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Original Article

ORIGINAL ARTICLE

Associations of MRI-derived kidney volume, kidney function, body composition and physical performance in ≈38 000 UK Biobank participants: a population-based observational study

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ABSTRACT

Background. Kidney volume is used as a predictive and therapeutic marker for several clinical conditions. However, there is a lack of large-scale studies examining the relationship between kidney volume and various clinicodemographic factors, including kidney function, body composition and physical performance.

Methods. In this observational study, MRI-derived kidney volume measurements from 38 526 UK Biobank participants were analysed. Major kidney volume–related measures included body surface area (BSA)-adjusted total kidney volume (TKV) and the difference in bilateral kidneys. Multivariable-adjusted linear regression and cubic spline analyses were used to explore the association between kidney volume–related measures and clinicodemographic factors. Cox or logistic regression was used to identify the risks of death, non-kidney cancer, myocardial infarction, ischaemic stroke and chronic kidney disease (CKD).

Results. The median of BSA-adjusted TKV and the difference in kidney volume were 141.9 ml/m^2 [interquartile range (IQR) 128.1–156.9] and 1.08-fold (IQR 1.04–1.15), respectively. Higher BSA-adjusted TKV was significantly associated with

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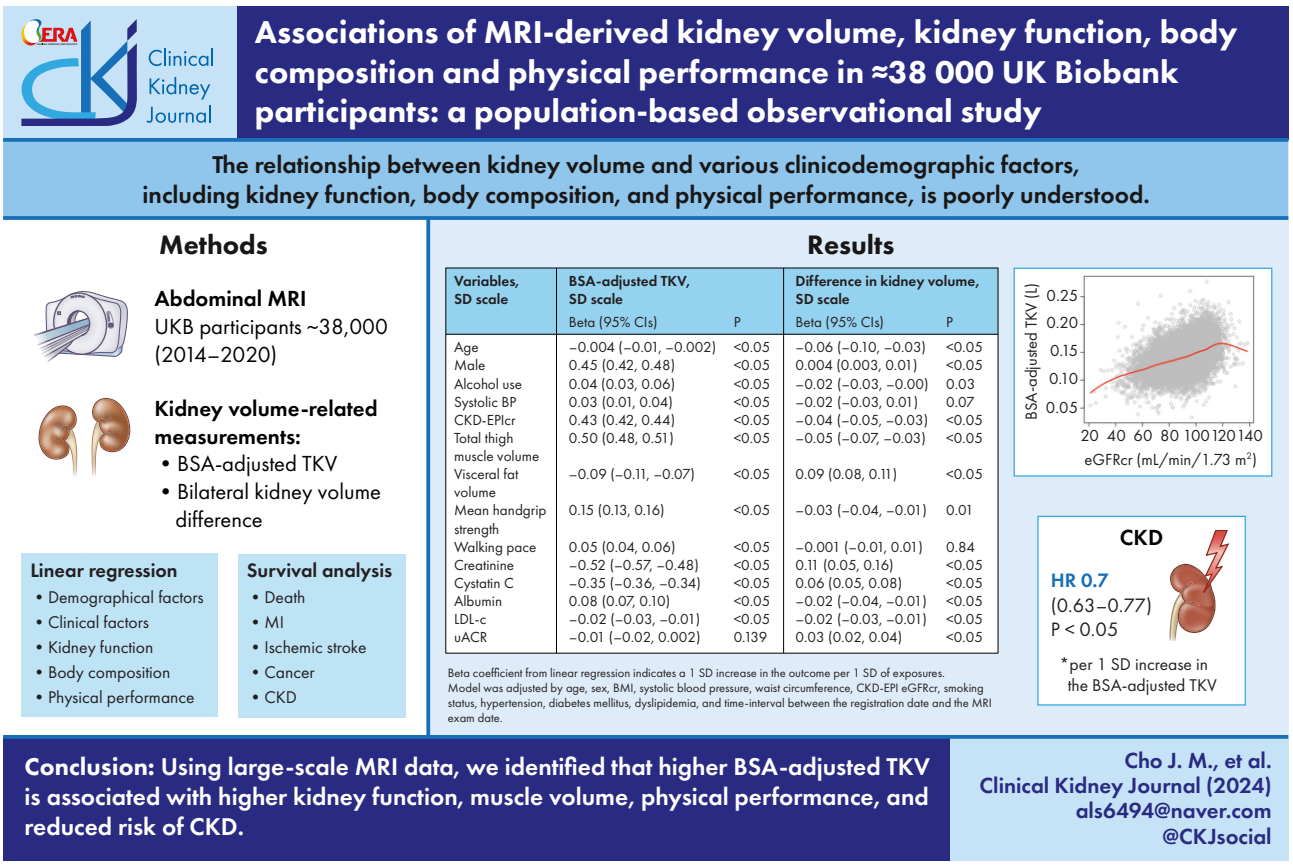
higher estimated glomerular filtration rate {eGFR; $\beta = 0.43$ [95% confidence interval (CI) 0.42–0.44]; $P < .001$}, greater muscle volume [$\beta = 0.50$ (95% CI 0.48–0.51); $P < .001$] and greater mean handgrip strength [$\beta = 0.15$ (95% CI 0.13–0.16); $P < .001$] but lower visceral adipose tissue volume [VAT; $\beta = -0.09$ (95% CI −0.11 to −0.07); $P < .001$] in adjusted models. A greater difference in bilateral kidney volumes was associated with lower eGFR, muscle volume and physical performance but with higher proteinuria and VAT. Higher BSA-adjusted TKV was significantly associated with a reduced risk of CKD [odds ratio (OR) 0.7 (95% CI 0.63–0.77); $P < .001$], while a greater difference in kidney volume was significantly associated with an increased risk of CKD [OR 1.13 (95% CI 1.07–1.20); $P < .001$].

Conclusion. Higher BSA-adjusted TKV and lower differences in bilateral kidney volumes are associated with higher kidney function, muscle volume and physical performance and a reduced risk of CKD.

GRAPHICAL ABSTRACT



Keywords: chronic kidney failure, glomerular filtration rate, kidney function tests, magnetic resonance imaging, organ size

INTRODUCTION

Kidney volume is an imaging biomarker used to determine renal function and disease progression in a range of kidney diseases [1–6]. The anatomical and functional capabilities of the kidneys are related to kidney volume, which is affected by factors such as the number and size of nephrons, alterations in kidney substructures and glomerular surface area [7–10]. Indeed, adverse clinical outcomes, such as progression of estimated glomerular filtration rate (eGFR) decline and kidney failure in autosomal dominant polycystic kidney disease (ADPKD) or post-transplant graft dysfunction in kidney recipients, were found to be associated with kidney volume [2, 11–13] Therefore, identifying the relationship between kidney volume and clinicodemographic factors is essential for detecting individuals at risk and improving their clinical outcomes.

Kidney size is determined by a complex interaction of hormonal, nutritional and environmental factors during development, along with the loss or merging of substructures after growth [9, 14–18]. In previous studies, kidney volume was associated with age, sex, height, body mass index (BMI), waist circumference and eGFR [12, 19–22]. Given the fundamental influence of an individual's body size on organ size, such an association between anthropometric measurements and kidney volume may not be unexpected [20]. Nevertheless, there is a need to determine the association between kidney volume and kidney function in a large population and to explore the clinical implications of kidney volume in relation to

clinicodemographic factors that may be important for health-related outcomes. Kidney volume is not fixed at a certain size in adults; it is subject to variations, with suggested associations including age, sex, body weight, protein intake and level of physical training [9, 23–26]. This indicates that kidney volume may be related to an individual's physiological homeostasis or stress, with a potential link to clinicodemographic, physical and functional parameters, including muscle mass and physical performance.

Recently, large-scale, whole-body magnetic resonance imaging (MRI) data released from the UK Biobank (UKB) have provided specific volumetric measurements of body composition, including organs, muscles and fat [11, 27]. Along with clinical data, it offers extensive phenotypic and functional information about kidney volume in the large population, enabling a comprehensive analysis of these factors. Because MRI is one of the non-invasive standards for measuring body composition [11, 28], using MRI-derived volumetric measurements from a large population might provide robust evidence for understanding the clinical implications of kidney volume.

In this study we aimed to identify the association between kidney volume–related measurements and various clinicodemographic, physical and functional factors in a large population. MRI-derived kidney volume and body composition measurements and physical performance data obtained from >38 000 participants in the UKB were used in the analysis.

MATERIALS AND METHODS

Ethical considerations

This study was approved by the Institutional Review Board of Seoul National University Hospital (2203-053-1303). This study was conducted in accordance with the principles of the Declaration of Helsinki. The data used in this study were accessed through the UKB consortium under application number 53799. Requirement for informed consent was waived because this study used a publicly available anonymous dataset.

Study setting

In this large-scale observational study, we analysed UKB participants using MRI-derived kidney volume measurements to identify the association between kidney volume and various factors, specifically kidney function, body composition and physical performance. The UKB is a large, population-based prospective cohort study of >500 000 adults 40–69 years of age recruited between 2006 and 2010 in the UK. Sociodemographic, lifestyle and medical history data were collected using touchscreen questionnaires, physical and functional measurements, biochemical assays and genome-wide genotyping at baseline. Dynamic linkages to the National Health Service provided data on deaths, cancer and hospital inpatient/outpatient episodes. Details for the UKB are provided elsewhere [29]. To provide researchers with measurements from different organ systems, including the brain, heart and abdominal organs, and body composition to explore the multifactorial mechanisms of complex diseases, a multimodal imaging study was initiated in 2014 [27]. Invitation for all UKB participants with comprehensive information about the project began in 2014 by email. By early 2020, ≈50 000 participants who consented to participate in the imaging study completed the imaging assessment. Fig. 1a presents an overview of the study timeline.

Kidney volume–related variables and study population

Approximately 40 000 participants completed an abdominal MRI (Siemens Aera 1.5T scanner, Siemens, Erlangen, Germany) between 2014 and 2020 [11, 27]. The Dixon protocol, with six separate series covering 1.1 m of the participants from neck to knees, was applied for the measurement of intra-abdominal organ volume and body composition. Details of image processing, quality control and data processing are described elsewhere [27]. Using deep learning models trained by expert manual annotation on UKB abdominal MRI data, automatic segmentation of key organs and volumetric measurements were conducted in a previous study [11]. Total kidney volume (TKV) was defined as the sum of the left and right kidney volumes. Furthermore, body surface area (BSA)-adjusted TKV was defined as the TKV/BSA to index TKV according to each participant's body size and to adjust the variation in kidney size due to differences in body size [7, 30, 31]. Dominant and non-dominant kidneys were determined according to their relative size superiority, regardless of the spatial location within the retroperitoneum. Difference in kidney volume was defined as the ratio of the volumes of the dominant and non-dominant kidneys (dominant kidney volume/non-dominant kidney volume). Kidney parenchymal volume was defined as the sum of the left and right kidney parenchymal volumes. Participants with a single kidney (defined as a difference in kidney volume ≥2.5) or kidney fusion were excluded from the study.

Clinicodemographic, body composition and physical performance variables

Sociodemographic variables, including age, sex, current smoking and alcohol intake frequency (1–2, 3–4 or 7 times/week); anthropometric measurements, including BMI, height, weight and waist circumference; clinical variables, including systolic and diastolic blood pressure (BP); comorbidities such as hypertension, diabetes mellitus (DM) and dyslipidaemia; and laboratory assays for haemoglobin, serum creatinine, cystatin C, glucose, albumin, uric acid, vitamin D, triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), glycated haemoglobin (HbA1c) and urine albumin:creatinine ratio (UACR) were utilized. The MRI-derived body composition measurements included total thigh fat-free muscle volume, visceral adipose tissue volume (VAT) and abdominal subcutaneous adipose tissue (ASAT) volume. Physical performances included mean handgrip strength (measured using a hydraulic hand dynamometer) and self-reported walking pace (slow, steady average or brisk). BSA was calculated using the Mosteller formula, which takes the square root of the height (cm) multiplied by the weight (kg) divided by 3600 [32]. To confirm the association between kidney volume–related measurements and kidney function, we used the following five equations to calculate the eGFR: creatinine-based 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI eGFRcr), cystatin C–based 2012 CKD-EPI (CKD-EPI eGFRcys), creatinine and cystatin C–based 2021 CKD-EPI (CKD-EPI eGFRcr-cys), creatinine-based European Kidney Function Consortium (EKFC eGFRcr) and cystatin C–based EKFC (EKFC eGFRcys) [33–36]. Details of the collected data are described in the Supplementary Methods.

Outcome data

Study outcomes included death, cancer, myocardial infarction (MI), ischaemic stroke and CKD. Diagnoses were recorded according to the World Health Organization's International

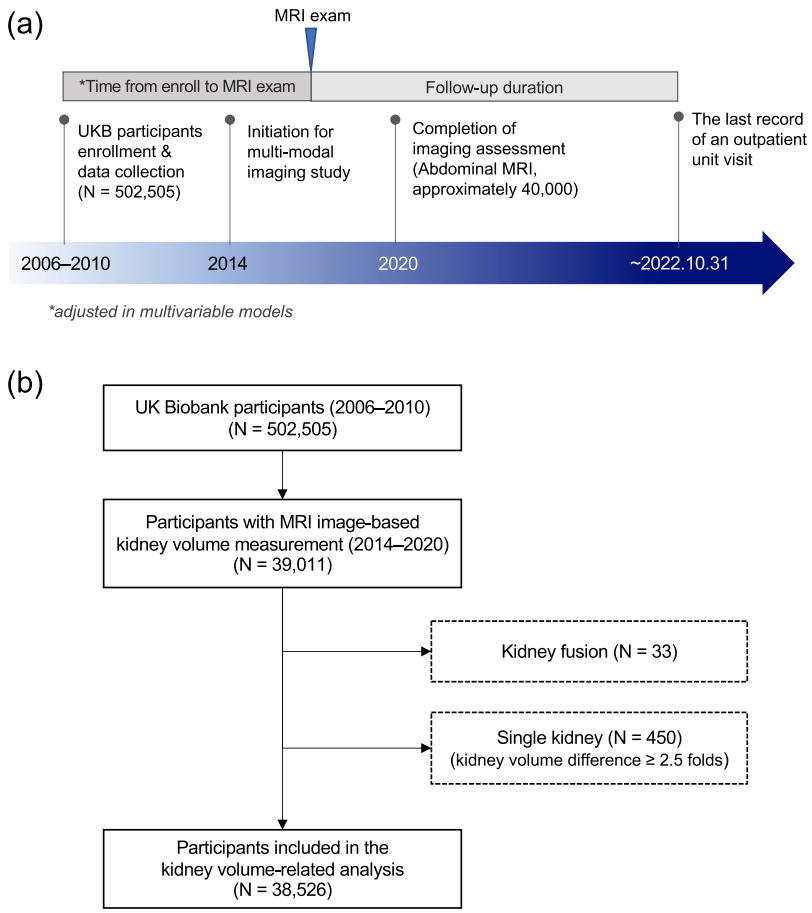


Figure 1: Study flowgram. **(a)** Overview of the timeline of UKB participant enrolment, data collection, imaging study initiation and completion and study outcome. Study outcome was identified between the completion of the MRI exam and the date of the last inpatient follow-up. Time between enrolment and MRI examination was adjusted in multivariable-adjusted models. **(b)** After excluding participants with kidney fusion and a single kidney, a total of 38 526 participants with MRI-derived kidney volume measurements were included for the analysis.

Classification of Diseases, 10th Revision (ICD-10) codes. When examining the association between kidney volume and cancer risk, individuals who developed kidney cancer (ICD-10 codes C64–66; $n = 67$) were excluded from the analysis because an increased kidney volume could potentially be indicative of an initial predisposition to kidney cancer. MI and ischaemic stroke data were obtained through algorithmic combinations of coded information from the UKB data collection, which included each participant's self-reported medical conditions, operations and medications at the baseline assessment, along with linked data from hospital admissions and death registries. CKD was identified by any of the ICD-10 codes N183 (CKD stage 3), N384 (CKD stage 4), N185 (CKD stage 5), N186 (end-stage renal disease) and their related subcodes.

Statistical analyses

Continuous variables with normal distribution, continuous variables with non-normal distribution and categorical variables were presented as mean [standard deviation (SD)], median [interquartile range (IQR)] and frequency, respectively. Distribution of both the BSA-adjusted and unadjusted TKV in the study population was visualized using histograms. A scatter plot with linear regression lines was used to visually represent the relationship between BSA-adjusted TKV, differences in kidney volume and kidney function, as indicated by the CKD-EPI eGFRcr.

As kidney volume–related measurements might be related to various sociodemographic and clinical factors, we explored the association between BSA-adjusted TKV and differences in kidney volume with such exposures. Linear regression models were used to explore the relationship between kidney volume–related measurements (BSA-adjusted TKV, differences in kidney volume) and kidney function, clinical factors, body composition and physical performance variables [β and 95% confidence intervals (CIs)]. For the main analysis, we examined the association with BSA-adjusted TKV because BSA-adjusted TKV offers kidney volume estimates that are less affected by variations in body size. Continuous variables were standardized by using SD to ensure scale independence and interpretability when included as exposure variables. Covariates previously associated with kidney volume and function, anthropometric measurements and body composition were adjusted in the multivariable models. Given the temporal gap between the time of study participation (when physical measurements and biochemical assays were conducted) and MRI examination, we further adjusted for time interval between the registration date and MRI examination date in the data. Cubic spline analysis was conducted to assess the linearity of association between kidney volume–related measurements and covariates [37]. Additionally, we performed a

Table 1: Characteristics of the study population

Variables	Total population ($N = 38\,526$)	Female ($n = 20\,028$)	Male ($n = 18\,498$)
Age (years), median (IQR)	55 (49–61)	55 (48–60)	56 (50–62)
Smoking status, *n* (%)			
Never smoker	23 324 (60.7)	12 864 (64.4)	10 460 (56.7)
Current smoker	12 688 (33.0)	6079 (30.4)	6609 (35.8)
Ex-smoker	2423 (6.3)	1039 (5.2)	1384 (7.5)
Alcohol consumption/week, median (IQR)	2 (2–3)	3 (2–4)	2 (1–3)
BMI (kg/m^2), *n* (%)	26.0 (23.7–28.8)	25.2 (22.9–28.4)	26.7 (24.6–29.2)
<30	31 552 (82.0)	16 598 (83.0)	14 954 (81.0)
≥30	6918 (18.0)	3400 (17.0)	3518 (19.0)
Waist circumference (cm), median (IQR)	88.0 (79.0–96.0)	80.0 (74.0–88.0)	94.0 (88.0–101.0)
Height (cm), median (IQR)	169.0 (163.0–176.6)	163.0 (159.0–167.0)	177.0 (172.0–181.0)
Weight (kg), median (IQR)	75.5 (65.8–86.0)	67.4 (60.8–75.9)	83.3 (75.8–91.9)
BSA (m^2), median (IQR)	1.89 (1.73–2.05)	1.75 (1.65–1.87)	2.02 (1.92–2.14)
Systolic BP (mmHg), median (IQR)	134.5 (123.0–148.0)	130 (119.0–144.0)	139 (128.5–151.5)
Diastolic BP (mmHg), median (IQR)	81 (74.5–88.0)	79 (72.5–85.5)	83.5 (77–90)
eGFR (ml/min/1.73 m^2), median (IQR)			
CKD-EPIcr	93.8 (84.5–100.7)	94.6 (84.8–101.5)	93.0 (84.1–99.7)
CKD-EPIcys	93.6 (82.6–105.0)	95.7 (83.8–106.8)	91.6 (81.5–102.6)
CKD-EPIcr-cys	93.8 (85.0–102.2)	94.9 (85.8–103.3)	92.7 (84.3–100.9)
EKFCcr	88.9 (80.8–96.3)	89.2 (80.6–96.8)	88.6 (81.0–95.9)
EKFCcys	92.2 (83.1–102.5)	96.4 (86.6–107.3)	88.2 (80.3–97.0)
eGFR category, *n* (%)			
≥120	288 (0.8)	189 (1.0)	99 (0.6)
≥90 and <120	21 862 (60.7)	11 864 (63.5)	9998 (57.8)
≥60 and <90	13 536 (37.6)	6505 (34.8)	7031 (40.7)
≥45 and <60	272 (0.8)	129 (0.7)	143 (0.8)
≥30 and <45	26 (0.1)	7 (0.0)	19 (0.1)
≥15 and <30	4 (0.0)	1 (0.0)	3 (0.0)
MRI-derived measures, median (IQR)			
BSA-adjusted TKV (ml/m^2)	141.9 (128.1–156.9)	137.4 (124.6–151.9)	146.9 (133.1–161.5)
TKV (ml)	266.5 (231.9–305.9)	241.7 (215.6–271.3)	296.2 (263.9–332.8)
LKV (ml)	133.5 (115.0–154.2)	121.2 (107.0–137.2)	148.6 (130.8–167.6)
RKV (ml)	133.0 (115.2–153.5)	120.6 (106.8–135.8)	148.1 (131.4–167.1)
Difference in kidney volume (fold)	1.081 (1.036–1.150)	1.084 (1.038–1.154)	1.078 (1.035–1.145)
Total thigh fat-free muscle volume (l)	9.709 (8.032–12.131)	8.110 (7.380–8.916)	12.229 (11.101–13.421)
Visceral adipose tissue volume (l)	3.290 (1.958–5.066)	2.342 (1.479–3.498)	4.697 (3.177–6.347)
Physical performance–related measures			
Mean handgrip strength (kg), mean (IQR)	31 (24–41)	25 (21–29)	41 (36–47)
Walking pace, *n* (%)			
Slow	1164 (3.0)	694 (3.5)	470 (2.5)
Steady/average	18 108 (47.1)	9480 (47.4)	8628 (46.7)
Brisk	19 182 (49.9)	9810 (49.1)	9372 (50.7)
Laboratory values, median (IQR)			
Haemoglobin (g/dl)	14.2 (13.3–15.1)	13.5 (12.9–14.0)	15.0 (14.4–15.6)
Creatinine (μmol/l)	71.0 (62.0–81.0)	63.0 (57.2–69.5)	80.1 (73.2–87.9)
Cystatin C (mg/l)	0.86 (0.79–0.94)	0.83 (0.76–0.91)	0.90 (0.83–0.97)
Urea (mmol/l)	5.2 (4.5–6.0)	5.0 (4.3–5.8)	5.4 (4.7–6.2)
Glucose (mmol/l)	4.9 (4.6–5.2)	4.9 (4.6–5.2)	4.9 (4.6–5.3)
Albumin (g/l)	45.3 (43.7–47.0)	45.1 (43.4–46.8)	45.7 (44.0–47.3)
Uric acid (μmol/l)	297.9 (246.4–354.2)	255.0 (219.3–295.9)	345.3 (303.9–392.6)
Vitamin D (nmol/l)	47.8 (22.5–63.0)	47.5 (33.2–62.9)	48.2 (33.9–63.2)
TG (mmol/l)	1.39 (0.99–2.03)	1.21 (0.90–1.72)	1.64 (1.15–2.36)
LDL-C (mmol/l)	3.54 (3.00–4.11)	3.53 (3.01–4.12)	3.55 (3.00–4.11)
HbA1c (mmol/mol)	34.6 (32.2–37.0)	34.5 (32.2–36.9)	34.7 (32.3–37.100)
UACR (mg/g)	9.5 (5.9–15.8)	12.2 (7.6–19.2)	7.3 (5.0–11.7)
Comorbidities, *n* (%)			
Hypertension	5163 (13.6)	2053 (10.4)	3110 (17.1)
Dyslipidaemia	4457 (11.8)	1386 (7.0)	3071 (16.9)
Diabetes mellitus	1005 (2.6)	369 (1.8)	636 (3.4)
CKD	302 (0.9)	137 (0.7)	165 (0.9)
Outcomes, *n* (%)			
Death	743 (1.9)	262 (1.3)	481 (2.6)
MI	704 (1.8)	180 (0.9)	524 (2.8)
Ischaemic stroke	328 (0.9)	117 (0.6)	211 (1.1)
Cancer	3312 (8.6)	1429 (7.1)	1883 (10.2)
CKD	720 (1.9)	301 (1.5)	419 (2.3)

The eGFR category was determined using eGFR calculated with the CKD-EPIcr-cys equation.
LKV: left kidney volume; RKV: right kidney volume; TG: triglyceride.

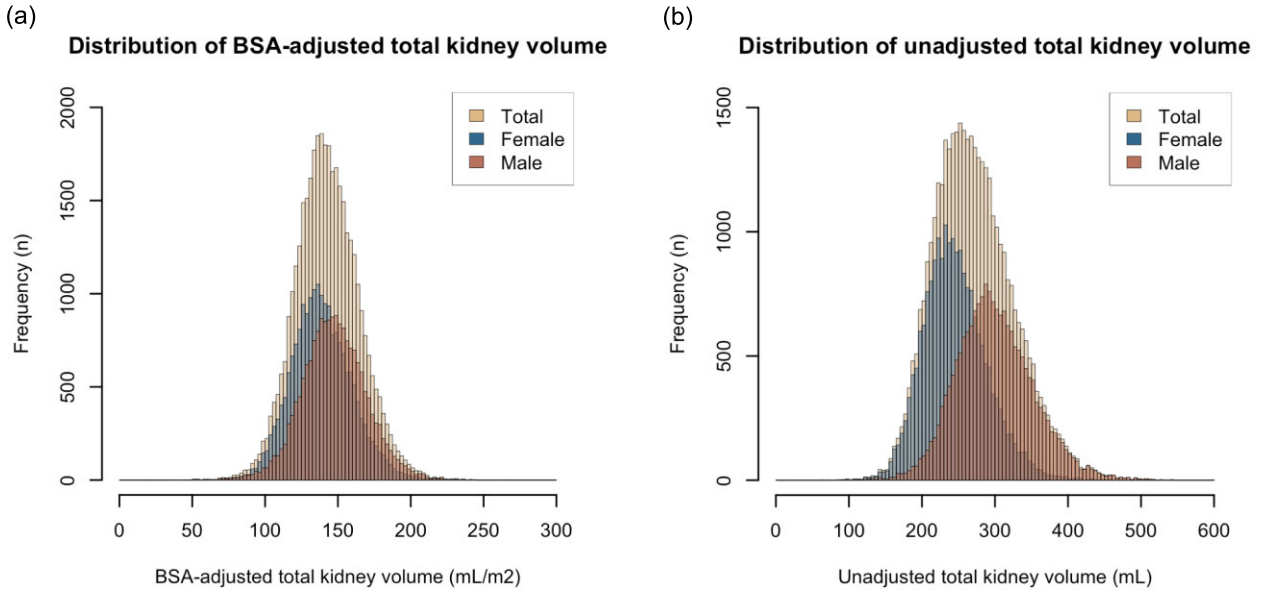


Figure 2: Distribution of **(a)** BSA-adjusted and **(b)** unadjusted TKV. Coloured bars represent the frequencies of total participants (ivory), males (brown) and females (dark blue). The median of BSA-adjusted and unadjusted TKV were 141.9 ml/m^2 (IQR 128.1–156.9) and 266.5 ml (IQR 231.9–305.9), respectively. In females, BSA-adjusted and unadjusted TKV was 137.4 ml/m^2 (IQR 124.6–151.9) and 241.7 ml (IQR 215.6–271.3), while in males the BSA-adjusted and unadjusted TKV was 146.9 ml/m^2 (IQR 133.1–161.5) and 296.2 ml (IQR 263.9–332.8).

subgroup analysis by stratifying the study population according to age (<65 and ≥65 years), sex, BMI (<30 and ≥30 kg/m^2), DM and kidney function (eGFR ≥120, ≥90 and <120, ≥60 and <90, and <60 ml/min/1.73 m^2). As a sensitivity analysis, we examined the association between height-adjusted TKV, BSA-adjusted kidney parenchymal volume and covariates.

Cox proportional hazards models were used to identify the associations between kidney volume–related measurements and the incidence of death, cancer, MI and ischaemic stroke. The duration of follow-up was calculated as the time between the MRI examination and first incidence of death, cancer, MI, ischaemic stroke, loss to follow-up or 31 October 2022, which was the last inpatient follow-up date. The association between kidney volume–related measurements and the risk of CKD was evaluated by logistic regression. CKD events that occurred between the MRI examination and the last inpatient follow-up date were identified. Cox and logistic regression models were adjusted for age, sex, BMI, CKD-EPI eGFRcr, hypertension, DM, dyslipidaemia and the time interval between study enrolment and MRI examination. Statistical significance was set at $P < .05$. All statistical analyses were performed using R version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Characteristics of the study population

Of 502 505 UKB participants, abdominal MRI–derived kidney volume data were available for 39 011 (7.8%) (Fig. 1b). After excluding participants with kidney fusion ($n = 33$) and those with a single kidney ($n = 450$), 38 526 participants were included in the analysis. Characteristics of the study population are summarized in Table 1. The median age of the study participants was 55 years (IQR 49–61) and 52% were females, with a median CKD-EPI eGFRcr of 93.8 ml/min/1.73 m^2 (IQR 84.5–100.7). The median BSA-adjusted TKV, TKV and difference in kidney volume were 141.9 ml/m^2 (IQR 128.1–156.9), 266.5 ml (IQR 231.9–305.9) and 1.08-fold (IQR 1.04–1.15), respectively. In males, the BSA-adjusted TKV was higher than that in females [146.9 ml/m^2 (IQR 133.1–161.5) versus 137.4 (124.6–151.9)], while the difference in kidney volume was lower [1.078-fold (IQR 1.035–1.145) versus 1.084 (1.038–1.154)]. Participants ≥65 years of age had a lower BSA-adjusted kidney volume [135.5 ml/m^2 (IQR 121.2–149.7) versus 142.65 (128.9–157.6)] and a higher difference in kidney volume [1.09-fold (IQR 1.04–1.18) versus 1.08 (1.04–1.15)] than participants <65 years of age (Supplementary Table 1). Fig. 2 shows that the distribution of the BSA-adjusted TKV was closer to the normal distribution than that of the unadjusted TKV. The median of total thigh fat-free muscle volume was 9.71 l (IQR 8.03–12.1) and VAT was 3.29 l (IQR 1.96–5.07). Participants had a mean handgrip strength of 31 kg (IQR 24–41) and 47.1% of participants had a 'steady average pace.'

Associations of BSA-adjusted TKV and difference in kidney volume with covariates

A higher BSA-adjusted TKV was significantly associated with a higher eGFR: [CKD-EPI eGFRcr: $\beta = 0.43$ (95% CI 0.42–0.44); CKD-EPI eGFRcr-cys: $\beta = 0.57$ (95% CI 0.56–0.58); CKD-EPI eGFR-cys: $\beta = 0.5$ (95% CI 0.49–0.51); EKFC eGFRcr: $\beta = 0.48$ (95% CI 0.47–0.49); EKFC eGFRcys: $\beta = 0.54$ (95% CI 0.53–0.55); $P < .001$, respectively] (Table 2). High systolic BP, smoking and alcohol consumption was associated with a higher BSA-adjusted TKV. Among the laboratory values, higher creatinine, cystatin C, uric acid and LDL-C levels were significantly associated with lower BSA-adjusted TKV, whereas higher serum glucose and albumin levels were associated with higher BSA-adjusted TKV. Notably, a higher BSA-adjusted TKV was associated with greater muscle volume [0.50 (95% CI 0.48–0.51), $P < .001$] and physical performance, such as mean handgrip strength [0.15 (95% CI 0.13–0.16), $P < .001$] or walking pace [0.05 (95% CI 0.04–0.06), $P < .001$], whereas it was associated with lower VAT [−0.09 (95% CI −0.11 to

Table 2: Multivariable-adjusted linear regression analyses for kidney volume–related measurements and clinicodemographic factors

Outcome	BSA-adjusted TKV, SD scale		Difference in kidney volume, SD scale	
Exposures, SD scale	Multivariable model, β (95% CI)	*P*-value	Multivariable model, β (95% CI)	*P*-value
Age	−0.004 (−0.01 to −0.002)	<.001	−0.06 (−0.10 to −0.03)	<.001
Male	0.45 (0.42–0.48)	<.001	0.004 (0.003–0.01)	<.001
Current smoking	0.09 (0.08–0.11)	<.001	0.003 (−0.02–0.02)	.73
Alcohol use	0.04 (0.03–0.06)	<.001	−0.02 (−0.03 to −0.002)	.03
BMI	0.01 (−0.01–0.03)	.29	−0.03 (−0.06 to −0.01)	.003
BSA	0.16 (0.14–0.18)	<.001	−0.02 (−0.04–0.002)	.07
Systolic BP	0.03 (0.01–0.04)	<.001	−0.02 (−0.03–0.01)	.07
eGFR				
CKD-EPIcr	0.43 (0.42–0.44)	<.001	−0.04 (−0.05 to −0.03)	<.001
CKD-EPIcr-cys	0.57 (0.56–0.58)	<.001	−0.06 (−0.08 to −0.05)	<.001
CKD-EPIcys	0.50 (0.49–0.51)	<.001	−0.06 (−0.07 to −0.04)	<.001
EKFCcr	0.48 (0.47–0.49)	<.001	−0.04 (−0.06 to −0.03)	<.001
EKFCcys	0.54 (0.53–0.55)	<.001	−0.06 (−0.07 to −0.04)	<.001
MRI-derived measures				
Total thigh fat-free muscle volume	0.50 (0.48–0.51)	<.001	−0.05 (−0.07 to −0.03)	<.001
Visceral adipose tissue volume	−0.09 (−0.11 to −0.07)	<.001	0.09 (0.08–0.11)	<.001
Abdominal subcutaneous adipose tissue volume	−0.12 (−0.13 to −0.10)	<.001	−0.03 (−0.05 to −0.01)	.003
Physical performance-related measures				
Mean handgrip strength	0.15 (0.13–0.16)	<.001	−0.03 (−0.04 to −0.01)	.01
Walking pace	0.05 (0.04–0.06)	<.001	−0.001 (−0.01 to 0.01)	.84
Laboratory values				
Haemoglobin	−0.02 (−0.03 to −0.01)	.001	0.001 (−0.01–0.02)	.84
Creatinine	−0.52 (−0.57 to −0.48)	<.001	0.11 (0.05–0.16)	<.001
Cystatin C	−0.35 (−0.36 to −0.34)	<.001	0.06 (0.05–0.08)	<.001
Glucose	0.03 (0.02–0.04)	<.001	−0.01 (−0.02–0.01)	.34
Albumin	0.08 (0.07–0.10)	<.001	−0.02 (−0.04 to −0.01)	<.001
Uric acid	−0.05 (−0.06 to −0.04)	<.001	0.01 (−0.01–0.02)	.35
LDL-C	−0.02 (−0.03 to −0.01)	<.001	−0.02 (−0.03 to −0.01)	<.001
UACR	−0.01 (−0.02–0.002)	.139	0.03 (0.02–0.04)	<.001
Comorbidities				
Hypertension	0.10 (0.07–0.13)	<.001	0.16 (0.13–0.19)	<.001
Dyslipidaemia	0.02 (−0.01–0.06)	.17	−0.002 (−0.04–0.04)	.94
Diabetes mellitus	0.05 (−0.01–0.11)	.11	0.07 (−0.01–0.14)	.07

β coefficient from linear regression indicates a 1 SD increase in the outcome (BSA-adjusted TKV or difference in kidney volume) per 1 SD for continuous or dichotomous exposures.

Multivariable model was adjusted by age, sex, BMI, systolic BP, waist circumference, CKD-EPI eGFRcr, smoking status, hypertension, diabetes mellitus, dyslipidaemia and time-interval between the registration date and the MRI exam date.

−0.07), $P < .001$] and ASAT [−0.12 (95% CI −0.13 to −0.1), $P < .001$] in adjusted models. The associations between adjusted TKV and covariates were consistent in the analysis where TKV was adjusted for height (Supplementary Table 2).

In contrast, an increased difference in kidney volume was significantly associated with a lower eGFR [CKD-EPI eGFRcr −0.04 (95% CI −0.05 to −0.03), $P < .001$], lower composition of muscle volume [−0.05 (95% CI −0.07 to −0.03), $P < .001$], higher VAT [0.09 (95% CI 0.08–0.11), $P < .001$] and reduced physical performance [mean handgrip strength −0.03 (95% CI −0.04 to −0.01), $P = .005$]. Furthermore, a higher UACR was significantly associated with a greater difference in kidney volume, whereas no significant association was observed with BSA-adjusted TKV.

Fig. 3 shows that a higher BSA-adjusted TKV was correlated with higher eGFR. The linear regression slope was steeper in the male group. Differences in kidney volume were negatively associated with the eGFR in both males and females. Supplementary Fig. 1 displays the association between laboratory values and BSA-adjusted TKV.

Sensitivity analysis

Since kidney structures such as the pelvis, ureter or fat may have been included in the measurement of TKV, we conducted a sensitivity analysis to examine any potential difference in the relationship between BSA-adjusted kidney parenchymal volume and factors compared with those of the adjusted TKV. Overall, we found that the association between BSA-adjusted kidney parenchymal volume and clinicodemographic, physical and functional factors was consistent with that of BSA-adjusted TKV (Supplementary Table 3), demonstrating that the associations between BSA-adjusted TKV and other factors are not significantly affected by structures that are not involved in kidney parenchymal function.

Non-linear association

We conducted a cubic spline analysis to identify whether kidney volume-related measurements and covariates with significant associations had a linear relationship (Fig. 4). In the unadjusted models, higher BSA-adjusted TKV was associated with younger age, higher serum albumin level and CKD-EPI eGFRcr, greater muscle volume and smaller adipose tissue volume. A greater difference in kidney volume was associated with a higher serum creatinine level, a lower albumin level and eGFR and a larger adipose tissue volume. Except for the non-linearity between the UACR and difference in kidney volume, there was no notable non-linearity among the significant findings

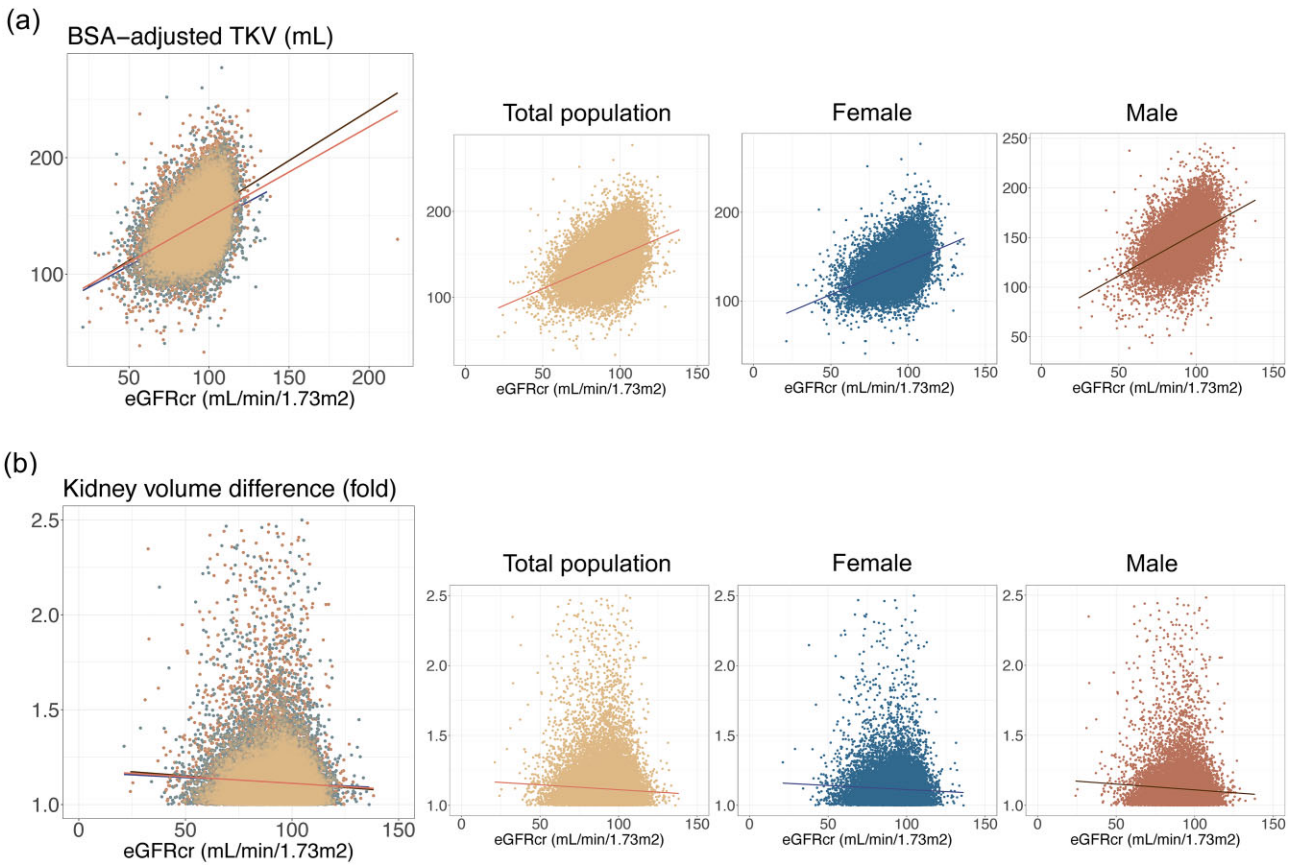


Figure 3: Scatter plots and linear regression of creatinine-based eGFR and **(a)** BSA-adjusted kidney volume and **(b)** the difference in kidney volume. eGFR and BSA-adjusted kidney volume showed a positive correlation in the total population, males and females, whereas difference in kidney volume showed a negative correlation in the total population, males and females. Dots and linear regression lines for total population, males and females are in ivory, brown and dark blue, respectively.

identified in the above linear regression analysis, suggesting that the linear regression captured the general trend of the dataset.

Subgroup analysis

The association between BSA-adjusted TKV, differences in kidney volume and clinical factors was examined in subgroups stratified by age, sex, obesity, DM and kidney function as kidney volume–related measurements and their association with covariates may differ across these subgroups (Supplementary Table 4-8). Notably, a significant link between higher BSA-adjusted TKV and higher eGFR, greater muscle volume, higher physical performance and lower VAT or ASAT were concordantly observed in all the subgroups in the multivariable-adjusted model. Furthermore, a greater difference in kidney volume was significantly associated with lower eGFR, smaller muscle volume, larger adipose tissue volume and reduced physical performance across the subgroups.

Outcomes according to kidney volume measurements

To evaluate the association between kidney volume and the risk of cardiovascular outcomes and cancer, Cox regression analysis was performed. During a median follow-up duration of 7.0 years (IQR 5.8–8.0), 743 (1.93%) death, 3312 (8.6%) cancer, 704 (1.83%) MI and 328 (0.85%) ischaemic stroke events were observed. In the multivariate-adjusted models for BSA-adjusted TKV, no significant association was found with the risks of death, MI, ischaemic stroke or cancer (Table 3). The adjusted models for the difference in kidney volume also showed no significant association with the study outcomes. On the other hand, adjusted logistic regression showed that higher BSA-adjusted TKV was significantly associated with a reduced risk of CKD [odds ratio (OR) 0.7 (95% CI 0.63–0.77); $P < .001$], while a greater difference in kidney volume was significantly associated with an increased risk of CKD [OR 1.13 (95% CI 1.07–1.20); $P < .001$].

DISCUSSION

In this study we demonstrated a significant association between BSA-adjusted TKV and the difference between kidney volume and function, body composition and physical performance using MRI-derived organ volumetry data from ≈38 000 UKB participants. We found that a higher BSA-adjusted TKV was associated with a higher eGFR, muscle volume and physical performance, whereas it was associated with a lower VAT and ASAT. Also, a greater difference in bilateral kidney volume was related to a lower eGFR, muscle volume and physical performance and a higher fat volume. Our study established that the BSA-adjusted kidney volume is not only an indicator of higher kidney function, but also positively correlates with muscle volume and physical performance, whereas an increased difference in

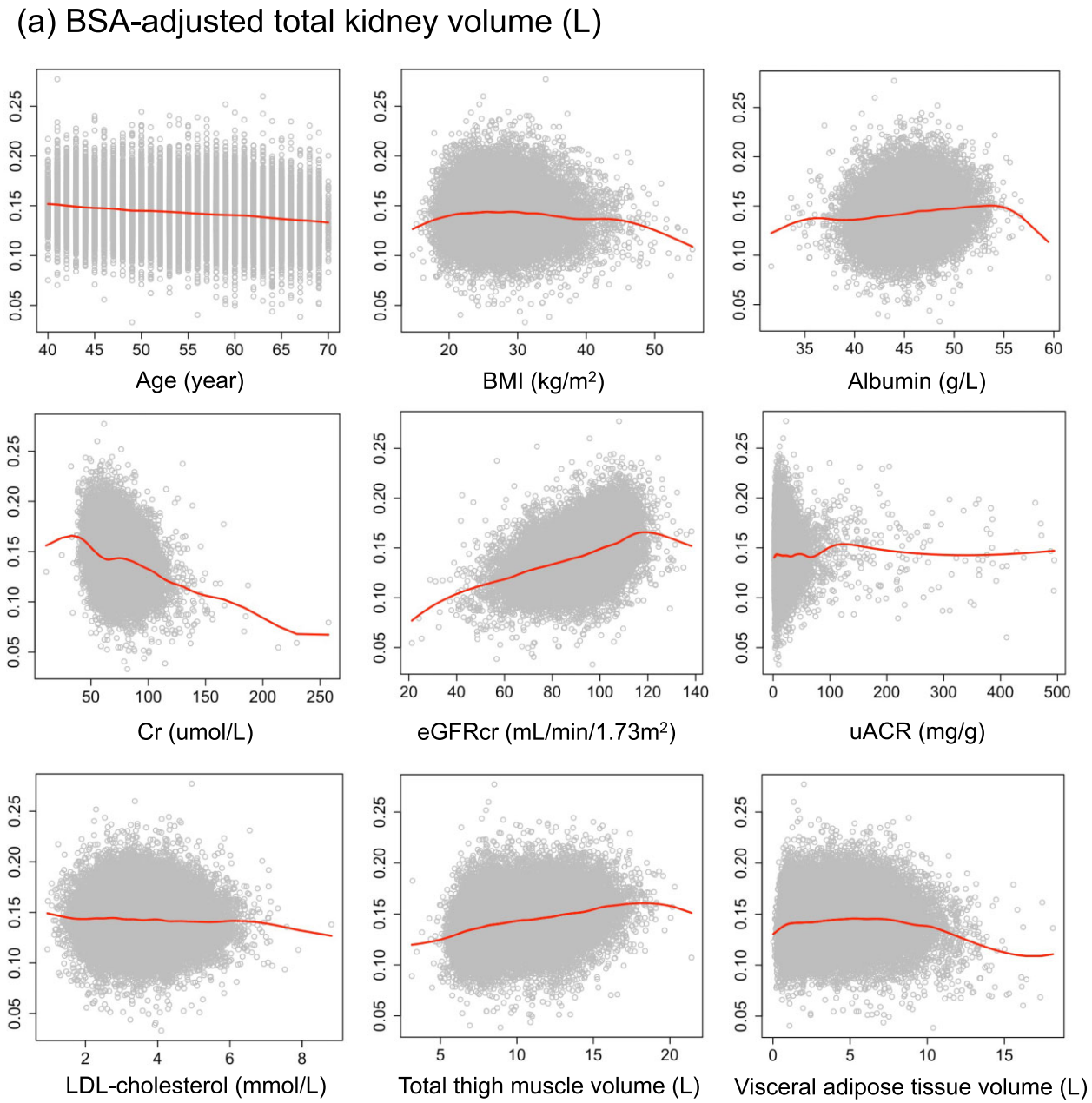


Figure 4a: Cubic splines for the relationship between various exposures with **(a)** BSA-adjusted TKV and **(b)** kidney volume difference. The red line represents a fit using flexible third-degree polynomials. eGFR was calculated using the CKD-EPI eGFRcr equation.

bilateral kidney volume is adversely associated with these factors.

The clinical implications of kidney volume in relation to clinicodemographic factors that may be critical for health-related conditions remain largely unclear. Previous studies have shown a linkage between kidney volume and function [12, 21, 38, 39] and a small kidney has been considered an indicator for increased risk of CKD or decreased renal function, as kidney volume is closely related to the number and size of nephrons, which determine kidney function [8, 40–43]. Interestingly, kidney volume has previously been indicated to be associated with age, sex, weight and even muscle mass or intense physical activity [9, 23–26]. In a recent study, a significant association was observed between BSA-adjusted kidney parenchymal volume and a higher height-normalized skeletal muscle index, along with a lower intramuscular adipose tissue index in non-diabetic participants [44]. Growing insights into the crosstalk between muscles and organs has revealed that skeletal muscles function as an endocrine organ by producing mytokines [45], which are linked to the growth and regeneration of damaged kidney and the suppression of fibrogenesis in the kidney [46–49]. However, studies that examine the linkage between kidney volume and clinicodemographic factors, particularly focused on kidney function, physical performance and body composition, are lacking. Thus

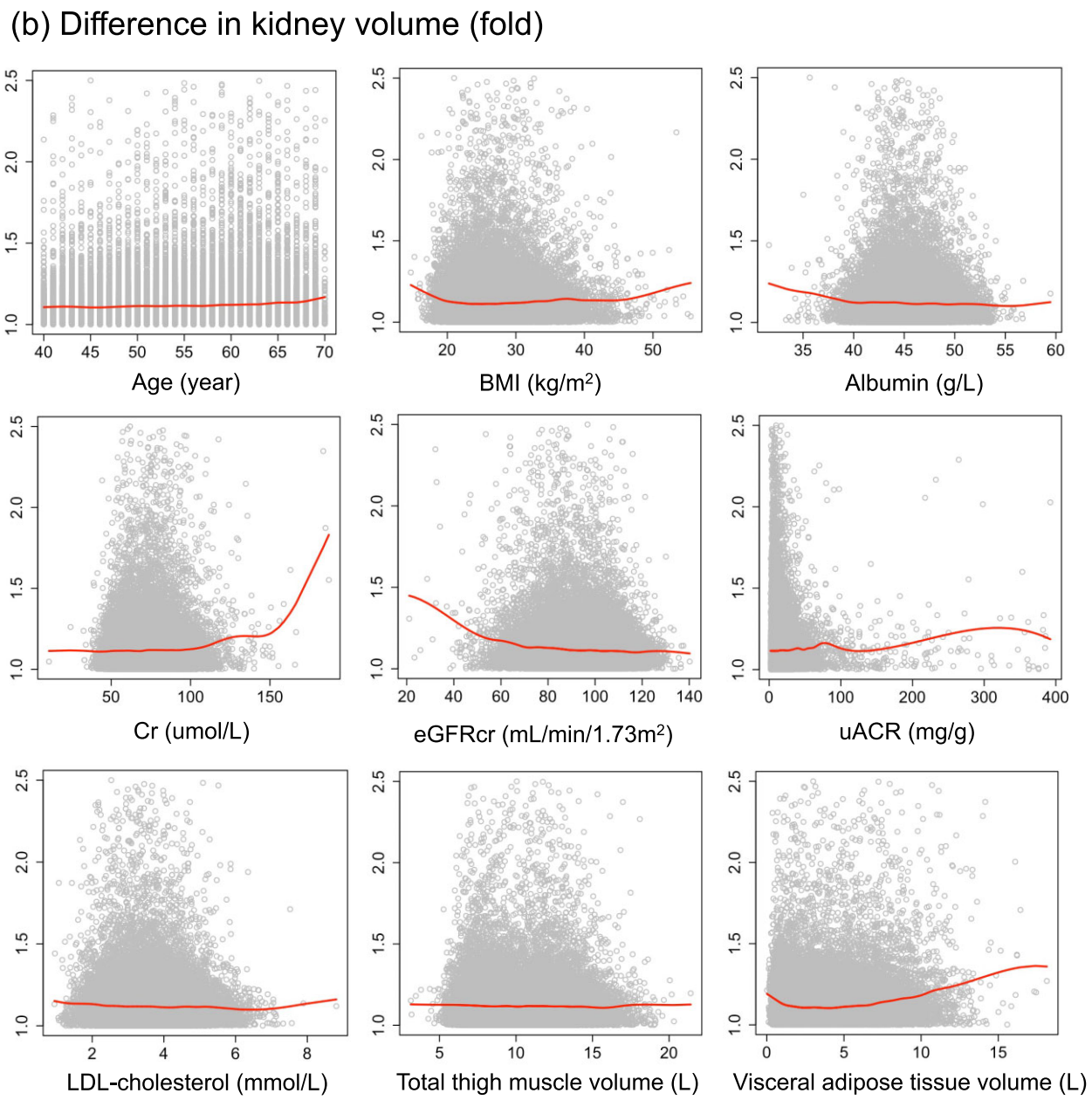


Figure 4b: Continued

we examined these associations in a large-scale UKB dataset comprising MRI-based data to enhance our comprehension and provide further perspectives.

Our study has several strengths. First, a large-scale MRI-derived kidney volume dataset computed using deep-learning models was used to provide high statistical power. Because MRI provides more precise measurements of body composition than other methods, such as ultrasonography [7] or body composition monitors [50], this offers strong evidence for an association between kidney volume and multiple factors. Second, the association of kidney volume with a wide range of clinicodemographic and functional factors, including laboratory data, body composition and physical performance, was analysed, providing valuable insights into our understanding of the factors that are potentially related to kidney volume. Third, five GFR estimation equations were used to identify the association between kidney volume–related measurements and eGFR and ascertain its robustness. As shown by the consistent associations observed between eGFR, regardless of the calculation method used and BSA-adjusted kidney volume or kidney volume difference, our study supports the finding that both BSA-adjusted TKV and kidney volume difference are significantly related to eGFR.

In regard to kidney function, we found significant associations with BSA-adjusted TKV and bilateral kidney volume differences in multiple subgroups. Specifically, a higher BSA-adjusted TKV was associated with a higher eGFR, whereas a higher difference in kidney volume was associated with a lower eGFR. This indicates that kidney function and CKD are associated not only with the absolute kidney volume but also with the discrepancies between bilateral kidneys. Furthermore, we identified

Table 3: Multivariable-adjusted analyses for kidney volume–related measurements and clinical outcomes

Exposures	BSA-adjusted TKV, SD scale				Difference in kidney volume, SD scale			
Outcome	Multivariable model 1, HR or OR (95% CI)	P-value	Multivariable model 2, HR or OR (95% CI)	P-value	Multivariable model 1, HR or OR (95% CI)	P-value	Multivariable model 2, HR or OR (95% CIs)	P-value
Death	1.05 (0.98–1.13)	.13	1.03 (0.95–1.12)	.47	0.99 (0.94–1.05)	.84	0.98 (0.92–1.04)	.46
MI	0.99 (0.91–1.07)	.74	0.98 (0.89–1.08)	.65	1.03 (0.96–1.10)	.38	1.00 (0.93–1.08)	.92
Stroke	1.10 (0.98–1.23)	.10	1.07 (0.94–1.23)	.30	1.00 (0.92–1.09)	.96	1.03 (0.94–1.14)	.47
Cancer	0.97 (0.94–1.00)	.07	0.97 (0.93–1.02)	.23	1.00 (0.97–1.04)	.83	1.00 (0.96–1.03)	.87
CKD	0.49 (0.45–0.53)	<.001	0.7 (0.63–0.77)	<.001	1.16 (1.1–1.22)	<.001	1.13 (1.07–1.2)	<.001

Multivariable model 1 was adjusted for age, sex, BMI and time interval between the registration date and the MRI exam date. Multivariable model 2 was adjusted for age, sex, BMI, CKD-EPI eGFRcr, hypertension, diabetes mellitus, dyslipidaemia and time interval between the registration date and the MRI exam date.
The association between kidney volume–related measurements and death, MI, ischaemic stroke and cancer was assessed by Cox regression analysis and CKD was assessed by logistic regression. The duration of follow-up was calculated as the time between the MRI examination and first incidence of death, cancer, MI, ischaemic stroke, loss to follow-up or 31 October 2022, which was the last inpatient follow-up date. The study outcomes included incident events, and those with pre-existing outcome events (172 MI, 1516 cancer, 62 ischaemic stroke and 260 CKD) were not included in the table.

that lower BSA-adjusted TKV and a higher difference in kidney volume were both significantly associated with an increased risk of CKD. This may be attributed to the association between kidney volume–related measurements and several risk factors of CKD, such as older age, elevated BP, current smoking, lower eGFR and serum albumin and higher LDL-C. Our findings are in line with those of previous studies that suggested low TKV is associated with lower eGFR [12, 21, 38, 39]. Although the left kidney has a physiologically larger volume than that of the right kidney [51], a higher degree of difference may be associated with reduced kidney function due to pathologic conditions that can cause a decrease in the unilateral kidney, such as renal artery stenosis [52], urinary tract obstruction [53], kidney stones [54] or CKD [55]. As identified in our study, a greater difference in the bilateral kidneys was associated with a reduced eGFR and higher albuminuria. This adverse relationship is in line with the previous studies that suggested a deficit in nephrons could lead to hypertension, CKD and an increased risk of albuminuria [56–58], as a larger difference in bilateral kidney volume may indicate nephron loss in the unilateral kidney. In addition, individuals exhibiting a greater difference in kidney volume may have a higher risk of chronic glomerular hyperfiltration, focal segmental glomerulosclerosis or atherosclerotic renal artery stenosis, which are associated with CKD or its risk factors [59]. Therefore, we suggest that a greater difference in bilateral kidney volume may be a risk factor for decreased kidney function.

Prolonged kidney stress, including interstitial inflammation and fibrosis, glomerular sclerosis and tubular atrophy, result in decreased kidney volume [9, 60, 61]. The observations from our study are concordant with the common concept that small kidneys are more prone to loss of kidney function, as low kidney volume might reflect underlying pathologic changes and a loss of functional nephrons [40]. Risk factors of CKD, including older age, lower albumin level and elevated serum uric acid and LDL-C, were also found to be associated with reduced BSA-adjusted TKV [60]. On the other hand, identifying the negative drivers that contribute to high TKV is also important, as high TKV could manifest in certain pathologic conditions associated with renal hypertrophy [62]. The current study demonstrated a significant association between higher BSA-adjusted TKV and several risk factors of CKD, including current smoking, higher systolic BP and elevated serum glucose levels. Although smoking and high glucose levels are well established to be associated with larger kidney volume [44, 63], results regarding the association between hypertension and kidney volume were inconsistent in previous studies due to limited sample sizes and differences in the characteristics of the participants [7, 64–66]. Overall, our findings confirm a relationship between hypertension and a larger kidney volume in a relatively healthy adult population. This association may potentially be related to glomerular hypertrophy and sclerosis resulting from increased BP and glomerular hyperfiltration [67]. In summary, it is essential to consider these factors when interpreting the implications of kidney volume in various clinical settings.

Interestingly, higher BSA-adjusted TKV was associated with greater muscle volume and physical performance, but with lower VAT and ASAT. Several studies have shown the crosstalk between skeletal muscle and kidney through mediators such as insulin-like growth factor 1, myostatin, interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) [45, 68, 69]. In an experimental study, an Akt1 mouse model, which mimics the muscle response to exercise, showed regeneration of functional and histologic defects in the kidney as well as a decrease in the expression of various inflammatory cytokines (i.e. IL-6, IL-1β and TNF-α) [47]. Also,

mice with muscle-specific peroxisome proliferator-activated receptor-γ co-activator-1α overexpression was associated with suppressed kidney fibrogenesis [48]. The previous research indicates muscle can affect regeneration of damaged kidney, supporting our findings that muscle volume might potentially be related to higher kidney volume. Moreover, body composition and physical capabilities are significantly associated with CKD risk [70, 71]. For example, higher muscle mass, lower fat volume and better physical performance determined by handgrip strength or walking pace were associated with a lower risk of incident CKD [72–75]. Thus these factors may serve as an important indicator in evaluating kidney prognosis in individuals.

This study has some limitations. First, is the differences in time points of study enrolment and MRI examination. Second, a causal relationship between kidney volume and function could not be identified because of the observational nature of the study. Finally, as the UKB participants are healthier and have a lower prevalence of CKD than the general population, generalizability is limited. The limitation might have led to the null findings related to the hard outcomes in the current data. In addition, our findings should be applied to the early changes of TKV in regards to a variety of CKD risk factors (e.g. high BP), as it would certainly lead to a decreased kidney volume in those with advanced CKD.

In summary, we identified significant associations between kidney volume parameters and kidney function in the UKB cohort using large-scale MRI data. We further demonstrated the relationship between physical performance and body composition, both of which are important factors in kidney function and CKD progression. Our findings provide valuable insights into the clinical implications of kidney volume.

SUPPLEMENTARY DATA

Supplementary data is available at *ckj* online.

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The data used in this study were accessed through the UKB consortium under application number 53799.

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AUTHORS' CONTRIBUTIONS

J.M.C., J.H.K., S.G.K., S.L., Y.K., S.C., Y.C.K., S.S.H., H.L. and J.P.L. performed the main statistical analysis, including data curation, formal analysis and investigation. K.K. contributed to the investigation and methodology. K.W.J., C.S.L., Y.S.K., D.K.K. and S.P. contributed to the conceptualization and design of the study. S.P. advised on statistical aspects and interpreted the data. D.K.K. and S.P. offered advice regarding the data interpretation and supervised. S.P. obtained funding and supervised the overall project. All of the authors participated in drafting the manuscript, reviewed the manuscript and approved the final version to be published.

DATA AVAILABILITY STATEMENT

The datasets analysed in the current study are publicly available and can be accessed through the UKB.

CONFLICT OF INTEREST STATEMENT

None declared.

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