Association of polygenic scores with chronic kidney disease phenotypes in a longitudinal study of older adults

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Risk of chronic kidney disease (CKD) is influenced by environmental and genetic factors and increases sharply in individuals 70 years and older. Polygenic scores (PGS) for kidney disease-related traits have shown promise but require validation in well-characterized cohorts. Here, we assessed the performance of recently developed PGSs for CKD-related traits in a longitudinal cohort of healthy older individuals enrolled in the Australian ASPREE randomized controlled trial of daily low-dose aspirin with CKD risk at baseline and longitudinally. Among 11,813 genotyped participants aged 70 years or more with baseline eGFR measures, we tested associations between PGSs and measured eGFR at baseline, clinical phenotype of CKD, and longitudinal rate of eGFR decline spanning up to six years of follow-up per participant. A PGS for eGFR was associated with baseline eGFR, with a significant decrease of 3.9 mL/min/1.73m^2 (95% confidence interval -4.17 to -3.68) per standard deviation (SD) increase of the PGS. This PGS, as well as a PGS for CKD stage 3 were both associated with higher risk of baseline CKD stage 3 in cross-sectional analysis (Odds Ratio 1.75 per SD, 95% confidence interval 1.66-1.85, and Odds Ratio 1.51 per SD, 95% confidence interval 1.43-1.59, respectively). Longitudinally, two separate PGSs for eGFR slope were associated with significant kidney function decline during follow-up. Thus, our study demonstrates that kidney function has a considerable genetic component in older adults, and that new PGSs for kidney disease-related phenotypes may have potential utility for CKD risk prediction in advanced age.

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Lay Summary

The sum of multiple small genetics contributors to a trait such as kidney function can be captured by polygenic risk scores (PGSs), derived from large-scale genome-wide association studies; however, the clinical significance of these scores is still being understood. We tested several recently developed PGSs for kidney traits in 11,813 European Australians, aged >70 years, from the ASPirin in Reducing Events in the Elderly population, with a mean estimated glomerular filtration rate (eGFR) of 72.9 ml/min per 1.73 m^2. We validated multiple PGSs for both eGFR and decline in eGFR. At a population level, those with higher PGSs had the lowest mean eGFR of 57 ml/min per 1.73 m^2, with significant individual variability. Overall, this study validated PGSs for kidney function in an older population, showing PGSs, which are static across the life span, still impact kidney function in later stages of life.

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Chronic kidney disease (CKD) is a significant and growing health care burden worldwide.[1] CKD prevalence increases with age, with peak incidence after the age of 60 years.[2] Risk is driven by conventional risk factors, including hypertension, diabetes, obesity, and smoking.[2,3] In

addition, CKD is strongly influenced by genetic factors, especially in monogenic kidney disorders.[4,5] Although rare monogenic variants are associated with severe, rare forms of CKD (e.g., autosomal dominant polycystic kidney disease and Alport syndrome), the relationship between common genetic variants and CKD risk is less well characterized, particularly in older individuals in whom CKD prevalence is high.[6,7]

Heritability estimates for kidney function generated from twin studies suggest a diminishing but still significant genetic component across the life span.[8] Genome-wide association studies predict lower heritability of CKD between 7% and 18%, depending on the population, but have been generated from younger populations.[9–12] Further studies are required to understand the relevance of genetic contributions to CKD in older age.[8] Accurate risk prediction remains a clinical challenge for CKD, especially in older people. Early identification of high-risk individuals for CKD through genetic profiling, before decline in kidney function, may help target interventions to high-risk individuals earlier and reduce disease burden.[6,7]

Polygenic scores (PGSs) are an aggregate measure of common-variant risk for a given disease or trait and are calculated by summing the effects of many different single-nucleotide polymorphisms together into a single score. PGSs for traits associated with kidney function have been recently developed, including from the CKDGen Consortium and UK Biobank, based on phenotypes related to kidney failure, estimated glomerular filtration rate (eGFR), rate of decline in eGFR, urine albumin-creatinine ratio (UACR), and other conditions, such as diabetes mellitus and coronary artery disease.[9,10,13] Older populations have more medical comorbidities, and PGSs for kidney function have been related to cardiac and metabolic disease (including diabetes mellitus) that are known to influence kidney function.[14,15] Validation and comparison of these scores in older people, aged >70 years, has been lacking despite the high burden of kidney disease in this older age group.

This study aims to assess the performance of recently developed kidney disease PGSs, with regard to association with the following: (i) CKD risk at baseline and (ii) more rapid decline in kidney function in older individuals, independent of environmental considerations and established risk factors. For the first question, we conducted a cross-sectional analysis using baseline measurements to examine whether a PGS for eGFR and, separately, UACR was associated with these measures in our cohort, and to compare the performance of a PGS for eGFR with PGSs from several studies specific to CKD phenotypes. For the second question, we examined 2 PGSs specific for the "decline in eGFR" phenotype to determine whether they were associated with a greater rate of eGFR decline prospectively using our longitudinal measures of eGFR. In addition, we investigated whether the PGS for eGFR was associated with metabolic disorders that strongly associate with CKD (baseline diabetes mellitus and incident cardiovascular disease and myocardial infarction), to better understand these linked risks.[16]

METHODS

Study design

The study includes genotyped Australian participants from the ASPirin in Reducing Events in the Elderly (ASPREE) trial, a randomized placebo-controlled trial of daily low-dose aspirin in older adults.[17–19] The analysis also includes recent data from the ASPREE-XT02 Longitudinal Data Set, which extends observational follow-up time beyond the original randomization period to a mean of 6.3 years. The ASPREE study design,[20,21] recruitment, and baseline characteristics[22] have been published previously. ASPREE participants were recruited in partnership with a network of general practitioners in Australia and the United States. The study was approved by the Alfred Hospital Human Research Ethics Committee (project 390/15) in accordance with the National Statement on Ethical Conduct in Human Research (2007). Written informed consent for genetic analysis was obtained from all study participants.

For the present genetic analysis, we include only Australian ASPREE participants with a baseline eGFR measurement who provided a sample for DNA analysis (Supplementary Figure S1). First, we conducted cross-sectional analysis of the baseline cohort. Second, we followed up participants with longitudinal data for analysis of eGFR decline. Finally, we excluded any participants with stage 5 CKD at baseline (those on dialysis treatment or those who received a kidney transplant).

Outcomes

There were 4 outcome measures for the cross-sectional analysis: (i) association with eGFR as a continuous variable; and (ii) the presence of CKD using established criteria, with CKD being defined according to 3 measures: (a) CKD_{KDIGO} was based on Kidney Disease: Improving Global Outcomes (KDIGO) criteria, where CKD was defined as either eGFR <60 ml/min per 1.73 m^2 or UACR >3.0 mg/mmol. CKD_{KDIGO} was derived for the subset of participants who had UACR available at baseline. (b) CKD_{eGFR} was defined as CKD using only eGFR <60 ml/min per 1.73 m^2); (c) a moderate to severe CKD phenotype (CKD_{eGFR_mod}) defined as eGFR <45 ml/min per 1.73 m^2.

The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation[23] and serum creatinine measured at baseline and annual study visits. UACR was measured at baseline (mg/mmol), with albuminuria defined as a UACR ≥3.0 mg/mmol.

For the longitudinal analysis, we used the annual eGFR measures in a statistical model to draw inferences about annual decline in ml/min per 1.73 m^2. Diabetes at baseline was based on presence of either self-report or fasting glucose ≥126 mg/dl, or medication for diabetes. Incident cardiovascular disease and myocardial infarction were classified as adjudicated outcomes in the original trial outcomes (adjudication assessed by expert committees, as described previously[18]).

Genotyping

Genotyping was performed on the Axiom 2.0 Precision Medicine Diversity Research Array (Thermo Fisher Scientific) following standard protocols and quality control. Variants were aligned to the human genome reference GRCh38; quality control steps were applied to match for predicted and expected sex, filter for relatedness (using PLINK 2.0 based on –king-table-filter 0.1) as well as missing samples and variants (–mind and –geno defaults), and exclude variants with Hardy-Weinberg $P < 0.000001$. Variants were imputed by TopMED Imputation Server Imputation (European samples).[24]

Variants that were multiallelic or with low imputation quality scores ($r^2 < 0.3$) were removed.

To mitigate the effect of population stratification bias on the PGS (i.e., confounding related to ethnicity), we included only individuals of European genetic ancestry, identified by principal component analysis and overlapping the European subset of the 1000 Genomes Project phase 3 reference population[25] (for details, see Supplementary Figure S2A and B). Briefly, the genotype data were combined with 1000 Genomes Project phase 3 data, with linkage disequilibrium (LD) pruned ($r^2 < 0.1$). The Z score of the first 2 principal component eigenvectors was calculated, and used to exclude samples with ±2 SDs in Z score compared with 1000 Genomes Project phase 3 reference populations, with the European population used to identify individuals used in this study (Supplementary Figure S2A and B).

Polygenic scores

The principal PGS for the cross sectional eGFR analysis was published by Yu et al, 2021 (PGS000883), hereby referred to as PGS_GFR.[26] This score was then compared with the recently developed PGS for CKD stage 3, referred to as PGS_CKD_S3. For the assessment of eGFR decline, we examined 2 PGSs for rapid decline of glomerular filtration rate: PGS000664, hereby referred to as PGS_GFR_decline_2021, and PGS_GFR_decline_2022.[9,27] We also examined a PGS for UACR (PGS000822, defined as PGS_ACR).[28] Table 1 briefly summarizes the PGSs examined, and lists details found in the primary publications.[27]

PGSs were calculated by PLINK2.0 using the score function.[29,30] This function sums the effect sizes for each effect allele present in each participant, creating a single score for each participant. We created 3 predicted eGFR risk groups for PGS_GFR: *high* for those with PGS > 95% above the mean, *medium* for those with PGS between 5% and 95%, and *low* for those with PGS < 5%. The *high* PGS group is predicted to have the lowest eGFR, and hence would be expected to have the highest risk of CKD (Supplementary Figure S3).

Statistical analysis

For the cross-sectional analysis, we used a linear regression to examine the relationship between PGS_GFR and eGFR at enrollment, and included the following covariates: age, sex, body mass index, alcohol use, smoking, hypertension, diabetes, and use of nonsteroidal anti-inflammatory drug or angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. For the binary CKD outcomes, logistic regression was used to examine the relationship between CKD and PGS_GFR, using the same covariates as the linear regression model.

For the longitudinal analysis, a linear mixed model examined the relationship between the PGS_GFR_decline_2021 and PGS_GFR_decline_2022 and repeated eGFR measurements over time in individual participants, with correlated random effects for participant-specific intercept and participant-specific slope using visit year as the time variable to yield annualized eGFR change (Supplementary Table S1). Covariates included in the model were baseline age, sex, body mass index, alcohol and smoking, hypertension, diabetes, and treatment arm (aspirin or placebo). To quantify the relationship between rate of decline of eGFR and PGS_GFR_decline_2021/2022, the linear mixed model included an interaction term between the PGS and visit year. We used the glht function from R package multcomp[31] to derive point estimates of the rate of change per year for individuals estimated to lie at: (i) 2 SDs above mean decline, (ii) 2 SDs below mean decline, and (iii) mean decline.

Cox proportional hazards models were used to examine the associations between PGS_GFR and each of incident coronary artery disease and incident myocardial infarction. Cause-specific hazard ratios for PGS_GFR were reported using the survival package,[32] with the same covariates as the linear regression. Logistic regression was used to examine the relationship between baseline eGFR and presence of diabetes mellitus. Results from statistical models are adjusted unless otherwise specified. Area under the curve (AUC) was used to compare the results between models. Hosmer-Lemeshow test was used to assess calibration of model.

RESULTS

Population characteristics

Of the 19,114 total participants randomized to receive aspirin or placebo in the ASPREE trial, 12,141 had a baseline eGFR measure and provided a sample for genomic analysis. A further 328 were excluded as they did not have European genetic ancestry and 5 further individuals had stage 5 CKD. Thus, the final study population consisted of 11,813 genotyped European ancestry individuals. For the analysis assessing albuminuria (UACR), 2911 had a missing baseline UACR measure; hence, this analysis was confined to a subset of 8902 individuals.

The baseline characteristics of the study sample are presented in Table 2. The mean age of the study population was 75.0 years (SD, 4.2 years), and 54.2% of participants were women. A total of 2904 participants (24%) met the CKD_{KDIGO} definition, and 2071 participants met the CKD_{eGFR} definition (eGFR < 60 ml/min per 1.73 m^2). The median follow-time up during which participants took aspirin or placebo was 4.7 years. Following the cessation of the trial, additional follow-up continued (ASPREE-XT02 Longitudinal Data Set), with the median follow-up time increasing to 6.3 years.

At baseline, the mean measured eGFR for the population was 72.9 ml/min per 1.73 m^2 (SD, 13.4 ml/min per 1.73 m^2). By 6 years of follow-up, 5127 measurements of eGFR were available, with the mean eGFR declining to 66.5 ml/min per 1.73 m^2 (SD, 14.9 ml/min per 1.73 m^2; Supplementary Table S2 and Supplementary Figure S4). For UACR, 8902 (75.4%) were measured at baseline, and 2946 were measured at 6 years. Baseline mean UACR was 2.34 mg/mmol (median, 0.8 mg/mmol); and the value was 3.93 mg/mmol (median, 1.2 mg/mmol) at 6 years.

Cross-sectional analysis

The PGS_GFR in our fully adjusted model was associated with eGFR at baseline; for each 1-SD decrease in the PGS_GFR, there was a difference in eGFR of –3.9 ml/min per 1.73 m^2 (95% confidence interval [CI], –4.2 to –3.7 ml/min per 1.73 m^2; $P < 0.001$). Hosmer-Lemeshow test did not indicate a lack of goodness of fit ($P > 0.05$). The mean eGFR values for participants in the <5% (predicted *high eGFR*), middle, and >95% (predicted *low eGFR*) groups were 81.9 ± 11.7, 72.9 ± 13.3, and 62.3 ± 12.5 ml/min per 1.73 m^2, respectively, with 281

Table 1 | Comparison of available PGSs for eGFR and decline in eGFR: multiple PGSs for CKD have been generated using alternative strategies, including population, definition of eGFR

PGS	Trait	Population	Discovery sample size	Discovery ancestry	Validation cohort	SNP-based heritability	Variance explained, %	Effect size in validation, HR or OR per SD (95% CI)	Limitations
PGS000883 (PGS_GFR)	Incident CKD = eGFR of 60 ml/min per 1.73m^2 plus ≥30% eGFR decline during a follow-up visit compared with baseline	UK Biobank + CKDGen	1,159,871	White = 82%; East Asian = 14.4%; South Asian = 1.8%; Black = 1.5%; Hispanic = 0.42%	ARIC	NA	7.3	HR =1.21 (1.16–1.26)	Generated in predominantly White population (83%) and validated in White population
PGP000269 (PGS_CKD_S3)	Case = eGFR <60 ml/min per 1.73 m^2 Control = eGFR >90 ml/min per 1.73 m^2	70% of UKBB Europeans	177,208	European/White = 100%	CKDGen, UK Biobank, eMERGE-III, Bio*Me*, UAB	NA	4	White = OR 1.46 (1.43–1.48) African = OR 1.23 (1.26–1.38) Latin = OR 1.42 (1.26–1.38) Asian = OR 1.68 (1.45 – 2.06)	Dichotomizes eGFR, to account for variability in eGFR by ancestry Strength is well-validated multiethnic cohort, and addition of APOL1 in African cohort
PGS000664 (PGS_decline_2021)	eGFRcrea decline: 3 ml/min per 1.73 m^2 per year, eGFRcrea decline ≥25%, and eGFRcrea <60 ml/min per 1.73 m^2 at follow-up among those with eGFRcrea 60 ml/min per 1.73 m^2	41 Studies from CKDGen and UK Biobank	>2,700,000	NA	Validated alternate kidney markers	NA	NA	NA	"Extreme" phenotype of eGFR decline, unable to validate in non-White population
Gorski 2022[27] (PGS_decline_2022)	Decline in eGFR ml/min per year (eGFR at follow-up – eGFR at baseline/number of follow-up years)	CKDGen, UK Biobank	343,339	White = 74%	The Trøndelag Health Study	Unadjusted eGFR decline = 1%	0.62	NA	Distinction between cross-sectional CKD and decline in eGFR limited by collider bias
PGS000822 (PGS_ACR)	Cases = urine ACR > 30 mg/g, Control = urine ACR < 10 mg/g	CKDGen, UK Biobank	564,257	White = 97% East Asian = 1.1% South Asian = 0.4% Black = 1.2% Latin = 0.3%	CKDGen Consortium	4.3%	0.69		Predominantly European population, variability in urine albumin/creatinine ratio, other studies have found variation in GWAS based on ancestory/disease states

ARIC, Atherosclerosis Risk In Communities study; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; eMERGE-III, Electronic Medical Records and Genomics Phase III; GWAS, genome-wide association study; HR, hazard ratio; NA, not applicable; OR, odds ratio; PGS, polygenic score; SNP, single-nucleotide polymorphism; UAB, University of Alabama at Birmingham; UKBB, United Kingdom Biobank.
Variances and heritability data are unavailable for some studies.

Table 2 | Baseline characteristics of the 11,831 ASPREE participants included in the analyses

Characteristic	Overall
N	11,813
Age, yr, mean (SD)	75.0 (4.2)
Age group, yr, n (%)	
70–74	7215 (61.1)
75–79	2958 (25.0)
80–84	1269 (10.7)
≥85	371 (3.1)
Female gender, n (%)[a]	6401 (54.2)
Smoker, n (%)	
Never	6568 (55.6)
Former	4878 (41.3)
Current	367 (3.1)
Alcohol consumption, n (%)	
None	2377 (20.1)
Moderate	5328 (45.1)
Excessive	4108 (34.8)
Hypertension, n (%)	8781 (74.3)
BMI, kg/m^2, mean (SD)	28.0 (4.5)
Diabetes, n (%)	1117 (9.5)
eGFR, ml/min per 1.73 m^2, mean (SD)	72.9 (13.4)
Family history of CKD, n (%)[b]	779 (6.6)
NSAID use, n (%)	1420 (12.0)
ACE inhibitor/ARB use, n (%)	4939 (41.8)
Has ACR measurement, n (%)	8902 (75.4)

ACE, angiotensin-converting enzyme; ACR, albumin-creatinine ratio; ARB, angiotensin receptor blocker; ASPREE, ASPirin in Reducing Events in the Elderly; BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; NSAID, nonsteroidal anti-inflammatory drug.
[a]Gender is reported here according to that personally identified by each participant of their own gender.
[b]Family history indicates first-degree family member with history of kidney disease.

individuals in the *low* group and 269 individuals in the *high* group (Figure 1a; Supplementary Table S3).

The PGS_GFR was not found to be associated with the baseline continuous measure of UACR (95% CI, –0.28 to 0.09; $P = 0.14$). However, the PGS for UACR (PGS_ACR) was associated with measured UACR at baseline; a 1-SD increase in PGS_ACR associated with a difference in UACR of 0.30 (95% CI, 0.11–0.49) mg/mmol. When comparing PGS_ACR with a binary outcome of CKD (CKD_{KDIGO}), we found it was associated with CKD with an odds ratio (OR) of 1.07 (95% CI, 1.02–1.11). Given the modest sized effect represented by this odds ratio, and small heritability estimates of UACR10 in genome-wide association studies, most of our subsequent analysis focused on eGFR.

We next examined binary end points related to eGFR and CKD using the PGS_GFR. The PGS_GFR was associated with CKD_{KDIGO} (OR, 1.39 per SD; 95% CI, 1.33–1.45), and with CKD_{eGFR} (OR, 1.75; 95% CI, 1.66–1.85). Individuals with the highest PGS_GFR (> 95%) had the highest risk for CKD_{eGFR} (OR, 3.39; 95% CI, 2.83–4.06, using the medium group as reference). Similar findings were observed for moderate to severe CKD (CKD_{eGFR_mod}; Tables 3 and 4). In adjusted analyses, we found that CKD_{eGFR} was still associated with PGS_GFR (OR, 1.75; 95% CI, 1.66–1.84) and with PGS_CKD_S3 (OR, 1.51; 95% CI, 1.43–1.59; Figure 2). Similar relationships were seen for CKD_{KDIGO} and CKD_{eGFR_MOD} (Tables 5 and 6; Supplementary Table S4). Performance metrics for PGS are included in Supplementary Figure S5.

We also performed a subgroup analysis to examine whether family history of kidney disease impacted the PGS associations. When excluding individuals with family history of kidney disease (remaining n = 10,462), PGS_GFR remained associated with CKD_{KDIGO} with OR of 1.37 (95% CI, 1.31–1.44), $P < 0.001$, and AUC of 0.69 (95% CI, 0.67–0.70). When examining only individuals with a family history of kidney disease (n = 743), PGS_GFR was associated with CKD_{KDIGO} with OR of 1.40 (95% CI, 1.18–1.66), $P < 0.001$, and AUC of 0.70 (95% CI, 0.65–0.74). In a model for CKD_{KDIGO} including all individuals and omitting the PGS, family history had an association in the unadjusted model with OR of 1.20 (95% CI, 1.02–1.41) and adjusted OR of 1.19 (95% CI, 1.00–1.41). Hosmer-Lemeshow test did not indicate a lack of goodness of fit ($P > 0.05$) in either subgroup.

Longitudinal analysis

PGS_GFR was not associated with decline in eGFR ($P = 0.15$). In contrast, PGS_GFR_decline_2021 was associated with more rapid decline in eGFR over the course of the trial ($P = 0.01$), as was PGS_GFR_decline_2022 ($P = 0.045$). Point estimates for the rate of yearly decline for an individual with a PGS_GFR_decline_2021 score in the 5th percentile was –1.14 ml/min per 1.73 m^2 (95% CI, –1.20 to –1.07 ml/min per 1.73 m^2) compared with –0.99 ml/min per 1.73 m^2 (95% CI, –1.06 to –0.93 ml/min per 1.73 m^2) for those in the 95th percentile. The estimated mean decline per year was –1.07 ml/min per 1.73 m^2 (95% CI, –1.10 to –1.03 ml/min per 1.73 m^2; Figure 3). For PGS_GFR_decline_2022, the rates of decline for those in the 5th and 95th percentiles were –1.12 (95% CI, –1.19 to –1.06) and –1.01 (95% CI, –1.07 to –0.94) ml/min per 1.73 m^2.

We next sought to assess the impact of possible collider bias when adjusting by baseline eGFR.[27] In a linear mixed model for eGFR measures at follow-up times only, with baseline eGFR added as a fixed effect, the results are no longer significant for PGS_GFR_decline_2021 ($P = 0.06$) or PGS_GFR_decline_2022 ($P = 0.17$).

Association of PGS for GFR with cardiometabolic disorders

We tested PGS_GFR against other cardiometabolic conditions in the ASPREE cohort to examine the specificity of CKD prediction. The PGS_GFR was not associated with development of coronary artery disease (hazard ratio, 1.01 [95% CI, 0.93–1.10] per 1 SD) or incident myocardial infarction (hazard ratio, 0.97 [95% CI, 0.85–1.11] per 1 SD) over the course of the study, nor with the presence or absence of diabetes mellitus at baseline (OR, 1.00 [95% CI, 0.94–1.06] per 1 SD; Table 7).

DISCUSSION

In this study, we demonstrated that PGSs for kidney-related traits are associated with CKD risk in older adults,

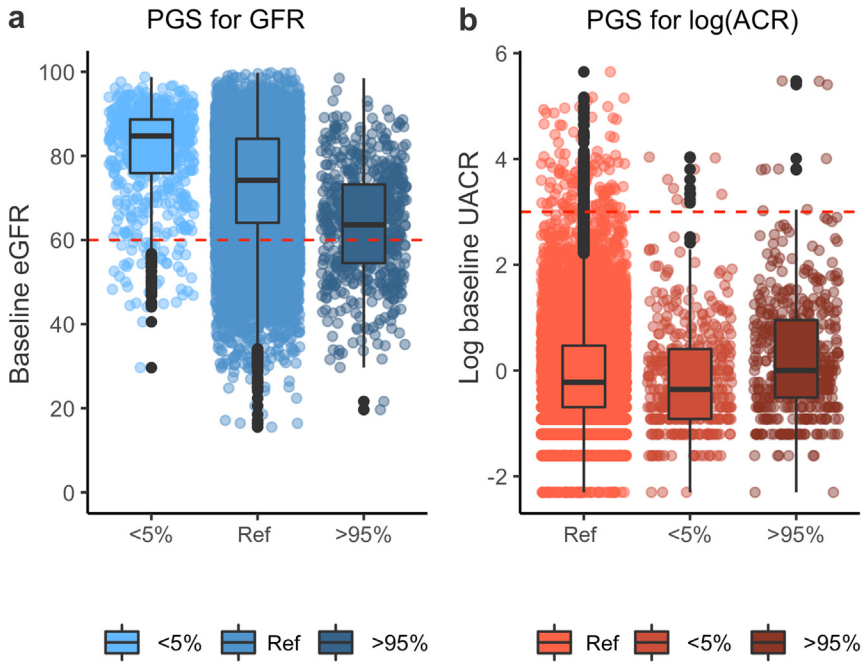

Figure 1 | Distribution of estimated glomerular filtration rate (GFR) and (natural) log urine albumin-creatinine ratio (UACR) compared with their polygenic scores (PGSs), stratified into low (<5%), medium (Reference [Ref]), and high (>95%) groups.

aged ≥70 years, highlighting the persisting influence of genetic factors for kidney function even in older age. Our results suggest that PGSs may have future utility for risk prediction of CKD in older people. The PGS_GFR was associated with baseline eGFR, whereas both PGS_GFR and PGS_CKD_S3 were associated with clinical CKD end points by KDIGO CKD stage. Older individuals with *high* PGSs had significantly higher risk of CKD than those with *low* PGSs. The PGS_GFR was not associated with UACR or other metabolic disorders strongly associated with CKD (cardiovascular disease, myocardial infarction, and diabetes mellitus). The PGSs for decline in GFR (PGS_GFR_decline_2021 and PGS_GFR_decline_2022) offer further insights into the role of different genetic factors associated with rates of decline. Overall, our study indicates that PGSs for kidney disease–related traits could help improve CKD risk prediction in older people.

The first key result of this study is the confirmation that higher PGS_GFR per SD is associated with –3.9 ml/min per 1.73 m^2 decrease in GFR per SD in the ASPREE population. Although this decrease per 1 SD is relatively small, this change is impactful for individuals with ≥2 SDs PGS score, who at age ≥70 years had a mean eGFR of 58 ml/min per 1.73 m^2 at the most recent follow-up, placing them considerably below the average study participant of 72.8 ml/min per 1.73 m^2. This result provides evidence that genetic profiling has the capacity to identify clinically meaningful subgroups for CKD, independently of other factors. When kidney function was modeled by CKD diagnosis or CKD stage (stage 3B–5), we found similar results, supporting validity of PGS for kidney function in this older population. The PGS_GFR, derived from baseline eGFR as a continuous measure, has a higher OR per SD than PGS_CKD_S3 in ASPREE, in both adjusted and unadjusted models. The PGS_GFR, derived from eGFR as a continuous measure, has a higher OR per SD than PGS_CKD_S3,[33] in ASPREE, in both adjusted and unadjusted models, when considering OR per SD and AUC. The PGS_CKD_S3, which separates CKD into eGFR <60 or > 90 ml/min per 1.73 m^2, may perform better if tested in a multiancestry population.[33] The PGS_GFR is associated with risk of CKD even in individuals without family history of CKD, limited by assessment in an older population with possible selection bias because of exclusion of cardiovascular disease at enrollment.

Table 3 | Cross-sectional analyses of PGS_GFR

CKD definition	Adjusted OR (95% CI)	*P* value	AUC (95% CI)	Unadjusted OR (95% CI)	*P* value	AUC (95% CI)
CKD_{KDIGO}	1.37 (1.31–1.43)	1.3×10^{-42}	0.69 (0.67–0.70)	1.36 (1.30–1.42)	8.5×10^{-44}	0.58 (0.57–0.60)
CKD_{eGFR}	1.75 (1.66–1.84)	1.7×10^{-90}	0.73 (0.72–0.75)	1.71 (1.63–1.80)	1.1×10^{-90}	0.64 (0.63–0.66)
CKD_{eGFR_MOD}	1.70 (1.52–1.90)	3.6×10^{-20}	0.79 (0.77–0.81)	1.70 (1.53–1.89)	1.5×10^{-21}	0.65 (0.62–0.68)

AUC, area under the curve; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; OR, odds ratio; PGS, polygenic score.

Table 4 | Cross-sectional analyses of PGS_CKD_S3

CKD definition	Adjusted OR (95% CI)	*P* value	AUC (95% CI)	Unadjusted OR (95% CI)	*P* value	AUC (95% CI)
CKD_{KDIGO}	1.24 (1.19–1.30)	9.8×10^{-22}	0.68 (0.67–0.69)	1.23 (1.18–1.29)	1.5×10^{-12}	0.56 (0.55–0.57)
CKD_{eGFR}	1.51 (1.43–1.59)	3.1×10^{-54}	0.71 (0.70–0.73)	1.48 (1.40–1.55)	1.2×10^{-52}	0.61 (0.60–0.62)
CKD_{eGFR_MOD}	1.47 (1.32–1.65)	5.0×10^{-12}	0.78 (0.75–0.80)	1.46 (1.31–1.63)	3.4×10^{-12}	0.62 (0.59–0.65)

AUC, area under the curve; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; OR, odds ratio; PGS, polygenic score.

OR and *P* values for adjusted logistic regression examining standardized (mean = 0; SD = 1) PGS_GFR for binary outcomes: CKD_{KDIGO} (eGFR < 60 ml/min per 1.73 m^2 or urine albumin-creatinine ratio > 3 mg/mmol), CKD_{EGFR} (eGFR < 60 ml/min per 1.73 m^2), and CKD_{EGFR_MOD} (eGFR < 45 ml/min per 1.73 m^2). Model adjusted for age, sex, alcohol, smoking, hypertension, diabetes, body mass index, nonsteroidal anti-inflammatory drug and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, and visit year. In the adjusted model, n = 11,205 as individuals with incomplete covariate data are removed; in the unadjusted model, the same set of individuals are used.

The PGS_GFR has previously been validated in a significantly younger US community-based cohort (mean age, 54 years), with higher eGFR (mean, 100 ml/min per 1.73 m^2) with a hazard ratio of 1.33 for CKD per 1-SD decrease of PGS.[26] Considering that a PGS is unchanging over the life span and can be measured in early life, the differences between the *low*, *middle*, and *high* PGS groups may help identify individuals at significant risk for CKD earlier than other risk stratification methods. For example, PGSs in cardiovascular disease were able to identify 13% of early-onset cardiovascular disease and reclassify certain individuals to lower risk of disease.[34] Potential clinical translation of PGS could identify those at higher risk to consider risk-reducing measures and targeted screening, whereas the broader research uses of PGS may include identifying new drug targets.[35]

The model we used with PGS_GFR was adjusted for demographics, body mass index, key comorbidities (hypertension and diabetes), and common medications that can affect kidney function (nonsteroidal anti-inflammatory drugs, angiotensin receptor blockers, or angiotensin-converting enzyme inhibitors), which highlights that the PGS is a source of risk information independent of conventional risk factors. However, as with other risk factors for CKD, a *high* PGS does not preclude individuals from having preserved kidney function, and translating PGS as part of a clinical risk prediction tool requires consideration of these limitations. Disease states are modifiable, with genetic risk predicted from PGS having significant variation in clinical phenotypes, as we demonstrated with eGFR, particularly compared with higher penetrance monogenic diseases, which exhibit more direct relationships to kidney function outcomes. The variability within *high* and *low* PGS groups demonstrated in our population supports the concept of modifiable genetic risk.[36,37]

In the studied population, the PGS_GFR did not correlate with development of coronary artery disease or myocardial infarction during follow-up or with baseline prevalence of diabetes mellitus. This suggests that the genetic signal captured by the PGS may be relatively specific to kidney function. However, the fact that the ASPREE population was free of overt cardiovascular disease at enrollment limits the conclusions that can be drawn about these phenotypes. Studies in populations with higher cardiovascular risk compared with the ASPREE cohort have found PGSs for CKD are associated with adverse end points of kidney failure, myocardial infarction, and death.[15] A PGS for CKD has also been associated with large-vessel stroke.[38] It is pertinent to consider differences in the choice of PGS and the populations they are generated from; PGS_GFR includes eGFR across a spectrum of individuals who may not have comorbidities, whereas a PGS for CKD is more likely to include individuals with cardiovascular disease and other comorbidities.

We also validated a PGS for albuminuria in the population. A 1-SD increase in the UACR PGS was associated with a 0.33 mg/mmol increase in UACR. However, the heritability of albuminuria varies from estimates of 0.03 to 0.04 in genome-

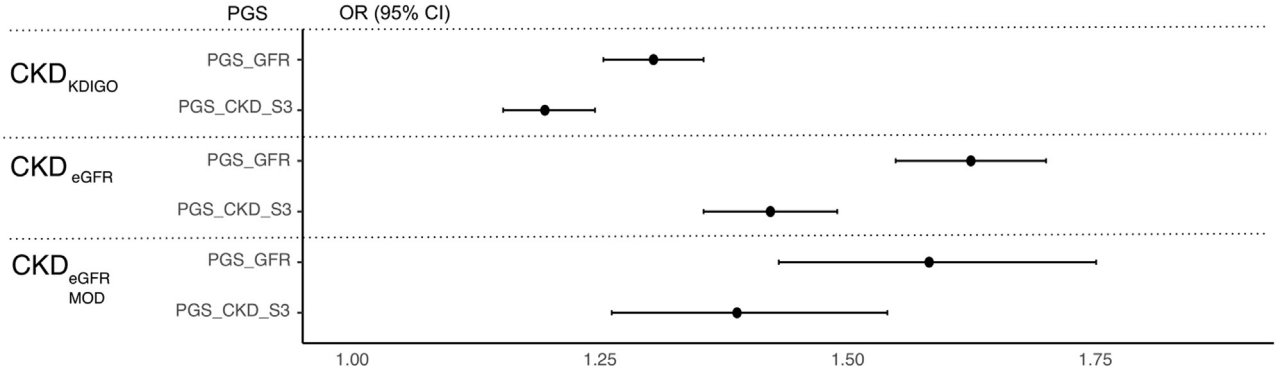

Figure 2 | Comparison of polygenic score (PGS)_glomerular filtration rate (GFR) with PGS_chronic kidney disease (CKD)_S3 for kidney function as CKD_{KDIGO} (estimated GFR [eGFR] < 60 ml/min per 1.73 m^2 or urine albumin-creatinine ratio > 3 mg/mmol), CKD_{EGFR} (eGFR < 60 ml/min per 1.73 m^2), and CKD_{EGFR_MOD} (eGFR < 45 ml/min per 1.73 m^2). CI, confidence interval; OR, odds ratio.

Table 5 | PGS_GFR for measures of CKD with PGS stratified by low and high risk of CKD

	Low (≤5% percentile)		High (≥95% percentile)	
End point	OR (95% CI)	*P* value	OR (95% CI)	*P* value
CKD_{KDIGO}	0.73 (0.58–0.90)	0.004	2.38 (1.99–2.85)	4.8×10^{-21}
CKD_{eGFR}	0.41 (0.29–0.55)	1.5×10^{-8}	3.39 (2.83–4.06)	1.0×10^{-39}
$CKD_{eGFR\ MOD}$	0.34 (0.13–0.71)	0.01	2.57 (1.80–3.58)	6.4×10^{-8}

CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; OR, odds ratio; PGS, polygenic score.
OR and *P* values for the fully adjusted logistic regression examining standardized (mean = 0; SD = 1) PGS_GFR stratified into categories (low, <5%; medium, 5%–95%; and high, >95% risk CKD) against binary outcomes: CKD_{KDIGO} (eGFR < 60 ml/min per 1.73 m^2 or urine albumin-creatinine ratio > 3), CKD_{eGFR} (eGFR < 60 ml/min per 1.73 m^2), and CKD_{eGFR_MOD} (eGFR < 45 ml/min per 1.73 m^2).

Table 6 | PGS_CKD_S3 for measures of CKD with PGS stratified by *low* and *high* risk of CKD

	Low (≤5% percentile)		High (≥95% percentile)	
End point	OR (95% CI)	*P* value	OR (95% CI)	*P* value
CKD_{KDIGO}	0.92 (0.74–1.13)	0.43	1.85 (1.53–2.23)	9.5×10^{-11}
CKD_{eGFR}	0.60 (0.46–0.78)	0.0002	2.43 (2.01–2.94)	3.4×10^{-20}
$CKD_{eGFR\ MOD}$	0.61 (0.31–1.07)	0.14	1.63 (1.06–2.41)	0.019

CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; OR, odds ratio; PGS, polygenic score.
OR and *P* values for the fully adjusted logistic regression examining standardized (mean = 0; SD = 1) PGS_GFR stratified into categories (low, <5%; medium, 5%–95%; and high, >95% risk CKD) against binary outcomes: CKD_{KDIGO} (eGFR < 60 ml/min per 1.73 m^2 or urine albumin-creatinine ratio > 3), CKD_{eGFR} (eGFR < 60 ml/min per 1.73 m^2), and CKD_{eGFR_MOD} (eGFR < 45 ml/min per 1.73 m^2).

wide association studies, up to 0.16 in the Framingham study and up to 0.30 in families with type 2 diabetes mellitus.[28,39,40] Given this variability, populations with greater heritability estimates may be more reflective of the duration of exposure to diabetes or poorly controlled hypertension. Given this heterogeneity, we focused predominantly on GFR for this study.

The second key outcome of our study was the validation of PGS for decline in eGFR (Figure 3) over time, based on serial eGFR measures of an average of 6 years of follow-up per participant. These results indicate a significant genetic component associated with more rapid decline in older ages. The result is informative, as to our knowledge the PGS_GFR_decline_2021 has not been validated in other populations to date, especially in this age range. The PGS_GFR_decline_2021 is a more "rapid" decline phenotype than PGS_GFR_decline_2022; however, both results were similar in our population, and we were unable to discriminate any significant advantage between either score, potentially related to absence of rapid decline phenotype in our population. Major limitations included a high dropout rate in later years and the fact that estimated rates of decline between the high and low PGS groups was small, corresponding to a 0.18 ml/min per 1.73 m^2 difference per year.

Although the heritability of eGFR decline from genome-wide association studies is 0.38, suggesting significant genetic factors,[9] the result of our analysis showed that the magnitude of change between the *high* and *low* PGS groups was small, and therefore may lack short- to middle-term clinical significance. This result may have been influenced by the overall health status of the ASPREE trial population at baseline. In a recent meta-analysis of 1.7 million patients, absolute reduction was more significant in those with a lower starting eGFR, suggesting that identifying those with a propensity toward lower eGFR could be useful for predicting who is at risk of more severe decline, and might be more useful than trying to predict decline using genetic information at older age.[41] The way in which baseline eGFR is handled in the analysis changes the conclusion of whether PGS_GFR_decline_2021 and PGS_GFR_decline_2022 are associated with eGFR decline, which may be related to collider bias. Collider bias is introduced when models for decline in eGFR incorporate baseline eGFR as part of the outcome, but which contain stronger genetic significance, and has been demonstrated in previous models, including PGS_GFR_decline_2022, suggesting studying genetic determinants of eGFR decline should be examined separately from genetics contributing to cross-sectional eGFR.[42]

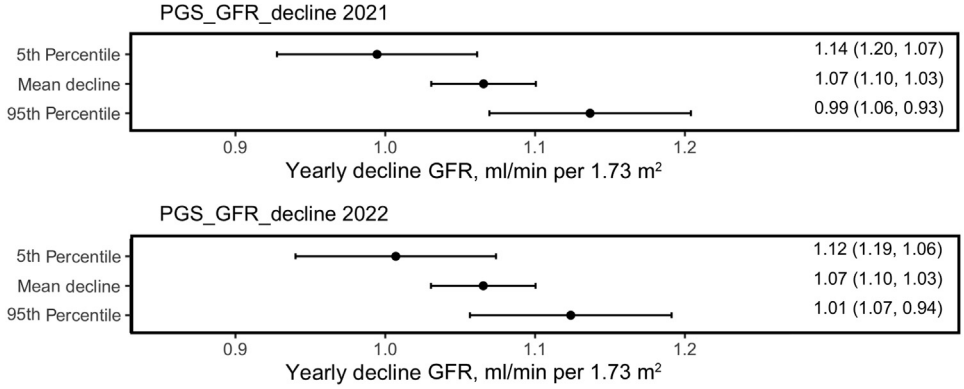

Figure 3 | Estimated difference in rate of decline of estimated glomerular filtration rate (GFR) per year according to the 2 polygenic score (PGS)_GFR_decline scores, showing estimates for mean, as well as point estimates for individuals in 5th and 95th percentiles.

Table 7 | Association of cardiometabolic disease over the course of the ASPREE study with PGS_GFR

Cardiometabolic trait	PGS_GFR per 1 SD (95% CI), *P* value	PGS_CKD_S3 per 1 SD (95% CI), *P* value
Incident coronary artery disease	1.01[a] (0.93–1.10), $P = 0.96$	0.98[a] (0.90–1.06), $P = 0.57$
Incident myocardial infarction over study	0.97[a] (0.85–1.11), $P = 0.66$	0.91[a] (0.80–1.05), $P = 0.19$
Baseline diabetes mellitus	1.00[b] (0.94–1.06), $P = 0.82$	0.99[b] (0.93–1.05), $P = 0.70$

ASPREE, ASPirin in Reducing Events in the Elderly; GFR, glomerular filtration rate; PGS, polygenic score.
[a]Hazard ratio.
[b]Odds ratio.
Covariates for coronary artery disease and myocardial infarction are age, sex, smoking, and alcohol use. The model for baseline diabetes mellitus is adjusted for age, sex, alcohol, smoking, hypertension, diabetes, body mass index, nonsteroidal anti-inflammatory drug and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, and visit year. In the adjusted model, n = 11,205 as individuals with incomplete covariate data are removed; in the unadjusted model, the same set of individuals are used.

A key strength of this study was validation of multiple PGSs for kidney phenotypes in an older, healthy population, across both eGFR and KDIGO stage. Models utilizing eGFR cutoff had stronger associations (and a greater AUC) than the same model when using KDIGO stage as the end point, but both are valid measures of kidney function. AUC scores showed comparable performance for both PGS_GFR and PGS_ CKD_S3 in all kidney phenotypes, with slightly higher AUC in PGS_GFR. The similarity is unsurprising as both are generated from CKDGen and UK Biobank data from predominantly European populations. PGS_CKD_S3 is unique with higher numbers of multiethnic populations, and incorporation of *APOL1* variation in the African ancestry cohort, with separation of eGFR into CKD status, to ensure discrimination of eGFR across ethnicities. Validation studies found that PGS_CKD outperforms PGS_CKD_S3 in patients of European ancestry, but not of Asian or African descent.[33] PGS_GFR_Decline_2021 was generated for >3 ml/min per 1.73 m^2 per year loss of eGFR, exceeding the rate in ASPREE, yet was still validated in this cohort. We were unable to discriminate this from PGS_GFR_Decline_2022, a phenotype with a lower rate of decline. Interestingly, the PGS_GFR_Decline_2022 noted a single-nucleotide polymorphism–for–age effect, supporting our findings of significance of PGS at older ages. Overall, kidney phenotypes in ASPREE were consistent with published literature, in their validation of recently developed PGSs.

Further strengths of this study lie in the high-quality longitudinal data and repeated measures of eGFR in an older population, validated in multiple phenotypes. The ASPREE cohort is a unique patient demographic, with exclusion criteria that ensure participants were free from cardiovascular disease, cancer, or dementia diagnoses at enrollment; thus, the general population is likely to have higher rates of CKD compared with ASPREE at equivalent age and a broader range of eGFR measures. A limitation of this study (as a result of the cohort ascertainment and related healthy survivorship bias) is that there were too few cases of CKD 4 to 5 and kidney failure to examine these phenotypes robustly, or to conclude on whether the PGS was associated with related metabolic or cardiovascular diseases. Nevertheless, individuals did retain some risks (such as high rates of hypertension) that are reflective of the broader population of older individuals.

A limitation found in many PGS studies is the risk of confounding by ethnicity (i.e., population stratification bias, where single-nucleotide polymorphisms strongly associated with one ethnicity may be more reflective of the shared environment in culture groups).[43] However, we mitigated against this risk by limiting the study to only individuals of European ethnicity. As a result, our findings cannot necessarily be generalized to other ethnicities, and PGS_CKD_S3 is more accurate for multiethnic populations, including incorporation of APOL1 status in African ancestry.[33]

The clinical translation of the investigated eGFR PGSs remains an open question, as novel approaches for improved long-term prognostication are explored. The results of this study suggest that identifying high-risk individuals earlier for CKD, before decline in eGFR, even at older ages may be a viable application of PGSs in the future. This may have specific benefit in older people, aged ≥70 years, in whom the prevalence of CKD increases sharply. Further validation of the PGSs tested is required in the general population, and across different ethnicities, age groups, and kidney-related conditions, to determine suitability for clinical implementation. PGSs for kidney disease–related traits could help improve CKD risk prediction and may offer a potentially modifiable risk factor that is amenable to early detection.

DISCLOSURE

AMM, KRP, and RW have received grants from the National Institutes of Health for the ASPREE trial and cohort. JBW has received grants from the National Institutes of Health, Merck, Glaco Smith Line, and Pfizer and meeting travel support and honoraria for educational events from Vifor, all outside of this work. AJM has received grants from the Medical Research Future Fund, Australian Government Department of Health, Townsville Hospital, and Health Services and meeting travel support from Otsuka, all outside of this work. All the other authors declared no competing interests.

DATA STATEMENT

Sequence and phenotype data that support the findings of this study have been deposited in the European Genome-Phenome Archive (EGAS00001005316). Access to analyze data from the ASPREE clinical trial and/or substudies, including biospecimens, can be applied for via the ASPREE Access Management Site (https://ams.aspree.org/public/#hero).

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SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary Figure S1. STROBE diagram of inclusion criteria for analysis.

Supplementary Figure S2. (**A,B**) Principal component (PC) analysis of the ASPirin in Reducing Events in the Elderly (ASPREE) cohort compared with the 1000 Genome Project.

Supplementary Figure S3. Histogram of polygenic scores (PGSs) investigated: scaled (mean, 0; SD, 1).

Supplementary Figure S4. Decline in estimated glomerular filtration rate (eGFR) over time (annualized) across the entire cohort.

Supplementary Figure S5. (**A–F**) Fully adjusted and unadjusted receiver operating characteristic (ROC) curve.

Supplementary Table S1. Number of individual measurements for estimated glomerular filtration rate (eGFR) and urine albumin-creatinine ratio (UACR) each year.

Supplementary Table S2. Mean estimated glomerular filtration rate (eGFR) measurements stratified by polygenic score (PGS) group and year.

Supplementary Table S3. Baseline attributes stratified by estimated glomerular filtration rate (eGFR) polygenic score (PGS) group.

Supplementary Table S4. Polygenic scores (PGSs) for chronic kidney disease (CKD) in models adjusted for principle component analysis.

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