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ORIGINAL ARTICLE

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 (3000*g* 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 ≥140 mmHg systolic or ≥90 mmHg diastolic or when they reported taking antihypertensive medication. Obesity was defined as body mass index (BMI) ≥30 kg/m^2 (weight in kg divided by height in m^2). 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^2)	25.63 ± 4.58	23.6 ± 3.05
BSA (m^2)	1.68 ± 0.20	1.65 ± 0.17
eGFR (mL/min/1.73 m^2)	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 ≥150–<500 (mg/g)	74 (1.8)	26 (1.2)
PCR ≥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 (>97.5 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

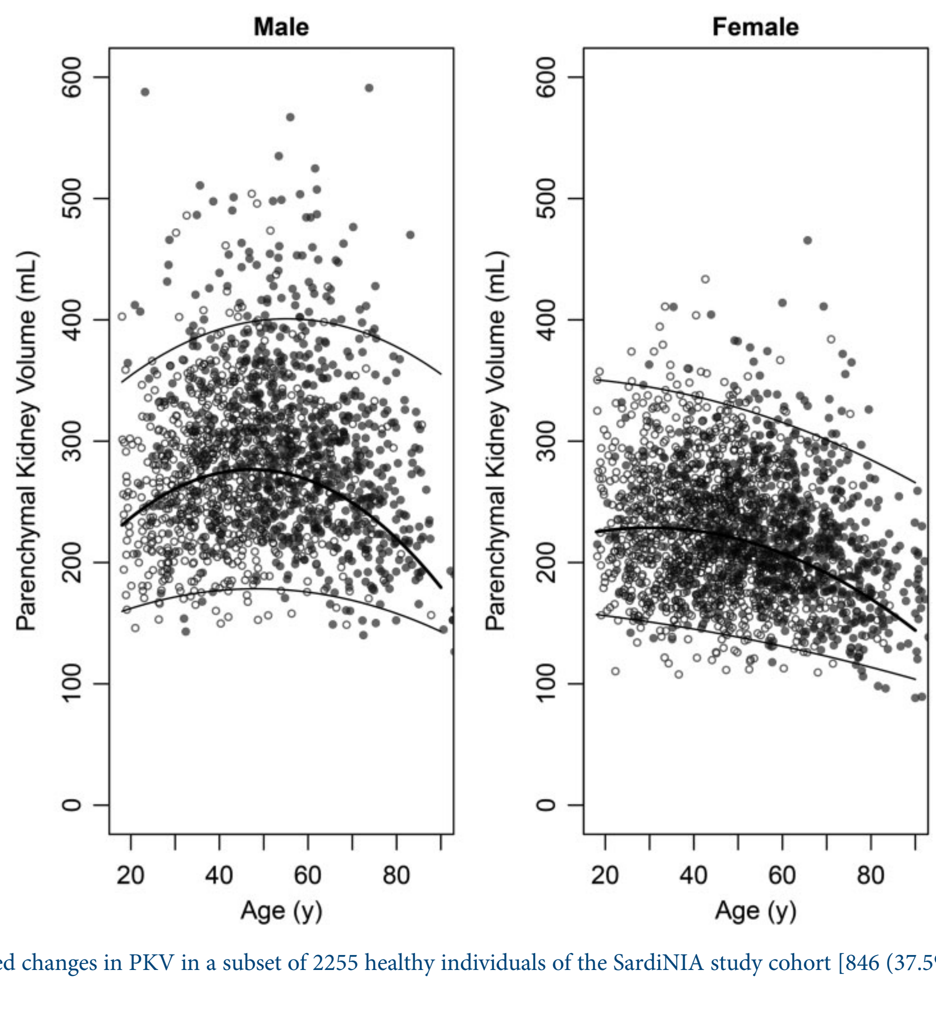

FIGURE 1: Age-related changes in PKV in a subset of 2255 healthy individuals of the SardiNIA study cohort [846 (37.5%) are men].

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^3), 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 (Pearsons'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.

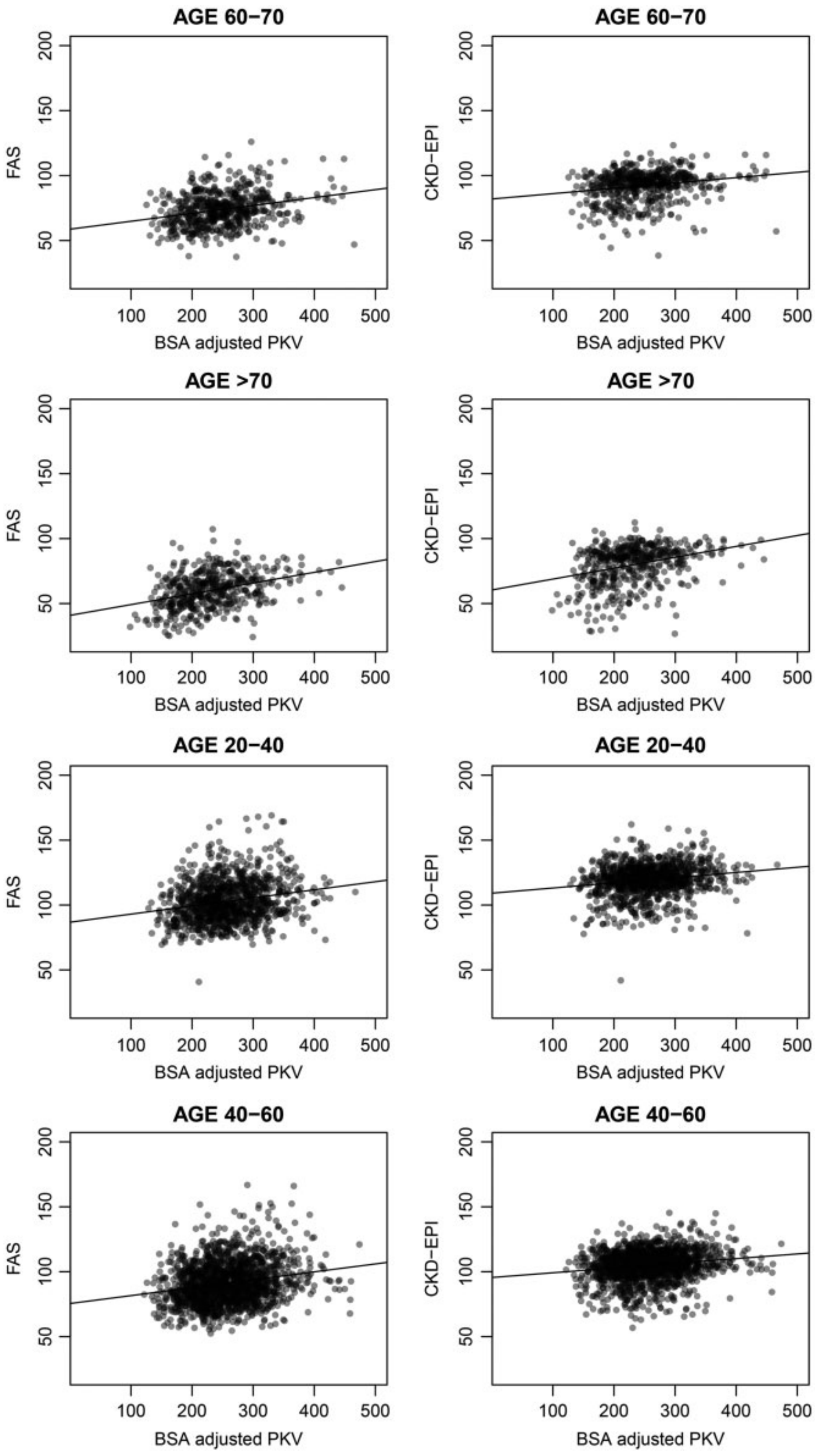

FIGURE 2: PKV and eGFR (estimated with the CKD-EPI and FAS equations) were directly related in all the age categories ($P < 0.001$). The strength of the association was greater in patients >70 years [Pearson's correlation $r = 0.36$ and 0.32, respectively, for FAS and CKD-EPI eGFR; 60–70 years: $r = 0.26$ (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 autoptic normal kidneys increased in size up to 7-fold from infancy to adulthood and then progressively shranked [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 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.

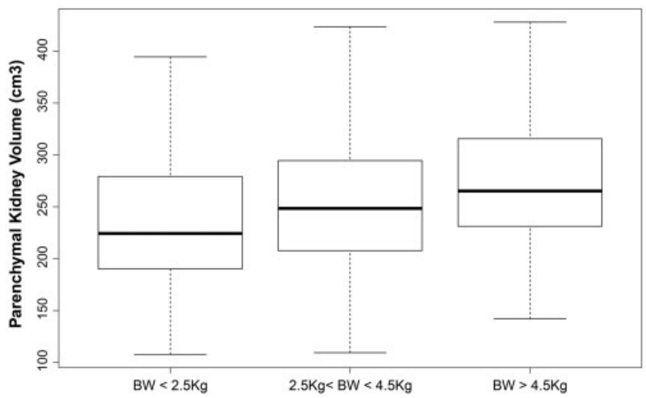

FIGURE 3: PKV by BW in a subset of 2057 individuals of the SardiNIA study cohort.

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

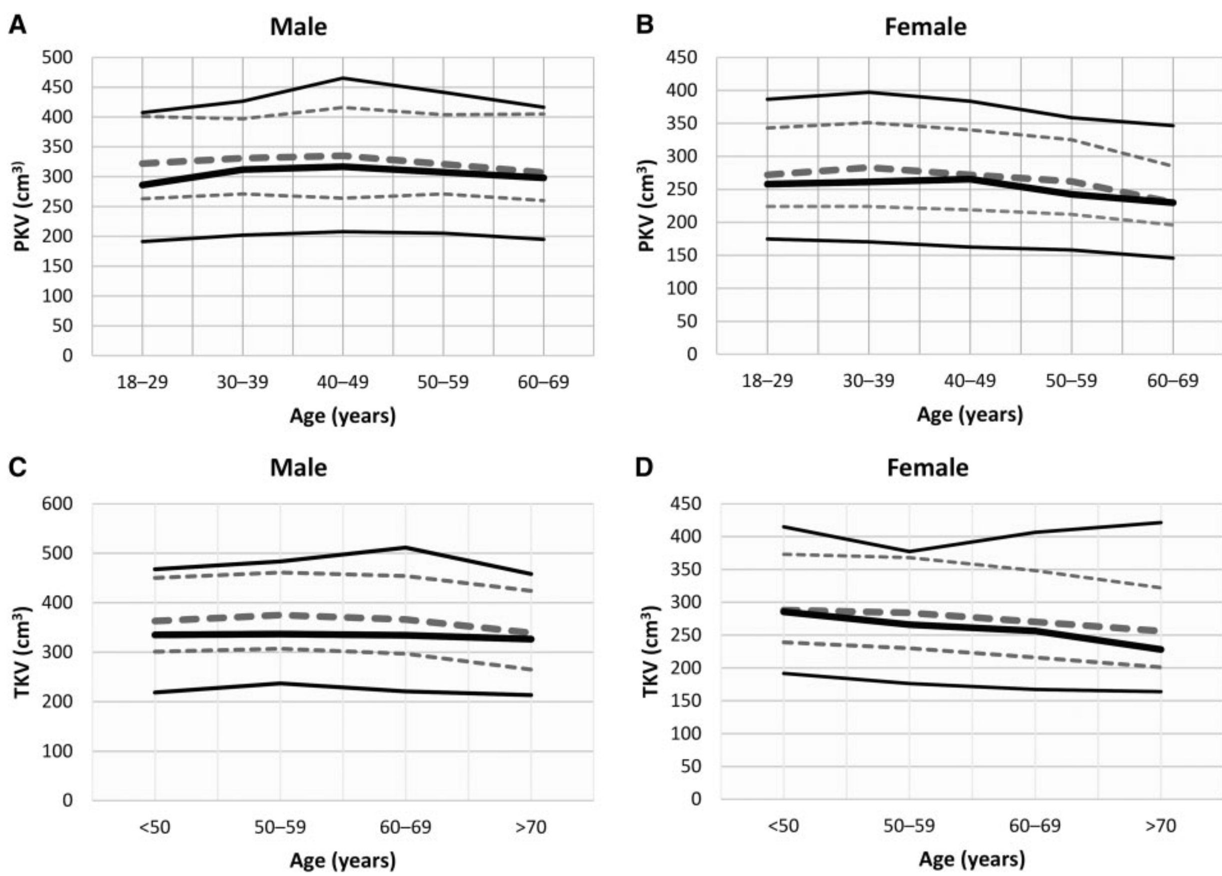

FIGURE 4: Comparison between PKV in healthy (**A**) women and (**B**) men of the SardiNIA kidney cohort (solid line) and of living kidney donors in Wang *et al.* [7] (dashed line). Comparison between TKV in healthy (**C**) women and (**D**) men of the SardiNIA kidney cohort (solid line) and the Framingham 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^2, 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 cormorbidities 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 online.

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CONFLICT OF INTEREST STATEMENT

None declared.

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