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Published in:
American Journal of Kidney Diseases

DOI:
10.1053/j.ajkd.2020.11.012

Publication date:
2021

Familial Aggregation of CKD and Heritability of Kidney Biomarkers in the General Population: The Lifelines Cohort Study

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Rationale & Objective: Chronic kidney disease (CKD) has a heritable component. We aimed to quantify familial aggregation of CKD in the general population and assess the extent to which kidney traits could be explained by genetic and environmental factors.

Study Design: Cross-sectional 3-generation family study.

Setting & Participants: Data were collected at entry into the Lifelines Cohort Study from a sample of the general population of the northern Netherlands, composed predominantly of individuals of European ancestry.

Exposure: Family history of CKD.

Outcomes: The primary outcome was CKD, defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, where GFR was estimated using the CKD Epidemiology Collaboration creatinine equation. Among a subsample for which urinary albumin concentration was available (n = 59,943), urinary albumin excretion was expressed as the rate of urinary albumin excretion (UAE) per 24 hours or urinary albumin-creatinine ratio (UACR).

Analytical Approach: Familial aggregation of CKD was assessed by calculating the recurrence risk ratio (RRR), using adapted Cox proportional hazards models. Heritability of continuous kidney-related traits was estimated using linear mixed models and defined as the ratio of the additive genetic variance to total phenotypic variance. All models were adjusted for age, sex, and known risk factors for kidney disease.

Results: Among 155,911 participants with available eGFR data, the prevalence of CKD was 1.19% (1,862 cases per 155,911). The risk of CKD in those with an affected first-degree relative was 3 times higher than the risk in the total sample (RRR, 3.04 [95% CI, 2.26-4.09). In those with an affected spouse, risk of CKD was also higher (RRR, 1.56 [95% CI, 1.20-1.96]), indicative of shared environmental factors and/or assortative mating. Heritability estimates of eGFR, UAE, and UACR were 44%, 20%, and 18%, respectively. For serum urea, creatinine, and uric acid, estimates were 31%, 37%, and 48%, respectively, whereas estimates for serum electrolytes ranged from 22% to 28%.

Limitations: Use of estimated rather than measured GFR. UAE data only available in a subsample.

Conclusions: In this large population-based family study, a positive family history was strongly associated with increased risk of CKD. We observed moderate to high heritability of kidney traits and related biomarkers. These results indicate an important role of genetic factors in CKD risk.

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Am J Kidney Dis. 77(6):869-878. Published online December 22, 2020.

doi: 10.1053/j.ajkd.2020.11.012

Chronic kidney disease (CKD) is recognized as a global public health problem[1] with prevalence ranging between 3.3% and 17.3% in adult European populations.[2] CKD is defined by decreased estimated glomerular filtration rate (eGFR) and/or increased albuminuria, and is associated with an increased risk of cardiovascular disease (CVD) and progression to kidney failure.[3-6]

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Established risk factors for CKD, such as hypertension and diabetes, explain 50%-70% of cases and are the main targets of current risk prediction models for CKD.[7] Familial clustering of CKD and kidney-related markers suggest that genetic factors or shared environmental factors are also important in the pathogenesis of this disease.[8-12] Indirect support for a genetic component to CKD comes from recent genome-wide association studies (GWAS) of eGFR[13] and albuminuria,[14] in which a large number of genetic loci have been reported to associate with the CKD-defining traits eGFR and albuminuria.

Several knowledge gaps exist with regard to the genetic contribution to CKD susceptibility in the general population. For example, most familial aggregation studies of CKD focused on its later stages (ie, kidney failure) using medical records and registry data.[8,9,12,15] Focusing on early-stage CKD rather than kidney failure may have added value for risk stratification.

In addition to assessing familial aggregation, one can estimate the heritability of disease traits. Heritability quantifies the relative importance of genetic and environmental factors in explaining the distribution of a trait or disease within a population.[16] Both kidney function and related blood biomarkers have been shown to be heritable.[11,17,18] Related blood biomarkers are, for example, alternative kidney function markers of creatinine (eg, serum urea, uric acid) or biomarkers for which homeostasis is regulated partly through kidney function (eg, serum electrolytes). To date, the heritability of kidney traits has been estimated in

twin studies,[17,19-22] in family studies with relatively small sample size,[11,18] and in studies in isolated founder or disease populations.[23,24] Due to the differences in family design (ie, twins vs pedigrees), relatively small sample sizes, and specific populations, random sampling error may have occurred,[16] thus, generalizability of those studies may be uncertain. Therefore, heritability estimates from a large, representative sample of the general population are needed.

This study aimed to quantify the familial aggregation of CKD and to obtain heritability estimates of kidney traits and related biomarkers in the general population.

Methods

Study Design and Population

In this cross-sectional family study, we used baseline data from the Lifelines Cohort Study and Biobank, a multidisciplinary prospective population-based cohort study of the northern Netherlands with a unique 3-generation design that included 167,548 participants, of whom >95% were of European ancestry. It uses a broad range of investigative procedures in assessing the sociodemographic, biomedical, physical, behavioral, and psychological factors that contribute to the health and disease of the general population, with a special focus on multimorbidity and complex genetics. The overall design and rationale of this study have been described in detail elsewhere.[25,26] Recruitment of participants and, subsequently, their families is detailed in Item S1. Briefly, kinship was derived from questionnaires and validated in those with genetic data (available in ~50,000 participants).[27] After signing informed consent, participants received a baseline questionnaire and an invitation to a health assessment at one of the Lifelines research sites. The Lifelines Cohort Study was conducted according to principles of the Declaration of Helsinki and in accordance with the research code of University Medical Center Groningen and was approved by its medical ethical committee. All participants gave written informed consent.

Measurements

Kidney Outcomes

Participants (≥8 years of age) were invited to 1 of 12 local research sites in northern Netherlands for their physical examinations. The baseline assessment consisted of 2 visits. During the first visit, a trained research nurse performed physical examinations and provided containers and oral and written instruction for collection of a 24-hour urine sample (for those ≥18 years of age). Two weeks later, during the second visit, a fasting blood sample (for those ≥8 years of age) and the 24-hour urine sample were collected.

Measurements of serum creatinine (Scr) were performed by using an isotope-diluted mass spectrometry–traceable enzymatic method on a modular analyzer, using reagents and calibrators from Roche Diagnostics, with intra- and interassay coefficients of variation of 0.9% and 2.9%, respectively. Urinary albumin concentration was measured by nephelometry, with a lower threshold of detection of 2.3 mg/L and intra- and interassay coefficients of variation of 2.2% and 2.6%, respectively (Dade Behring Diagnostic), and multiplied by urine volume to obtain a value of urinary albumin excretion (UAE) in milligrams per 24 hours. Urinary albumin-creatinine ratio (UACR) was determined from spot urine (for those ≥8 years of age). After addition of a constant of 1 to handle zero values, UAE and UACR were natural log–transformed to approximate a normal distribution prior to statistical analyses.

CKD was defined in the primary analysis as eGFR <60 mL/min/1.73 m^2 (CKD_{Scr}) in the complete sample. In secondary analyses in a subsample where urinary albumin was available (in ~60,000 participants), we applied 2 additional definitions of CKD that incorporated albuminuria according to KDIGO (Kidney Disease: Improving Global Outcomes) guidelines.[28,29] The first additional definition took into account UAE ($CKD_{Scr+UAE}$: eGFR <60 mL/min/1.73 m^2 and/or UAE ≥30 mg/d); and the second definition took into account UACR rather than UAE ($CKD_{Scr+UACR}$: eGFR <60 mL/min/1.73 m^2 and/or UACR ≥30 mg/g). In addition, in this subsample, we repeated our analyses using moderately increased albuminuria alone (CKD_{UAE}: UAE ≥30 mg/d; CKD_{UACR}: UACR ≥30 mg/g).

We calculated eGFR using the 2012 CKD Epidemiology Collaboration (CKD-EPI) creatinine equation[30] for adults and the bedside Schwartz equation for juveniles (age <18 years).[31]

Kidney-Related Biomarkers

Kidney-related biomarkers were determined using standard methods for serum uric acid, an enzymatic colorimetric assay; for serum urea an ultraviolet kinetic assay on a Roche Modular analyzer; and for serum electrolytes (calcium, potassium, and sodium) a Roche Modular P chemistry analyzer (Roche).

Covariates

Known CKD risk factors (body mass index [BMI], hypertension, diabetes mellitus, hypercholesterolemia, smoking status, and history of CVD) were included as covariates (details in Item S1).

Statistical Analysis

Baseline Characteristics

Baseline characteristics were examined for the total population and separately for adults and in juveniles.

Recurrence Risk Ratio

Mean eGFR and prevalence of CKD were calculated for the general population and for individuals with affected

first-degree relatives. Recurrence risk ratio (RRR) of CKD was defined as the adjusted prevalence ratio between first-degree relatives of an affected individual and the general population according to the Risch definition.[32] We used Cox proportional hazards models, adapted according to Breslow,[33] to estimate prevalence ratios in a cross-sectional study by applying an equal follow-up time for all participants. This method produces consistent estimates for prevalence ratios close to true limits.[34,35] A marginal proportional hazards model was used to handle correlated observations due to familial clustering. This model estimates the mean population hazard function and uses a robust sandwich method to estimate confidence intervals (CI).[36,37] This approach has been applied and validated in previous studies of other diseases.[38–40]

For each CKD definition (CKD_{Scr}, CKD_{UAE}, CKD_{UACR}, $CKD_{Scr+UAE}$, $CKD_{Scr+UACR}$), we calculated RRR for individuals with an affected first-degree relative of any kinship. Models based on type of kinship and sex of affected relatives (eg, parents, siblings, offspring, and their sex) were explored. Additionally, we estimated RRR for individuals with an affected spouse to assess effects of shared environment and/or assortative mating. We adjusted for age, age squared, sex, and CKD risk factors.

Heritability Estimates

For all continuous traits, we estimated narrow-sense heritability, defined as the ratio of the additive genetic variance, which reflects transmissible resemblance between relatives, to the total phenotypic variance. We used the residual maximum likelihood-based variance decomposition method[41] implemented in ASReml software (VSNi).[42] With this method, the overall phenotypic variance is decomposed into genetic and environmental components. We also included household or spousal effects in the model to estimate the influence of shared environment by using family identifier or spouse identifier as a proxy. This allowed us to distinguish between shared genes and shared environment as potential sources of familial resemblance. In addition, we calculated spousal correlations for all continuous traits. *P* values for heritability were derived from likelihood ratio tests, which compare the likelihood of a heritability model to that of a model in which heritability is constrained to zero. Age, age squared, sex, and CKD risk factors were included as covariates, regardless of their statistical significance. We report the percentage of variance explained by these covariates (PVC).

To ascertain bias due to missingness, we examined the consistency of RRR estimates for CKD_{Scr}, as well as heritability estimates for eGFR, Scr, and serum potassium within the full sample and the subsample.

All analyses were performed using ASReml 4.1 software[42] and R version 3.3.1 software.[43] A two-sided significance level for analyses was set at $\alpha = 0.05$.

Results

Baseline Characteristics

From the 167,548 Lifelines participants at baseline, we included 155,911 participants (within 29,703 family clusters; 39,836 singletons) with available eGFR data during the baseline visit (Fig 1). In a subsample of 59,938 (including 743 juveniles), both eGFR and UACR were available, whereas in a subsample of 59,145 participants (only adults), both eGFR and UAE were available (Fig S1-S2). Table S1 provides more details on family structure.

In the full sample (N = 155,911; 58.1% female participants; mean age, 43.1 ± 14.7 [SD] years) participants had a mean eGFR of 97.2 ± 15.7 mL/min/1.73 m^2. In the subsample with albuminuria measurements, a median UAE of 3.86 (interquartile range [IQR], 2.33-6.92) mg/d and a median UACR of 2.72 (IQR, 1.58-7.33) mg/g were observed (Table 1). Male participants had a slightly less favorable kidney risk profile than female participants (ie, higher prevalence of smoking, hypertension, diabetes, and high cholesterol) but similar distributions in CKD risk and kidney markers (ie, eGFR and UAE) (Table S2). Participants with a family history of CKD_{Scr} had a less favorable kidney profile than those without a family history (Table S3). Distributions of age, sex, and covariates in the subsample were similar to those in the full sample (Table S4).

We identified 1,862 CKD_{Scr} cases, translating to a crude prevalence of 1.19% (Table 1). In 1,725 of 29,703 families (5.8% of family clusters), there was at least 1 CKD_{Scr} case. A total of 2,211 individuals had at least 1 first-degree relative with CKD_{Scr}: 1,680 with at least 1 affected parent, 56 with at least 1 affected offspring, and 499 with at least 1 affected sibling.

There was a dramatically greater prevalence of CKD_{Scr} in those older than 60. Mean eGFR was lower at a higher age, and age-specific mean values of eGFR were lower among individuals with affected first-degree relatives than among the general population (Fig 2A). Accordingly, the age-specific prevalence rates were significantly higher in those with a first-degree relative affected with CKD_{Scr} (Fig 2B). In the subsample, the crude prevalence rates of $CKD_{Scr+UAE}$ and $CKD_{Scr+UACR}$ were 5.5% and 6.8%, respectively (Table 1).

Recurrence Risk Ratio for CKD_{Scr}

Estimates of RRR for CKD_{Scr} are shown in Fig 3. Generally, having a first-degree relative affected with CKD_{Scr} was associated with an RRR of 3.04 (95% CI, 2.26-4.09). Familial recurrence showed no clear pattern by kinship type or sex of the affected family member. Spouses of affected individuals had higher risk than the general population (RRR, 1.56 [95% CI, 1.20-2.00]).

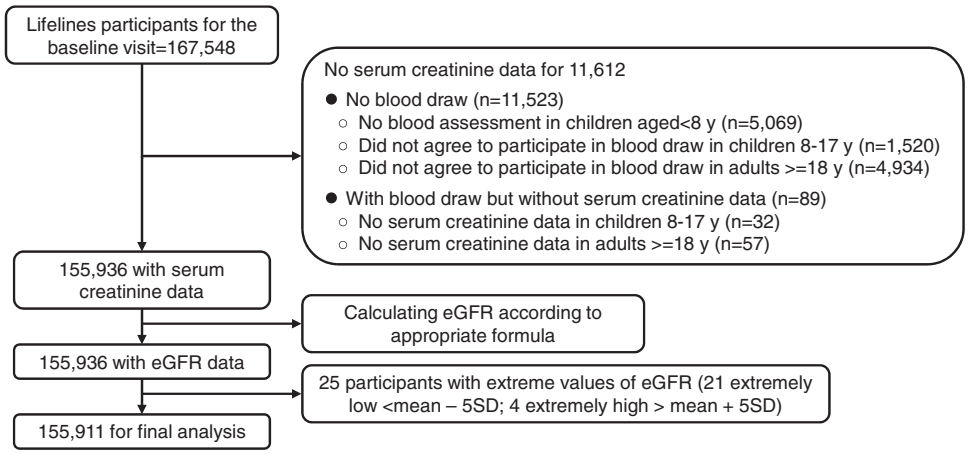

Figure 1. Flow chart of eGFR analysis. There were 21 participants with extremely low eGFR values (1 <−5 SD from the mean) who were considered CKD patients and retained in analyses of CKD. Abbreviations: eGFR, estimated glomerular filtration rate; SD, standard deviation.

Recurrence Risk Ratio for $CKD_{Scr+UAE}$ and CKD_{UAE}

In the subsample (~60,000 participants), prevalence of $CKD_{Scr+UAE}$ was higher than that of CKD_{Scr} (Fig S3). $CKD_{Scr+UAE}$ was more prevalent in those with an affected first-degree relative (Fig S4), although the trend was less pronounced compared to that for CKD_{Scr}. In the subsample, the

Table 1. Baseline Characteristics of Adult and Juvenile Participants

	Adults (Age ≥18)	Juveniles (Age 8-17)	Total
Complete sample			
No. of participants	147,715	8,196	155,911
Age, y	44.83 ± 13.12	12.21 ± 2.76	43.11 ± 14.71
Male sex	61,512 (41.64%)	3,891 (47.47%)	65,403 (41.95%)
BMI, kg/m^2	26.07 ± 4.33	18.91 ± 3.18	25.69 ± 4.56
Current smoker	31,156 (21.38%)	NA[a]	NA[a]
Hypertension	38,605 (26.13%)	NA[a]	NA[a]
Diabetes	5,673 (3.84%)	NA[a]	NA[a]
Hypercholesterolemia	29,888 (20.23%)	NA[a]	NA[a]
Serum potassium, mEq/L	3.86 ± 0.30	3.84 ± 0.28	3.86 ± 0.3
Serum creatinine, mg/dL	0.83 ± 0.14	0.61 ± 0.13	0.82 ± 0.15
eGFR, mL/min/1.73 m^2	96.41 ± 15.29	111.46 ± 16.81	97.2 ± 15.74
CKD_{Scr}[b]	1,858 (1.26%)	4 (0.05%)	1,862 (1.19%)
Subsample			
No. of participants	59,195	748	59,943
Serum calcium, mg/dL	9.14 ± 0.32	9.50 ± 0.28	9.14 ± 0.32
Serum sodium, mmol/L	141.74 ± 1.84	141.63 ± 1.68	141.73 ± 1.84
Uric acid, mg/dL	4.88 ± 1.18	4.37 ± 1.01	4.88 ± 1.18
Serum urea, mg/dL	14.48 ± 3.56	12.41 ± 2.75	14.45 ± 3.56
UACR, mg/g	2.72 [1.57-5.05]	2.93 [1.84-4.84]	2.72 [1.58-7.33]
UAE, mg/d	3.86 [2.33-6.92]	NA[a]	NA[a]
UACR ≥30 mg/g	1,622 (2.73%)	20 (2.68%)	1,642 (2.73%)
UAE ≥30 mg/d	2,431 (4.10%)	NA[a]	NA[a]
$CKD_{Scr+UACR}$	3,338 (5.52%)	24 (3.20%)	3,362 (5.49%)
$CKD_{Scr+UAE}$	4,127 (6.83%)	NA[a]	NA[a]

Data for continuous variables given as mean ± SD or median [interquartile range], and for categorical variables, as number (%). Conversion factors for calcium in mg/dL to mmol/L, ×0.2495; creatinine in mg/dL to μmol/L, ×88.4; uric acid in mg/dL to μmol/L, ×59.48; serum urea in mg/dL to mmol/L, ×0.357.
Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CKD_{Scr}, CKD defined by eGFR <60 mL/min/1.73 m^2; $CKD_{Scr+UACR}$, CKD defined by eGFR <60 mL/min/1.73 m^2 and/or UACR ≥30 mg/g; $CKD_{Scr+UAE}$, CKD defined by eGFR <60 mL/min/1.73 m^2 and/or UAE ≥30 mg/d; eGFR, estimated glomerular filtration rate; NA, not available; Scr, serum creatinine; UACR, urinary albumin-creatinine ratio; UAE, urinary albumin excretion.
[a]Data were not available for juveniles.
[b]These included 21 participants with extremely low eGFR values (less than −5 SD from the mean) who were considered CKD patients and were retained in analyses of CKD recurrence but were excluded from heritability analyses.

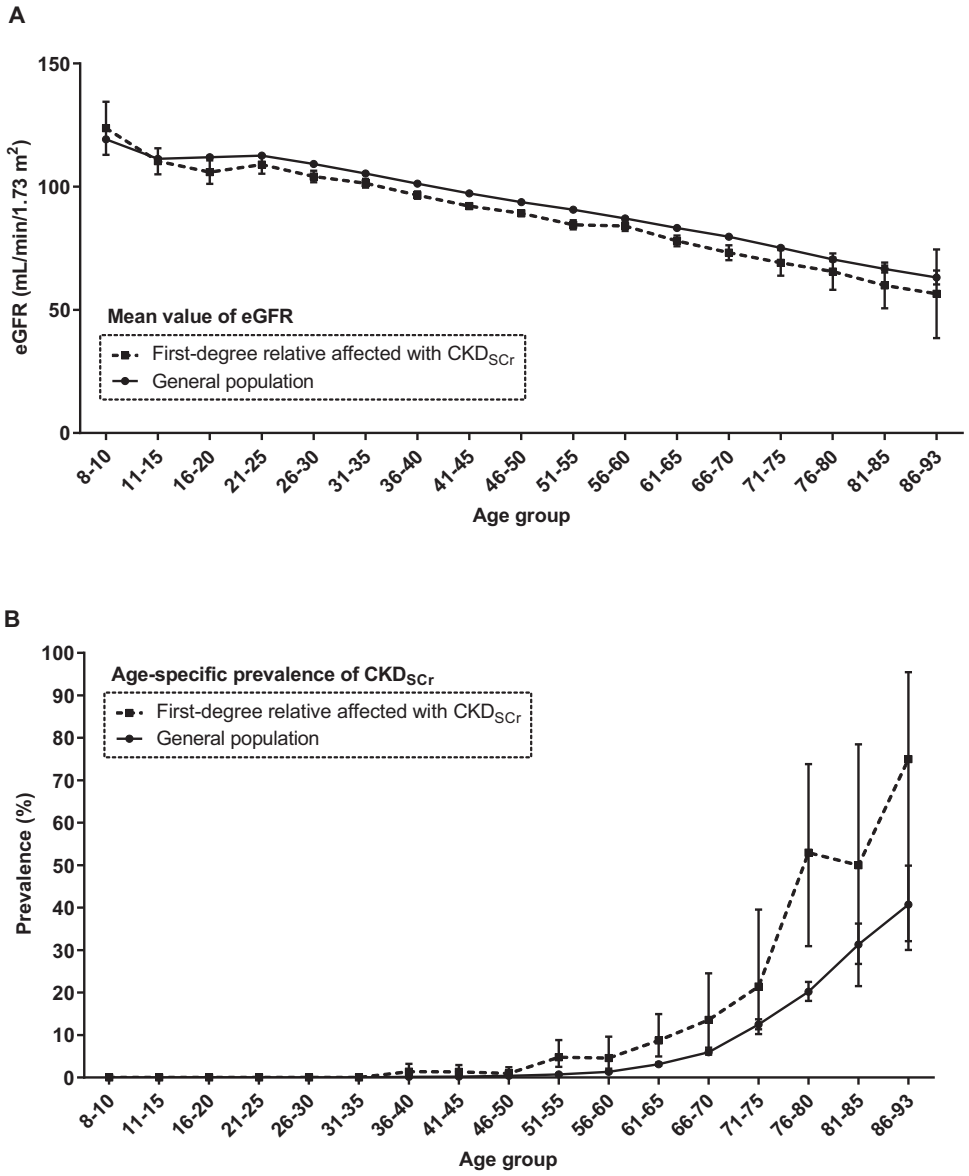

Figure 2. Comparisons of (A) age-specific mean values of eGFR and (B) age-specific prevalence of CKD_{Scr} between individuals with affected first-degree relatives and the general population. Error bars indicate 95% CI. Abbreviation: CKD_{Scr}, CKD defined by eGFR<60 mL/min/1.73 m^2.

RRR for $CKD_{Scr+UAE}$ was 1.34 (95% CI, 1.14-1.58), whereas for CKD_{Scr} this was 2.35 (95% CI, 1.74-3.17) (Fig S5). Use of UACR instead of UAE as a measurement of albuminuria yielded highly similar results (Figs S4-S8). Sensitivity analysis excluding juveniles yielded similar results (Fig S9).

We repeated our analyses using CKD_{UAE}. On average, those with a first-degree relative affected by CKD_{UAE} had higher UAE (Fig S6). Higher prevalence of CKD_{UAE} was observed among those with an affected first-degree relative (Fig S7). The RRR for CKD_{UAE} was 1.60 (95% CI, 1.26-2.03). Risk was elevated mainly in those with an affected mother or sibling. No elevated spousal risk was observed (Fig S8). Results for CKD_{UACR} were highly similar.

Heritability Estimates

We report heritability estimates of the CKD-defining traits eGFR (44%), UAE (20%), and UACR (19%), for the kidney biomarkers serum urea (31%), Scr (37%), and uric acid (48%), and for the serum electrolytes potassium (28%), calcium (27%), and sodium (22%) (Table 2). In the subsample, heritability estimates of eGFR, Scr, and serum potassium were consistent with the estimates in the full sample but less precise (Table S5), indicating low risk of bias due to missingness. Heritability estimates did not change when accounting for household or spousal effects. These effects explained <0.1% of the variance in each outcome, which was corroborated by the modest spousal correlations (Table S6). Inclusion of additional covariates did not substantially change

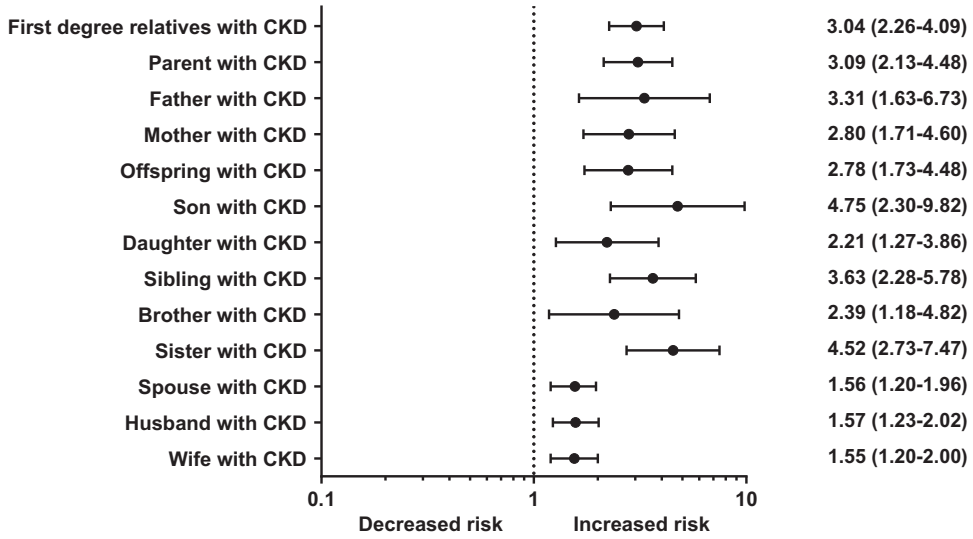

Figure 3. Recurrence risk ratios for CKD_{Scr}, adjusted for age, age^2, sex, BMI, hypertension, diabetes, high cholesterol, history of cardiovascular disease, and smoking status. Error bars indicate 95% CI. Abbreviations: BMI, body mass index; CKD_{Scr}, CKD defined by eGFR <60 mL/min/1.73 m^2.

the estimates of heritability. Age and sex explained 42% of the phenotypic variance of eGFR and only 2.6% of UAE and 8.3% of UACR. Inclusion of additional covariates increased the PVC for most traits only slightly, with the exception of uric acid, which showed a substantial increase in PVC of 10.3 percentage points. The PVC for model 2 ranged from 4.6% for potassium to 44.1% for uric acid (Table 2). Sensitivity analysis excluding juveniles yielded slightly higher heritability estimates for eGFR and serum creatinine (Table S7).

Discussion

In this large population-based family study, we investigated the familial aggregation of CKD by comparing the risk of CKD in individuals with an affected first-degree relative to that in the general population. Participants with an affected first-degree relative were observed to have a 3-fold higher risk of CKD than that in the general population, independent of BMI, hypertension, diabetes, hypercholesterolemia, history of CVD, and smoking status. We observed a 1.56-fold higher risk in those with an affected spouse, suggesting that shared environmental factors and/or assortative mating play a role. Heritability of eGFR was considerable (44%), whereas heritability of UAE was moderate (20%). Heritability of kidney-related markers and serum electrolytes ranged between 20% and 50%. These results indicate an important role for genetic factors in modulating susceptibility to kidney disease in the general population.

In this study, participants with an affected first-degree relative were observed to have a 3-fold higher risk of

Table 2. Heritability of Kidney Traits and Related Biomarkers

		Model 1		Model 2	
Traits	N	h^2 ± SE	PVC	h^2 ± SE	PVC
eGFR	155,911	0.435 ± 0.007	0.420	0.436 ± 0.007	0.423
ln(UAE)[a]	59,145	0.199 ± 0.014	0.026	0.193 ± 0.014	0.048
ln(UACR)[a]	59,938	0.185 ± 0.014	0.083	0.178 ± 0.014	0.103
Uric acid[a]	58,519	0.481 ± 0.013	0.338	0.498 ± 0.013	0.442
Serum creatinine	155,911	0.373 ± 0.007	0.374	0.379 ± 0.007	0.377
Serum urea[a]	58,481	0.307 ± 0.013	0.218	0.308 ± 0.013	0.219
Serum potassium	155,842	0.279 ± 0.007	0.041	0.278 ± 0.007	0.050
Serum calcium[a]	58,488	0.268 ± 0.013	0.059	0.267 ± 0.013	0.079
Serum sodium[a]	58,444	0.217 ± 0.013	0.066	0.221 ± 0.013	0.074

Model 1, adjusted for age, age^2, sex. Model 2, adjusted for age, age^2, sex, body mass index, diabetes, hypertension, high cholesterol, history of cardiovascular disease, and smoking status. $P < 0.001$ for all heritability estimates. UAE and UACR were natural log (ln)-transformed; eGFR and other markers were normally distributed.
Abbreviations: eGFR, estimated glomerular filtration rate; h^2, heritability; PVC, proportion of variance due to covariates; SE, standard error; UACR, urinary albumin-creatinine ratio; UAE, urinary albumin excretion.
[a]Data were available only for a subsample of adult participants.

CKD. Previous studies that examined familial aggregation of CKD focused on its end stage (ie, kidney failure). Recurrence risk of kidney failure in the case of an affected first-degree relative has been estimated in African Americans (9-fold higher risk),[44] Taiwanese Han-Chinese (2.5-fold higher risk),[12] and in a multiancestry (African and European) US population-based case-control study (1.3- to 10-fold higher risk).[8] Relative risk in a large Norwegian registry-based study was 7.2.[15] Among dialysis patients in End-Stage Renal Disease Network 6 in the United States, 23% have close relatives receiving kidney replacement therapy for kidney failure,[45] and individuals with a family history of kidney replacement therapy are at increased risk for CKD.[46]

In registry data, early stages of CKD remain unrecognized. The present study is unique in that it is based on objective laboratory measurements of eGFR and UAE spanning data from 3 generations, and is therefore more sensitive to nonsymptomatic, early-stage CKD. Data for familial recurrence of CKD may guide clinical decision making with regard to CKD diagnosis and prevention. Further study is warranted to assess the added value of family history in CKD risk stratification, and to investigate the potential impact of targeting families of CKD patients in screening and prevention.

The RRR of $CKD_{Scr+UAE}$ was significant, although considerably lower than that of CKD_{Scr}. This may be explained by our observation that familial patterns of CKD_{UAE} were less pronounced than those of CKD_{Scr}. Furthermore, we observed only moderate heritability (~20%) for measures of albuminuria (ie, genetic factors contribute relatively little to between-individual variation in urinary albumin excretion, whereas eGFR was highly heritable (~44%). The comparatively higher RRR of CKD_{Scr} is therefore expected.

Spouses of those affected by CKD were at a 1.56-fold higher risk of CKD; in addition, kidney traits showed weak but significant positive correlations between spouses. As spouses are unrelated, the increased risk of CKD in spouses and spousal correlations of kidney traits may reflect effects of shared environmental factors or assortative mating. To further assess the effects of shared environment on kidney traits, we examined family and spouse effects as variance components in our heritability models. These effects were negligible, therefore the elevated risk in spouses seems more related to assortative mating (ie, partner selection based on phenotypes that convey higher risk of CKD). Strong evidence of assortment exists for factors such as smoking,[47] height, BMI, and educational attainment,[48] each of which is a potential determinant of CKD risk. In the present study, however, spousal correlations of eGFR and UAE did not diminish after adjustment for renal risk factors (including BMI and smoking status). Thus, assortment likely occurs on factors other than currently known CKD determinants, which may be explored in future study in spousal pairs.

Between-study comparisons of heritability estimates are not straightforward, as phenotypic variance and contribution of genetic factors depend on population, ethnicity, environment, measurement methods, and sampling error. Some variability in estimates can therefore be expected. Previously, the heritability of eGFR was described in several twin studies and a few community-based studies. In the present large-scale study, we observed a heritability of 44% for eGFR, corroborating estimates from previous, relatively small-scale population-based studies, such as from Switzerland (46%)[18] and from South Tyrol, Italy (39%).[13] In pedigree data from the population-based Framingham Heart Study, the heritability estimate for eGFR was lower (33%),[49] similar to that in Zuni Indians (33%).[24] The lower estimates are possibly due to population differences, random sampling error, or use of older, less precise GFR estimating methods.[50] As generally observed for most traits, twin studies (50%-67.3%)[21,22,51] yielded somewhat higher heritability estimates for eGFR than family-based studies (33%-46%).[13,18,24,52]

The heritability estimate of urinary albumin (ie, UAE and UACR) in the present study (20%) was similar to that in a previous Swiss population-based study (23%)[18] that also collected 24-hour urine samples. The heritability of UACR was 21% in Pima Indians,[45] and 25% in Zuni Indians.[24] Heritability of UACR in European ancestry twins was 45%.[53] Previous studies in patients with diabetes reported highly variable heritability estimates (21%-46%) of albuminuria measured in spot urine samples.[54-58] Finally, we observed 22%-28% heritability for the serum electrolytes potassium, calcium, and sodium, confirming the potential for identifying genetic variants involved in electrolyte homeostasis in the general population.

Across all traits studied in twins, heritability is on average ~49%.[59] Heritability for kidney traits is comparable with those estimated for, for example, blood pressure traits (h^2: 17-52%).[60]

The heritability estimates in the present study provide an upper bound to the amount of phenotypic variance that can be attributed to genetic factors. Large-scale GWAS thus far identified 306 common single-nucleotide polymorphisms (SNPs) for Scr-based eGFR, explaining 7.1% of phenotypic variance,[13] whereas the present study estimates the heritability of Scr-based eGFR to be 44%. Similarly, the 59 SNPs thus far identified in GWAS on UACR explain 0.7%, which is modest compared to our heritability estimate of 20%.[14] Future genetic study of rare variants may potentially explain this "missing" heritability.[61,62]

For the present work, CKD was defined according to an age-independent eGFR cutoff value of <60 mL/min/1.73 m^2 as described in international guidelines.[29,63] It has been argued that an age-dependent eGFR cutoff for CKD is also appropriate, as the current definition has been suggested to lead to overdiagnosis of CKD in elderly[64] and misclassification of CKD. Future study may involve analyzing heritability using alternative definitions of CKD.

We present the largest family-based study of kidney traits that uses laboratory-defined CKD and the first study to quantify the familial clustering of CKD including early (ie, non–kidney failure) stages of CKD. Furthermore, the Lifelines Cohort Study is representative of the general population of northern Netherlands,[65] facilitating precise heritability estimation. Additionally, albuminuria was determined in both spot urine samples and in 24-hour urine collections, the latter being considered the gold standard to assess albuminuria and available to few large-scale epidemiological studies.

Several limitations need to be addressed. First, although the gold standard 24-hour albuminuria measurements were available, this was only true for a subsample of approximately 60,000 participants. However, age, sex, and covariate distributions were highly similar between the subsample and the full sample, as were heritability estimates of eGFR, Scr, and serum potassium. Thus, missingness was likely random and unlikely to have seriously biased our results. Second, GFR was not measured but was estimated from Scr. Therefore, bias is possible due to creatinine metabolism. In addition, GFR estimating equations are known to be less precise in the higher range (>60 mL/min/1.73 m^2),[66-68] possibly causing downward bias in our heritability estimates. Third, no kidney biopsy data were available, nor could we exclude Mendelian forms of inherited kidney disease; we therefore could not distinguish between the different etiologies of CKD. Fourth, potential preferential missingness of data from nonparticipating affected family members may have caused underestimation of recurrence risk ratios. Fifth, the low prevalence of CKD in our study population (CKD_{Scr}: 1.19%) may have inflated relative risk estimates. Finally, >95% of Lifelines Cohort Study participants were of European ancestry[69]; therefore, we cannot generalize our results to other ancestries.

In summary, we demonstrate that CKD clusters in families in the general population, given that risk of CKD was strongly elevated in those with an affected relative. Considerable heritability (20-50%) of kidney traits was observed. Therefore, much of the familial clustering may be attributed to genetic factors. The data presented in this study inform future work on risk stratification based on family history, and provide a step forward in disentangling genetic and environmental risk factors in CKD.

Supplementary Material

Supplementary File (PDF)

Figure S1: Flow chart of eGFR and UACR analysis.

Figure S2: Flow chart of eGFR and UAE analysis.

Figure S3: Age-specific prevalence of CKD in the general population diagnosed by different criteria.

Figure S4: Comparisons of age-specific prevalence of CKD between individuals with affected first-degree relatives and the general population.

Figure S5: RRRs for CKD in individuals with affected first-degree relatives or spouse.

Figure S6: Comparisons of age-specific geometric means of UAE and UACR.

Figure S7: Comparisons of age-specific prevalence of UAE ≥ 30 mg/d and UACR ≥ 30 mg/g.

Figure S8: RRRs for UAE ≥ 30 mg/d and UACR ≥ 30 mg/g.

Figure S9: Recurrence risk of CKD_{Scr} in adult participants only.

Item S1: Detailed methods.

Table S1: Family structure.

Table S2: Baseline characteristics of adult and juvenile participants stratified by sex and age.

Table S3: Baseline characteristics of participants with and without CKD_{Scr} family history.

Table S4: Baseline characteristics of adult and juvenile participants in the subsample, stratified by sex and age.

Table S5: Heritability of eGFR, Scr, and potassium in subsample participants only.

Table S6: Spousal correlations.

Table S7: Heritability of eGFR, Scr, and potassium in adult participants only.

Article Information

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Support: The Lifelines Cohort Study was supported by the Netherlands Organization of Scientific Research NWO grant 175.010.2007.006; the Economic Structure Enhancing Fund (FES) of the Dutch Government; the Ministry of Economic Affairs; the Ministry of Education, Culture and Science; the Ministry for Health, Welfare and Sports; the Northern Netherlands Collaboration of Provinces (SNN); the Province of Groningen; the University Medical Center Groningen; the University of Groningen; the Dutch Kidney Foundation; and the Dutch Diabetes Research Foundation. Dr Zhang was awarded a personal grant by China Scholarship Council (CSC) during his study period in the Netherlands. The

funders had no role in study design, data collection, analysis, reporting, or the decision to submit for publication.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Acknowledgements: We acknowledge the services of the Lifelines Cohort Study, the contributing research centers delivering data to Lifelines, and all study participants. We also thank Dr Chang Fu Kuo for modeling the recurrence risk ratio of CKD in the general population, and Arthur Gilmour for technical support with ASReml software.

Peer Review: Received March 1, 2020. Evaluated by 2 external peer reviewers, with direct editorial input from a Statistics/Methods Editor, an Associate Editor, and the Editor-in-Chief. Accepted in revised form November 6, 2020.

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