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The Heritability of Kidney Function Using an Older Australian Twin Population

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Introduction: Twin studies are unique population models which estimate observed rather than inferred genetic components of complex traits. Nonmonogenic chronic kidney disease (CKD) is a complex disease process with strong genetic and environmental influences, amenable to twin studies. We aimed to assess the heritability of CKD using twin analysis and modeling within Older Australian Twin Study (OATS) data.

Methods: OATS had 109 dizygotic (DZ) and 126 monozygotic (MZ) twin pairs with paired serum creatinine levels. Heritability of kidney function as estimated glomerular filtration rate (eGFR CKD Epidemiology Collaboration [CKD-EPI]) was modeled using the ACE model to estimate additive heritability (A), common (C), and unique (E) environmental factors. Intratwin pair analysis using mixed effects logistic regression allowed analysis of variation in eGFR from established CKD risk factors.

Results: The median age was 69.71 (interquartile range 78.4–83.0) years, with 65% female, and a mean CKD-EPI of 82.8 ml/min (SD 6.7). The unadjusted ACE model determined kidney function to be 33% genetically determined (A), 18% shared genetic-environmental (C), and 49% because of unique environment (E). This remained unchanged when adjusted for age, hypertension, and sex. Hypertension was associated with eGFR; however, intertwin variance in hypertension did not explain variance in eGFR. Two or more hypertension medications were associated with decreased eGFR ($P = 0.009$).

Conclusion: This study estimates observed heritability at 33%, notably higher than inferred heritability in genome-wide association study (GWAS) (7.1%–18%). Epigenetics and other genomic phenomena may explain this heritability gap. Difference in antihypertension medications explains part of unique environmental exposures, though discordance in hypertension and diabetes does not.

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There is a complex relationship between aging and key risk factors including hypertension and diabetes and the development of CKD. In Australians aged between 65 and 74 years, 20.9% have CKD, and 42% >75 years have CKD with a high burden on health care admissions.[1] Complex genetic and environmental factors underpin the development of CKD. It is important to consider the interplay between genetic predisposition to kidney function in elderly populations in conjunction with established environmental risk factors.

Twin and family studies provide powerful tools to investigate genetic and environmental factors in human disease. A twin study found that the heritability of nephrolithiasis was 46% in females and 57% in men, highlighting genetic and gender-related environmental contributions.[2] Norwegian cohorts have found kidney failure clusters in families, where nonhereditary nephropathies increase the relative risk of kidney failure 3.7-fold in first-degree relatives.[3] A longitudinal study of healthy twins investigated change in kidney function because of metabolic syndrome and found that that genetic correlation was significant for high-density lipoprotein cholesterol and kidney function. Waist circumference, glucose, blood pressure (BP),

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triglycerides, and body mass index had significant environmental correlation with kidney function.[4] Thus, family studies can assess both genetic and environmental factors in CKD.

The field of genetics in CKD is expanding our understanding of disease processes, from classic Mendelian and monogenic inheritance to polygenic complex traits analysis identifying new genes and pathways of interest. Autosomal dominant polycystic kidney disease and Alport syndrome are well-described monogenic disorders. Autosomal dominant polycystic kidney disease involves single mutations in *PKD1* or *PKD2* with significant phenotypic variation.[5] Of people with CKD, 10% have identifiable genetic abnormalities underpinning their disease process, using whole exome sequencing data from a 625-gene panel.[6] The most common cause of CKD in children is nephronophthisis, an autosomal recessive ciliopathy, which is associated with at least 25 genes.[7] Nephronophthisis exhibits significant variability, even within families, and genetic diagnosis has furthered our understanding in adult CKD.[8] *APOL1* G1/G2 have been linked with progression to end-stage kidney disease with focal segmental glomerulosclerosis and lupus nephritis in African American populations.[9] Genes involved in biological pathways contributing to the major risk factors for progression of CKD such as hypertension and diabetes are of particular interest. A meta-analysis of 23 studies with 7918 cases and 6905 controls found that *AGTR1A A1166C*, a polymorphism in a gene involved in the renin-angiotensin system and significantly implicated in hypertension, was not associated with incidence of CKD, although more data in the South Asian populations are required.[10] A 2005 meta-analysis of 14,727 subjects supports a genetic association in the *ACE* gene locus with diabetic nephropathy.[11] Two single nucleotide polymorphisms (SNPs) in *SLC19A3*, an intracellular thiamine transporter, seem to be protective against microvascular complications including retinopathy and nephropathy in type 1 diabetics.[12] GWAS have estimated the genetic contribution to kidney function between 7% and 19.6%, with higher estimates in more targeted groups such as those with diabetes mellitus.[13,14] These examples highlight the important interplay between genetic variation and environmental factors leading to kidney disease, in addition to and outside the traditional and more deterministic modes of Mendelian inheritance.

Twin studies are able to determine heritability, the amount of phenotypic variation in trait in a population attributable to genetic differences. Heritability is estimated using data from MZ (identical genetic background) and DZ (sibling models with 50% shared genetic material) twins. The identified genetic determination of kidney function varies between GWAS and familial studies, and studies in elderly populations are often missing from GWAS data sets. Twin study analyses in populations with elderly cohorts which have inherently more time opportunity for experiencing comorbidities, senescence, and kidney phenotypes are lacking. This study aims to determine the genetic contribution to kidney function through a twin study of older people and to determine the potential influence of high-risk medical conditions such as hypertension and diabetes.

METHODS

Participant Recruitment

Twins aged ≥65 years were recruited by the OATS through the Twins Research Australian as described previously.[15] The inclusion criteria were age ≥65 years, ability to consent, having a consenting co-twin, having completed education in English, and being at least of low-average intelligence quotient. The exclusion criteria included diagnosis of malignancy or other life-threatening medical illness and current diagnosis of acute psychotic disorder. Participants provided written informed consent.

Clinical Assessment

Sociodemographic data, medical and psychiatric history, detailed family history, and risk factor schedule were collected, and a standard medical examination was performed. Medication lists were collected on a per patient basis and categorized into number of antihypertensives, oral hypoglycemics, or insulin. The lowest of 3 clinic systolic and diastolic BP measures was included for analysis. Only twin pairs who donated a blood sample for clinical chemistry were included in the analysis. Kidney function was calculated using the CKD-EPI equation from serum creatinine, age, gender, and ethnicity data.[16] Of the OATS participants, 77% were included in the analysis.

Analysis

Twins were paired and labeled as MZ or DZ. Twins who did not have both serum creatinine collected were excluded from the analysis. There were 470 twins (126 MZ pairs, 109 DZ pairs) with paired serum creatinine available. Data were analyzed in STATA 15 (StataCorp, 2017, College Station, TX). Statistical significance was indicated at a $P < 0.05$.

The ACE classical twin model for quantitative traits was used to establish concordance and heritability.[17] Linear mixed effect models were run, 1 for MZ only and 1 for DZ twins only with twin pair as a random effect, 1 for all twins with twin pair as a random effect, and 1 for all twins where separate effects for MZ and DZ twins

Table 1. Characteristics and medical history of twin participants

	MZ (n = 252)		DZ (n = 218)	
Variables	***n***	**Summary, *n* (%)**	***n***	**Summary, *n* (%)**
Sex, *n* (%)	252		218	
Male/male		48 pairs (38.1)		14 pairs (12.8)
Female/female		78 pairs (61.9)		56 pairs (51.4)
Male/female		0 pairs (0.0)		39 pairs (35.8)
Age, median (IQR)	252	69.7 (66.7–74.2)	218	69.7 (66.8–74.1)
BMI, kg/m^2, median (IQR)	245	26.1 (23.7–28.5)	209	26.2 (23.8–28.9)
Type 2 diabetes, *n* (%)	252	24 (9.5)	217	22 (10.1)
No. diabetes medications, *n* (%)	252		218	
0		234 (92.9)		201 (92.2)
1		13 (5.2)		11 (5.0)
2		5 (2.0)		3 (1.4)
3		0 (0.0)		3 (1.4)
eGFR, mean (SD)	252	82.4 (6.8)	218	83.2 (6.6)
SBP, mean (SD)	245	132.2 (19.3)	207	132.6 (18.7)
DBP, mean (SD)	245	77.6 (11.0)	207	78.1 (10.9)
Hypertension, *n* (%)	250	134 (53.6)	216	114 (52.8)
No. hypertension medications, *n* (%)	252		218	
0		138 (54.8)		109 (50.0)
1		49 (19.4)		58 (26.6)
2		41 (16.3)		31 (14.2)
3		15 (6.0)		14 (6.4)
4		8 (3.2)		4 (1.8)
5		1 (0.4)		2 (0.9)

BMI, body mass index; DBP, diastolic blood pressure; DZ, dizygotic; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MZ, monozygotic; SBP, systolic blood pressure.

were included where twin number was nested within twin pair. Models were also adjusted for age and sex based on clinical reasoning and separately adjusted for age and hypertension based on a backward elimination variable selection process. Intraclass correlations, DZ covariance, and ACE variance components were derived from these unadjusted and adjusted models. Nested models were compared using the likelihood ratio test.

To determine the genetic and environmental determinants of kidney function, the following 3 analyses were run: "initial multivariable" analysis to determine significant factors for eGFR in our population; "intrapair" analysis to assess differences within twin sets; and "intra- and interpair" analysis to consider if twin pairs, considered separately and together, are different from other paired twins. The "initial multivariable" analysis was performed using mixed effects models with twin pair ID as a random effect to identify whether variables were associated with eGFR. These models of eGFR were performed using age, sex, weight, height, diabetes, and hypertension status as covariates or using age, sex, weight, height, diabetes medication, and hypertension medications as covariates. These covariates are to kidney function as measured by eGFR (CKD-EPI).

As a part of the "intrapair" analysis, the difference in the outcome of eGFR between twins and the difference between covariates between twins were computed, resulting in 1 record per twin pair. The same covariates used in the "initial multivariable" analysis were computed except for age, as it was reasonably assumed that there would be no variability in ages within twins. These "difference" covariates (excluding age) were then used to model the "difference" in GFR between twin pairs using multivariable linear regressions. Zygosity was not accounted for in these models.

"Intrapair and interpair" analysis was used to examine twins as paired sets and considers the impact of each factor, that is, each twin's hypertensive status, on the paired twin eGFR. This analysis models eGFR including both the twin pair mean and the twin pair difference from the twin pair mean for each covariate in the model. All covariate twin pair means and differences were calculated and included in the analysis, except for the twin pair difference in age, owing to twin pairs sharing the same age. The analyses presented used mixed effects models with twin pair as a random effect.

Ethics

The OATS has been approved prospectively by the University of New South Wales Human Research Ethics Committee (approval HC17414), and the data request for this specific project was approved by the OATS governance committee. This specific project was

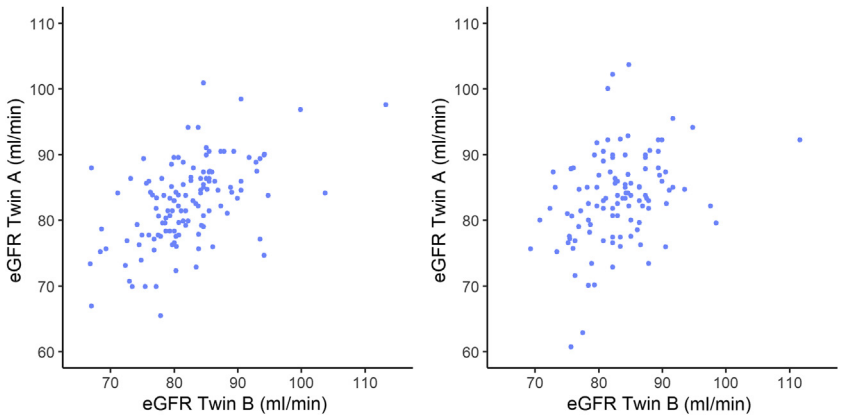

Figure 1. Scatterplot of eGFR as an estimate of kidney function between twin pairs. The correlation in MZ twins (0.51 [95% CI 0.41–0.65]) was slightly less than twice that of DZ twins (0.35 [95% CI 0.22–0.56]). DZ, dizygotic; eGFR, estimated glomerular filtration rate; MZ, monozygotic.

further approved by the Royal Brisbane and Women's Hospital Human Research Ethics Committee (approval LNR/2018/QRBW/44085).

RESULTS

Table 1 illustrates the baseline demographics of MZ and DZ twins. This was an older population, with a median age of 69.7 years. The population had a high female prevalence in both MZ (61.9%) and DZ (69.3%) twins. Within the DZ twins, 12.8% were male/male, 51.4% female/female, and 35.8% male/female. Only 9.5% of MZ and 10.1% of DZ twins had type 2 diabetes, whereas more than half of the twins had hypertension (MZ 53.6%, DZ 52.8%).

Concordance

As expected, estimated eGFR was more similar between MZ than DZ twins (Figure 1). The correlation in MZ twins (0.51 [95% CI 0.41–0.65]) was less than twice that of DZ twins (0.35 [95% CI 0.22–0.56]) (Table 2), indicating additive genetic effects contributing to eGFR.[18] Correlations of eGFR between MZ and between DZ twins were also similar in sex- and hypertension-adjusted and sex- and age-adjusted models. Comparisons of unadjusted models for all twins and all twins with separate effects for MZ and DZ twins indicated a significant difference between MZ and DZ correlations ($P = 0.044$), which remained after adjustment for sex and hypertension ($P = 0.032$) and adjustment for sex and age ($P = 0.044$). The ACE model (Figure 2, Table 3) determined unadjusted heritability at A = 0.33, C = 0.18, and E = 0.49, which did not change markedly when adjusted for sex and hypertension or sex and age. All unadjusted and adjusted comparisons of ACE and AE models resulted in P values < 0.001, indicating the ACE model is most appropriate.

Genetic and Environmental Determinants of eGFR

Two linear mixed effect models (models 4.1 and 4.2; Table 4) were run to evaluate the association between established risk factors and kidney function. Model 4.1 (included age, weight, height, gender, hypertension, and type 2 diabetes) identified hypertension as statistically significantly associated with a decrease in eGFR (β −1.59 [95% CI −2.82 to −0.36], $P = 0.011$). For kidney function, model 4.2 (included age, weight,

Table 2. Correlation and covariance of eGFR between twins by zygosity

	Unadjusted				Sex and hypertension adjusted				Sex and age adjusted			
Model	Zygotic covariance	(95% CI)	ICC	(95% CI)	Zygotic covariance	(95% CI)	ICC	(95% CI)	Zygotic covariance	(95% CI)	ICC	(95% CI)
MZ twins only	23.6	(16.2–34.5)	0.52	(0.39–0.64)	22.8	(15.5–33.5)	0.52	(0.39–0.65)	22.2	(15.1–32.7)	0.50	(0.38–0.63)
DZ twins only	14.5	(8.0–26.0)	0.34	(0.19–0.52)	12.9	(6.9–24.2)	0.31	(0.17–0.50)	13.3	(7.1–24.6)	0.32	(0.18–0.50)
All twins—no MZ/DZ effects	19.5	(14.2–26.9)	0.44	(0.34–0.54)	18.2	(13.0–25.3)	0.43	(0.32–0.53)	18.2	(13.1–25.3)	0.42	(0.32–0.53)
All twins—MZ/DZ effects												
MZ	22.8	(16.7–31.1)	0.51	(0.41–0.65)	21.7	(15.8–29.8)	0.51	(0.40–0.65)	21.4	(15.5–29.5)	0.50	(0.39–0.64)
DZ	15.4	(9.1–26.0)	0.35	(0.22–0.56)	13.8	(7.8–24.4)	0.32	(0.19–0.55)	14.1	(8.0–24.6)	0.33	(0.20–0.55)

DZ, dizygotic; eGFR, estimated glomerular filtration rate; ICC, intraclass correlation; MZ, monozygotic.
Covariance models first consider "MZ only" or "DZ only" twin pairs, then consider "All twins—no MZ/DZ effect," which does not consider for zygosity, and "All twins—MZ/DZ effects," which incorporates zygosity into the modeling.

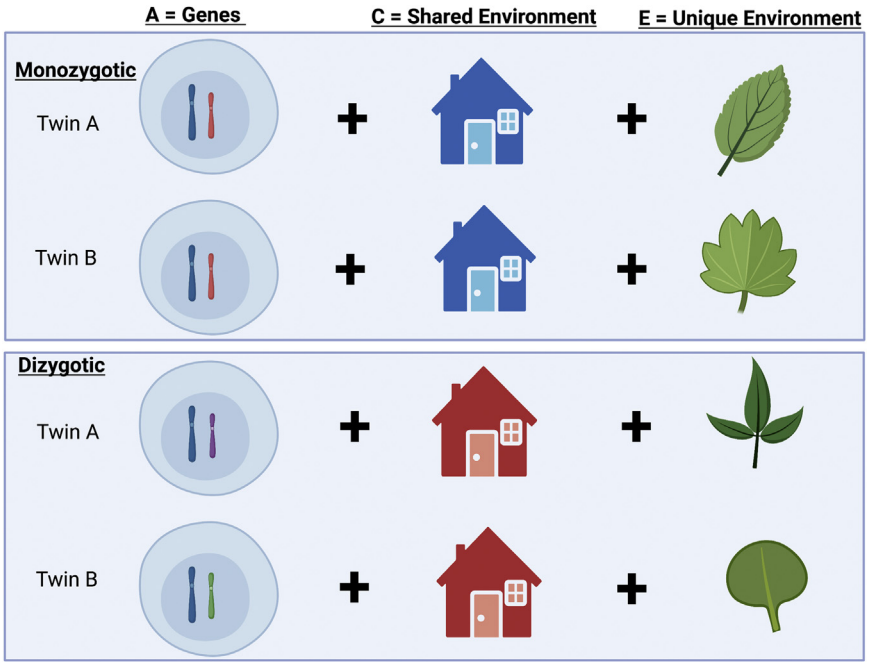

Figure 2. ACE model. A refers to additive genetic effects, which are considered 100% in monozygotic twins and 50% in dizygotic twins. C refers to common environment effects, presumed shared environment until age 18 years. E refers to unshared environmental effects, such as difference in smoking status.

height, gender, number of hypertension medications, and type 2 diabetes medications) revealed that taking >2 hypertension medications was significantly associated with a decrease in estimated eGFR (β −1.96 [95% CI −3.42 to −0.49], $P = 0.009$), although diabetes medications were not ($P = 0.69$). The number of medications was included as a marker of exposure level for hypertension and diabetes. A third model was run combining hypertension, hypertension medications, diabetes status, and diabetes medications that did not reveal any further significant associations with eGFR (results not presented).

Table 5 outlines the results of the intrapair analysis, where the twin pair difference in GFR is modeled by the twin pair differences in covariates. Hypertension and diabetes status (model 5.1) were modeled separately to antihypertensive and diabetes medication (model 5.2). The multivariable linear regressions (Table 5) did not identify any significant relationship between intratwin pair variation in eGFR and intratwin pair differences in height, weight, hypertension, diabetes, or medications.

An intratwin and intertwin analysis, as found in Table 6, similarly did not identify any associations between the twin pair mean or twin pair difference covariates and eGFR.

Table 7 illustrates the heritability estimates for kidney function from 9 twin studies. Measures of eGFR estimates varied across populations, including Sweden, Hungary, California, Australia, and Vietnam.[19–26]

Table 3. ACE and AE models for eGFR

	Unadjusted				Sex and hypertension adjusted				Sex and age adjusted			
Model	Covariance (95% CI)		Prop. variance (95% CI)		Covariance (95% CI)		Prop. variance (95% CI)		Covariance (95% CI)		Prop. variance (95% CI)	
ACE												
A	14.8	(4.5–48.2)	0.33	(0.07–0.74)	15.9	(5.3–47.3)	0.37	(0.08–0.77)	14.7	(4.5–47.9)	0.37	(0.08–0.77)
C	8.0	(1.2–53.9)	0.18	(0.01–0.65)	5.8	(0.4–76.5)	0.14	(0.004–0.69)	6.7	(0.7–63.2)	0.14	(0.004–0.69)
E	21.6	(17.0–27.4)	0.49	(0.37–0.61)	20.9	(16.4–26.6)	0.49	(0.37–0.61)	21.6	(17.0–27.4)	0.49	(0.37–0.61)
AE												
A	22.8	(16.8–30.9)	0.51	(0.40–0.63)	21.7	(15.8–29.7)	0.51	(0.39–0.63)	21.3	(15.6–29.3)	0.51	(0.39–0.63)
E	21.6	(17.0–27.4)	0.49	(0.37–0.60)	20.9	(16.4–26.6)	0.49	(0.37–0.61)	21.5	(17.0–27.3)	0.49	(0.37–0.61)

A, additive genetic; C, common environment; E, unique environment; eGFR, estimated glomerular filtration rate.
The partitioning of the total variance of kidney function as eGFR into variance components for A, C, and E effects where the proportion of variance because of A, C, and E is also listed. All unadjusted and adjusted comparisons of ACE and AE models resulted in $P < 0.001$.

Table 4. Relationship of environmental factors to eGFR-initial modeling using mixed effect models

	Model 4.1			Model 4.2		
Variable	β	(95% CI)	*P* value	β	(95% CI)	*P* value
Age	−0.13	(−0.27 to 0.01)	0.070	−0.13	(−0.26 to 0.01)	0.070
Weight	−0.04	(−0.10 to 0.01)	0.13	−0.04	(−0.09 to 0.01)	0.13
Height	0.01	(−0.08 to 0.10)	0.90	−0.003	(−0.09 to 0.09)	0.95
Sex						
Female	Ref			Ref		
Male	−1.58	(−3.51 to 0.36)	0.11	−1.22	(−3.12 to 0.68)	0.21
Hypertension						
No	Ref					
Yes	−1.59	(−2.82 to −0.36)	0.011			
Type 2 diabetes						
No	Ref					
Yes	0.74	(−1.32 to 2.81)	0.48			
Hypertension medications						
0				Ref		
1				−1.08	(−2.53 to 0.37)	0.14
2+				−1.96	(−3.42 to −0.49)	0.009
Diabetes medications						
No				Ref		
Yes				−0.47	(−2.79 to 1.84)	0.69

eGFR, estimated glomerular filtration rate; Ref, reference.

DISCUSSION

In a population of Australian twins >65 year of age, we estimate heritability of kidney function at 33%, 49% determined by unique environmental factors and 18% from shared environment. Correlation was higher in MZ than DZ twins, which suggests additive genetic effects contributing to eGFR. Results suggest that hypertension and >2 antihypertensive medications were associated with eGFR. Intrapair analysis, evaluating for differences between pairs, suggested that a trend toward hypertension status contributing to differences in eGFR, although not statistically significant, is an area for future exploration with a larger sample size. Analysis between twin pairs found no association with diabetes status, although the overall number of participants with diabetes was low. "Intra- and intertwin models" assess twins both as pairs and at a population level. Our analysis suggested that number of hypertension medications, which may represent severity of hypertension exposure, accounts for significant variance in eGFR between twins. Together, these analyses are in keeping with previous research that hypertension is a modifiable environmental factor that influences eGFR. In a broader context, we found that heritability estimates from twin studies are greater than those found in GWAS and highlight the importance of twin studies to understand the interplay between environmental and genetic factors.

Correlation of CKD-EPI between MZ twins (0.52) was higher than DZ twins (0.35), which indicates a genetic component with additive genes and a shared environment. When DZ correlation is more than half of the MZ correlation, this suggests both additive genetic effects and shared environmental effects.[18] Other studies estimate correlation of kidney function in MZ twins at 0.50 to 0.57 and DZ twins at 0.24 to 0.31, which is similar to our results, and supports that eGFR is

Table 5. Multivariable linear regression of twin pair difference (twin 2–twin 1) in eGFR

	Model 5.1			Model 5.2		
Twin pair difference covariate	β	(95% CI)	*P* value	β	(95% CI)	*P* value
Age						
Weight	−0.01	(−0.09 to 0.06)	0.75	−0.01	(−0.09 to 0.06)	0.71
Height	−0.01	(−0.14 to 0.13)	0.94	−0.03	(−0.16 to 0.11)	0.69
Sex	−1.29	(−4.46 to 1.87)	0.42	−0.56	(−3.63 to 2.52)	0.72
Hypertension	−1.51	(−3.20 to 0.19)	0.081			
Type 2 diabetes	−1.21	(−4.02 to 1.61)	0.40			
Hypertension medications				−0.76	(−1.71 to 0.19)	0.12
Diabetes medications				0.60	(−2.39 to 3.60)	0.69

eGFR, estimated glomerular filtration rate.

Table 6. Within pair and between pair analysis

	Model 6.1			Model 6.2		
Covariate[a]	β	(95% CI)	*P* value	β	(95% CI)	*P* value
Age (mean)	−0.13	(−0.28 to 0.01)	0.069	−0.12	(−0.26 to 0.02)	0.10
Weight (mean)	−0.06	(−0.14 to 0.02)	0.14	−0.05	(−0.12 to 0.03)	0.22
Weight (dif)	−0.02	(−0.10 to 0.05)	0.59	−0.02	(−0.10 to 0.05)	0.53
Height (mean)	0.003	(−0.12 to 0.13)	0.96	0.0001	(−0.12 to 0.12)	1.00
Height (dif)	0.01	(−0.13 to 0.14)	0.92	−0.01	(−0.15 to 0.12)	0.85
Sex (mean)	−1.32	(−3.83 to 1.18)	0.30	−1.25	(−3.70 to 1.20)	0.32
Sex (dif)	−1.62	(−4.70 to 1.46)	0.30	−0.97	(−3.97 to 2.04)	0.53
Hypertension (mean)	−1.74	(−3.60 to 0.12)	0.067			
Hypertension (dif)	−1.40	(−3.06 to 0.25)	0.097			
T2DM (mean)	0.28	(−2.81 to 3.38)	0.86			
T2DM (dif)	−1.57	(−4.32 to 1.18)	0.26			
Hypertension medications (mean)				−1.13	(−2.28 to 0.01)	0.052
Hypertension medications (dif)				−0.82	(−1.75 to 0.11)	0.086
Diabetes medications (mean)				−3.25	(−6.96 to 0.46)	0.086
Diabetes medications (dif)				1.17	(−1.73 to 4.07)	0.43

T2DM, type 2 diabetes mellitus.
[a]Mean indicates mean of twin pairs, dif indicates difference of twin pair from twin mean.
This model analyzes eGFR variation within and between twin pairs and includes both the twin pair mean and the twin pair difference from the twin pair mean for each covariate in the model.

genetically determined.[20,21] In female-only twin analysis, correlation of creatinine clearance in MZ (0.77) and DZ twins (0.52) was higher than our study, which may reflect the younger age (<50 years) of the cohorts and average normal kidney function, with median calculated creatinine clearance >90 ml/min.[22] Our population was older with more variation in kidney function, although all participants had an eGFR >60 ml/min per 1.73 m^2, limiting assessment of CKD. A key assumption of twin modeling is shared environment until age 18 years. The prevalence of kidney disease rises dramatically in older populations, from 7.9% in 55 to 64 years to 20.9% in 65 to 74 years, which our twins all had preserved kidney function limits

Table 7. Twin study heritability estimates of kidney function in different age groups

Population		Twins	Mean age (yr)	Gender (% female)	Renal function estimate (mean)		Heritability (A)	Shared environment (C)	Unique environment (E)
Australian NHMRC registry	Total MZ DZ	412 170 242	23.1	51	Serum creatinine (μmol/l)	84.9 male, 72.2 female	0.47 (SEM 0.17)	0.21	0.40
Southern California twin registry	Total MZ DZ	741	41.7 (SEM 0.5)	73	CKD-EPI (ml/min)	103.6 (SEM 0.76)	67.3 (SEM 4.7)	—	—
Southern California twin registry	Total MZ DZ	374 258 116	40.7 (SEM 0.85)	76	Modification of diet in renal disease (ml/min)	92.2 (SEM 1.36)	0.776 (SEM 0.034)	—	—
Hungary twin population	Total MZ DZ	202 63 38	47.4 (SD 15.5) 38.3 (SD 13.5)	73 71.1	Serum creatinine (μmol/l)	70 (SD 9.8) 72.3 (SD 11.4)	0.623 (95% CI 0.449–0.784)	0 (95% CI 0–0.562)	0.377 (95% CI 0.216–0.539)
St Thomas' UK Adult Twin registry	Total MZ DZ	3494 1078 2416	48 (SD 13.6) 46.8 (SD 11.5)	100 100	Creatinine clearance (ml/min)	93.9 (SD 22.3) 99.3 (SD 27)	0.63 (95% CI 0.54–0.72)	0.18 (95% CI 0.10–0.26)	0.19 (95% CI 0.16–0.22)
Emory Twin Study (Vietnam Era Twin registry)	Total MZ DZ	515 304 206	55 (SD 3.0)	0	CKD-EPI(ml/min)	88.3 (SD 12.5)	0.51 (95% CI 0.39–0.61)	—	0.49 (95% CI 0.39–0.61)
TwinGene	Total MZ DZ	10,682 2499 8183	65 (SD 8)	52	Cystatin C eGFR (ml/min)	—	0.38 (95% CI 0.23–0.52)	—	—
Older Australian Twin Study	Total MZ DZ	470 252 218	71.06 (SD 5.13) 71.19 (SD 5.59)	65 61.9 69.3	CKD-EPI (ml/min)	82.4 (SD 6.8) 83.2 (SD 6.6)	0.33 (95% CI 0.07–0.74)	0.18 (95% CI 0.01–0.65)	0.49 (95% CI 0.37–0.61)
Origins of variance in the old-old: octogenarian twins	Total MZ DZ	432 192 240	84.4 (range 81–95 yr)	64	Serum creatinine (μmol/l)	91.8 (SD 28.4)	0.18 (95% CI 0–0.55)	0.02 (95% CI 0–0.33)	0.52 (95% CI 40–0.68)

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DZ, dizygotic; MZ, monozygotic.
Heritability estimates (h^2) for kidney function were extracted from published twin studies.

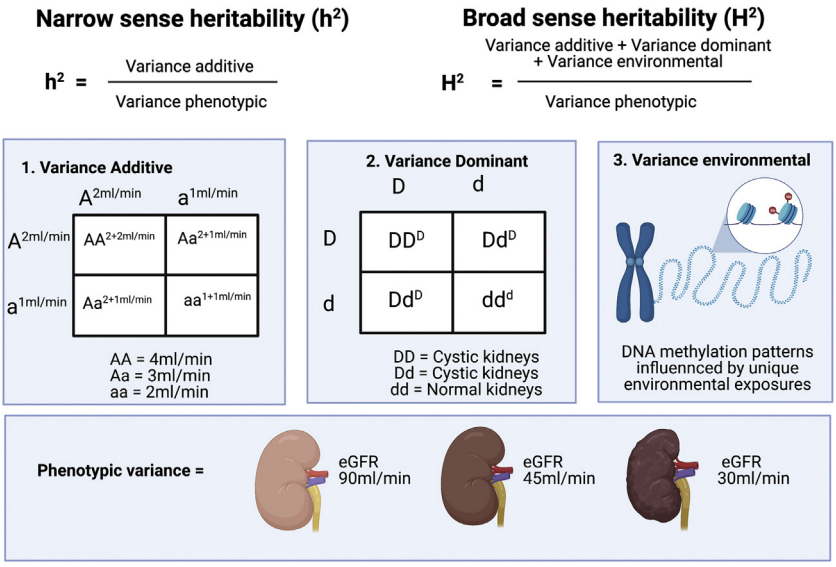

Figure 3. Difference between narrow and broad sense heritability. Heritability is a measure of much of a characteristic that is determined by underlying genetics. Narrow sense heritability (panel 1) estimates heritability only using additive genetic effects. *Va* is where if allele A contributes 2 ml/min of eGFR and allele a contributes 1 ml/min of eGFR, then AA will contribute 4 ml/min, Aa 3 ml/min, and aa 2 ml/min. Broad sense heritability takes into consideration *Vd*, Va, and *Ve*. *Vd* found in panel 2, where the dominant allele is the genetic determinant, an example of which is ADPKD—either you have cystic kidneys or not. *Ve* is the environmental modulator on genes, such as histone modifications, as found in panel 3. Phenotypic variance reflects the population level of a trait, such as measured eGFR. ADPKD, autosomal dominant polycystic kidney disease; eGFR, estimated glomerular filtration rate; Va, variance additive; Vd, variance dominant; Ve, variance environmental. Created with BioRender.com.

modeling of CKD, but variation in eGFR between twins still enables study of determinants of healthy kidney function.[1]

Our adjusted twin modeling estimates that 37% of kidney function at a median cohort age of 69 years is based on genetic factors, 14% because of shared environment, and 49% because of unique environmental exposures. These values are in keeping with male twins from Vietnam, who at age 55 years had heritability of eGFR at 48% and 52% from environmental factors.[21] The largest study with 10,682 twins at age 65 years had estimated heritability at 38%, similar to our study and higher than the heritability estimates found using GWAS SNP models (32%).[20] A younger female twin population had estimated genetic contribution of 63%, 18% shared environment, and 19% unique factors.[22] Table 7 summarizes the estimated narrow sense heritability (h^2), in a variety of populations, with varying estimates of eGFR. eGFR reduces with age of the population, and as such, studying h^2 estimates in these populations may reflect disease status over the life time. As the average population age increases, the h^2 diminishes, such that by the eighth decade of life, approximately 18% of kidney function is attributed to genetics.[25] Tarnoki *et al.*[27] modeled kidney size in twins, finding that kidney length was 50% heritable, whereas kidney width was primarily driven by environmental factors. Together, these twin studies suggest that a proportion of kidney function is genetically determined, with increasing influence of environmental determinants over the lifespan.

Decline in kidney function is considered a normal part of aging, and accurately estimating kidney function and its clinical significance in this process of physiological senescence is complex. In a population of adults aged >65 years with treated hypertension, the rate of decline in eGFR was associated with increased mortality.[28] Healthy populations with a lower eGFR at 50 years had more preserved eGFRs at older ages, whereas unhealthy groups with higher eGFRs at younger ages had lower eGFRs at older ages. Interestingly, preserved eGFR at older ages was not associated with better health in older age.[29] This highlights the complexities of using eGFR as a measure of health status in populations which include elderly participants. It may be that our standard measure is not the most informative. Cystatin C may be more accurate than creatinine for measuring eGFR in elderly populations.[30] Furthermore, higher measures of eGFR (>97.5 centile) can represent renal hyperfiltration, typically associated with diabetes mellitus, cardiovascular risk, and mortality outcomes in both healthy and unhealthy populations.[31,32] Renal hyperfiltration has similar cardiovascular mortality to CKD stage 3a.[33] Fluctuations in kidney function over time can represent both healthy and unhealthy aging, and a comparison of rate of decline of eGFR is warranted.

Narrow sense h^2 is the estimate of the additive genetic effects and is well suited to study polygenic traits including kidney function. Broad sense h^2 includes dominant and environmental impacts on genetics, illustrated in Figure 3. Classic twin modeling reports h^2 and excludes dominant genetics effects (i.e., autosomal dominant conditions such as autosomal dominant polycystic kidney disease) and interactions between genes (i.e., epigenetic factors). GWAS only account for h^2 as they use SNPs that can only be modeled as additive genetic effects. Additive genetic traits models are generally sufficient to model human traits, and when MZ correlation is <2 DZ correlation, this suggests contributing environmental factors.[34] That MZ is <2 DZ suggests that in our population, kidney function has important environmental determinants. A criticism of twin models is shared environmental factors are stronger between MZ than between DZ twins, which can overestimate the narrow sense heritability.[35] Our study may overestimate heritability; however, the fact that we still see stronger correlation between MZ than DZ twins supports the important genetic contribution to kidney function, in addition to the influence of shared environment. In studying human disease, heritability estimates are useful to provide a measure of risk between genes. In polygenic traits, this is less clear cut, and studying families could help guide risk factor management, such as management of CKD and hypertension based on a familial risk calculator or polygenic risk scores.

The estimated heritability of kidney function (proportion of kidney function caused by underlying genetics) is much greater from family and twin studies compared with GWAS owing to this being an observed rather than inferred phenomena. A GWAS of >1 million patients found 309 SNPs that explained 7.1% of the variance of eGFR and 19.6% of heritability.[13] A study of 122 SNPs associated with kidney function found that eGFR was 15% heritable in nondiabetes, nonhypertensive, non-Hispanic individuals and 13% heritable in non-Hispanic Blacks.[14] The Hong Kong Diabetes Registry has 8000 patients with diabetic nephropathy and using a GWAS analysis found the heritability of eGFR was 7%, CKD was 23%, and end-stage kidney disease was 31%.[36] A study of 10,682 twins from the Swedish TwinGene project compared classic twin models with the SNP model of heritability. Traditional twin analysis estimated eGFR h^2 as 0.35, where SNP based h^2 was 0.32, with 84% of the traditional twin model heritability explained by SNPs.[20] Heritability estimates derived from family studies, including twin studies described previously, are much greater. A higher GWAS derived h^2 of 0.36 for kidney function was found when related families were included.[37] In a study of siblings in 310 families with diabetes mellitus, heritability of eGFR was 0.69 and heritability of urine albumin creatinine ratio was 0.40.[38] A GWAS in 1703 patients with type 1 diabetes found that heritability for rate of decline of eGFR was 0.36.[39] The differences in heritability estimates could be attributed to epigenetic interactions with risk factor genes that drive pathogenesis of CKD. Families have higher degree of shared environment exposures which could confound heritability estimates. An example of modifiable risk is high salt diets, which potentiates CKD in certain populations.[40]

Epigenetic markers may account for differences in heritability estimates found between GWAS and family/twin studies and as markers of environmental determinants of disease.[41] Epigenetic modifications are acquired in utero, throughout early childhood (which may be shared within twin pairs) and even into older adulthood. Interestingly, 81% of female twins have the same X inactivation methylation pattern, which is higher than would be expected randomly.[42] A recent meta-analysis of DNA methylation age correlation in twins over the life span found that DNA methylation age is not similar at birth and increases in adolescence and adulthood, most notably in MZ twins, potentially reflecting the shared environment.[42] When genome-wide average methylation was used as a measure of methylation, there was a high degree of correlation in DNA methylation in twins at birth (0.8), which was not different between MZ and DZ twins, suggesting methylation was determined by environmental (in utero) rather than genetic factors. In adolescence, concordance between twins reduces and plateaus in adulthood. The OATS group genome-wide average methylation correlation was 0.31.[43] Older twins (>65 years) exhibit differences in expression of 5-methylcytosine DNA and histone acetylation, markers of epigenetic modifications.[42,44] Epigenetic changes may explain discordant disease states, as found with twins with differing activities of lupus and rheumatoid arthritis related to DNA methylation patterns.[45,46] In CKD, established epigenetic markers include microRNAs that prognosticate progression of diabetic nephropathy.[47] MicroRNAs miR-17, miR-21, miR-150, miR-126, miR-196a, and miR-9 are associated with progression of CKD.[47,48] The epigenetic contribution to kidney function is an exciting area of future research.

We found that hypertension and 2+ hypertension medications were associated with eGFR, which is consistent with hypertension as an established risk for CKD (Table 4). Using number of antihypertensives, we found that the twin mean number of antihypertensive medications was trending toward significantly being associated with eGFR ($P = 0.052$). This trend could

reflect that twins on higher numbers of antihypertensive agents had more challenging hypertension associated with a higher decline in eGFR, or that better controlled hypertension had less risk of CKD. This could indicate that hypertension and hypertension medications may influence eGFR, which can be both environmental and genetic. That this is not statistically significant could be because of our relatively small study sample, with well controlled hypertension (average measured BP 132/78 mm Hg). Use of antihypertensive medication with an elevated BP is associated with a slower eGFR decline.[38,49] The heritability of kidney function in hypertensive families in the Seychelles was 0.41 to 0.82 and suggests that kidney impairment is higher in patients with 2 first-degree relative with hypertension.[50] Heritability of hypertension in GWAS is estimated at 0.263, although the heritability estimate also diminishes with age, similar to what we have found with kidney function.[51] A GWAS found that genetic proxies, which are drug target genetic variants, for angiotensin-converting enzymes and calcium channel blockers were associated with higher eGFRs, where beta-blocker–associated proxies were associated with lower levels of kidney function.[52] Kidney function and hypertension have a complex relationship, and a recent Mendelian analysis using GWAS data was able to reveal that higher kidney function is associated with lower BP, where BP did not influence kidney function.[53] Hypertension is a well-established risk factor for CKD, is known to be heritable within families, and may reflect a modifiable factor which interplays with genetic determinants of kidney function. These studies suggest that kidney function has genetic determinants which are contributors to hypertension, with a genetic susceptibility, and targeting kidney health may reduce hypertension and associated disease burden.

Diabetes status and number of diabetes medications did not account for differences found in kidney function. In our population, 9.8% had diabetes, although only 24 people took 1 diabetes medication and 11 took >1, suggesting reasonable diabetic control. Relatively low numbers of twins were discordant for diabetes mellitus in our study, limiting analysis. The DISCOTWIN consortium has pooled 32,000 twins, including our OATS population, and found that only 5.9% of MZ twins and 8% of DZ twins were discordant for diabetes. There is 87% concordance of diabetes between MZ twins.[54] Studying these rare discordant twin sets will offer insight into the pathogenesis of diabetes, and proteomic analysis is underway.

Identifying polygenic contributors to human disease is an exciting area of future research, and understanding diseases with a significant degree of heritability warrants development of genetic risk prediction tools. Polygenic risk scores have recently been validated in major diseases, including coronary artery disease, type 2 diabetes, and breast cancer. This landmark study found, using polygenic risk, that 8% of the population has a 3-fold higher risk for coronary artery disease, based on polygenic risk scores.[55] Several polygenic risk scores have been calculated for kidney function and will further our understanding of CKD as a complex trait.[55–57]

Limitations of this study include the small sample size, Caucasian population-limiting generalizability, and relatively preserved kidney function, although the kidney function is more variable than other twin studies. Data including urine protein/creatinine ratio or Hba1c were not collected in this data set. We also used single measures of eGFR and have no temporal information regarding rate of decline in eGFR. Our strengths were use of CKD-EPI, mixed genders, and the focus on older twins.

We found in an older population of Caucasian twins that the kidney function as modeled by eGFR has both significant genetic and environmental determinants. This study highlights the heritability gap between genetic arrays and family-based studies. In the genomic era, family studies are still powerful models to further our understanding of human disease and offer insights into both genetic predisposition and significant environmental risk factors and the interplay between these. Further studies using family history to inform of disease risk and modifiable risk factors are intriguing, including establishing polygenic risk scores.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

STROBE Statement.

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