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Solitary kidney and risk of chronic kidney disease

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Abstract

The renal outcome of solitary kidney remains controversial. We examined the longitudinal association of congenital or acquired solitary kidney with the development of chronic kidney disease (CKD). A cohort study was performed involving 271,171 Korean men and women free of CKD at baseline who underwent a health screening program and who were followed annually or biennially for an average of 5.4 years. Solitary kidney was determined based on ultrasonographic findings. CKD was defined as an estimated glomerular filtration rate of < 60 ml/min/1.73 m^2 and/or the presence of proteinuria in two or more consecutive visits. During 1,472,519.6 person-years of follow-up, 2989 participants developed CKD (incidence rate: 2.0 per 1000 person-years). After adjustment for potential confounders, the aHR (95% CIs) for incident CKD comparing solitary kidney to the control was 3.26 (1.63–6.54). In analyses of cause-specific solitary kidney, aHR (95% CIs) for CKD comparing unilateral nephrectomy and congenital solitary kidney to the control were 6.18 (2.31–16.49) and 2.22 (0.83–5.92), respectively. The association between solitary kidney and CKD was stronger in men. Having a solitary kidney was independently associated with an increased risk of CKD development. Therefore, preventive strategies for reducing the risk of CKD are required in individuals with a solitary kidney.

Keywords Solitary kidney · Chronic kidney disease · Cohort study

Introduction

Chronic kidney disease (CKD) is a global public health issue with increasing associated health and economic burdens [1]. CKD is a predisposing factor for progression to end-stage renal disease (ESRD). There is also an increasing recognition that CKD is a strong risk factor for all-cause and cardiovascular mortality [1]. In addition, health-related quality of life in patients with CKD is considerably compromised and declines over time [2]. Therefore, it is important to develop preventive strategies to identify high-risk individuals before they develop CKD and to identify potentially modifiable risk factors.

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Solitary kidney is mainly caused either by unilateral renal agenesis; congenital hypoplasia and dysplasia; and surgical removal of the kidney due to disease, injury, or kidney donation. In the 1980s, Brenner et al. [3, 4] proposed that a reduced nephron number predisposes a patient to hypertension, proteinuria, and a decline in glomerular filtration rate (GFR) in the long run. There is a body of evidence suggesting that either a congenital or acquired reduction in renal mass is related with an increased risk of renal impairment [5–10]. On the other hand, the renal function of patients with unilateral nephrectomy due to donation is relatively well-preserved over time [11–15]. Although clinical outcomes in patients with solitary kidney including renal insufficiency have been largely explored in previous studies, the renal outcome of solitary kidney is still controversial. Conflicting findings related with the presence of the solitary kidney could be due to insufficient sample size, absent or inappropriate control groups, and/or the loss of follow-up data [11, 13, 15, 16].

Thus, our study aims to assess the association between having a solitary kidney and the development of CKD in a large cohort of Korean men and women free of CKD at baseline who participated in a health screening examination program.

Methods

Study population

The Kangbuk Samsung Health Study is an ongoing dynamic cohort study of Koreans aged 18 years or older who underwent a comprehensive annual or biennial examination from 2002 to present at the Kangbuk Samsung Hospital Total Healthcare Center in either Seoul or Suwon, South Korea. This study was a part of the KSHS, which is designed to use data routinely collected as part of health screening examinations comprising questionnaires, blood tests, imaging examination, and procedures (e.g., ultrasound, endoscopy) [17, 18]. More than 80% of examinees were employees of various companies or local governmental organizations and their spouses. In South Korea, the Industrial Safety and Health Law requires annual or biennial health checkups of all employees to be completed free of charge. This type of health checkup can be performed at any authorized hospital and the Total Healthcare Center of Kangbuk Samsung Hospital is the largest health checkup center in Korea. The remaining participants voluntarily paid for screening examinations at the health screening center. In this study, to examine the association between solitary kidney and CKD, we included all participants with at least one follow-up visit who underwent a comprehensive health examination between 2002 and 2015 and were followed annually or biannually until December 2015 (N = 294,418). Among these participants, 22,701 were excluded based on exclusion criteria noted at the first visit: missing estimated GFR (eGFR) or abdominal ultrasonography (US) data (n = 573); a history of cancer (n = 3553); a history of CKD (n = 4253); proteinuria at baseline (n = 13,454); CKD at baseline (n = 1824); chronic kidney disease, renal tumor, renal cancer on US; and/or partial or total nephrectomy due to renal diseases including renal tuberculosis, renal stone, nephritis, and renal tumor (n = 97). Because some participants met one or more of the exclusion criteria, the total number of participants eligible for this study was 271,717. The study was approved by the institutional review board of Kangbuk Samsung Hospital (IRB No. KBSMC 2017-08-042), which waived the requirement for informed consent due to the use of de-identified data obtained as part of routine health screening exams.

Measurement

Data on demographic characteristics; smoking status; alcohol consumption; physical activity; educational level; medical history of hypertension, diabetes, chronic kidney disease, and/or cancer; and medication use were collected via standardized, self-administered questionnaires, as previously described [18, 19]. Smoking status was categorized into never, former, and current smokers. Alcohol consumption was categorized into ≤ 20 g/day and > 20 g/day. The weekly frequency of moderate- or vigorous-intensity physical activity was assessed and categorized into at least three times per week of moderate to vigorous intensity aerobic activity versus < 3 times per week. High education level was defined as college graduate or more. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, self-reported history of hypertension, or self-reported use of antihypertensive medication. Diabetes was defined as fasting glucose ≥ 126 mg/dl, HbA1c ≥ 6.5%, self-reported history of diabetes, or self-reported use of antidiabetic medication.

Trained nurses assessed all physical tests including body weight, height, and sitting blood pressure (BP). Sitting BP was measured by use of standard mercury sphygmomanometers. Body weight and height were measured and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Obesity was defined as BMI ≥ 25 kg/m^2 according to Asian-specific criteria [20].

Blood samples were taken from the antecubital vein after a fast of at least 10 h. Laboratory tests included fasting glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase (GGT), high sensitive C-reactive protein (hsCRP), insulin, and creatinine. Serum creatinine was measured using the kinetic alkaline picrate (Jaffe) method in an automated chemistry analyzer (specifically, an Advia 1650 Autoanalyzer from Bayer AG, Leverkusen, Germany between 2002 and 2009 and a Modular D2400 from Roche AG, Basel, Switzerland from 2010 to 2015). CKD was defined as estimated GFR < 60 ml/min/1.73 m^2 and/or the presence of proteinuria in two or more consecutive visits. Estimated GFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [21]. Since we did not use an isotope dilution mass spectrometry (IDMS) method to determine serum creatinine from 2002 to 2009, we reduced the creatinine level by 5%, which has been used as the calibration factor to be standardized to IDMS [22, 23.] To measure urine protein semi-quantitatively, we used urine dipsticks (URiSCAN urine test strips) and results were reported in six grades (i.e., absent, trace, 1+, 2+, 3_, and 4+). The presence of proteinuria was indicated as grade 1+ or greater. Insulin resistance was assessed with the homeostatic model assessment of insulin resistance (HOMA-IR) equation: fasting blood insulin (uU/ml) × fasting blood glucose (mmol/l)/22.5. [24].

Experienced radiologists who were unaware of the aim of the study performed abdominal US using a Logic Q700 MR 3.5 MHz transducer (GE, Milwaukee, WI, USA). Abdominal US was performed for all examinees at the first and each subsequent visit. Images were taken in a standard position with the examinees in the supine decubitus position with the right arm raised above the head. When a kidney was not identified in the renal fossa, the pelvis and abdomen were scanned to assess for an ectopic kidney. In the present study, congenital solitary kidney was defined as the non-visualization of unilateral kidney on US without any history of surgical removal and non-identifiable ectopic kidney on US. Unilateral nephrectomy was defined as evidence of a nephrectomy, the nonvisualization of a unilateral kidney ("empty renal fossa"), and an ipsilateral abdominal scar with a self-reported history of radical uninephrectomy in accordance with standard criteria. Renal compensatory hypertrophy was diagnosed based on the increase in longitudinal length of the contralateral remaining kidney and body size. The cause of having a solitary kidney was collected via a self-administered questionnaire. The solitary kidney group was subclassified into a renal agenesis group and nephrectomy group. Then, the nephrectomized subgroup was further divided into a donor nephrectomy group, an accident group, and an unknown cause group.

Statistical analyses

All data were presented as mean (standard deviation), median (interquartile range), or number (percentage). Characteristics of study participants were presented according to the presence or absence of solitary kidney. Also, we evaluated the difference of baseline characteristics between participant who were followed and those who were not. To compare between two groups, we used Student's *t* test for continuous variables with normal distribution, Kruskal–Wallis test for variable with non-normal distribution and a Chi square test for categorical variables.

The primary endpoint of this study was the development of CKD in two or more consecutive visits. Each participant was followed from the time of their baseline exam until either the development of CKD or until the conduction of their last health exam prior to December 31, 2015—whichever came first. Incidence rate was calculated as the number of incident cases divided by person-years during the follow-up time. Since, in cases of CKD, we could postulate that it had occurred between two visits but we could not determine the precise time of development, a parametric Cox model was used to account for this type of interval censoring (*stpm* command in Stata) [25]. In these models, the baseline hazard function was parameterized with restricted cubic splines in logarithmic time with four degrees of freedom.

The hazard ratio (HR) and 95% confidence interval (CI) were calculated for incident CKD. Data were initially adjusted for age, sex, center, and year of screening exam (Model 1); and were then further adjusted for smoking status, alcohol intake, regular exercise, education level, history of diabetes and hypertension, medication use for dyslipidemia, hypertension and diabetes, and baseline eGFR (Model 2). Finally, Model 3 was further adjusted for the presence of compensatory hypertrophy. The proportional hazards assumption was assessed by examining graphs of estimated log (−log) survival. To determine linear trends of incidence, the number of categories was used as a continuous variable and tested on each model. The same analyses were also performed separately using the development of eGFR < 60 ml/min/1.73 m^2 and/or the development of proteinuria as the outcome. The cumulative incidence of CKD by the cause of solitary kidney was assessed by Kaplan–Meier plots.

Participants usually underwent health examination annually or biennially and were recruited into the study continuously beginning in 2002; thus, some participants recruited in the screening program in more recent years have not been seen long enough to undergo a follow-up examination. To account for differences between participants with no follow-up visit and those with at least one follow-up visit, we estimated the probability of follow-up as a function of baseline characteristics. In our sensitivity analysis, each individual was weighted by the inverse of the predicted probability of selection (inverse probability weight analysis [IPW]) to address the question "What is the association between solitary kidney and CKD if there was no selection bias from the baseline study sample?" [26].

In addition, we performed stratified analyses in subgroups defined by age (< 50 vs. ≥ 50 years); sex (women vs. men); smoking status (never or ever vs. current smokers); alcohol intake (< 20 vs. ≥ 20 g/day); BMI (< 25 vs. ≥ 25 kg/m^2); hsCRP (< 1.0 vs. ≥ 1.0 mg/l); HOMA-IR (< 2.5 vs. ≥ 2.5); diabetes (no vs. yes); and hypertension (no vs. yes). Interactions between solitary kidney and subgroup characteristics were tested using likelihood ratio tests, comparing models with and without multiplicative interaction terms.

Statistical analyses were carried out using STATA version 14.0 (StataCorp LP, College Station, TX, USA). All *P* values less than 0.05 were considered statistically significant.

Results

Among the 271,717 participants, 217 individuals with a solitary kidney were identified (153 presenting with congenital solitary kidney and 64 presenting with nephrectomy). The causes of nephrectomy were donation in 31 participants, trauma in 11 participants, and unknown in 22 participants (Supplementary Table 1). Table 1 shows the baseline characteristics according to the presence of solitary kidney. Participants who had a solitary kidney were more likely to be female and to have history

Table 1 Baseline characteristics of participants according to the presence of solitary kidney

Characteristic	Overall	Normal	Solitary kidney	*P* value
Number	271,717	271,500	217	
Age (years)*	37.6 (8.0)	37.6 (8.0)	38.1 (9.3)	0.353
Men (%)	58.6	58.6	49.3	0.006
Current smoker (%)	26.2	26.2	23.6	0.415
Alcohol intake (%)‡	16.8	16.8	17.4	0.829
Vigorous exercise (%)§	14.8	14.8	18.2	0.159
High education (%)	79.0	79.0	68.7	0.002
History of diabetes (%)	1.5	1.5	1.8	0.638
Medication for diabetes (%)	1.0	1.0	0.9	0.957
History of hypertension (%)	5.7	5.7	8.8	0.049
Medication for hypertension (%)	3.4	3.4	6.0	0.037
Medication for dyslipidemia (%)	1.0	1.0	2.3	0.067
Renal compensation hypertrophy (%)	0.0	0.0	46.5	< 0.001
eGFR (ml/min/1.73 m^2)	84.2 (14.2)	84.2 (14.2)	78.2 (14.2)	< 0.001
Systolic BP (mmHg)*	112.3 (13.7)	112.3 (13.7)	113.5 (13.3)	0.173
Diastolic BP (mmHg)*	72.4 (10.0)	72.4 (10.0)	72.6 (10.1)	0.708
Glucose (mg/dl)*	93.7 (13.9)	93.7 (13.9)	92.1 (10.0)	0.080
Total cholesterol (mg/dl)*	193.7 (34.3)	193.7 (34.3)	194.1 (33.3)	0.871
LDL-C (mg/dl)*	114.2 (30.2)	114.2 (30.2)	112.0 (28.5)	0.296
HDL-C (mg/dl)*	56.5 (13.4)	56.5 (13.4)	57.5 (14.9)	0.321
Triglycerides (mg/dl)†	98 (69–145)	98 (69–145)	98 (71–153)	0.333
ALT (U/l)†	20 (14–30)	20 (14–30)	19 (14–26)	0.214
AST (U/l)†	21 (18–26)	21 (18–26)	21 (18–26)	0.527
GGT (U/l)†	19 (12–34)	19 (12–34)	17 (11–30)	0.017
hsCRP (mg/l)†	0.4 (0.2–0.9)	0.4 (0.2–0.9)	0.4 (0.2–0.8)	0.456
HOMA-IR†	1.58 (1.08–2.18)	1.58 (1.08–2.18)	1.65 (1.05–2.21)	0.883
Year of screening exam				0.913
2002–2004	30.1	30.1	29.5	
2005–2007	19.7	19.7	18.0	
2008–2010	21.3	21.3	26.3	
2011–2013	26.5	26.5	23.5	
2014–2015	2.4	2.4	2.8	

eGFR estimated glomerular filtration rate, *BP* blood pressure, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein-cholesterol, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *GGT* gamma-glutamyltransferase, *hsCRP* high sensitivity C-reactive protein, *HOMA-IR* homeostasis model assessment of insulin resistance

Values are *means (standard deviation), †medians (interquartile range), or percentages

‡≥ 20 g of ethanol per day; §≥ 3 times per week of hypertension or antihypertensive medication and lower levels of eGFR, GGT, and education. The participants who were not followed were on average 4.5 years older, less likely to be male and highly educated, and more likely to have chronic disease at baseline including hypertension, diabetes, and dyslipidemia than those who were followed (Supplementary Table 2).

During 1,472,519.6 person-years of follow-up, 2989 participants developed CKD (incidence rate: 2.0 per 1000 person-years). In Model 1, following adjustment for age, sex, center, and year of screening exam, a significantly higher risk of CKD was observed in participants with solitary kidney compared with those with two kidneys (adjusted HR: 3.45, 95% CI 1.73–6.91). This association persisted after adjusting for baseline eGFR, smoking status, alcohol intake, regular exercise, education level, history of diabetes, history of hypertension, medication use for dyslipidemia, hypertension and diabetes, and the presence of renal compensatory hypertrophy (adjusted HR: 4.82, 95% CI 2.30–10.14, Model 3). In analyses performed according to the cause of having a solitary kidney, multivariable adjusted HR (95% CIs) values in Model 2 for CKD comparing participants with nephrectomy and congenital solitary kidney to normal subjects were 6.18 (2.31–16.49) and 2.22 (0.83–5.92), respectively. In analyses done according to the cause of nephrectomy, multivariable-adjusted HR (95% CIs) values in Model 2 for CKD comparing donor nephrectomy to normal subjects was 8.63 (2.78–26.84). These results were not qualitatively changed after further adjustment for the presence of renal compensatory hypertrophy (Model 3).

When the analyses were performed separately for decreased GFR and/or incident proteinuria as the outcome, solitary kidney was associated with the development of both decreased GFR and proteinuria. After adjustment for age, sex, center, year of screening exam, baseline eGFR, smoking status, alcohol intake, regular exercise, education level, history of diabetes and hypertension, and medication use for dyslipidemia, hypertension and diabetes, adjusted HR (95% CIs) values for the development of decreased GFR comparing participants with nephrectomy and congenital solitary kidney to normal subjects were 8.13 (2.60–25.37) and 1.83 (0.26–12.98), whereas corresponding HR values for incident proteinuria were 3.48 (0.49–24.72) and 1.60 (0.40–6.39). In an analysis done according to the cause of nephrectomy, multivariable adjusted HR (95% CI) for decreased GFR comparing donor nephrectomy to normal subjects was 7.99 (1.99–32.13), whereas multivariable-adjusted HR (95% CIs) value for incident proteinuria comparing donor nephrectomy was 7.61 (1.07–54.13), respectively (Table 2). Figure 1 illustrates the Kaplan–Meier curves for the cumulative incidence of CKD according to the cause of solitary kidney.

In pre-specified subgroup analyses, associations between solitary kidney and CKD were similar across the subgroups of study participants, except with respect to sex: notably, the association tended to be stronger in individuals aged ≥ 50 and in men (P for interaction = 0.06 and P for interaction = 0.07, respectively). Otherwise, there were no significant interactions by smoking status (never vs. current smokers), alcohol intake (< 20 vs. ≥ 20 g/day), BMI (< 25 vs. ≥ 25 kg/m^2), hsCRP (< 1.0 vs. ≥ 1.0 mg/l), HOMA-IR (< 2.5 vs. ≥ 2.5), diabetes (no vs. yes), or hypertension (no vs. yes) (Table 3).

Also, we performed analysis of the association between solitary kidney and annual eGFR change. The average difference of annual eGFR change of solitary kidney compared to normal kidney was −0.046 (−0.237 to 0.145), suggesting that annual eGFR loss was slightly higher in the solitary kidney group than the normal group, although the difference was not statistically significant (Supplementary Table 3).

The results with IPW, while accounting for differences between participants with no follow-up visit and those with at least one follow-up visit, were slightly attenuated but similar to those of the original analysis without IPW (Supplementary Table 4). When we analyzed the association between solitary kidney and the development of CKD which was defined as decreased eGFR and/or the presence of proteinuria at a single time point instead of two or more consecutive visits, the positive relationship of solitary kidney with the development of decreased eGFR and proteinuria was consistently observed (Supplementary Table 5).

Discussion

In this large cohort study of young and middle-aged Korean men and women free of CKD at baseline, having a solitary kidney was independently and moderately associated with an increased risk of CKD. This association persisted even after adjusting for possible confounders, indicating that having a solitary kidney is an independent risk factor of CKD. The risk of CKD was higher in individuals with acquired solitary kidney than in those with congenital solitary kidney, even though the increased risk of incident CKD was observed in those with either congenital or acquired solitary kidney.

The risk of impaired renal function in solitary kidney has been largely studied during the last three decades. Experimental animal studies revealed that, following renal ablation, structural and functional changes occurred in the remnant kidney [27, 28]. Brenner et al. [4] suggested that renal ablation lead to progressive glomerular injury, which is associated with glomerular hypertrophy, hyperfiltration, and systemic hypertension. They also suggested that congenital nephron endowment is an important factor in the progression of chronic renal disease [29]. These findings have been supported by many clinical observations, which have predominantly been conducted in patients with congenital renal

Table 2 Hazard ratios for persistent chronic kidney disease according to the presence of solitary kidney

	Person-years (PY)	Median follow-up period (IQR)	No. of incident cases	Incidence rate (per 10^3 PY)	Multivariable HR[a] (95% CI)		
					Model 1	Model 2	Model 3
eGFR < 60 ml/min/1.73 m^2 or proteinuria							
Normal	1,470,011.5	4.2 (2.1–8.0)	2969	2.0	1.00 (reference)	1.00 (reference)	1.00 (reference)
Solitary kidney	1125.9	4.0 (2.1–7.7)	8	7.1	3.45 (1.73–6.91)	3.26 (1.63–6.54)	4.82 (2.30–10.14)
Congenital	869.6	5.0 (2.3–8.0)	4	4.6	2.18 (0.82–5.81)	2.22 (0.83–5.92)	3.61 (1.20–10.85)
Nephrectomy	256.3	3.5 (1.8–4.7)	4	15.6	8.29 (3.11–22.11)	6.18 (2.31–16.49)	6.58 (2.46–17.61)
Donor	119.0	3.3 (1.8–5.8)	3	25.2	13.63 (4.39–42.29)	8.63 (2.78–26.84)	8.72 (2.80–27.12)
Accident	74.1	3.9 (3.2–11.7)	0	–	–	–	–
Unknown	63.2	2.3 (1.6–3.7)	1	15.8	9.41 (1.32–66.80)	6.94 (0.97–49.52)	7.64 (1.07–54.70)
eGFR < 60 ml/min/1.73 m^2							
Normal	1,479,419.2	4.2 (2.1–8.1)	938	0.6	1.00 (reference)	1.00 (reference)	1.00 (reference)
Solitary kidney	1138.1	4.1 (2.1–7.7)	4	3.5	5.72 (2.14–15.28)	4.36 (1.63–11.65)	5.80 (2.17–15.52)
Congenital	879.7	5.2 (2.3–8.2)	1	1.1	2.09 (0.29–14.86)	1.83 (0.26–12.98)	2.88 (0.41–20.52)
Nephrectomy	258.4	3.5 (1.8–4.7)	3	11.6	13.61 (4.37–42.38)	8.13 (2.60–25.37)	8.76 (2.80–27.37)
Donor	121.0	3.5 (1.8–5.8)	2	16.5	34.18 (8.53–137.05)	7.99 (1.99–32.13)	8.01 (1.99–32.20)
Accident	74.1	3.9 (3.2–11.7)	0	–	–	–	–
Unknown	63.2	2.6 (1.7–3.7)	1	15.8	22.49 (3.15–160.53)	13.68 (1.88–99.43)	18.89 (2.55–140.0)
Proteinuria							
Normal	1,460,894.3	4.2 (2.1–8.1)	1972	1.3	1.00 (reference)	1.00 (reference)	1.00 (reference)
Solitary kidney	1131.5	4.1 (2.1–7.7)	3	2.7	1.78 (0.57–5.53)	1.95 (0.63–6.05)	3.84 (1.24–11.93)
Congenital	880.9	5.1 (2.3–8.1)	2	2.3	1.44 (0.36–5.77)	1.60 (0.40–6.39)	3.86 (0.96–15.46)
Nephrectomy	250.6	3.5 (1.8–5.4)	1	4.0	3.37 (0.47–23.95)	3.48 (0.49–24.72)	3.81 (0.54–27.06)
Donor	112.1	3.5 (1.8–5.9)	1	8.9	7.05 (0.99–50.03)	7.61 (1.07–54.13)	7.84 (1.10–55.76)
Accident	74.1	3.9 (3.2–11.7)	0	–	–	–	–
Unknown	64.4	2.4 (1.7–3.7)	0	–	–	–	–

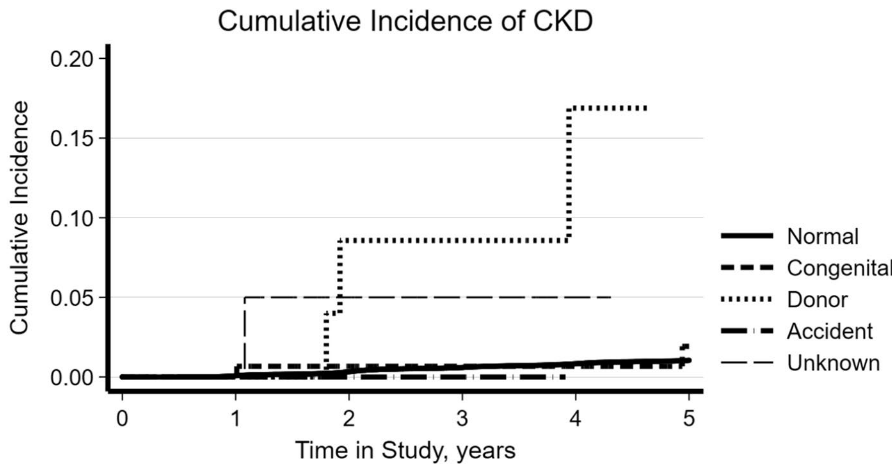
eGFR estimated glomerular filtration rate, *CI* confidence interval, *HR* hazard ratio

[a]Estimated from parametric proportional hazard models. Multivariate Model 1 was adjusted for age, sex, center, and year of screening exam; Model 2: Model 1 plus adjustment for baseline eGFR, smoking status, alcohol intake, regular exercise, education level, history of diabetes, history of hypertension, medication use for diabetes, medication use for hypertension and medication use for dyslipidemia; Model 3: Model 2 plus adjustment for renal compensation hypertrophy

disease [5–9]. In a retrospective review, Sanna-Cherchi et al. [5] reported that the risk for dialysis was significantly higher in patients with congenital solitary kidney, suggesting that subclinical defects of the solitary kidney may be responsible for a poorer renal outcome.

Although the theory of Brenner et al. has been supported by a number of studies, several observational studies have documented conflicting results [11–14, 16, 30–33]. In a study of 28 United States Army personnel who lost a kidney due to trauma during World War II, authors suggested that unilateral nephrectomy in young adults has few major adverse consequences over 45 years [16]. Similarly, the development of CKD in individuals with trauma nephrectomy was not observed in our study. However, the sample size was too small to provide reliable estimates.

Short-term and long-term renal outcomes of living kidney donors (LKDs) have also been examined in previous observational studies. Some longitudinal studies of LKDs with a mean follow-up time from 10.7 years to 25 years reported that renal function was well-maintained after unilateral nephrectomy [11–15]. Most previous studies that have used unselected general populations as the control group have reported that the long-term risk of end-stage renal disease in LKDs was similar to that in the general



No. at Risk

	0	1	2	3	4	5
Normal	271500	261853	217824	179994	145642	120240
Congenital	153	149	129	105	89	77
Donor	31	28	19	17	10	8
Accident	11	11	11	10	5	5
Unknown	22	21	13	10	4	2

Fig. 1 Kaplan-Meier curves for cumulative incidence of CKD according to the cause of solitary kidney

population [34–36]. However, theoretically, the long-term outcome in LKDs should be better rather than equal to that in the general population given that LKDs are selected from among the healthiest individuals based on strict criteria [34]. Furthermore, kidney donation itself might be related with strong personal motivation and implementation of lifestyle changes, which can affect the incidence of CKD. Recently, two matched cohort studies from the United States and Norway reported that the ESRD risk of LKDs increased 8–11 times [36, 37]. In our study, the CKD risk of LKDs was similar to the results observed in the former two studies (adjusted HR: 8.63, 95% CI 2.78–26.84).

Furthermore, our study is the first cohort study to demonstrate the renal outcome of solitary kidney based on cause of solitary kidney. In our study, the risk of CKD in kidney donors was higher than those of solitary kidney due to congenital form or nephrectomy for other reason. A possible explanation for higher risk in kidney donors seen in our study may be the presence of certain genetic factors, as donors are likely to be immediate family members of the patient [37]. In Korea, the majority of transplants tend to come from living blood-related donors [38]. A family history of renal disease is one of the risk factors of CKD, with a corresponding OR of 1.63 [39]. Unfortunately, in our study, information on family history of renal disease and the relationship of the kidney recipient to the donor was not available; thus, it is possible that a confounding effect related with a family history of renal disease might have led to an overestimation of the result. To address the potential effect of unmeasured confounding, we calculated the E-value. The HR of 8.63 (95% CI, 2.78–26.84) in donor nephrectomy could be explained by an unmeasured confounder that was associated with both solitary kidney and CKD with an HR of 16.74-fold each, above and beyond the measured confounders, but weaker confounding could not do so. The confidence interval could be moved to include the null by an unmeasured confounder that was associated with both treatment and outcome by a risk ratio of 5.0-fold each, above and beyond the measured confounders, but weaker confounding could not do so [40].

The difference in renal outcome between congenital and acquired solitary kidney is also not clearly demonstrated. In this study, the risk of CKD was higher in participants with unilateral nephrectomy than in those with congenital solitary kidney. Similarly, Jaoude et al. reported an inverse relationship between GFR and follow-up time in patients with acquired solitary kidney but not in those with congenital solitary kidney. They suggested that the adaptive response following renal mass reduction may begin much earlier in the case of congenital solitary kidney than in that of acquired solitary kidney. Furthermore, because mature glomeruli have low mitotic activity, acquired solitary kidney can have a worse functional adaption [41].

In our study, the association between solitary kidney and CKD was stronger in men. A previous study by Muzaale et al. reported that the cumulative incidence of ESRD at 15 years per 10, 000 in LKDs was higher in men than in women; notably, for men, cumulative incidence was 44.1 (95% CI 32.9–59.1), while, for women, it was 21.1 (95% CI 14.9–29.9) [36]. Another study showed a twofold higher risk of ESRD rate after LKD in men than in women [42]. Although the reasons for the gender difference in the association between solitary kidney and risk of CKD are not fully understood, gender differences have been documented in the risk of CKD [43–45]. Men appear to be at a greater risk of predisposal to kidney disease and unfavorable outcomes with

Table 3 Hazard ratios for persistent chronic kidney disease (eGFR < 60 ml/min/1.73 m^2 or proteinuria) by the presence of solitary kidney in clinically relevant subgroup

Subgroup	Normal	Solitary kidney	*P* value	*P* value for interaction
Age				0.06
< 50 years (*n* = 249,037)	1.00 (reference)	2.30 (1.03–5.13)	0.042	
≥ 50 years (*n* = 22,680)	1.00 (reference)	10.56 (2.62–42.55)	0.001	
Sex				0.07
Female (*n* = 112,593)	1.00 (reference)	1.23 (0.31–4.92)	0.771	
Male (*n* = 159,124)	1.00 (reference)	5.38 (2.41–12.01)	< 0.001	
Smoking				0.65
Non- or ex-smoker (*n* = 188,732)	1.00 (reference)	2.95 (1.32–6.58)	0.008	
Current smoker (*n* = 66,860)	1.00 (reference)	1.80 (0.25–12.80)	0.557	
Alcohol intake (g of ethanol per day				0.97
< 20 g/day (*n* = 213,301)	1.00 (reference)	3.24 (1.54–6.81)	0.002	
≥ 20 g/day (*n* = 42,977)	1.00 (reference)	3.39 (0.48–24.13)	0.223	
BMI				0.43
< 25 mg/kg^2 (*n* = 195,273)	1.00 (reference)	2.46 (1.02–5.92)	0.045	
≥ 25 mg/kg^2 (*n* = 76,427)	1.00 (reference)	4.36 (1.40–13,56)	0.011	
HsCRP				0.34
< 1.0 mg/l (*n* = 202,743)	1.00 (reference)	2.39 (0.99–5.75)	0.052	
≥ 1.0 mg/l (*n* = 66,014)	1.00 (reference)	4.83 (1.55–15.02)	0.007	
HOMA-IR				0.99
< 2.5 (*n* = 222,245)	1.00 (reference)	3.78 (1.89–7.56)	< 0.001	
≥ 2.5 (*n* = 43,538)	1.00 (reference)	–	–	
Diabetes				1.00
No (*n* = 264,974)	1.00 (reference)	3.02 (1.51–6.06)	0.002	
Yes (*n* = 6740)	1.00 (reference)	–	–	
Hypertension				0.85
No (*n* = 237,883)	1.00 (reference)	3.03 (1.44–6.37)	0.003	
Yes (*n* = 33,578)	1.00 (reference)	2.49 (0.35–17.75)	0.362	

Estimated from parametric proportional hazard models adjusted for age, sex, center, year of screening exam, baseline eGFR, smoking status, alcohol intake, regular exercise, education level, history of diabetes, history of hypertension, medication use for diabetes, medication use for hypertension and medication for dyslipidemia

eGFR estimated glomerular filtration rate, *hsCRP* high sensitivity C-reactive protein, *HOMA-IR* homeostasis model assessment of insulin resistance

a rapid decline in renal function [44, 46–48]. Estrogen has been shown to have an antioxidative effect and appears to be renoprotective via the renal nitric oxide system, the attenuation of oxidative stress, or its effect on the components of the renin–angiotensin system [43, 49]. Due to the small sample of postmenopausal women included in our study, we were not able to perform a stratified analysis of women; indeed, most of our female participants were pre-menopausal. Thus, in our study, the association between solitary kidney and CKD in women can represent their relation only before menopause. Further researches on gender differences in the association between solitary kidney and CKD are needed.

Notably, the strengths of our study include its large sample size and the use of carefully standardized clinical, laboratory and imaging procedures including abdominal US which was routinely performed as a part of a health checkup program in all participants at baseline and at each subsequent visit. Additionally, all subjects of our study including those in the control group come from a single cohort of asymptomatic apparently healthy examinees, possibly minimizing the bias related with the selection of the control group. With this in consideration, we were able to demonstrate an independent association between solitary kidney and CKD. Also, our study findings reaffirm the necessity of proper surveillance for patients with solitary kidney and suggest that renal outcome may be different according to the cause of solitary kidney.

Several limitations of the current study also need to be considered. First, information on smoking, alcohol use, physical activity, and medical history including the cause of nephrectomy was obtained via a self-administered structured questionnaire used in health checkup programs in Korea as a part of the National Health Insurance plan. Thus, we cannot exclude the potential for measurement error in these variables, which might have resulted in some degree of residual confounding. Second, we have no data for specific medications that can affect renal outcome. Instead, we adjusted for antihypertensive, antidiabetic and lipid-lowering agents. Third, solitary kidney was determined based only on US without confirmation using renal scintigraphy. Thus, we cannot discard the possibility that some participants categorized as having a congenital solitary kidney might have an ectopic functioning kidney. However, if the congenital solitary kidney group had another functioning kidney, the association between solitary kidney and incident CKD could be attenuated. Fourth, the time of nephrectomy was not available in this study. Fifth, renal compensatory hypertrophy was diagnosed by experienced radiologists based on the increase in longitudinal length of the contralateral remaining kidney and body size. Therefore, there might have been misclassification of renal compensatory hypertrophy, which was determined at the discretion of the performing radiologists. Finally, the majority of participants in the present study were young to middle-aged Korean adults; hence, these results should be generalized to use in other age or race/ethnicity groups with caution.

In conclusion, having a solitary kidney was independently associated with an increased risk of CKD in this large cohort study of young to middle aged Korean adults. This association was more prominent in participants with acquired solitary kidney than with congenital solitary kidney. Preventive strategies for reducing the risk of CKD are required in individuals with either congenital or acquired solitary kidney.

Author contributions Research idea and study design: SK, YC, SR; data analysis/interpretation: SK, YC, YRL, YC, KEY, HSJ; statistical analysis: SR; supervision or mentorship: SR, YRL, YYH, KBL, KJJ, HS. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. SR and YC take responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to disclose.

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