

# Kidney size in relation to ageing, gender, renal function, birthweight and chronic kidney disease risk factors in a general population

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## ABSTRACT

**Background.** The relationship of kidney size to ageing, kidney function and kidney disease risk factors is not fully understood.

**Methods.** Ultrasound length and parenchymal kidney volume were determined from a population-based sample of 3972 Sardinians (age range 18–100 years). We then identified the subset of 2256 ‘healthy’ subjects to define age- and sex-specific reference ranges (2.5–97.5 percentile) of kidney volume. Logistic regression (accounting for family clustering) was used to identify the clinical characteristics associated with abnormally large kidneys or abnormally small kidneys.

**Results.** In the healthy subset, kidney volume and length increased up to the fourth to fifth decade of life followed by a progressive decrease in men, whereas there was a gradual kidney volume decrease throughout the lifespan of women. In the whole sample, independent predictors of lower kidney volume (<2.5 percentile for age and sex) were male sex, low body mass index, short height, low waist:hip ratio and high serum creatinine (SCr); the independent predictors of larger kidney volume (>97.5 percentile for age and sex) were younger age, female sex, diabetes, obesity, high height, high waist:hip ratio and lower SCr. Estimated heritability for kidney volume was 15%, and for length 27%; kidney volume correlated strongly with birthweight.

**Conclusions.** Overall, in a general healthy population, kidney measures declined with age differently in men and women. The determinants of kidney parenchymal volume include genetic factors and modifiable clinical factors.

**Keywords:** age, elderly, epidemiology, gender, ultrasonography

## INTRODUCTION

Renal function is known to decrease progressively with age even in healthy individuals, a process called nephrosenescence [1, 2]. Correspondingly, the increased rates of chronic kidney disease (CKD) observed in the elderly result from ageing-related decreases in function and from the increasing frequency of risk factors such as atherosclerosis or diabetes [3, 4]. As apparent indicators of nephrosenescence, imaging findings routinely show renal atrophy and reduced kidney size in patients with CKD, particularly at advanced stages [5]. Previous work also suggested an age-related loss of total or parenchymal kidney volume (PKV) in normal subjects, and it has even been suggested that in healthy kidney donors kidney volume could be a surrogate for kidney function [6, 7]. The relationship between renal volume and function during ageing remains unclear [8] and not always proportional, because the kidney has a considerable functional reserve and homeostatic adaptive mechanisms [9]. For example, glomerular filtration rate (GFR) can be sustained within the normal range in kidney donors even after the loss of functional parenchyma [10] and can be increased as required in pregnancy [11] or after partial or radical nephrectomy in adults [12].

Furthermore, complicating inferred links between kidney volume and function during ageing, there may be possible differential effects in men and women [7]. Other relevant

ageing-related factors include the increase of renal sinus fat, parenchymal cysts [13] and CKD risk factors such as diabetes and obesity [14]. Different ethnicity and a limited number of observed aged individuals may constitute additional limits [15–17].

Here we aimed to extend previous analyses about the ageing-dependent decline of estimated GFR (eGFR) [1] in a large cohort of Sardinians, including substantial numbers of individuals >70 years of age. In this cross-sectional study we further analysed the relationship of PKV and length with age, renal function, CKD risk factors, birthweight (BW) and heritability characteristics in both women and men.

## MATERIALS AND METHODS

### Study design

Clinical and genetic data were obtained as part of the longitudinal SardiNIA Project (<https://sardinia.irp.nia.nih.gov/>), supported by the National Institute on Aging (NIA), started in 2001. The cohort underwent a study visit every 3–4 years. Analysis for this study was based on the fourth visit of 3688 participants that completed evaluations for PKV by ultrasound, laboratory testing and an administered survey and lacked renal cysts that would bias PKV calculations. A subset of 2421 ‘healthy’ individuals was used to define reference levels for PKV. The healthy subset was defined by the absence of diabetes, obesity, metabolic syndrome, hypertension, protein:creatinine ratio (PCR) >150 mg/g or a history of cardiovascular (CV) disease.

The study was approved by the ethics committee and written consent was obtained from all the participants.

Among 4531 individuals (57.1% female), 559 (49% female) were excluded from analyses of kidney size because they had cysts or polycystic kidney disease.

### Kidney parenchymal measures

Ultrasound examination was used to determine kidney length and PKV. A medical sonographer used the convex array probe C5-2 MHz of the Philips Healthcare ATL HDI 3500 ultrasound device. Ultrasound images for each kidney were collected in the longitudinal and transverse planes, assessing maximum length, anteroposterior diameter and width and thickness of the parenchyma. Renal length was measured as the maximum distance between the upper and lower pole in the longitudinal plane at the median level. The anteroposterior diameter and width were measured in the transverse plane perpendicular to the longitudinal axis of the kidney, in the hilum. The anteroposterior diameter and the width were measured in orthogonal directions. Parenchymal thickness was measured in the longitudinal scan as the distance between the renal capsule and the border of the renal sinus fat separation. We considered the mean of three consecutive measures. PKV was estimated using ellipsoid volume equations [18] (see [Supplementary data](#) for details).

### Clinical characteristics

Participants were interviewed to collect sociodemographic information, medical and family history, BW, lifestyle, health behaviours (smoking, drinking, coffee intake etc.) and medications. Anthropometric measures (height, weight and waist

circumference) and resting blood pressure (BP) were determined. Blood samples were collected by venipuncture after an overnight fast of at least 12 h at each visit. Blood tests included serum creatinine (SCr), uric acid, glucose, haemoglobin A1c and lipid levels. SCr was measured with a kinetic alkaline picrate assay (Biosystem A25) and calibrated to standardized values [1]. GFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and full age spectrum (FAS) equations. PCR was expressed as mg/g. Urine samples were centrifuged (3000g for 10 min) and the supernatant was then processed for the pyrogallol red molybdate (PRM) dye-binding assay from BioSystems (PROTEIN Urine 12501). The proteins in urine reacted with PRM dye reagent to form a blue–purple colour complex with maximum absorbance at 600 nm and the tests were performed using the A25 autoanalyser (BioSystems, Spain). Diabetes was defined according to the guidelines of the American Diabetes Association [19]. BP was measured using a calibrated desktop sphygmomanometer after at least 5 min of supine rest. Volunteers were classified as hypertensive when BP was  $\geq 140$  mmHg systolic or  $\geq 90$  mmHg diastolic or when they reported taking antihypertensive medication. Obesity was defined as body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup> (weight in kg divided by height in m<sup>2</sup>). Body surface area (BSA) was calculated with the Dubois formula. Metabolic syndrome was defined according to the International

**Table 1. Demographic and clinical characteristics of 3972 individuals of the SardiNIA study cohort**

Characteristics	Whole sample (n = 3972)	Healthy (n = 2256)
Age (years)	49.96 ± 16.14	43.82 ± 13.18
Age range (years)		
20	52 (1.3)	42 (1.9)
20–39	1131 (28.5)	881 (39)
40–59	1693 (42.6)	1060 (47)
60–69	606 (15.3)	199 (8.8)
>70	490 (12.3)	74 (3.3)
Men	1657 (41.7)	847 (37.5)
Height (cm)	160.5 ± 9.4	161.4 ± 8.84
Waist:hip ratio	0.895 ± 0.083	0.869 ± 0.072
BMI (kg/m <sup>2</sup> )	25.63 ± 4.58	23.6 ± 3.05
BSA (m <sup>2</sup> )	1.68 ± 0.20	1.65 ± 0.17
eGFR (mL/min/1.73 m <sup>2</sup> )	104.33 ± 17.78	110.5 ± 14.02
SCr (mg/dL)	0.85 ± 0.17	0.82 ± 0.14
High SCr	100 (2.5)	0
PCR $\geq 150$ –<500 (mg/g)	74 (1.8)	26 (1.2)
PCR $\geq 500$ (mg/g)	29 (0.8)	0
Small PKV	93 (2.3)	57 (2.5)
Large PKV	183 (4.6)	59 (2.6)
Diabetes	297 (7.5)	0
Hypertension	1119 (28.2)	0
Previous cardiac disease	232 (5.8)	0
Uric acid (mg/dL)	4.57 ± 1.45	4.23 ± 1.29
HDL cholesterol (mg/dL)	63.71 ± 14.29	65.64 ± 14.29
LDL cholesterol (mg/dL)	126.25 ± 34.36	126.25 ± 33.98
Triglycerides (mg/dL)	97.35 ± 62.83	86.73 ± 51.33
Smoker	745 (18.1)	509 (22.6)
Former smoker	956 (24.1)	453 (20.1)

Values are presented as mean ± SD or n (%). Healthy individuals are those without the following comorbidities/risk factors: diabetes, obesity, hypertension, previous cardiac disease, high SCr. Small and high PKVs are defined as, respectively, <2.5 and >97.5 percentiles for sex and age. High SCr is defined as >97.5 percentile for sex and age. GFR is estimated with the CKD-EPI equation.

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Diabetes Federation guidelines [20]. Cigarette smoking was assessed as never, current or former at the time of the clinic visit; individuals who smoke 1 cigarette/day and those who have quit smoking for 1 year were defined, respectively, as current or former smokers. Previous CV events, including coronary heart disease, heart attack, heart failure and stroke, were self-reported.

Low and high BW were defined as <2.5 and >4.5 kg, respectively. Age, sex and BSA-adjusted heritability were assessed for PKV using the POLY software program (freely available with source code from <http://csg.sph.umich.edu//chen/public/software/poly/Download.htm>).

### Statistical analysis

The distributions of clinical characteristics in the overall sample and the health subset were described. All regression analysis used generalized estimating equations to account for the familial relationships of the sample. Quantile regression was used to determine how PKV changes with age in both men and women with the 2.5 percentile, median and 97.5 percentile reported. Multivariable logistic regression models were fit to identify the clinical characteristics that independently associated with abnormally large kidneys (>97.5 percentile for age and sex) and the clinical characteristics that associated with abnormally small kidneys (<2.5 percentile for age and sex) in the whole sample.

Statistical analyses used R (<http://www.r-project.org/>). A significance level of 0.05 was used.

## RESULTS

### Population sample

The SardiNIA project includes 6921 individuals, representing >60% of the adult population of 4 villages in the Lanusei valley in Sardinia. All individuals included in the study were of Sardinian origin and participate in a longitudinal study of age-related quantitative traits on the island. Detailed description of the cohort have been published previously [1]. The main clinical and demographic characteristics of the 3688 SardiNIA participants studied here are described in Methods section and are shown in the Table 1.

### Kidney sizes

PKV varied in a nonlinear fashion according to age and sex. It remained almost stable until the fourth decade in women and then gradually declined, sharply after the seventh decade ( $P < 0.001$ ). In contrast, it increased in men from youth to the fifth decade before a progressive decline, resulting in a parabolic curve over time ( $P < 0.001$ ) with a sharp decline after the seventh decade (Figure 1).

The median PKV among 2256 healthy individuals was 266 cc (2.5–97.5 percentiles 173–389). As shown in Table 2, men had larger PKVs than women ( $P < 0.01$  for all age groups). As a further notable sex difference, PKV increased gradually up to age 45 years in men and then gradually declined, whereas

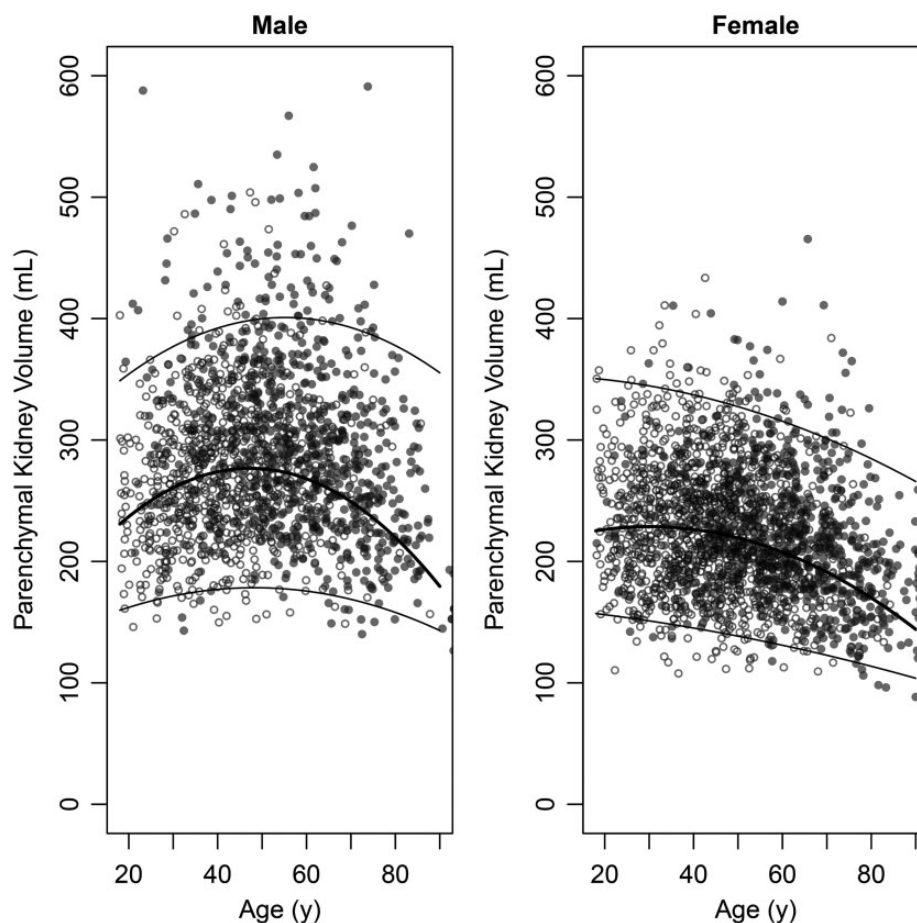


FIGURE 1: Age-related changes in PKV in a subset of 2255 healthy individuals of the SardiNIA study cohort [846 (37.5%) are men].

PKVs in women was relatively stable up to the age of 40–50 years, with a subsequent decline (Table 2). The results were similar when PKV was adjusted for BSA or height and for kidney length (Supplementary data, Figures 1S and 2S). Those results were more evident in the ‘comorbid’ group (data not shown).

### Clinical characteristics and CKD risk factors associated with small and large PKVs

Independent predictors of small PKV (defined as PKV <2.5 percentile for age and sex) were male sex, high BMI, low height, low waist:hip ratio and high SCr (Table 3).

Independent statistically significant predictors of large PKV (>97.5 percentile for age and sex in the healthy group) were female sex, diabetes, obesity, high height, high waist:hip ratio and low SCr (Table 3). The results were similar when PKV was adjusted for BSA, but the anthropometric variables lost their statistical significance (Supplementary data, Table 1S).

**Table 2. The median (2.5–97.5 percentiles) PKV by sex and age group in a subset of 2256 healthy individuals of the Sardinia study cohort**

Age group (years)	PKV (cm <sup>3</sup> ), median (2.5–97.5 percentiles)	
	Male	Female
Overall (n = 847–1409)	266.2 (173.5–389.1)	220.0 (137.3–331.9)
18–30 (n = 153–217)	249.7 (167.0–355.7)	225.0 (152.6–337.3)
30–40 (n = 231–321)	272.2 (176.5–372.3)	227.9 (148.7–346.6)
40–50 (n = 239–408)	276.6 (181.5–406.1)	231.7 (141.9–334.8)
50–60 (n = 134–279)	268.5 (179.3–385.3)	211.6 (138.1–313.1)
60–70 (n = 63–136)	260.2 (170.1–363.4)	200.6 (127.3–302.4)
70–80 (n = 23–41)	250.5 (174.6–372.8)	190.0 (122.5–322.5)
80–90 (n = 3–7)	207.0 (159.1–308.2)	164.5 (134.1–196.2)

Men had larger kidney PKVs than women (P < 0.01 for all age groups).

In contrast to the strong effects of metabolic variables, genetic heritability was modest (15% on PKV and 27% on kidney length).

### Kidney volume and renal function

BSA-adjusted PKV was directly related to GFR estimated with either the CKD-EPI or FAS equation, and the association was stronger in the >70-years-old group (Pearson’s correlation coefficient 0.32 and 0.35, respectively, with CKD-EPI and FAS equations; Figure 2).

### BW

When the cohort was split according to BW as low (<2.5 kg), normal (2.5–4.5 kg) and high (>4.5 kg), we observed that higher BW (>4.5 kg) was associated with larger kidney volume and lower BW (<2.5 kg) was associated with smaller kidney volume. For BWs between 2.5 and 4.5 kg, intermediate values of PKV were observed (Figure 3).

## DISCUSSION

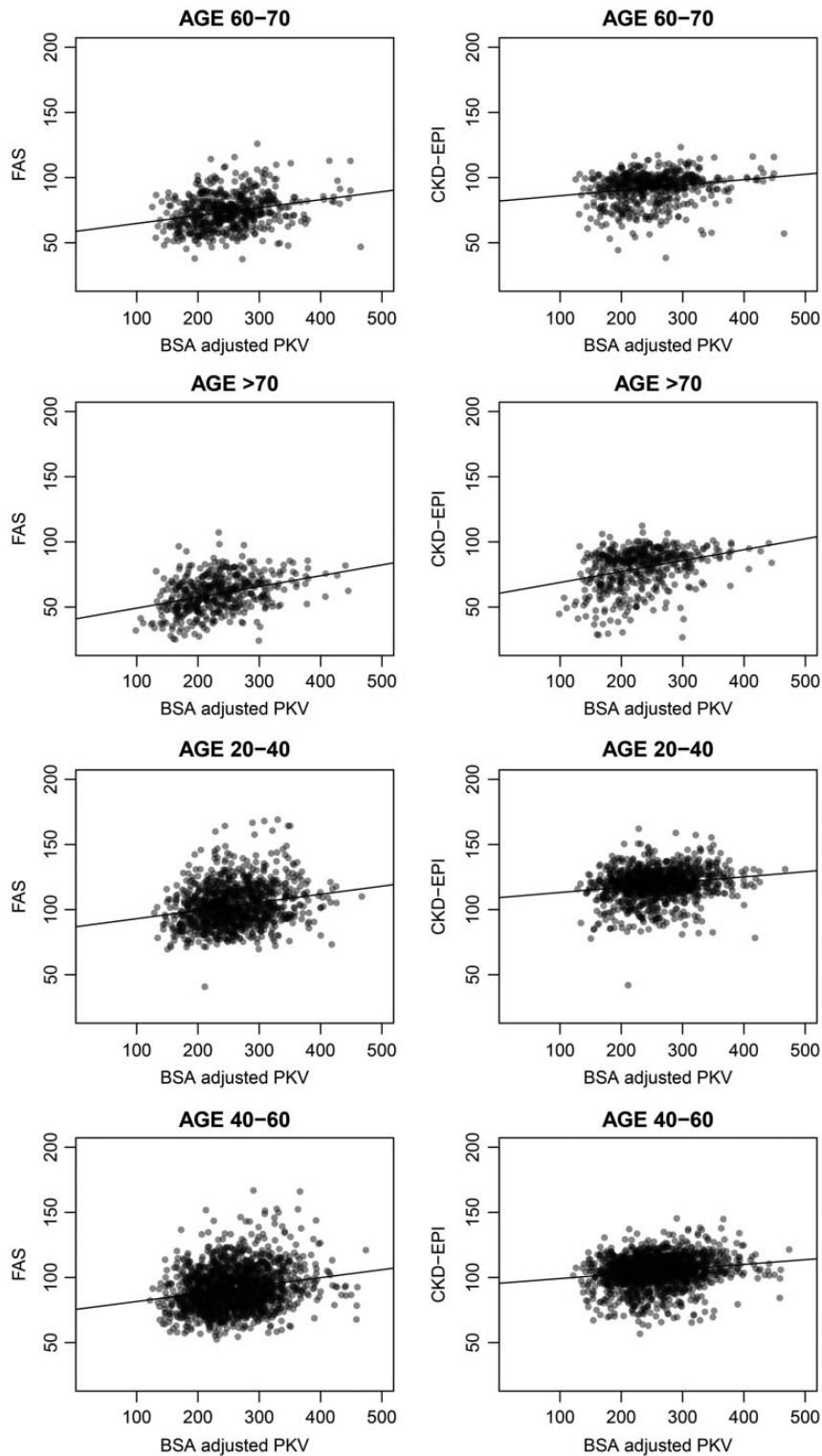
Gender- and age-related changes in kidney size parameters over the lifespan were clear in our cohort of 2431 healthy individuals. PKVs in males increased up to middle age and then progressively declined, more sharply after 70 years of age, whereas females trended towards a gradual kidney volume decrease through life. This tendency may be an early expression of nephrosenescence and can reflect an ‘adaptive volume augmentation’ in early adulthood, that is, a volume compensation for some progressive loss of functional nephrons [3]. Consistent with such a notion, measured GFR (mGFR) is stable or declines slowly before a steeper decrease after the fourth decade [21, 22]. Since the human nephrogenesis is complete by 36 weeks of

**Table 3. Predictors of small and large kidney PKVs in a cohort of 3972 individuals of the Sardinia study cohort**

	Small PKV				Large PKV			
	Univariate		Multivariate		Univariate		Multivariate	
	OR	P-value	OR	P-value	OR	P-value	OR	P-value
Age (years)	1.006	0.5	–	–	1.007	0.8	–	–
Female	0.941	0.9	0.235	<0.001	0.517	0.5	2.035	0.01
Obesity	0.264	0.8	–	–	7.106	0.18	4.368	<0.001
Diabetes	1.095	1.0	–	–	2.892	0.4	1.723	0.03
Previous CV disease	2.363	0.7	–	–	0.803	0.9	–	–
High BP	0.768	0.9	–	–	2.219	0.4	–	–
Smoker	0.716	0.9	–	–	1.285	0.8	–	–
Former smoker	1.112	0.9	–	–	1.603	0.6	–	–
BMI, SD	0.394	<0.001	0.302	<0.001	2.171	0.03	–	–
Height, SD	0.708	0.003	0.425	<0.001	1.621	<0.001	2.336	<0.001
Waist:hip ratio, SD	0.664	0.5	0.670	0.019	1.972	<0.001	1.766	<0.001
SCr, SD	1.391	0.5	1.853	<0.001	0.811	0.02	0.508	<0.001
PCR >500 mg/g	0.00	1.0	–	–	3.089	0.7	–	–
HDL cholesterol, SD	1.288	0.02	–	–	0.788	0.004	–	–
LDL cholesterol, SD	0.803	0.07	–	–	1.035	0.9	–	–
Triglycerides, SD	0.770	0.06	–	–	1.202	0.01	–	–
Uric acid, SD	0.875	0.8	–	–	1.250	0.05	–	–

Family-based, logistic univariate and multivariate regression of low and large PKVs. Quantitative variables are scaled for continuous variables, ORs are expressed for each increase of 1 SD of the variable.

OR, odds ratio; SD, standard deviation.



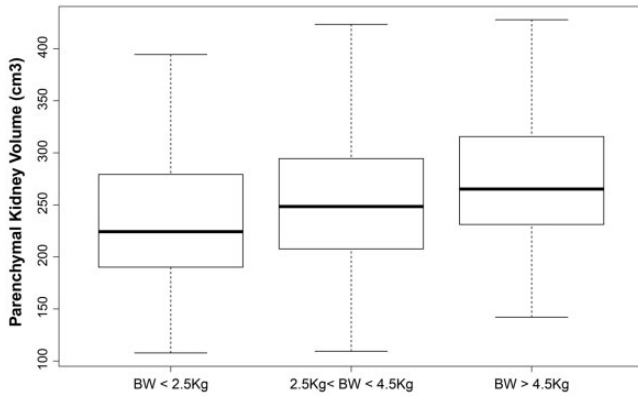
**FIGURE 2:** PKV and eGFR (estimated with the CKD-EPI and FAS equations) were directly related in all the age categories ( $P < 0.001$ ). The strength of the association was greater in patients  $>70$  years [Pearson's correlation  $r = 0.36$  and  $0.32$ , respectively, for FAS and CKD-EPI eGFR; 60–70 years:  $r = 0.26$  (FAS) and  $0.20$  (CKD-EPI); 40–60 years:  $r = 0.21$  (FAS) and  $0.17$  (CKD-EPI); 20–40 years:  $r = 0.21$  (FAS) and  $0.18$  (CKD-EPI)].

gestation [23], the initial increase in kidney volume in early adulthood in men (Figure 1) cannot be due to increased nephron numbers but most likely reflects nephron hypertrophy. Consistent with this interpretation, adaptive hyperfiltration in 21 kidney donors [24] and in rats [25] after nephrectomy was

attributed to hypertrophy of the remaining nephrons [26]. During the lifespan, in fact, microdissected glomeruli from autopsied normal kidneys increased in size up to 7-fold from infancy to adulthood and then progressively shrank [25] with nephrosclerosis and tubular atrophy [27]; and nephron

hypertrophy has indeed been proposed as a compensation for the progressive loss of more superficial glomeruli during nephrosclerosis in ageing [28–30]. A concomitant decrease in podocyte density in hypertrophic glomeruli may further increase the risk of glomerulosclerosis [31].

According to previous studies, cortical volume declines late in life [7]: again, this could reflect increased sclerosis [32, 33] and atubular glomeruli [34]. Nephrosclerosis and nephron hypertrophy would thus have opposite effects on cortical volume



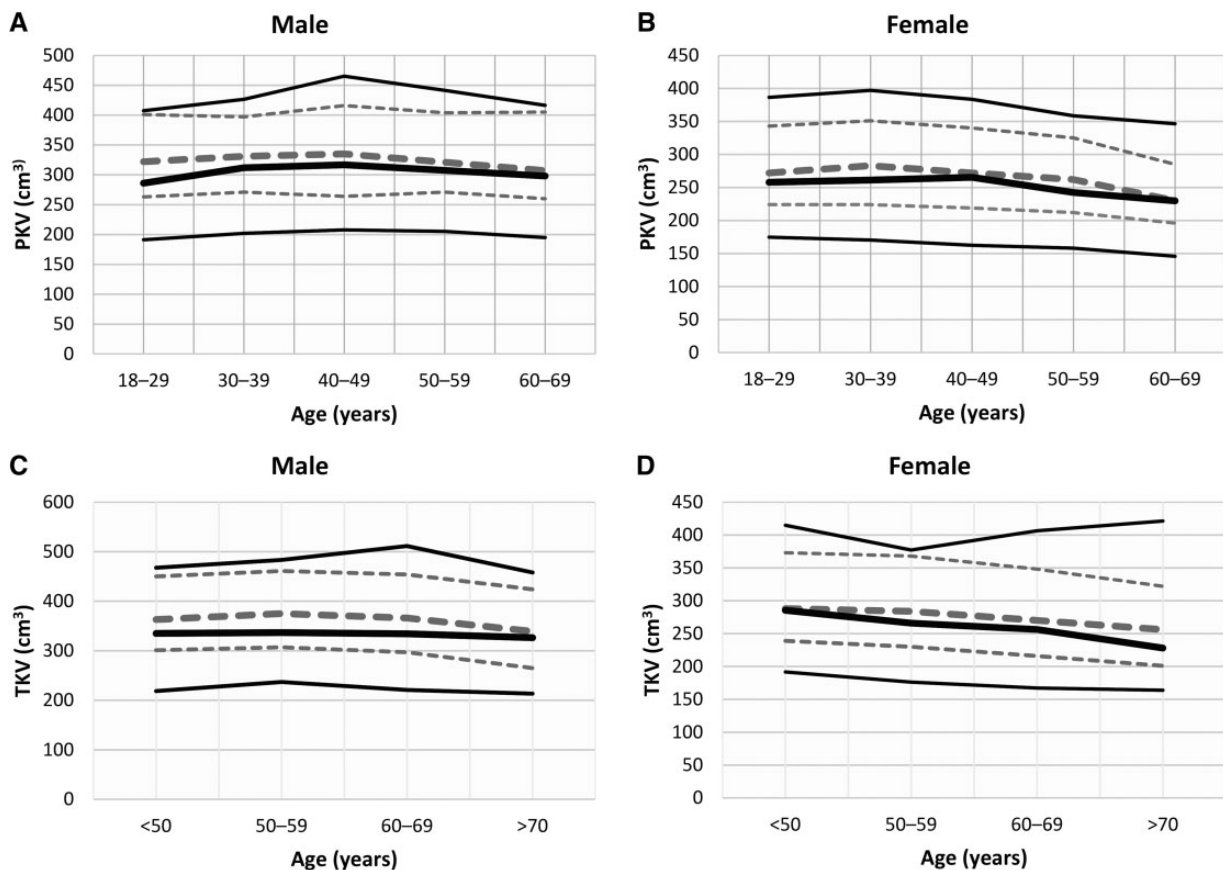
**FIGURE 3:** PKV by BW in a subset of 2057 individuals of the SardiNIA study cohort.

and the net effect can rationalize the biphasic curve we observed during ageing: total PKV increases, followed after the fourth decade by progressively increasing loss of total parenchymal and cortical volume from nephrosclerosis and ischaemia. Thus when we compared our PKV mean values (yellow) to those of the kidney donors in Wang *et al.* [7] (blue) in females (Figure 4A) and males (Figure 4B), the profiles were quite similar.

Likewise, the trend of total kidney volume (TKV) mean values of the SardiNIA cohort (yellow) was similar to that in the Framingham study (blue) for males (Figure 4C) and females (Figure 4D) [35]. The mean values of Sardinians were consistently lower (Supplementary data, Figures 3S and 4S)—likely because of their smaller body size, because the means were almost the same when adjusted for BSA levels. The distribution was wider in our cohort, reflecting greater population variability or the different imaging techniques.

### Sex differences

We found notable initial hypertrophy, especially in men. A previous study of computed tomography (CT) scans of potential kidney donors found somewhat similar results [7]: cortical volumes showed age-related reduction in both men and women, whereas medullary volume showed a slight, constant increase in men but an initial increase followed by a subsequent



**FIGURE 4:** Comparison between PKV in healthy (A) women and (B) men of the SardiNIA kidney cohort (solid line) and of living kidney donors in Wang *et al.* [7] (dashed line). Comparison between TKV in healthy (C) women and (D) men of the SardiNIA kidney cohort (solid line) and the Framingham study (Roseman *et al.* [35], dashed line). The thick lines are the median values, the thin lines the 2.5 and 97.5 percentiles. PKV and TKV are adjusted for body surface area (1.9 and 1.78 m<sup>2</sup>, respectively).

decline in women (Figure 1). Physiological differences in the kidneys in men and women may be driven by the kidney sex hormone receptors [36, 37]. In a murine model of uninephrectomy, glomerular volume of the remnant kidney increased more in males than in females, dependent on testosterone stimulus [38]. Androgens also increased kidney weight in rat models, may upregulate angiotensin II and are profibrotic, stimulating mesangial extracellular matrix accumulation, whereas oestrogens can suppress mesangial growth and extracellular matrix accumulation [39].

### Comorbidities

The whole sample and healthy sample had the same prevalence of small PKV, but large PKV was almost half as prevalent in healthy individuals. (Pathologically small kidneys were not detected, probably because individuals with advanced or end-stage kidney disease were excluded from the analysis.)

Adjusted analyses showed diabetes and obesity as independent predictors of large PKV. These comorbidities are associated with hyperfiltration via overstimulation of the renin–angiotensin–aldosterone system (RAAS) [40], provoking intraglomerular hypertension and adaptive functional augmentation. Thus diabetic nephropathy and obesity are characterized by enlarged kidneys with hyperfiltration and glomerulomegaly [41, 42]. The effect of obesity was marked and the waist:hip ratio was further associated with large PKV independent of BMI.

The effects of size and comorbidities on kidney function are hard to quantitate, but age correlates qualitatively with eGFR (data not shown), and even more clearly with the reported initial stable or slowly declining level of mGFR followed by a much faster decrease as age progresses [21, 22, 43]. Moreover, eGFR correlates significantly with kidney volume, in all age categories, especially in the elderly.

### BW and heritability

Our observational study is cross-sectional. Kidney measures were obtained with ultrasound, which cannot differentiate between cortical and medullary parenchyma; moreover, kidney volume was calculated with an ellipsoid formula. Furthermore, because there is currently no acceptable way to determine nephron number in living individuals, it is difficult to assess glomerulus/nephron decline quantitatively. But as a crude index, number correlates with BW: deceased neonates born small for their gestational age have fewer nephrons than controls [23, 44]. Low-BW newborns have reduced ultrasonographic kidney sizes in childhood [45], and we find that higher BW is associated with larger adult kidney volume and, we infer, correspondingly greater or lower numbers of glomeruli in adult life, but with no significant differences in eGFR. Overall, as suggested earlier, low BW and reduced kidney size could thus be a surrogate for low nephron number [46]. Although *PAX2* [47] and *OSR1* variation [48], for example, are associated with a reduction of newborn kidney size, there is less evidence for a substantial effect of genetic factors on size measures in adults. Two small studies [49, 50] estimated the heritability of renal length as ~45–50%. However, we found only modest heritability of 15% for PKV and 27% for kidney length in this large general

population cohort, which is especially well suited to assess heritability accurately [51, 52]. Instead, the results underline—especially for volume—the strong environmental component in the development of kidney size, including the effect of associated nutritional factors that could respond to intervention.

Such factors likely account for the small kidney size associated with low BW, but it remains unclear whether those individuals show earlier or more advanced CKD or whether their kidney size corresponds to their level of metabolic need, with no increased risk of CKD.

### CONCLUSIONS

In our general population cohort, ages 18–100 years, we characterized renal size in relation to ageing, gender, function and CKD risk factors. Overall, a biphasic trend with age was observed in males and, in a more pronounced way, in individuals with diabetes and obesity. We suggest that the early increase could reflect an adaptive volume augmentation, with hypertrophy responding to higher metabolic needs, particularly in those with metabolic comorbidities. Heritability was modest, whereas lifestyle effects were apparent. In addition to high BW, obesity, high waist:hip ratio, height and female sex were independent predictors of large PKV, whereas SCr was an independent predictor of small kidneys. Further studies could assess whether resultant adult renal sizes determined sonographically could represent a useful index of the level of adaptive volume augmentation and later nephrosenescence, especially in the progressive CKD in middle age and thereafter.

### SUPPLEMENTARY DATA

Supplementary data are available at [ndt](http://ndt.oxfordjournals.org/) online.

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### CONFLICT OF INTEREST STATEMENT

None declared.

### REFERENCES

1. Pani A, Bragg-Gresham J, Masala M. Prevalence of CKD and its relationship to eGFR-related genetic loci and clinical risk factors in the SardiNIA study cohort. *J Am Soc Nephrol* 2014; 25: 1533–1544

2. Rule AD, Glassock RJ. The aging kidney. In: JC Curhan, AQ Lam (eds). *UpToDate*. Waltham, MA: UpToDate. Last updated version: 15 April 2016
3. Glassock RJ, Rule AD. Aging and the kidneys: anatomy, physiology and consequences for defining chronic kidney disease. *Nephron* 2016; 134: 259
4. Glassock RJ, Rule AD. The implications of anatomical and functional changes of the aging kidney: with an emphasis on the glomeruli. *Kidney Int* 2012; 82: 270–277
5. Buturović-Ponikvar J, Visnar-Perovic A. Ultrasonography in chronic renal failure. *Eur J Radiol* 2003; 46: 115–122
6. Choi DK, Choi SM, Park BH *et al*. Measurement of renal function in a kidney donor: a comparison of creatinine-based and volume-based GFRs. *Eur Radiol* 2015; 25: 3143–3150
7. Wang X, Vrtiska T, Avula R *et al*. Age, kidney function, and risk factors associate differently with cortical and medullary volumes of the kidney. *Kidney Int* 2014; 85: 677–685
8. Johnson S, Rishi R, Andone A *et al*. Determinants and functional significance of renal parenchymal volume in adults. *Clin J Am Soc Nephrol* 2011; 6: 70–76
9. Sharma A, Zaragoza JJ, Villa G *et al*. Optimizing a kidney stress test to evaluate renal functional reserve. *Clin Nephrol* 2016; 86: 18–26
10. Chen KW, Wu MW, Chen Z *et al*. Compensatory hypertrophy after living donor nephrectomy. *Transplant Proc* 2016; 48: 716–719
11. Davison JM. Kidney function in pregnant women. *Am J Kidney Dis* 1987; 9: 248–252
12. Takagi T, Mir MC, Sharma N *et al*. Compensatory hypertrophy after partial and radical nephrectomy in adults. *J Urol* 2014; 192: 1612–1618
13. Rule AD, Sasiwimonphan K, Lieske JC *et al*. Characteristics of renal cystic and solid lesions based on contrast-enhanced computed tomography of potential kidney donors. *Am J Kidney Dis* 2012; 59: 611–618
14. Päivänsalo MJ, Merikanto J, Savolainen MJ *et al*. Effect of hypertension, diabetes and other cardiovascular risk factors on kidney size in middle-aged adults. *Clin Nephrol* 1998; 50: 161–168
15. Gourtsoyiannis N, Prassopoulos P, Cavouras D *et al*. The thickness of the renal parenchyma decreases with age: a CT study of 360 patients. *Am J Roentgenol* 1990; 155: 541–544
16. Emamian SA, Nielsen MB, Pedersen JF *et al*. Kidney dimensions at sonography: correlation with age, sex, and habitus in 665 adult volunteers. *Am J Roentgenol* 1993; 160: 83–86
17. Glodny B, Unterholzner V, Taferner B *et al*. Normal kidney size and its influencing factors – a 64-slice MDCT study of 1.040 asymptomatic patients. *BMC Urol* 2009; 9: 19
18. Hricak H, Lieto RP. Sonographic determination of renal volume. *Radiology* 1983; 148: 311–312
19. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2018. *Diabetes Care* 2018; 41(Suppl 1): S13–S27
20. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome—a new world-wide definition. A consensus statement from the International Diabetes Federation. *Diabet Med* 2006; 23: 469–480
21. Davies DF, Shock NW. Age changes in glomerular filtration rate, effective renal plasma flow and tubular excretory capacity in adult males. *J Clin Invest* 1950; 29: 496–507
22. Lindeman RD, Tobin J, Shock NW. Longitudinal studies on the rate of decline in renal function with age. *J Am Geriatr Soc* 1985; 33: 278–285
23. Hinchliffe SA, Sargent PH, Howard CV *et al*. Human intrauterine renal growth expressed in absolute number of glomeruli assessed by the disector method and Cavalieri principle. *Lab Invest* 1991; 64: 777–784
24. Lenihan CR, Busque S, Derby G *et al*. Longitudinal study of living kidney donor glomerular dynamics after nephrectomy. *J Clin Invest* 2015; 125: 1311–1318
25. Cortes P, Zhao X, Dumler F *et al*. Age-related changes in glomerular volume and hydroxyproline content in rat and human. *J Am Soc Nephrol* 1992; 2: 1716–1725
26. Hayslett JP, Kashgarian M, Epstein FH. Functional correlates of compensatory renal hypertrophy. *J Clin Invest* 1968; 47: 774–782
27. Denic A, Alexander M, Kaushik V *et al*. Detection and clinical patterns of nephron hypertrophy and nephrosclerosis among apparently healthy adults. *Am J Kidney Dis* 2016; 68: 58–67
28. Denic A, Glassock RJ, Rule AD. Structural and functional changes with the aging kidney. *Adv Chronic Kidney Dis* 2016; 23: 19–28
29. Denic A, Mathew J, Lerman LO *et al*. Single-nephron glomerular filtration rate in healthy adults. *N Engl J Med* 2017; 376: 2349–2357
30. Hoy W, Douglas-Denton R, Hughson M *et al*. A stereological study of glomerular number and volume: preliminary findings in a multiracial study of kidneys at autopsy. *Kidney Int* 2003; 63(Suppl 83): S31–S37
31. Puelles VG, Douglas-Denton RN, Cullen-McEwen LA *et al*. Podocyte number in children and adults. Associations with glomerular size and numbers of other glomerular resident cells. *J Am Soc Nephrol* 2015; 26: 2277–2288
32. Rule AD, Amer H, Cornell LD *et al*. The association between age and nephrosclerosis on renal biopsy among healthy adults. *Ann Intern Med* 2010; 152: 561–567
33. Rule AD, Semret MH, Amer H *et al*. Association of kidney function and metabolic risk factors with density of glomeruli on renal biopsy samples from living donors. *Mayo Clin Proc* 2011; 86: 282–290
34. Chevalier RL, Forbes MS. Generation and evolution of atubular glomeruli in the progression of renal disorders. *J Am Soc Nephrol* 2008; 19: 197–206
35. Roseman DA, Hwang SJ, Oyama-Manabe N *et al*. Clinical associations of total kidney volume: the Framingham Heart Study. *Nephrol Dial Transplant* 2017; 32: 1344–1350
36. Jelinsky S, Harris H, Brown E *et al*. Global transcription profiling of estrogen activity: estrogen receptor  $\alpha$  regulates gene expression in the kidney. *Endocrinology* 2003; 144: 701–710
37. Wilson C, McPhaul M. A and B forms of the androgen receptor are expressed in a variety of human tissues. *Mol Cell Endocrinol* 1996; 120: 51–57
38. Mulrony SE, Woda C, Johnson M, Pesce C. Gender differences in renal growth and function after uninephrectomy in adult rats. *Kidney Int* 1999; 56: 944–953
39. Kwan G, Neugarten J, Sherman M *et al*. Effects of sex hormones on mesangial cell proliferation and collagen synthesis. *Kidney Int* 1996; 50: 1173–1179
40. Thethi T, Kamiyama M, Kobori H. The link between the renin-angiotensin-aldosterone system and renal injury in obesity and the metabolic syndrome. *Curr Hypertens Rep* 2012; 14: 160–169
41. Zerbin G, Bonfanti R, Meschi F *et al*. Persistent renal hypertrophy and faster decline of glomerular filtration rate precede the development of microalbuminuria in type 1 diabetes. *Diabetes* 2006; 55: 2620–2625
42. Kambham N, Markowitz GS, Valeri AM *et al*. Obesity related glomerulopathy: an emerging epidemic. *Kidney Int* 2001; 59: 1498–1509
43. Wesson LG. Renal hemodynamics in physiological states. In: LG Wesson (ed). *Physiology of the Human Kidney*. New York: Grune and Stratton, 1969, 96–108
44. Hughson M, Farris AB 3rd, Douglas-Denton R *et al*. Glomerular number and size in autopsy kidneys: the relationship to birth weight. *Kidney Int* 2003; 63: 2113–2122
45. Spencer J, Wang Z, Hoy W. Low birth weight and reduced renal volume in Aboriginal children. *Am J Kidney Dis* 2001; 37: 915–920
46. Luyckx VA, Brenner BM. The clinical importance of nephron mass. *J Am Soc Nephrol* 2010; 21: 898–910
47. Quinlan J, Lemire M, Hudson T *et al*. A common variant of the *PAX2* gene is associated with reduced newborn kidney size. *J Am Soc Nephrol* 2007; 18: 1915–1921
48. Zhang Z, Iglesias D, Eliopoulos N *et al*. A variant *OSRI* allele which disturbs *OSRI* mRNA expression in renal progenitor cells is associated with reduction of newborn kidney size and function. *Hum Mol Genet* 2011; 20: 4167–4174
49. Pruijm M, Ponte B, Ackermann D *et al*. Heritability, determinants and reference values of renal length: a family-based population study. *Eur Radiol* 2013; 23: 2899–2905
50. Tarnoki DL, Tarnoki AD, Bata P *et al*. Different genetic impact in the development of renal length and width: a twin study. *Intern Med J* 2015; 45: 63–67
51. Pilia G, Chen WM, Scuteri A *et al*. Heritability of cardiovascular and personality traits in 6,148 Sardinians. *PLoS Genet* 2006; 2: e132
52. Orrù V, Steri M, Sole G *et al*. Genetic variants regulating immune cell levels in health and disease. *Cell* 2013; 155: 242–256

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