEAS), total testosterone (TT), and androstenedione were measured by enzyme immunoassay (Diagnostic Biochem Canada). Sex hormone binding globulin was measured by immunoenzymometric assay (Mercodia). All enzyme-linked immunosorbent assay (ELISA) tests were performed using the Sunrise ELISA Reader (Tecan). The free androgen index was calculated using the following formula: TT (nmol/L) _ 100/sex hormone binding globulin (nmol/L). The intra-assay and interassay coefficients of variation for TT were 3.6% and 6.0%, for DHEAS 1.9% and 3.2%, for sex hormone-binding globulin 1.1% and 4.1%, and for androstenedione 2.2% and 3.5%. Serum creatinine (cr) levels were assayed 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% in 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). Assay performance was monitored after every 25 tests using lyophilized serum controls in normal and pathologic ranges and all samples were analyzed when the internal quality control met the standard and acceptable criteria. [20]

2.3. Terms definitions

Since the study was begun in 1998, the diagnosis of PCOS was based on the U.S. National Institutes of Health (NIH) criteria, including chronic oligo/anovulation, and either biochemical or clinical hyperandrogenism after exclusion of other known related disorders. [21] Oligo/anovulation was defined as either regular or irregular menstruation ≥ 34 days or a history of eight or fewer menstrual cycles in a year. The clinical symptoms of hyperandrogenism included hirsutism diagnosed based on a standardized scoring system of modified Ferriman-Gallwey scale ≥8, acne, or androgenic alopecia. Biochemical hyperandrogenism was assessed as an increased level of one or more serum androgens—including dehydroepiandrosterone sulfate, testosterone, or androstenedione— above the 95th percentile, determined in the selected healthy non-hirsute eumenorrheic women in the study population. [22]

According to American Diabetes Association criteria, diabetes was defined as fasting plasma glucose ≥ 126 mg/dL, or 2-hour plasma glucose ≥ 200 mg/dL, or using medications for a previous diagnosis of DM (23). Hypertension was defined based on criteria of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation,

and Treatment of High Blood Pressure as a mean systolic blood pressure ≥ 140 mm Hg, mean diastolic blood pressure ≥ 90mmHg, or undergoing treatment for hypertension. [24]

According to the Kidney Disease Outcome Quality Initiative guidelines (K/DOQI), chronic kidney disease is defined as Glomerular Filtration Rate (GFR) <60 mL/min/1.73 m^2 for >3 months (25). In this study, GFR was estimated using the abbreviated prediction equation, provided by the Modification of Diet in Renal Disease (MDRD) study as follows: $GFR = 186 \times (scr^{2} - 1.154) \times (age^{2} - .203) \times 0.742$. In this equation, estimated GFR (eGFR) is expressed as mL/min per 1.73 m^2 and serum creatinine (Scr) is expressed as mg/dL. According to guidelines, CKD is considered as eGFR below than 60 mL/min/1.73 m^2 occurring at any time during the follow-up period. [25, 26]

2.4. Statistical Analysis

Baseline characteristics of study participants in two groups were compared using independent t-tests, and Mann-Whitney test based on the normal distribution of continuous variables and the chi-square test for categorical variables.. The event date for the incident of CKD was defined as the midpoint between the date of the follow-up visit at which the CKD was diagnosed for the first time and the most recent follow-up visit before the diagnosis. The follow-up time was drawn from the difference between the calculated midpoint date and the date of entry into the study for each participant. For censored participants, the time was calculated as the interval between the first and the last observation dates. The incidence rate of CKD was calculated per 1000 person-years among the PCOS and control groups.. The cumulative incidence of CKD which was estimated using the Kaplan-Meier method and was compared among women with PCOS and the healthy women using the log-rank statistic are shown in Figure 2. Univariate and multiple Cox proportional hazards regression models were used to estimate the hazard ratio (HR) of CKD in relation to PCOS. In this model, age was considered as the time scale and as well as the baseline hazard assumes that each woman's observed risk period was started at birth and was not adjusted for age truncation. The proportional hazards assumption of the model was assessed via the Schoenfeld residual test (p=0.725 and p=0.738 respectively for Univariate and multiple models) and rechecked graphically by log (-log) survival curves that were appropriated. BMI, hypertension (HTN), type 2 diabetes (T2DM) and current smoking status at both baseline and during the follow-up of study and also anti DM (including metformin) and anti HTN medications usage during the follow-up of study were evaluated as confounding covariates. All statistical tests were two-tailed, and $P < 0.05$ was considered statistically significant. The Statistical Package for Social Sciences (SPSS version 16; SPSS Inc.) and STATA software (version 12; STATA Inc.) were used for data analysis.

3. RESULTS

In total, 156 patients with PCOS and 1304 healthy women were observed for a median (IQR) follow-up time of 12.9 (10.8-14.0) years. The characteristics of the study participants are presented in Table 1. The women with PCOS were significantly younger than the healthy controls (26.4 ± 8.5 *vs.* 28.7 ± 8.6 years, respectively; P = 0.002). The mean BMI and WC in the PCOS patients and healthy women were similar (26 ± 5.2 *vs.* 25.3 ± 4.7, P = 0.085) and (82.7 ± 12.5 *vs.* 81.3 ± 11.6, P = 0.172), respectively. However, the exception for androgens levels there were not any statistically significant differences between the two groups in the other characteristics at the baseline of the study.

Among the 1460 women who were free of CKD at baseline, 25 PCOS cases (14.8 per 1000 person-years; 95% CI, 10-22) and 305 healthy women (21.5 per 1000 person-years; 95% CI, 19.2-24.1developed CKD over 15833 person-year of follow up. The results of Cox model showed that the risk of CKD among women with PCOS and healthy women are comparable and women with PCOS did not have a higher risk of developing CKD compared to healthy women (unadjusted HR: 0.886; 95% CI: 0.883-1.328–3.9; P = 0.551). The results remained unchanged after adjustment for potential confounders of smoking status, BMI, hypertension and diabetes at baseline and follow-up of study (multiple adjusted HR: 0.911; 95% CI: 0.600-1.383; P = 0.661).

4. DISCUSSION

This study was a long-term, prospective, population-based study that presents new findings describing the incidence rate and risk of CKD between women with PCOS and healthy controls. The results of the present study suggest that the risk of developing CKD among women with PCOS is comparable with the general female population after adjustment for potential related confounders.

PCOS and CKD are important and common noncommunicable disorders globally (12, 27). CKD, a state of progressive loss of kidney function, mostly relates to underlying cardio-metabolic disturbances. However, there are some literature showed that women with PCOS may have a higher prevalence of cardio-metabolic risk factors mainly due to hyperandrogenism, insulin resistance, [4, 28, 29] obesity and central obesity which may lead to disturbances of growth factors, adipokine hormones, and pro-inflammatory factors [30, 31] and also higher serum level of endothelin-1 and subsequently potential endothelial dysfunction. [32] This evidence led to the theory that PCOS patients may have higher cardio-metabolic related events, including CKD in later life.

However, much less is known regarding the underlying mechanism of kidney function in PCOS. There is some evidence showed that hyperandrogenism as one of the main criteria of PCOS is correlated with kidney dysfunction, particularly in tubular epithelial cell injury. In this respect, it is showed that higher testosterone levels could activate the apoptotic pathway in human renal tubule cells which stimulates apoptosis and inflammation in kidney tubulogenic cells and further tubular proteinuria and chronic renal diseases. [16, 33] In addition, although all PCOS patients did not suffer from IR, [34] but its high prevalence and compensatory hyperinsulinemia may be associated with impaired long-term renal function in PCOS. Hyperinsulinemia may stimulate mesangial hyperplasia, increases low-grade inflammation, glomerular filtration and vascular permeability which may lead to urinary albumin extraction (UAE). [13, 35] However, the role of insulin is still not fully understood and in some studies, an association between UAE and insulin was not observed. [36]

Limited efforts have been made to investigate PCOS-related kidney dysfunction. Some studies have reported some evidence including the higher prevalence of pre-microalbuminuria [15, 37, 38] and microalbuminuria (13, 39), increased level of cystatin C [40] and urinary albumin excretion, [13] higher rate of glomerular filtration rate [14, 41] as well as hyperuricemia [14, 41, 42] which may be associated with kidney dysfunction among women with PCOS. Likewise, Duleba et al. (2010) in the observational study of 63 normotensive and non-diabetic PCOS patients evaluated the overt microalbuminuria and urinary albumin excretion (UAE) as a key indicator of renal function and endothelial dysfunction. However, overt microalbuminuria was detected in a significant proportion of subjects with PCOS, and UAE was related to established cardiovascular risk factors in PCOS. [13] In line with these findings, Patil et al. (2017) in

PCOS animal models showed that chronic and persistent hyperandrogenism in PCOS significantly increased the risk for the development of chronic kidney disease with advanced age. [13] In a recently published study, Song et al. (2019) performed a prospective survey to establish a link of PCOS with kidney injury. In this study, 55 PCOS patients and 69 healthy controls were selected from reproduction medicine hospital and correlation analyses between serum testosterone and some renal functional manifestations were assessed. The results of the study showed that urinary albumin to creatinine ratio (UACR), as a glomerular injury indicator among PCOS patients was significantly higher than non-PCOS controls, suggesting that PCOS is closely associated with kidney injury. Further, the serum testosterone level in PCOS had a positive association with the urinary protein excretion levels than potentially shows the injury in renal tubules. They concluded that PCOS associated with kidney injuries and serum testosterone plays a critical role in PCOS-associated kidney injury. [16]

However, our present population-based study found no increase in the incidence of CKD in women with PCOS compared with the non-PCOS controls and did not confirm those reports. The probable reason for this discrepancy was that all those studies reported these associations have been limited by several biases. The clinical-based setting of studies that may include severe phenotype of PCOS patients, un-adjustment for potential confounders such as age or BMI that strongly associated with renal function, the cross-sectional design of studies and lack of comparison with healthy control group means that those findings should be interpreted with cautious.

Notably, since hyperandrogenism and IR as critical factors in PCOS-associated kidney injury, [16] are correlated with a spectrum of clinical, biochemical and cardio-metabolic severity of PCOS [5, 34] this may suggest that severe form PCOS are associated with CKD. Likewise, Although the available evidence supporting this assumption is insufficient, however, community-based setting studies with including milder phenotypes of PCOS who might have never been referred to a clinic, reported that PCOS is not associated with worsening of cardio-metabolic health later in life. [43-46] However, results from these studies cannot be directly compared with our results since these studies did not investigate the risk of CKD in PCOS. But these studies suggest that representative of PCOS population sampling is strongly associated with the cardio-metabolic associated events findings.

One potential hypothesis is that there is evidence demonstrating that women with PCOS are more likely to have their lifestyle modification with various interventions, including diet, exercise or medication. [47-49] Given the better lifestyle of PCOS women, similar risk of CKD in women with PCOS compared to healthy women in later life might be explained. However, since we did not evidence to support this hypothesis, further studies are warranted to explore it. Moreover, it is worth noting that estrogen has nephroprotective effects due to attenuating the glomerulosclerosis and tubulo-interstitial fibrosis. [50] However, since women with PCOS have extended exposure to endogenous estrogen due to later age at menopause and lower conception rate, [51] this could be a benefit for kidney function among PCOS patients.

However, Since we used NIH criteria for PCOS diagnosis, the prevalence of PCOS in this study was relatively lower than studies that used Rotterdam or Androgen Excess Society (AES) for PCOS definition. [52] In addition, The mean BMI at baseline among women with PCOS and healthy women showed no statistically significant difference in our study and were much less than observed in Western countries. The population-based nature of our study, which included less severe phenotypes that might have never been referred to a clinic, may explain these findings. [53] In addition, the overall prevalence of obesity among the Iranian population is less than in the U.S. population. [54]

This study has some strengths and limitations. The longitudinal nature of the data with a long-term follow-up period helped us to present the valuable estimation of the CKD risk among women with PCOS. Moreover, the population-based setting of the study let us have a representative sample of the PCOS population due to reducing selection bias. Therefore the findings may not be comparable with those studies with clinical-based studies. In addition, adjustment of the related potential confounders produced valuable results. However, lifestyle modifications that would give more precise information for tracking of CKD in PCOS were not assessed in this study. Moreover, our results are limited to a specific urban population in one geographical area among population who willing to participate in a study and therefore it cannot be generalized to all other geographical and ethnicity population. Moreover, since the study was begun in 1998, the diagnosis of PCOS was based on the U.S. National Institutes of Health (NIH) criteria, including chronic oligo/anovulation, and either biochemical or clinical hyperandrogenism after exclusion of other known related disorders. Hence, all PCOS women in our study had both hyperandrogenism and oligo/anovulation; as a result subgroup analysis according to the PCOS phenotypes was not possible.

In conclusion, our population-based study with a long-term follow-up period showed that the incidence and risk of CKD were similar to the general female population, may suggest an individualized approach for the monitoring of the development and progression of CKD in women with PCOS. However, large studies, with long term follow up and more diverse phenotypes are needed to confirm the findings.

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CONFLICT OF INTEREST

Authors have no conflict of interest to declare.

Data Availability Statement

Data is available after publication if requested, via email to the corresponding author.

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Table 1. Baseline characteristics of PCOS and healthy control groups.

Characteristic	PCOS n=156	Healthy control n=1304	Unadjusted P-value
Age (y)	26.4 (8.5)	28.7 (8.6)	0.002
BMI (kg/m^2)	26 (5.2)	25.3 (4.7)	0.085
WC (cm)	82.7 (12.5)	81.3 (11.6)	0.172
WHR	0.8	0.8	0.543
SBP (mm Hg)	107.6 (11.6)	108.5 (11.8)	0.380
DBP (mm Hg)	73.1 (9.1)	72.8 (9.1)	0.659
TC (mg/dL)	189.2 (44.3)	185.8 (39.9)	0.317
TG (mg/dL) *	106 (80.2-160)	99 (73-147)	0.058
HDL-C (mg/dL)	44.4 (11.4)	44.5 (10.6)	0.934
LDL-C (mg/dL)	118.6 (36.5)	117.5 (34.4)	0.694
FBS (mg/dL)	87.1 (9.1)	88.1 (17.6)	0.518
Bs-2hPG (mg/dL)	108 (32)	105.5 (34.7)	0.492
Total T (ng/mL)	0.5 (0.3–0.7)	0.4 (0.2–0.6)	0.001
SHBG (nmol/L)	37.0 (27.0–43.0)	45.5 (39.0–54.8)	0.001
FAI	3.1 (2.2–3.8)	2.3 (1.5–4.2)	0.001
DHEAS (mg/dl)	120.0 (77.0–162.3)	125.2 (75.5–145.3)	0.001
A4 (ng/mL)	1.4 (0.6–2.3)	0.8 (0.5–1.7)	0.001
Modified FG score	10.0 (9–12)	1 (0–4)	0.001
Medical history			
Diabetes, n (%)	2 (1.2)	30 (2.3)	0.569
Hypertension, n (%)	10 (6.5)	58 (4.4)	0.309
Current smoking status, n (%)	2 (1.2)	23 (1.7)	0.543

Note: Data were presented as mean (standard deviation) or median(IQR) or number(%) as were appropriated. BMI = body mass index; BS-2hPG = 2-hour postprandial blood sugar; DBP = diastolic blood pressure; FBS = fasting blood sugar; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure; TC = total cholesterol; TG = triglyceride; WC = waist circumference; WHR = waist-to-hip ratio;

Figure 1. Study flowchart.

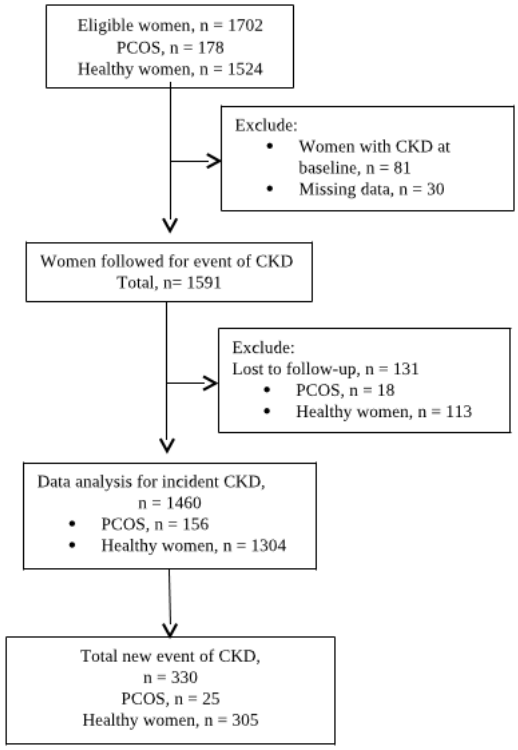

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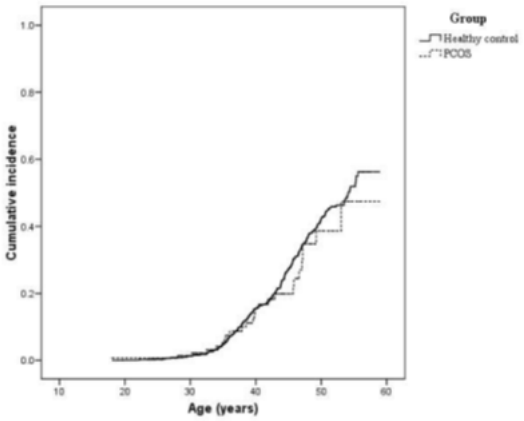
Figure 2. Kaplan-Meier cumulative incidence of CKD in women with polycystic ovary syndrome and healthy women. Age is used as the time scale. (log-rank test P = 0.551).



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