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# The HALT Polycystic Kidney Disease Trials – Analysis of baseline parameters

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## Abstract

HALT-PKD consists of two randomized trials comparing treatment with an angiotensin converting inhibitor (ACEI)-angiotensin receptor blocker (ARB) combination vs ACEI alone and standard vs low blood pressure target in Study A (eGFR >60 ml/min/1.73 $m^2$) and ACEI-ARB vs ACEI alone in Study B (eGFR 25-60 ml/min/1.73 $m^2$). It includes the largest cohort of systematically studied ADPKD patients (558 A and 486 B) to date. We used correlation and multiple regression cross-sectional analyses to ascertain associations of baseline parameters with total kidney (TKV) and liver (TLV) or liver cyst (LCV) volumes measured by MRI in Study A and with eGFR in both studies. Lower eGFR and higher natural log transformed urine albumin excretion are independently associated with larger natural log transformed TKV adjusted for height (HtTKV). Higher BSA is independently associated with higher ln(HtTKV) and lower eGFR. Men have larger HtTKV and smaller LCV than women. A weak correlation was found between ln(HtTKV) and ln(HtTLV) or ln(LCV) in women only. Women have higher urine aldosterone excretions and lower plasma potassium levels. In summary, this analysis 1) confirms a strong association between renal volume and functional parameters, 2) shows that gender and other factors differentially affect the development of polycystic disease in the kidney and liver, and 3) suggests an association between anthropomorphic measures reflecting preand/or post-natal growth and the severity of the disease.

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Competing Financial Interests

Dr. Torres is an investigator and Chair of the Steering Committee for several Otsuka studies on ADPKD, is an investigator in a clinical trial for ADPKD sponsored by Novartis Pharmaceuticals, and has served as consultant for Wyeth Pharmaceuticals, Hoffman-La Roche Inc., and Primrose Therapeutics. Dr. Perrone is an investigator and member of the Steering Committee for several Otsuka studies on ADPKD and is the coordinating and site investigator for a clinical trial for ADPKD sponsored by Novartis Pharmaceuticals. Dr. Chapman is an investigator and member of the Steering Committee for several Otsuka studies on ADPKD.

## Introduction

Autosomal dominant polycystic kidney disease (ADPKD) occurs in 1/400 - 1/1000 live births and accounts for ~4.6% of the prevalent kidney replacement population in the United States.[1] Hypertension is its most common manifestation and an important risk factor for its progression to end stage renal disease (ESRD) and cardiovascular morbidity and mortality.[2]

Substantial experimental and clinical data has implicated the renin-angiotensin-aldosterone system (RAAS) in the pathogenesis of ADPKD and associated hypertension. However, evidence that treatments targeting the RAAS are superior to other antihypertensive therapies is inconclusive. Past studies have been limited by small sample sizes with inadequate power, short periods of follow-up, study of relatively late stages of disease and/or use of low doses of angiotensin I converting enzyme inhibitors (ACEI), which may not effectively block the RAAS.[2]

Because of the importance of hypertension in ADPKD and uncertainties surrounding its treatment, the NIH/NIDDK funded two distinct multicenter double-blind randomized clinical trials, adequately powered to assess the effect of RAAS blockade on renal progression at early (Study A) and late (Study B) stages of the disease (NCT00283686, http://clinicaltrials.gov). Their rationale, design and implementation have been discussed in detail elsewhere.[3]

Here we perform a cross-sectional analysis of the baseline characteristics in this large cohort of patients to identify factors affecting the development and progression of this disease.

## Results

### Baseline patient characteristics

Gender, race, education level, marital status, employment, ages at the times of enrollment into the study and diagnoses of ADPKD and hypertension, and manifestations leading to and mode of diagnosis of ADPKD, by study and, in Study A, BP target assignment, are shown in Table 1.

The baseline clinical, laboratory and imaging characteristics of participants in Studies A and B are shown in Table 2. Study B participants who by design have lower eGFR than Study A patients, are older, have higher BMI, higher serum concentration of potassium and urine excretion of albumin, and lower urine excretion of aldosterone and urine sodium/potassium ratio. Serum potassium concentration is lower in women in both studies, whereas urine aldosterone excretion is higher in women compared to men in Study A.

Kidney and liver volumes were measured only in Study A. Total kidney volume (TKV) and TKV adjusted for height (HtTKV) or BSA are significantly greater in men than in women (Table 2). LCV is greater in women.

Baseline clinical, laboratory, and imaging characteristics of participants in Study A by BP group assignment are shown in Table 3. Except for slightly lower urine aldosterone excretion in participants assigned to rigorous BP control, there are no significant differences between the standard and rigorous BP control groups.

### Associations of baseline parameters with kidney volume

(Table 4). Age and natural log transformed HtTKV, ln(HtTKV), are significantly correlated in men, but not in women (Figure 1). BSA and height are positively correlated with ln(HtTKV); these correlations are seen in men but not in women. BSA and height are also

positively correlated with unadjusted lnTKV or with lnTKV adjusted for BSA (not shown). Office (and home, not shown) BPs and ln(urine albumin excretion) correlate positively, whereas eGFR and RBF correlate negatively with ln(HtTKV). Weak positive correlations exist between urine volume, urine sodium excretion, ln(HtTLV) and ln(HtLCV) with ln(HtTKV) in women only.

Multiple regression analysis shows independent associations of baseline BSA, ln(urine albumin excretion), and eGFR with baseline ln(HtTKV) (Table 5), unadjusted lnTKV or lnTKV adjusted for BSA. The association of BSA with baseline ln(HtTKV) remains statistically significant if kidney weights (estimated from TKV) are subtracted from body weights to calculate BSA, indicating that the association is not due to a bias introduced by the contribution of kidney volume to body weight. BMI cannot replace BSA in the model.

### Associations of baseline parameters with eGFR

(Table 6). Age (Figure 2), office systolic blood pressure, serum potassium, and ln(urine albumin excretion) are negatively correlated, whereas sodium/potassium ratio is positively correlated with baseline eGFR. BSA, BMI, office diastolic blood pressure, and urine potassium excretion are negatively correlated with eGFR in men only. Urine aldosterone excretion is positively correlated with eGFR in women only. In Study A, age and ln(HtTKV) are negatively and RBF is positively correlated with eGFR (Figure 3).

Multiple regression analysis shows independent associations of baseline age, RBF, and ln(HtTKV) with eGFR (Table 7). Excluding RBF and ln(HtTKV) from the model, age, BSA, ln(urine albumin), serum potassium, and urine aldosterone are independently associated with eGFR (Table 7). BMI cannot replace BSA in the model.

## Discussion

The HALT PKD A and B population constitutes the largest cohort of systematically analyzed hypertensive ADPKD patients published to date. Analysis of the baseline characteristics of the study population demonstrates adequate randomization between the low and standard BP arms of Study A. It also identifies novel factors impacting the development and progression of ADPKD.

### Associations of baseline parameters with ln(HtTKV)

Baseline eGFR, ln(urine albumin excretion), and BSA, independently associate with ln(HtTKV) in the current study. Previous studies had shown a negative correlation between TKV and GFR [4] and direct associations of TKV with urine protein and albumin excretions.[5] More recently, the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) used MRI to measure TKV annually in a cohort of ADPKD patients with well-preserved renal function at the initiation of the study. Age-adjusted TKV was negatively correlated with GFR and urine albumin excretion at baseline.[6] During the initial CRISP study period of three years, TKV was modestly associated with a decline in GFR measured by iothalamate clearance.[7] A more recent CRISP report with eight years of follow up, has found increasingly strong associations between baseline HtTKV and the follow-up iothalamate clearances and progression through the K/DOQI stages.[8] These observations demonstrate that renal cyst burden, reflected by HtTKV, is a very important determinant of renal functional decline in ADPKD.

In the current study BSA is independently associated with ln(HtTKV), unadjusted lnTKV or lnTKV adjusted for BSA. The association between the anthropomorphic marker BSA and TKV, even when TKV is adjusted for height or BSA, points to biological factor or factors associated with, but distinct from body size. Genetic and environmental factors affect birth

weights and postnatal growth velocities which ultimately determine adult height, weight, and BSA. Genome-wide association studies have identified loci associated with height variation.[9, 10] Associations between height and risks for particular diseases may reflect common genetic effects on growth and disease predisposition rather than direct associations of phenotypic traits. Low birth weights increase the risk for insulin resistance, type 2 diabetes, obesity, and hypertension in adult life,[11] whereas high birth weights are associated with increased risk for various childhood[12-15] and adult[16-19] malignancies. Low birth weights have been associated with lower nephron numbers which in turn could increase the risk for hypertension, proteinuria and GFR decline in ADPKD, as it has been reported in other renal diseases.[20, 21] On the other hand, enhanced nephrogenesis could accelerate cyst development as shown in conditional mouse models[22-24] and a higher nephron number could make larger number of cells susceptible to somatic mutations and cyst development in the same way that a large nephron number and mammary gland mass increase the risk for renal cell and breast cancers.[16, 25] Postnatal growth may be as or more important than prenatal growth for programming pathways predisposing to adult diseases. Faster postnatal growth associated with high nutrient formula feeding increases the risk for obesity, insulin resistance, low HDL cholesterol, hypertension, and cardiovascular disease.[26-30] Since newborns with low birth weights usually show faster postnatal growth whereas large newborns show growth deceleration, it has been suggested that the association of low birth weight with higher risk for cardiovascular disease reflects at least in part the adverse effects of postnatal growth acceleration.[28, 31-33] At present we can only speculate on which genetic and environmental factors affecting growth can also affect the progression of ADPKD. A large body of evidence, for example, indicates that the insulin-like growth factor-I (IGF-I) system plays a major role in prenatal and postnatal growth[34-37] and mediates epithelial cell proliferation in polycystic kidney disease.[38, 39]

That the association between BSA and ln(HtTKV) in the current study is mostly restricted to men is intriguing but not unique. Gender differences are common in animal model[40-43] and human[44, 45] examples of developmental programming. Males appear more susceptible to perinatal programming of metabolic and cardiovascular homeostasis than females. The associations of birth weight with development of chronic kidney disease[46-48] and of renal cell cancer[16] are stronger in male individuals. Gender differences in hormonal systems affecting fetal and renal development, such as the IGF-I[37] and the renin-angiotensin systems,[49] may be responsible for these gender effects.

### Associations of baseline parameters with eGFR

In Study A, age, RBF and ln(HtTKV) were independently associated with baseline eGFR. These results are consistent with those of the CRISP study.[50] In Studies A and B, age, BSA, serum potassium, ln(urine albumin excretion) and urine aldosterone excretion were independently associated with eGFR. As in the case of ln(HtTKV), the association of BSA and eGFR is restricted to men. The positive correlation between urine aldosterone excretion and eGFR and the lower urinary aldosterone excretion in Study B compared to Study A participants, despite higher serum potassium concentrations, suggests that as renal function declines extracellular fluid volume expansion suppresses the circulating renin-angiotensin system. In chronic kidney disease aldosterone production depends on the extracellular volume status, increases in response to sodium restriction, and may contribute to renal disease progression regardless of its level.[51-53]

### Distinct factors affect the severity of polycystic kidney and liver disease

A number of observations in this study suggest that the renal involvement in ADPKD may be more severe in men than in women. In Study A, TKV is significantly greater in men than in women, even when adjusted by height or BSA and despite the fact that men are

significantly younger than women. The significant direct correlation between age and ln(HtTKV) in men, but not in women, may reflect a higher rate of renal enlargement in men. In Study B, men have significantly higher BP and urine albumin excretion than women. The significantly older age of women in both studies, A and B, probably reflects a selection bias introduced by the fact that men have more progressive disease than women and therefore had to be younger at enrollment into the study in order to meet the eGFR entry criteria. Nevertheless, we cannot find an independent association of gender with disease severity reflected by a higher ln(HtTKV) or a lower eGFR in the multiple regression analysis. Interestingly, a recent study based on data from the Danish National Registry on Regular Dialysis and Transplantation has shown that during 1990-2007 the mean age of ESRD increased by 5.0 and 4.4 years in male and female ADPKD patients and that the age adjusted male/female ratio at onset of ESRD fell from 1.6 in 1.1, suggesting that male gender has become less important as a risk factor for progression in ADPKD in the last two decades.[54]

It has been hypothesized that patients with more severe polycystic kidney disease also have more severe liver involvement, reflecting a higher systemic severity of the disease.[55] This was not confirmed by the CRISP study where a correlation between LCV and TKV became non-significant when adjusted for age.[56] The current study detects only a weak association between ln(HtTKV) and either ln(HtTLV) or ln(LCV) in women, but not in men. Furthermore, while men had higher HtTKV than women, women had higher LCV than men, suggesting opposite sex-linked hormonal effects on disease progression in polycystic kidneys and polycystic livers. These observations indicate that, in addition to the *PKD* mutations, other factors distinct for each organ are important for the development and progression of polycystic kidney and polycystic liver disease.

### Gender differences in urine aldosterone excretion and plasma potassium concentrations

Other observations in this analysis deserve comment. Higher urine aldosterone excretions in women compared to men in Study A are consistent with higher serum aldosterone values in women compared to men and in premenopausal compared to postmenopausal women in the Framingham Heart Study. [57] Aldosterone production significantly increases in the luteal phase due to high progesterone levels[58, 59] because progesterone is a precursor of aldosterone[60, 61] and a mineralocorticoid receptor antagonist with a natriuretic effect that can activate the renin-angiotensin system.[62] Luteinizing hormone may also stimulate aldosterone synthesis in the adrenal cortex.[63]

Lower plasma potassium concentrations in women compared to men have been reported in previous human and animal studies[64-66] and attributed to estrogen effects, enhancing the action of mineralcorticoids on the kidney and increasing $\beta_2$ adrenoreceptor density, affinity or G protein coupling to adenylate cyclase in skeletal muscle and red blood cells thus causing an intracellular influx of potassium into the cells.[66, 67]

In summary, a cross-sectional analysis of baseline parameters in HALT-PKD, the largest cohort of systematically studied ADPKD patients to date confirms a strong association between renal volume and functional parameters, shows that gender and other factors differentially affect the development of polycystic disease in the kidney and liver, and suggests the intriguing possibility that intrauterine development and developmental programming (reflected by BSA and height) affect the natural history of this disease.

## Methods

The design and implementation of the HALT PKD trials have been described in detail elsewhere. [3] The Polycystic Kidney Disease Treatment Network (HALT PKD) includes four Participating Clinical Centers (PCCs), three Satellite Clinical Sites, and a Coordinating

Center (CC). The PCC's include Emory University, Mayo Clinic with Kansas University Medical Center and the Cleveland Clinic, Tufts Medical Center with Beth Israel Deaconess Medical Center, and University of Colorado Health Sciences. The Coordinating Center initially at Washington University is now at the University of Pittsburgh. HALT-PKD began enrolling subjects in 2006, and concluded enrollment in mid-2009. Follow-up will continue until 2014.

### Organization of the HALT-PKD trials

The HALT PKD trials are prospective randomized double blind placebo controlled multicenter interventional trials comparing treatment with angiotensin converting inhibitor (ACEI) - angiotensin receptor blocker (ARB) combination vs ACEI alone and standard vs low BP target in 15-49 year-old ADPKD patients with eGFR >60 ml/min/1.73 $m^2$ (n=558, Study A) and ACEI-ARB vs ACEI alone in 18-64 year-old patients with eGFR 25-60 ml/min/1.73 $m^2$ (n=486, Study B). All participants have hypertension or high–normal BP defined as systolic BP greater than or equal to 130 mm Hg and/or diastolic BP greater than or equal to 80 mm Hg on three separate readings within the past year, or current use of antihypertensive agents for BP control. Standard BP control for this study is defined as 120-130/70-80 and low BP as 95-110/60-75.

### Washout period and home BP measurements

Participants are trained at the screening visit to perform home BP measurements at least every other day during the drug washout period. BP measurements are obtained at least 30 minutes after awakening, before eating breakfast, smoking or consuming caffeine, after sitting for at least 5 minutes with the arm resting at heart level. The average of the 2nd and 3rd of three measurements 30 seconds apart is used for decision-making. If the difference between the two systolic or diastolic readings is >10 mm Hg, participants record a 4th and $5^{th}$ reading and the average of the last 4 readings is used. For those taking antihypertensive medications, existing antihypertensives are gradually discontinued and a 2-4 week drug washout period is completed. Labetalol or clonidine is taken during the washout period for BP control, unless indicated otherwise. BP drugs taken for non-hypertensive indications are continued at the discretion of the principal investigator.

### Participant baseline visits and randomization procedures

Within 10 weeks of the screening visit participants return to the center for a standardized baseline visit including complete history and physical examinations, sitting and standing clinic BP measurements following the same protocol used for home BP measurements, serum creatinine (see below) and biochemical measurements, MRI acquisitions in Study A patients, and completion of 24 hour urine collections for determination of albumin and aldosterone excretion, as well as health related questionnaires.

Two blood samples, drawn a minimum of one hour apart, are sent to the central laboratory (Cleveland Clinic Foundation Reference Laboratory) for analysis to establish the baseline serum creatinine measurement. Consistency of the two serum creatinine measurements (< 20% variation) is required. If the two measurements differ by greater than 20%, a second set of serum creatinine samples is obtained shortly after and sent for repeat analysis. Glomerular filtration rate is estimated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.[68] A 24-hour urine collection is performed for measurements of sodium, potassium, creatinine, albumin and aldosterone excretions, which are performed at the Diagnostic Laboratory Facility at Brigham and Women's Hospital, Boston. Adequacy of the collection is assessed based on creatinine excretion compared to the predicted value from lean body weight for age and gender.

MR imaging is performed in Study A patients for the determination of total kidney volume (TKV), total liver volume (TLV), liver cyst volume (LCV), left ventricular mass and renal blood flow (RBF). MR images (including RBF images) are obtained at each center using a protocol developed by the HALT PKD Imaging Subcommittee. Following acquisition, MR images are reviewed locally and then transferred electronically to the Image Analysis Center at the University of Pittsburgh. The cardiac MR imaging results will be reported separately.

### Randomization procedures

Randomization was performed by the coordinating center at the baseline visit in equal proportions to combined lisinopril plus telmisartan or lisinopril plus placebo using random permuted blocks with stratification by center, participant age, gender, race and baseline eGFR. Study A patients were additionally randomized in equal proportions to either a standard BP (120-130/70-80 mm Hg) or low BP (95-110/60-75 mm Hg) target.

### Statistical Methods

The data were analyzed using STATA/SE 11.1 (College Station, TX). Group comparisons were conducted using two-sample t-tests, and correlations were reported using Pearson correlation coefficients. The comparison of categorical variables across groups was conducted using chi-square tests. Continuous data was investigated for violations of normality as well as outliers. In the event that these violations occurred, suitable transformations were taken (i.e. natural logarithm).

Multiple regression models were built to examine how clinical and laboratory baseline variables were associated with baseline TKV or eGFR. Predictor variables for each of the initial multivariate models were chosen based on significant ($p<0.10$) univariate correlations with the respective outcome. The predictor variables were also checked for multicollinearity using variance inflation factors. Stepwise selection, with probabilities to enter and remove as 0.05 and 0.10 respectively, was used for model building. Only variables with p-values $<0.05$ were further considered for the final models. Finally, regression coefficients were standardized to facilitate the comparison of predictor variables. Due to the exploratory nature of the analyses, adjustments for multiplicity were not performed.

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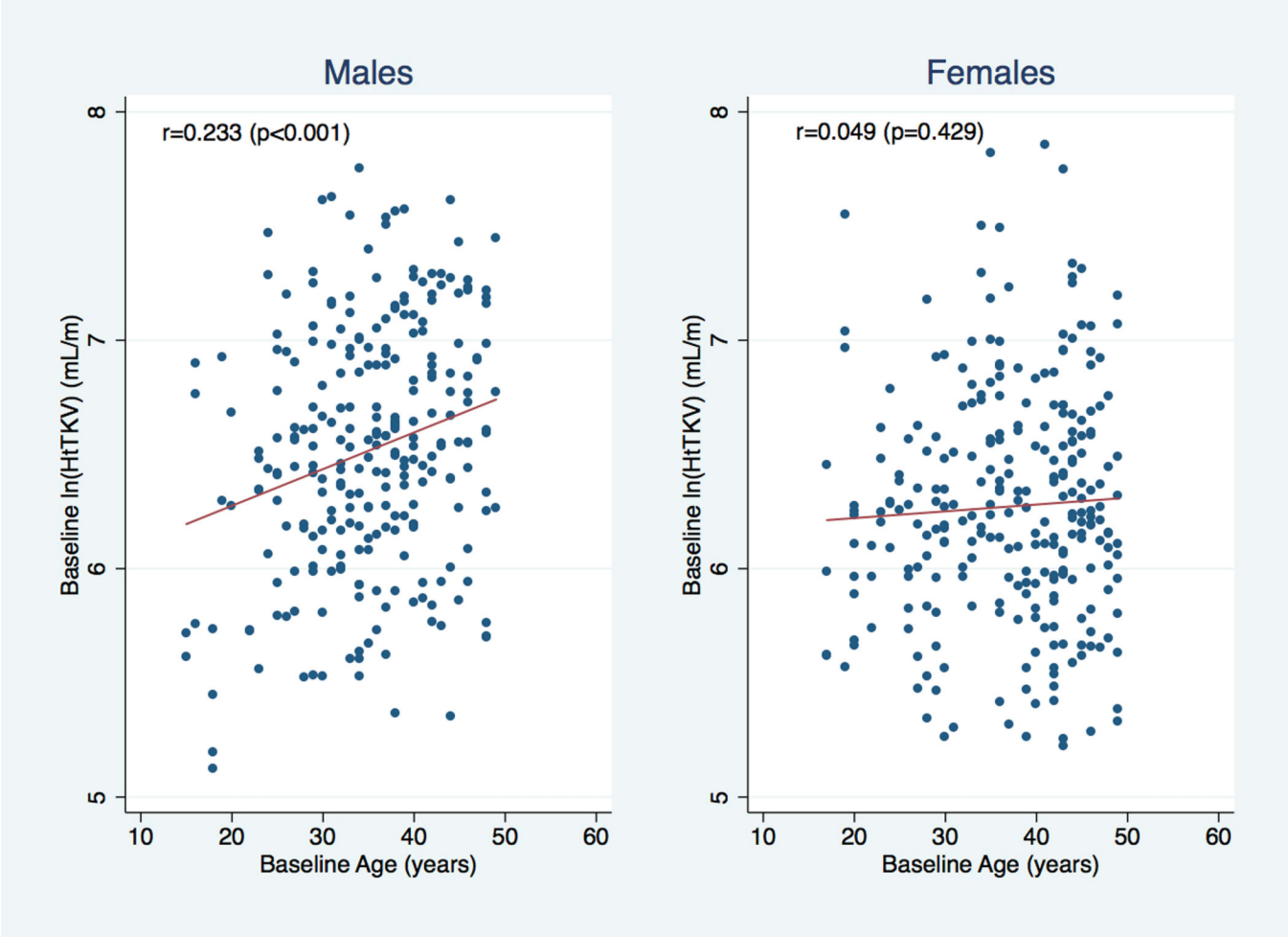


**Figure 1.**
Plots of ln(HtTKV) by_age in male and female subjects in Study A.

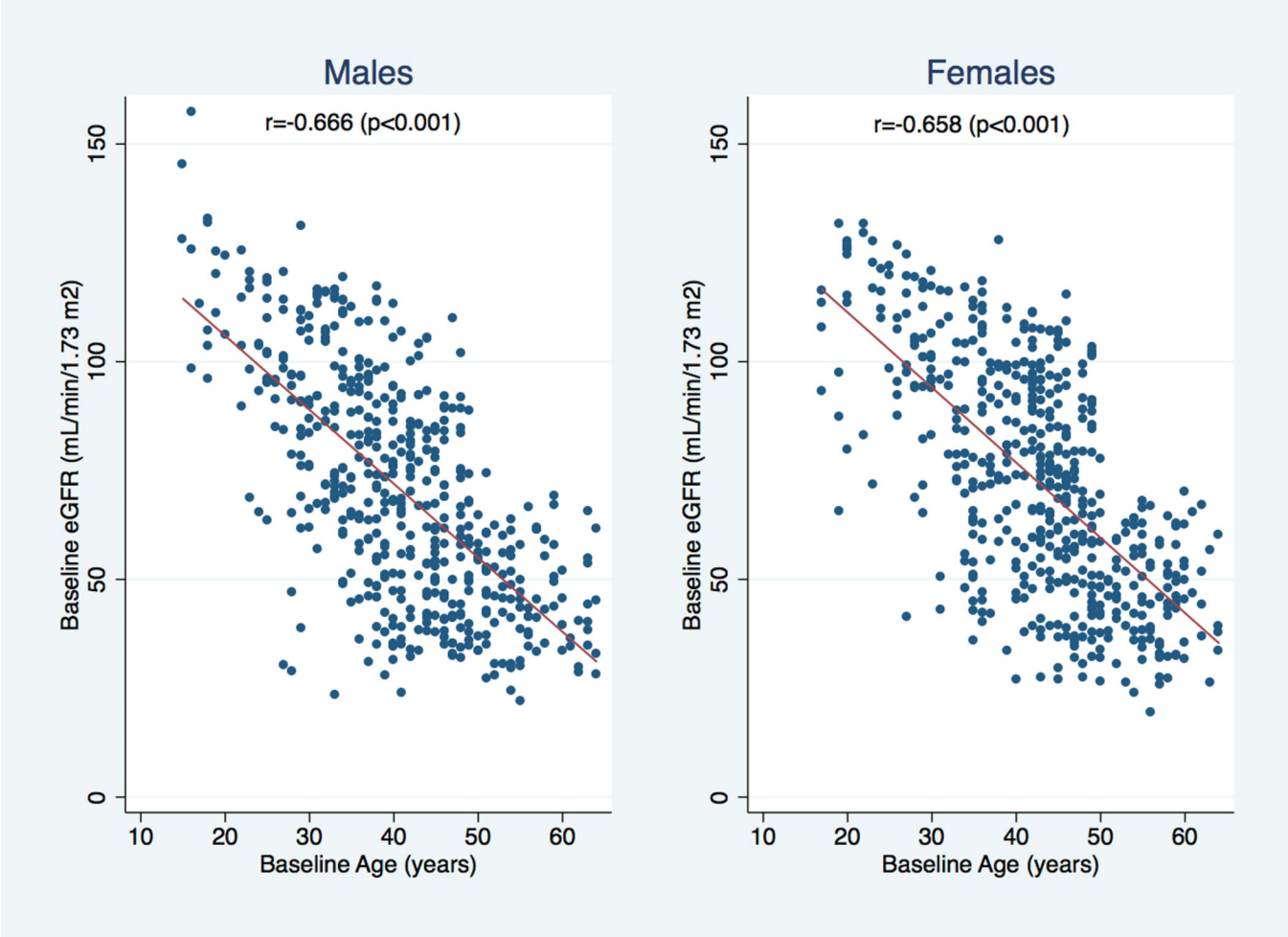


**Figure 2.**
Plots of eGFR by age in male and female subjects in Studies A and B.

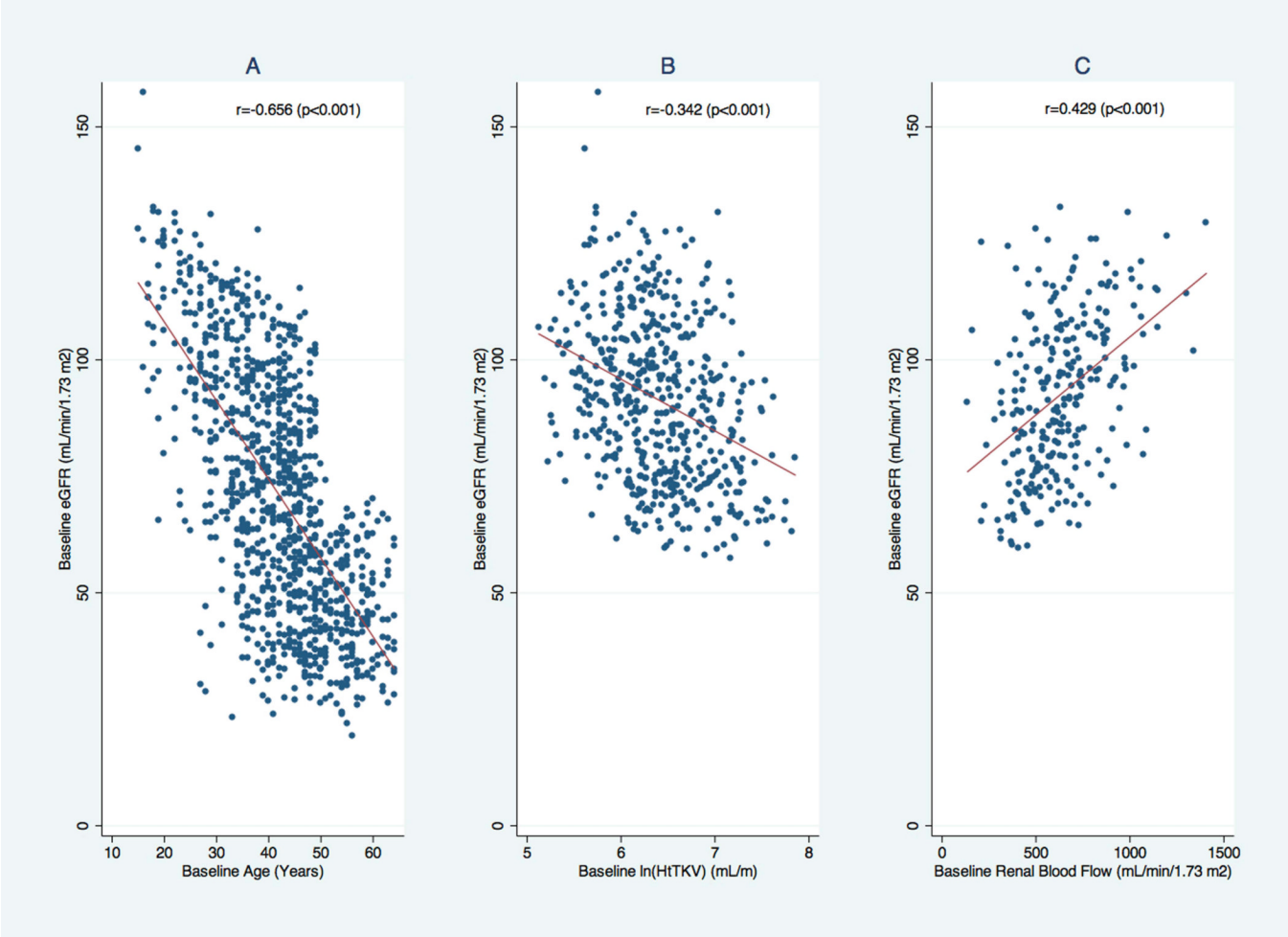


**Figure 3.**
Correlations of age (A), ln(HtTKV) (B) and RBF (C) with eGFR at baseline.

## Table 1

Demographic characteristics of the study population

| | | Study A, Standard (n=284) | Study A, Low (n=274) | Study B (n=486) |
|---|---|---|---|---|
| Gender | Male (n, %) | 143 (50.4) | 140 (51.2) | 235 (48.4) |
| Race | Caucasian (n, %) | 258 (90.9) | 259 (94.5) | 454 (93.6) |
| | African American (n, %) | 7 (2.5) | 7 (2.6) | 12 (2.5) |
| Age at enrollment | Years (mean ± SD) | 35.9 ± 8.4 | 36.5 ± 8.2 | 48.2 ± 8.3 |
| Educational level | Some high school (n, %) | 12 (4.2) | 7 (2.6) | 2 (0.4) |
| | Completed high school (n, %) | 33 (11.6) | 31 (11.4) | 53 (11.0) |
| | Some college (n, %) | 70 (24.7) | 57 (21.0) | 117 (24.2) |
| | Completed college (n, %) | 104 (36.6) | 111 (40.8) | 160 (33.1) |
| | Graduate studies (n, %) | 65 (22.9) | 66 (24.3) | 152 (31.4) |
| Marital status | Single (n, %) | 82 (29.0) | 80 (29.4) | 52 (10.7) |
| | Married (n, %) | 171 (60.4) | 175 (64.3) | 363 (74.9) |
| | Divorced/separated (n, %) | 27 (9.5) | 16 (5.9) | 57 (11.8) |
| | Widowed/other (n, %) | 3 (1.1) | 1 (0.4) | 13 (2.6) |
| Employment | Student (n, %) | 25 (8.8) | 27 (9.9) | 11 (2.3) |
| | Homemaker (n, %) | 18 (6.3) | 22 (8.0) | 43 (8.9) |
| | Part-time employment (n, %) | 34 (12.0) | 32 (11.7) | 50 (10.3) |
| | Full-time employment (n, %) | 204 (71.8) | 197 (71.9) | 342 (70.5) |
| | Other/disabled/retired (n, %) | 13 (4.6) | 11 (4.0) | 60 (12.4) |
| Diagnosis of ADPKD, age | Years (mean ± SD) | 27.1 ± 9.7 | 28.0 ± 10.3 | 33.1 ± 12.3 |
| Diagnosis due to | Screening (n, %) | 113 (39.8) | 93 (34.2) | 184 (37.9) |
| | Incidental Imaging (n, %) | 37 (13.0) | 30 (11.0) | 47 (9.7) |
| | Pain (n, %) | 42 (14.8) | 34 (12.5) | 52 (10.7) |
| | Hypertension (n, %) | 36 (12.7) | 50 (18.4) | 69 (14.2) |
| | Routine Physical (n, %) | 10 (3.5) | 8 (2.9) | 26 (5.4) |
| | Hematuria (n, %) | 15 (5.3) | 25 (9.2) | 33 (6.8) |
| | UTI (n, %) | 5 (1.8) | 9 (3.3) | 9 (1.9) |
| | Other (n, %) | 26 (9.1) | 23 (8.5) | 65 (13.4) |
| Diagnosis of ADPKD, mode | Ultrasound (n, %) | 205 (72.2) | 195 (71.7) | 350 (72.2) |
| | CT (n, %) | 46 (16.2) | 42 (15.4) | 54 (11.1) |
| | MRI (n, %) | 17 (6.0) | 16 (5.9) | 23 (4.7) |
| | IVP (n, %) | 7 (2.5) | 11 (4.0) | 31 (6.4) |
| | Other (n, %) | 9 (0.1) | 8 (0.0) | 27 (0.6) |
| Diagnosis of hypertension, age | Years (mean ± SD) | 30.2 ± 8.7 | 30.9 ± 9.1 | 36.2 ± 10.6 |

*Kidney Int*. Author manuscript; available in PMC 2013 February 25.

**Table 2**

Baseline Characteristics by Gender in Study A and Study B

| | Study A | | | Study B | | |
|---|---|---|---|---|---|---|
| | **Male** | **Female** | **Both** | **Male** | **Female** | **Both** |
| | **Mean ± SD (N)** | **Mean ± SD (N)** | **Mean ± SD** | **Mean ± SD (N)** | **Mean ± SD (N)** | **Mean ± SD** |
| Age years | **35.2 ± 8.1** (283) | **37.2 ± 8.4**$^{\dagger}$ (275) | **36.2 ± 8.3** | **47.4 ± 8.7** (235) | **49.0 ± 7.9**$^{*}$ (251) | **48.2 ± 8.3**$^{\S}$ |
| Height cm | **181.0 ± 7.8** (275) | **166.3 ± 7.8**$^{\S}$ (271) | 173.7 ± 10.7 | **180.3 ± 8.9** (231) | **166.4 ± 20.5**$^{\S}$ (246) | 173.1 ± 17.4 |
| BSA $m^2$ | **2.1 ± 0.2** (274) | **1.8 ± 0.2**$^{\S}$ (271) | 2.0 ± 0.2 | **2.1 ± 0.2** (231) | **1.8 ± 0.2**$^{\S}$ (246) | 2.0 ± 0.3 |
| BMI kg/ $m^2$ | 27.6 ± 4.7 (274) | 27.2 ± 10.4 (271) | **27.4 ± 8.0** | 29.0 ± 5.9 (231) | 28.2 ± 12.9 (246) | **28.6 ± 10.1**$^{*}$ |
| Office Systolic BP mmHg | **127.2 ± 14.3** (280) | **122.9 ± 14.5**$^{\S}$ (274) | 125.1 ± 14.5 | 127.9 ± 15.0 (235) | 125.4 ± 15.8 (251) | 126.6 ± 15.4 |
| Office Diastolic BP mmHg | 80.0 ± 11.4 (280) | 78.6 ± 11.8 (274) | 79.3 ± 11.6 | **80.3 ± 9.7** (234) | **76.8 ± 10.9**$^{\S}$ (251) | 78.5 ± 10.5 |
| HtTKV mL/m | **780.7 ± 419.5** (262) | **608.9 ± 367.2**$^{\S}$ (266) | 694.1 ± 403.0 | NA | NA | NA |
| RBF mL/min/1.73 $m^2$ | **665.0 ± 224.3** (130) | **610.5 ± 205.4**$^{*}$ (138) | 636.9 ± 216.1 | NA | NA | NA |
| HtTLV mL/m | 1114 ± 402 (265) | 1137 ± 513 (269) | 1126 ± 461 | NA | NA | NA |
| Liver cyst volume mL | **146.2 ± 703.0** (226) | **343.9 ± 795.6**$^{*}$ (241) | 248.2 ± 757.9 | NA | NA | NA |
| eGFR mL/min/1.73 $m^2$ | 90.4 ± 17.8 (282) | 92.7 ± 17.1 (275) | **91.5 ± 17.5** | 47.1 ± 11.3 (235) | 49.2 ± 12.3 (251) | **48.2 ± 11.8**$^{\S}$ |
| S. sodium mEq/L | 139.3 ± 2.2 (283) | 138.6 ± 7.8 (275) | 138.9 ± 5.7 | 138.6 ± 11.8 (234) | 139.3 ± 2.4 (249) | 138.9 ± 8.4 |
| S. potassium mEq/L | **4.2 ± 0.4** (283) | **4.0 ± 0.4**$^{\S}$ (275) | **4.1 ± 0.4** | **4.3 ± 0.5** (234) | **4.2 ± 0.5**$^{*}$ (249) | **4.3 ± 0.5**$^{\S}$ |
| Urine volume mL | 2639 ± 1201 (272) | 2457 ± 1150 (265) | 2550 ± 1179 | **2794 ± 1114** (222) | **2541 ± 974**$^{*}$ (240) | 2662 ± 1050 |
| Urine sodium mEq/24 hrs | **194.0 ± 75.3** (254) | **161.0 ± 78.5**$^{\S}$ (260) | 177.3 ± 78.6 | **202.7 ± 86.6** (211) | **153.8 ± 68.1**$^{\S}$ (224 | 177.5 ± 81.3 |
| Urine potassium mEq/24 hrs | **62.9 ± 26.4** (251) | **53.5 ± 25.0**$^{\S}$ (257) | **58.1 ± 26.1** | **68.7 ± 28.3** (211) | **56.3 ± 23.0**$^{\S}$ (224) | **62.3 ± 26.4**$^{*}$ |
| Urine sodium/potassium ratio | 3.5 ± 1.6 (251) | 3.3 ± 1.6 (257) | **3.4 ± 1.6** | 3.2 ± 1.2 (211) | 3.0 ± 1.5 (224) | **3.1 ± 1.3**$^{\dagger}$ |
| Urine aldosterone μg/24 hrs | **10.0 ± 5.9** (217) | **15.8 ± 12.0**$^{\S}$ (223) | **12.9 ± 9.9** | 10.0 ± 7.7 (173) | 10.3 ± 7.6 (190) | **10.2 ± 7.6**$^{\S}$ |
| Urine albumin mg/24 hrs | 40.8 ± 73.2 (254) | 42.3 ± 183.6 (260) | **41.5 ± 140.2** | **109.1 ± 195.6** (210) | **64.9 ± 124.1**$^{*}$ (224) | **86.3 ± 163.9**$^{\S}$ |

Characters in bold indicate statistically significant differences between genders within Study A and Study B or between Study A and Study B. P-values:

* ≤0.05

† ≤0.005

§ ≤0.0005

**Table 3**

Baseline characteristics in Study A by blood pressure group assignment

| | Study A Standard | | Study A Low | | p value |
|---|---|---|---|---|---|
| | **N** | **Mean ± SD** | **N** | **Mean ± SD** | |
| Age years | 284 | 35.9 ± 8.4 | 274 | 36.5 ± 8.2 | 0.401 |
| Female | 284 | 49.6% | 274 | 48.9% | 0.861 |
| Height cm | 280 | 173.4 ± 11.5 | 266 | 174.0 ± 9.8 | 0.533 |
| BSA $m^2$ | 279 | 2.0 ± 0.2 | 266 | 2.0 ± 0.2 | 0.938 |
| BMI $kg/m^2$ | 279 | 27.8 ± 10.1 | 266 | 27.0 ± 5.1 | 0.225 |
| Office Systolic BP mmHg | 282 | 125.2 ± 14.6 | 272 | 125.0 ± 14.5 | 0.883 |
| Office Diastolic BP mmHg | 282 | 79.9 ± 11.7 | 272 | 78.7 ± 11.5 | 0.227 |
| HtTKV TKV/m | 269 | 704.2 ± 406.1 | 259 | 683.7 ± 400.2 | 0.558 |
| RBF mL/min/1.73 $m^2$ | 131 | 623.2 ± 215.0 | 137 | 650.0 ± 217.2 | 0.311 |
| HtTLV mL/m | 273 | 1128.4 ± 380.4 | 261 | 1122.9 ± 532.4 | 0.892 |
| Liver cyst volume mL | 241 | 237.1 ± 596.9 | 226 | 260.1 ± 899.6 | 0.751 |
| eGFR mL/min/1.73 $m^2$ | 283 | 91.7 ± 17.8 | 274 | 91.4 ± 17.2 | 0.820 |
| S. sodium mEq/L | 284 | 139.1 ± 2.3 | 274 | 138.8 ± 7.8 | 0.572 |
| S. potassium mEq/L | 284 | 4.1 ± 0.4 | 274 | 4.1 ± 0.4 | 0.368 |
| Urine volume mL | 271 | 2577 ± 1223 | 266 | 2522 ± 1133 | 0.595 |
| Urine sodium mEq/24 hrs | 260 | 176.4 ± 77.7 | 254 | 178.2 ± 79.7 | 0.786 |
| Urine potassium mEq/24 hrs | 257 | 57.9 ± 24.4 | 251 | 58.4 ± 27.8 | 0.818 |
| Urine sodium/potassium ratio | 257 | 3.4 ± 1.6 | 251 | 3.4 ± 1.6 | 0.784 |
| Urine aldosterone μg/24 hrs | 226 | **13.9 ± 11.1** | 214 | **11.9 ± 8.3** | **0.033** |
| Urine albumin mg/24 hrs | 260 | 34.9 ± 56.6 | 254 | 48.3 ± 191.0 | 0.284 |

Characters in bold indicate statistically significant differences

**Table 4**

Correlations between ln(htTKV) and other baseline parameters in Study A

| | ln(htTKV) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Men | | | Women | | | Both | | |
| | N | r | P | N | r | P | N | r | P |
| Age years | 262 | 0.233 | **0.0001*** | 266 | 0.049 | 0.4288 | 528 | 0.109 | **0.0121*** |
| Height cm | 262 | 0.142 | **0.0215*** | 266 | 0.075 | 0.2198 | 528 | 0.236 | **<0.0001*** |
| BSA $m^2$ | 261 | 0.243 | **<0.0001*** | 266 | 0.101 | 0.0998 | 527 | 0.275 | **<0.0001*** |
| BMI kg/ $m^2$ | 261 | 0.157 | **0.0112*** | 266 | 0.055 | 0.3675 | 527 | 0.084 | 0.0541 |
| Office Systolic BP mmHg | 261 | 0.190 | **0.0020*** | 266 | 0.106 | 0.0840 | 527 | 0.178 | **<0.0001*** |
| Office Diastolic BP mmHg | 261 | 0.193 | **0.0017*** | 266 | 0.088 | 0.1533 | 527 | 0.152 | **0.0005*** |
| RBF mL/min/1.73 $m^2$ | 128 | -0.241 | **0.0062*** | 137 | -0.169 | **0.0489*** | 265 | -0.181 | **0.0032*** |
| eGFR mL/min/1.73 $m^2$ | 262 | -0.375 | **<0.0001*** | 266 | -0.289 | **<0.0001*** | 528 | -0.339 | **<0.0001*** |
| S. sodium mEq/L | 262 | 0.043 | 0.4916 | 266 | 0.018 | 0.7691 | 528 | 0.035 | 0.4184 |
| S. potassium mEq/L | 262 | 0.056 | 0.3647 | 266 | -0.054 | 0.3765 | 528 | 0.044 | 0.3101 |
| Urine volume mL | 254 | -0.042 | 0.5020 | 256 | 0.129 | **0.0397*** | 510 | 0.055 | 0.2156 |
| Urine sodium mEq/24 hrs | 236 | 0.044 | 0.5018 | 251 | 0.139 | **0.0276*** | 487 | 0.142 | **0.0017*** |
| Urine potassium mEq/24 hrs | 233 | 0.027 | 0.6777 | 248 | 0.069 | 0.2775 | 481 | 0.096 | **0.0351*** |
| Urine sodium/potassium ratio | 233 | -0.005 | 0.9342 | 248 | 0.008 | 0.9054 | 481 | 0.015 | 0.7423 |
| Urine aldosterone μg/24 hrs | 201 | 0.058 | 0.4135 | 216 | -0.017 | 0.7997 | 417 | -0.062 | 0.2031 |
| ln(Urine albumin) | 236 | 0.286 | **<0.0001*** | 251 | 0.446 | **<0.0001*** | 487 | 0.360 | **<0.0001*** |
| ln(HtTLV mL/m) | 262 | 0.081 | 0.1895 | 262 | 0.136 | **0.0264*** | 527 | 0.112 | **0.0098*** |
| ln(Liver Cyst Volume mL) | 215 | 0.040 | 0.5581 | 233 | 0.171 | **0.0088*** | 448 | 0.066 | 0.1641 |

Characters in bold indicate statistically significant correlations

## Table 5

Final regression model to predict ln(HtTKV)

| | $R^2$ =0.287 (n=486) | |
|---|---|---|
| | **Beta** | **P** |
| BSA $m^2$ | 0.247 | **<0.001** |
| ln(Urine albumin mg/24 hrs) | 0.324 | **<0.001** |
| eGFR mL/min/1.73 $m^2$ | -0.286 | **<0.001** |

Characters in bold indicate statistically significant independent predictors

**Table 6**

Correlations between eGFR and other baseline parameters in both studies (A and B)

| | eGFR | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Men | | | Women | | | Both | | |
| | N | r | P | N | r | P | N | r | P |
| Age years | 517 | -0.666 | **<0.0001*** | 526 | -0.658 | **<0.0001*** | 1043 | -0.656 | **<0.0001*** |
| Height cm | 505 | 0.019 | 0.6627 | 517 | 0.035 | 0.4280 | 1022 | 0.012 | 0.7043 |
| BSA $m^2$ | 504 | -0.147 | **0.0010*** | 517 | 0.000 | 0.9961 | 1021 | -0.073 | **0.0202*** |
| BMI kg/ $m^2$ | 504 | -0.188 | **<0.0001*** | 517 | -0.026 | 0.5618 | 1021 | -0.072 | **0.0219*** |
| Office Systolic BP mmHg | 514 | -0.093 | **0.0360*** | 525 | -0.093 | **0.0330*** | 1039 | -0.095 | **0.0022*** |
| Office Diastolic BP mmHg | 513 | -0.136 | **0.0020*** | 525 | 0.061 | 0.1621 | 1038 | -0.035 | 0.2571 |
| S. sodium mEq/L | 516 | 0.021 | 0.6331 | 524 | -0.035 | 0.4214 | 1040 | -0.003 | 0.9228 |
| S. potassium mEq/L | 516 | -0.198 | **<0.0001*** | 524 | -0.246 | **<0.0001*** | 1040 | -0.223 | **<0.0001*** |
| Urine volume mL | 494 | -0.088 | 0.0506 | 505 | -0.070 | 0.1158 | 999 | -0.081 | **0.0104*** |
| Urine sodium mEq/24 hrs | 465 | -0.001 | 0.9881 | 484 | 0.050 | 0.2712 | 949 | 0.014 | 0.6675 |
| Urine potassium mEq/24 hrs | 462 | -0.100 | **0.0311*** | 481 | -0.063 | 0.1680 | 943 | -0.088 | **0.0068*** |
| Urine sodium/potassium ratio | 462 | 0.178 | **0.0001*** | 481 | 0.125 | **0.0059*** | 943 | 0.148 | **<0.0001*** |
| Urine aldosterone μg/24 hrs | 390 | 0.003 | 0.9496 | 413 | 0.279 | **<0.0001*** | 803 | 0.173 | **<0.0001*** |
| ln(Urine albumin) | 464 | -0.308 | **<0.0001*** | 484 | -0.263 | **<0.0001*** | 948 | -0.287 | **<0.0001*** |

Characters in bold indicate statistically significant correlations

## Table 7

Final regression models to predict eGFR

| | Including ln(HtTKV) and RBF $R^2$ = 0.404 (n = 265) | | Excluding ln(HtTKV) and RBF $R^2$ = 0.521 (n = 770) | |
|---|---|---|---|---|
| | **Beta** | **P** | **Beta** | **P** |
| Age yrs | -0.433 | **<0.001** | -0.619 | **<0.001** |
| BSA $m^2$ | ---- | ---- | -0.078 | **<0.01** |
| Serum potassium mEq/L | ---- | ---- | -0.085 | **<0.001** |
| Urine aldosterone μg/24 hrs | ---- | ---- | 0.096 | **<0.001** |
| ln(Urine albumin mg/24 hrs) | ---- | ---- | -0.254 | **<0.001** |
| ln(HtTKV mL/m) | -0.182 | **<0.001** | ---- | ---- |
| RBF mL/min/1.73 $m^2$ | 0.300 | **<0.001** | ---- | ---- |

Characters in bold indicate statistically significant independent predictors