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Influence of common genetic variants on childhood kidney outcomes

Kozeta Miliku^{1,2,3}, Suzanne Voegelzang^{1,2,3}, Oscar H. Franco², Albert Hofman², Vincent WV Jaddoe^{1,2,3}, and Janine F Felix^{1,2,3}

¹The Generation R Study Group, Erasmus MC, University Medical Center, Rotterdam, the Netherlands ²Department of Epidemiology, Erasmus MC, University Medical Center, Rotterdam, the Netherlands ³Department of Pediatrics, Erasmus MC, University Medical Center, Rotterdam, the Netherlands

Abstract

Background—Kidney measures in early life are associated with kidney disease in later life. We hypothesized that these associations are partly explained by common genetic variants that lead to both smaller kidneys with lower kidney function in early childhood and kidney disease in adulthood.

Methods—We examined in a population-based prospective cohort study among 4,119 children the associations of a weighted genetic risk score combining 20 previously identified common genetic variants related to adult eGFR_{creat} with kidney outcomes in children aged 6.0 years (95% range 5.7–7.8). Childhood kidney outcomes included combined kidney volume, glomerular filtration rate (eGFR) based on creatinine levels, and microalbuminuria based on albumin and creatinine urine levels.

Results—We observed that the genetic risk score based on variants related to impaired kidney function in adults was associated with a smaller combined kidney volume (P-value 3.0×10^{-3}) and with a lower eGFR (P-value 4.0×10^{-4}) in children. The genetic risk score was not associated with microalbuminuria.

Conclusion—Common genetic variants related to impaired kidney function in adults already lead to subclinical changes in childhood kidney outcomes. The well-known associations of kidney

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Corresponding author: Dr. J.F. Felix, MD, PhD, The Generation R Study Group (Na-2906), Erasmus MC, University Medical Center Rotterdam, PO Box 2040, 3000 CA Rotterdam, the Netherlands; Phone: +31 (0) 10 7043997, Fax: +31 (0) 10 4089382; j.felix@erasmusmc.nl.

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Category of study:

Population study

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measures in early life with kidney disease in later life may at least be partly explained by common genetic variants.

Introduction

End stage kidney disease seems to partly originate in early life (1, 2). Smaller kidneys in early life with a reduced number of nephrons lead to glomerular hyperfiltration and sclerosis and predispose to kidney disease in adulthood (3, 4). Also, risk factors for impaired kidney function track from childhood to adulthood (5, 6). Early kidney growth and development is a complex developmental process and is influenced by many environmental factors (7, 8). Various nutritional and environmental exposures have been suggested to affect early kidney development and may subsequently influence the risk of kidney disease in later life (9, 10).

However, the associations between early life kidney characteristics and kidney disease in later life may also be explained by common genetic variants. These variants may affect early kidney development and function and thereby predispose individuals to kidney disease in later life. Several genes are known to be involved in kidney development (8). Rare mutations in these genes are rare can cause severe anomalies, such as agenesis or dysgenesis of the kidney (7). These mutations do not explain variation in kidney development within normal range. However, large genome wide association studies (GWAS) in adults have identified 30 common genetic variants associated with impaired kidney function (11–13). For this study, we hypothesized that these genetic variants also affect kidney growth and function in early childhood, and thereby partly explain the well-known associations of early life kidney measures with kidney disease in later life.

To test this hypothesis, we examined, in a population-based prospective cohort study among 4,119 children, the associations of genetic risk scores combining previously identified common genetic variants related to impaired kidney function in adults with kidney outcomes in school-age children.

Results

Participant characteristics

The flowchart of study participants is given in the Figure 1. Table 1 shows the characteristics of the participants. In the full group the mean combined kidney volume and $\text{eGFR}_{\text{creat}}$ were 120 cm^3 ($\text{SD} \pm 23.3$) and $119 \text{ ml/min/1.73m}^2$ ($\text{SD} \pm 16$), respectively. Of all the children, 7.9% had microalbuminuria and 0.07% had an $\text{eGFR} < 60 \text{ ml/min/1.73 m}^2$. The characteristics of the subgroup of European children only were similar to those of the full group (Supplemental Table S1 (online)).

Individual genetic variants and childhood kidney outcomes

Results for the associations of the individual SNPs with childhood kidney outcomes are given in the Supplemental Material. Of the 20 available SNPs known to be associated with $\text{eGFR}_{\text{creat}}$ and the single SNP associated with microalbuminuria in adults, none were individually significantly associated with kidney volume, $\text{eGFR}_{\text{creat}}$, $\text{eGFR}_{\text{cystC}}$, and microalbuminuria, in the full group (Supplemental Table S2 (online)). In both the full group

and the European ancestry subgroup, rs3925584, located upstream of MPPED2, was associated with childhood creatinine blood levels (P values 1.8×10^{-3} and 5.6×10^{-4} , respectively). In addition, in the European ancestry subgroup, rs11078902 in CDK12 was associated with childhood creatinine blood levels and with eGFR_{creat} (P values 1.1×10^{-3} and 2.3×10^{-3} , respectively) (Supplemental Tables S3, S4 and S5 (online)). The 20 adult kidney function SNPs together explained 1.3%, 1.4%, and 0.6% of the variance in combined kidney volume, eGFR_{creat} and eGFR_{cystC} in childhood, respectively.

Genetic risk score and childhood kidney outcomes

Table 2 presents the associations of the weighted genetic risk score based on 20 SNPs known to be associated with impaired adult eGFR_{creat} with childhood kidney outcomes. The weighted risk score ranged from 13 to 33 with a mean of 22.8 (SD 2.8) and was significantly associated with childhood combined kidney volume (*P value* 3.0×10^{-3}). For each additional average risk allele, combined kidney volume was -0.39 cm^3 (95% Confidence Interval (CI) $-0.64, -0.13$) smaller. The difference in combined kidney volume between the lowest and highest risk categories (22 and 33 risk alleles, respectively) was 2.62 cm^3 (Figure 2, panel a), which corresponds with a 2.2% difference. A higher weighted genetic risk score was also associated with a lower eGFR_{creat} (*P value* 4.0×10^{-4}). For each additional average risk allele, eGFR_{creat} was $-0.38 \text{ ml/min/1.73m}^2$ (95% CI $-0.60; -0.17$) lower. The difference in mean eGFR_{creat} between the lowest and highest risk categories was $4.46 \text{ ml/min/1.73m}^2$ (Figure 2, panel b), which corresponds with a 3.7% difference. Similarly, per additional average risk allele of the adult risk score, childhood eGFR_{cystC} was $-0.27 \text{ ml/min/1.73m}^2$ (95% CI $-0.47; -0.07$) lower. The difference in mean eGFR_{cystC} between the lowest and highest risk categories was $3.38 \text{ ml/min/1.73m}^2$ (Figure 2, panel c). We did not observe an association of the weighted risk score with the risk of childhood microalbuminuria (data not shown).

Results from the unweighted risk score (mean 21.8, SD 2.8) were similar to those of the weighted score (Table 2). Supplemental Table S6 (online) shows that higher genetic risk scores were also associated with higher childhood creatinine blood levels and cystatin C blood levels (*P values* <0.05). Results in the subgroup of only European children tended to be similar to those in the full group, although the association of both risk scores with eGFR_{cystC} lost its significance and the unweighted risk score lost its significance with combined kidney volume in this group (Supplemental Table S7 (online)). The effect of the genetic risk score on combined kidney volume did not change after adjusting our model additionally for child height (Supplemental Table 8 (online)).

The genetic risk scores including 27 SNPs, with 7 additional SNPs related to creatinine metabolism in adults, and the genetic risk score including 11 SNPs which may have a known function related to kidney development, revealed similar results as our main risk score. Results are shown in Supplemental Tables S9 and S10 (online). In the Supplemental Table S11 (online), is shown the effect of the unweighted risk score which includes the additional 2 SNPs related to eGFR_{cystC}. The results did not change, but the effect estimates on eGFR_{cystC} and cystatin C were larger.

Discussion

We observed in a large population-based prospective cohort study, that a higher genetic risk score combining previously identified common genetic variants related to lower kidney function in adults was also associated with a smaller combined kidney volume and lower eGFR_{creat} and eGFR_{cystC} in childhood.

Previous GWAS have identified many common genetic variants related to impaired kidney function in adults (11–13). Of the 20 available SNPs known to be associated with adult eGFR_{creat} and the single SNP associated with adult microalbuminuria, only 2 were individually associated with childhood kidney outcomes. First, we observed an association of rs3925584, located upstream of *MPPED2*, with creatinine blood levels both in the full group and in the subgroup of European children only. In zebrafish, knockdown of *MPPED2* caused abnormal podocyte anatomy (11). Rs3925584 has also been associated with magnesium levels in a large GWAS (14). Rs3925584 is also located close to *DCDC5*, which has been associated with bone mineral density (15). Second, rs11078902 in *CDK12* was associated with eGFR_{creat} and creatinine blood levels in the subgroup of European children only (11). *CDK12*, cyclin-dependent kinase 12, regulates the expression of genes involved in DNA repair and is required for the maintenance of genomic stability. *CDK* inhibitors have been described to play a role in human glomerular disease (16). All these associations were directionally consistent with results reported in previous GWAS among adults (11, 13). None of the included common genetic variants were associated with childhood microalbuminuria. The results for the associations of individual SNPs with childhood kidney outcomes should be interpreted carefully. The original GWAS meta-analysis discovery studies in adults were performed in much larger samples than the current study and our negative results may have occurred due to a lack of power.

In the current study, the weighted genetic risk score related to impaired kidney function in adults was associated with smaller combined kidney volume and lower eGFR in childhood. For an average child in our population, the observed effect estimates correspond with a 0.3% smaller combined kidney volume, a 0.3% lower eGFR_{creat} and a 0.3% lower eGFR_{cystC} per each additional risk allele. We did not observe an association of the genetic risk score with microalbuminuria. We found similar results for the weighted and unweighted risk genetic scores, suggesting that the adult weights used in this score did not strongly influence the observed associations. Adding to the risk score 7 SNPs previously reported to play a role in creatinine production and secretion revealed similar results. Restricting the genetic risk score to the 11 SNPs with a likely or known function related to kidney development revealed similar results with slightly stronger effect estimates. This restricted genetic risk score may be more specific to our outcomes because of the young age range. Including in the unweighted risk score two additional SNPs known to be associated with eGFR_{cystC} (13, 17), showed similar associations, with stronger effect estimates on eGFR_{cystC} and cystatin C, suggesting a strong influence of the 2 added SNPs on these 2 markers. Ideally, the weights in the genetic risk score would be child-specific, as these best reflect the relative importance of the variants in children. For this, we would need results from large-scale GWAS with independent replication samples on childhood kidney function outcomes. However, a GWAS focused on kidney function among healthy children is not available yet. A recent paper

described a GWAS to identify common genetic variants influencing renal function in children with CKD. Although no genome-wide significant associations were found, a number of potentially interesting subthreshold SNPs were identified (18). This underlines the need for large-scale GWAS efforts to discover the genetic background of kidney function in children, both with and without CKD.

We hypothesized that common genetic variants may partly explain the associations of early life kidney measures with kidney function in later life. The observed associations of the genetic risk scores related to kidney function in adults with kidney outcomes in childhood support this hypothesis. However, confirmation of our findings in other children cohorts and further functional studies are required to establish the causal genes and the mechanisms underlying the associations of these variants with kidney function in childhood and disease in adulthood. In the same cohort as the current study, we have reported associations of smaller kidneys with lower kidney function (19). To explore if the associations of the genetic risks score with kidney function outcomes were explained by kidney volume, we additionally adjusted the kidney function measures for combined kidney volume. However, the results did not change. Also, adding childhood height to the models associating the genetic risk score with combined kidney volume did not materially change the results. The observed effect estimates in the present study are small, but important from an etiological perspective. They provide further insights into pathways leading to changes in kidney function from the earliest phase of life. Whether common genetic variants related to kidney outcomes in childhood and disease in adulthood are clinically useful for identification of groups at risk needs further study.

Some methodological issues need to be considered. Major strengths of the current study are the detailed phenotypes and the relatively large number of subjects. Still, our sample size was too small to identify many of the associations of individual common genetic variants with childhood kidney outcomes, assuming similar effect sizes as in adults. It has been shown that kidney function and the prevalence of chronic kidney disease vary across ethnic groups in adults (20). Our study population was multi-ethnic, but a sensitivity analysis in European children only, as the largest ethnic subgroup, revealed similar results as in the full group. The other ethnic subgroups were too small to analyze individually. Of all children with genetic information, data on kidney outcomes was available in 72%. As compared to children with kidney follow-up measurements, those without these measurements had a lower birth weight (P value <0.05) (data not shown). A selective loss to follow-up may have reduced variation in birth weight and early kidney size and therefore reduced the power to detect differences. We performed detailed measurements of childhood kidney outcomes. Kidney size correlates with the number of glomeruli and can be used as a measure of kidney development (21). In children the estimation of GFR is challenging. Blood creatinine is most commonly used to calculate eGFR. In addition to blood creatinine levels, we also calculated eGFR based on cystatin C levels using Zappitelli's formula (22, 23). It has been suggested that blood cystatin C levels might be a better biomarker to estimate GFR because the production rate is constant, it is freely filtered, and less dependent on child weight, height and sex compared to creatinine (24, 25). Finally, in our study we have captured the vast majority of, but not all, known SNPs related to kidney function, as not all SNPs were available in the GWAS dataset.

Conclusion

Our results suggest that common genetic variants related to kidney function in adults could influence kidney structure and function from early childhood onwards. The previously observed associations of early life kidney measures with kidney disease in later life seem to be partly explained by common genetic variants.

Methods

Design and study population

This study was embedded in the Generation R Study, a multiethnic population-based prospective cohort study from fetal life onwards in Rotterdam, the Netherlands, which has been described in detail previously (26). The study has been approved by Medical Ethical Committee of Erasmus MC, University Medical Center Rotterdam. All children were born between April 2002 and January 2006 and form a largely prenatally enrolled birth cohort that is currently being followed until young adulthood. Written consent was obtained for every participant. A genome wide association screen was available in 5,732 children (see below for details). The present analyses were performed among 4,119 singleton live births for whom we have detailed information on kidney outcomes at the median age of 6 years (95% range 5.7, 7.8). The flowchart of study participants is given in the Figure 1.

Genetic variants

DNA was isolated from cord blood samples. If DNA samples from cord blood were missing (in 6.3% of the participants), DNA was isolated from blood samples at follow-up measurements. Genome-wide association arrays were run using the Illumina 610 Quad and 660 platforms (27). A stringent process of quality control was applied. Individuals with low sample call rates or sex mismatches were excluded. Before imputation, Single Nucleotide Polymorphisms (SNPs) were excluded in case of high levels of missing data (SNP call rate <98%), highly significant departures from Hardy-Weinberg equilibrium ($P < 1 \times 10^{-6}$), or low minor allele frequencies (<1%) (26). MACH software was used to impute genotypes to the cosmopolitan panel of HapMap II (release 22) (28, 29). Three SNPs (rs6431731, rs2453580, and rs881858) had imputation qualities between 0.68 and 0.9, indicating reasonable imputation. All other SNPs had imputation qualities above 0.9, indicating good imputation. Based on previous studies, we identified 30 SNPs robustly associated with adult kidney function: 29 for adult eGFR_{creat} and 1 for adult microalbuminuria (11–13). Of these 30 SNPs, information on 26 was available in the GWAS. Information on rs11078903, rs7805747, rs2279463, and rs7422339, all previously associated with adult eGFR_{creat}, was not available. However, rs3798156 was used as a perfect proxy ($R^2=1$) for rs2279463 and rs11078902 was used as a perfect proxy for rs11078903. No perfect proxies were available in the GWAS dataset for the other two SNPs. As the focus of this study was to examine SNPs related to estimated glomerular filtration rate and not to creatinine metabolism, 20 out of these 28 SNPs were used for the genetic risk score analyses. The individual SNPs used are shown in Supplemental Tables S2 (online).

Childhood kidney outcomes

Kidney outcomes were assessed at a dedicated research center in the Erasmus MC - Sophia Children's Hospital in Rotterdam by well-trained staff (30). We measured kidney volume with ultrasound, using an ATL-Philips HDI 5000 instrument (Seattle, WA), with a 2.0-5.0 MHz curved array transducer. We identified the left and right kidneys in the sagittal plane along its longitudinal axis. Also, we performed measurements of maximal bipolar kidney length, width and depth. Kidney width and depth were measured at the level of the hilum. The cross-sectional area in which the kidney appeared symmetrically round at its maximum width was used. Kidney volume was calculated using the equation for a prolate ellipsoid: volume (cm³) = 0.523 x length (cm) x width (cm) x depth (cm) (31). Combined kidney volume was calculated by summing right and left kidney volume. We previously reported good intra-observer and inter-observer correlation coefficients (32).

Non-fasting blood samples were drawn by antecubital venipuncture. Creatinine concentrations were measured with enzymatic methods and cystatin C levels with a particle enhanced immunoturbidimetric assay (using Cobas 8000 analyzers, Roche, Almere, the Netherlands). Quality control samples demonstrated intra-assay and inter-assay coefficients of variation of 0.51% for creatinine and 1.65% for cystatin C, and 1.37% for creatinine and 1.13% for cystatin C, respectively. We estimated glomerular filtration rate (eGFR) according to the revised Schwartz 2009 formula: $eGFR_{creat} = 36.5 * (\text{height (cm)} / \text{serum creatinine } (\mu\text{mol/l}))$ (33). Additionally, we estimated the glomerular filtration rate using Zappitelli's formula based on cystatin C levels: $eGFR_{cystC} = 75.94 / [CysC^{1.17}]$ (22).

Urine creatinine (mmol/l) and urine albumin (mg/l) levels were determined with a Beckman Coulter AU analyser, creatinine levels were measured with the Jaffe reaction. We also calculated the albumin-creatinine ratio. In line with clinical cut-offs, microalbuminuria was defined as an albumin-creatinine ratio >2.5 mg/mmol for boys and > 3.5 mg/mmol for girls (34).

Statistical analysis

First, we performed multiple linear and logistic regression analyses, adjusted for sex, age at measurements and the first four principal components, to examine the associations of the 21 SNPs (20 SNPs for kidney function per se and 1 for microalbuminuria) individually with combined kidney volume, creatinine and cystatin C levels, $eGFR_{creat}$ and $eGFR_{cystC}$ and the risk of microalbuminuria in childhood, assuming additive genetic effects. To adjust for multiple testing in the analyses of the individual SNPs, we applied Bonferroni correction for the number of SNPs tested. A *P* value of $< 2.4 \times 10^{-3}$ ($0.05/21$) was considered statistically significant. Second, for each outcome we calculated the percentage of variance explained by all SNPs combined by deducting the unadjusted R^2 of the model including only the covariates from the unadjusted R^2 of the full model including all SNPs and the covariates, which were sex, age at measurements, and the first four principal components from our genome wide data. Third, we combined the 20 SNPs related to adult $eGFR_{creat}$ in a genetic risk score that summed the number of $eGFR_{creat}$ -decreasing alleles weighted by their previously reported effect sizes in adults. As for every SNP, the number of effect alleles can be 0, 1, or 2, the weighted risk score was rescaled to a score ranging from 0 to 40, the

maximum number of effect alleles, and rounded to the nearest integer. Additionally, we computed an unweighted genetic risk score based on the 20 adult $eGFR_{creat}$ SNPs to see whether the results were independent of the weight based on adults findings, by adding the number of risk alleles for the 20 SNPs. Linear and logistic regression analyses were performed to examine the association of these risk scores with combined kidney volume, creatinine and cystatin C, levels, $eGFR_{creat}$, $eGFR_{cystC}$ and the risk of microalbuminuria in childhood, adjusted for the same covariates as mentioned above. All analyses were performed first in the full group and subsequently repeated as sensitivity analyses in the subgroup of children of European ethnicity, the largest ethnic subgroup in our population. A child was classified as European if he/she was within four standard deviations from the HapMap CEU panel mean value for all first four principal components, based on the genetic data. To assess whether the associations were different by child sex we evaluated the statistical interaction by adding the product term of the child sex and individual SNPs to the models. However, no significant interactions were observed. We also aimed to explore whether child height affected the associations of the genetic risk score with combined kidney volume. We performed a sensitivity analysis to explore whether adding 7 SNPs related to creatinine metabolism (rs10774021, rs10794720, rs491567, rs6465825, rs9895661, rs2453533, rs3798156) to the genetic risk score would affect the results (11). In addition, we explored the association of a genetic risk score including only 11 of the 20 SNPs, which may have a role related to kidney developmental outcomes (nephrogenesis (rs881858, VEGFA; rs626277, DACH1); glomerular filtration barrier and podocyte function (rs11959928, DAB2; rs3925584, MPPED2; rs13538, NAT8), metabolic function of the kidney (rs1260326, GCKR; rs10109414, STC1), solute transport (rs12460876, SLC7A9; rs6420094, SLC34A1) and renal cell structure development (rs12917707, UMOD; rs17319721, SHROOM3)) (13, 17, 35, 36). Furthermore, we explored the effect of 2 SNPs known to be associated with $eGFR_{cystC}$, by adding them to the unweighted risk score. All analyses were performed using the Statistical Package for the Social Sciences version 21.0 for Windows (SPSS IBM, Chicago, IL).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Flow chart of the study participants

Figure 2.

panels a-c Effect of the weighted adult $eGFR_{creat}$ genetic risk score on childhood kidney outcomes (N= 4,119)

a. Effect of adult $eGFR$ creatinine-based genetic risk score on childhood combined kidney volume:

The x axis gives the categories of the risk score (overall sum of risk alleles, weighted by previously reported effect sizes, rescaled and rounded to the nearest integer). The left y axis gives the number of individuals in each risk-score category, whereas the right y axis gives the mean combined kidney volume. The histogram reflects the observed number of individuals in each risk-score category. The dots and regression line reflect the estimated mean combined kidney volume for each risk-score category. P value is based on the continuous risk score, as presented in Table 2. **** P value 3.0×10^{-3}**

b. Effect of adult $eGFR$ creatinine-based genetic risk score on childhood $eGFR$ creatinine-based:

The x axis gives the categories of the risk score (overall sum of risk alleles, weighted by previously reported effect sizes, rescaled and rounded to the nearest integer). The left y axis gives the number of individuals in each risk-score category, whereas the right y axis gives the mean $eGFR_{creat}$. The histogram reflects the observed number of individuals in each risk-

score category. The dots and regression line reflect the estimated mean $eGFR_{creat}$ for each risk-score category. *P value* is based on the continuous risk score, as presented in Table 2. **
P value 4.0×10^{-4}

c. Effect of adult eGFR creatinine-based genetic risk score on childhood eGFR cystatin C-based:

The *x* axis gives the categories of the risk score (overall sum of risk alleles, weighted by previously reported effect sizes, rescaled and rounded to the nearest integer). The left *y* axis gives the number of individuals in each risk-score category, whereas the right *y* axis gives the mean $eGFR_{cystC}$. The histogram reflects the observed number of individuals in each risk-score category. The dots and regression line reflect the estimated mean $eGFR_{cystC}$ for each risk-score category. *P value* is based on the continuous risk score, as presented in Table 2. **
P value 8.0×10^{-3}

Table 1**Subjects characteristics (N=4,119)**

Girls (%)	49.7
Gestational age at birth (weeks)	40.1 (36.4-42.3)
Birth weight (g)	3464 (515)
Age at kidney measurements (y)	6.0 (5.7-7.8)
Height at kidney measurements (m)	1.20 (0.06)
Weight at kidney measurements (kg)	23.3 (4.2)
Combined kidney volume (cm ³)	120.0 (23.3)
Creatinine (μmol/l)	37.4 (5.7)
Cystatin C (μg/l)	783 (83)
eGFR _{creat} (ml/min/1.73m ²)	119 (16)
eGFR _{cystC} (ml/min/1.73m ²)	103 (15)
Microalbuminuria (%)	7.9

Values are valid percentages for categorical variables, means (SD) for continuous variables with a normal distribution, or medians (95% range) for continuous variables with a skewed distribution.

Abbreviations: eGFR_{creat} estimated glomerular filtration rate calculated based on creatinine blood levels; eGFR_{cystC} estimated glomerular filtration rate calculated based on cystatin C blood levels.

Table 2Associations of the genetic risk score based on adult kidney function with childhood kidney outcomes (N= 4,119)^a

	Genetic risk score					
	Weighted			Unweighted		
	Difference (95% Confidence Interval)	P value	% of explained variance	Difference (95% Confidence Interval)	P value	% of explained variance
Childhood kidney outcomes (N)						
Kidney volume (cm ³) ^b (3,784)	-0.39 (-0.64; -0.13)	3.0*10⁻³	0.3	-0.38 (-0.63; -0.13)	3.2*10⁻³	0.3
eGFR _{creat} (ml/min/1.73m ²) ^b (2,847)	-0.38 (-0.60; -0.17)	4.0*10⁻⁴	0.4	-0.40 (-0.61; -0.20)	1.7*10⁻⁴	0.7
eGFR _{cystC} (ml/min/1.73m ²) ^b (2,854)	-0.27 (-0.47; -0.07)	8.0*10⁻³	0.2	-0.28 (-0.48; -0.09)	5.0*10⁻³	0.3

^a Analyses were performed in children with complete data on genetics, at least one outcome under study, and covariates.^b Values are beta coefficients from linear regression models adjusted for child age, sex and the first four principal components from the genetic data.

Abbreviations: eGFR_{creat} estimated glomerular filtration rate calculated based on creatinine blood levels; eGFR_{cystC} estimated glomerular filtration rate calculated based on cystatin C blood levels. *P* value for the significant associations < **0.05**. The percentage of variance explained by the genetic risk score, was calculated by comparing the unadjusted R² between a model including the risk score and the covariates and a model including only the covariates, which were sex, age at measurements, and the first four principal components.