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Non-GFR Determinants of Low Molecular Weight Serum Protein Filtration Markers in CKD

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Supplementary Material

Note: The supplementary material accompanying this article (doi:_____) is available at www.ajkd.org

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Abstract

Background—Unlike the case with creatinine, the conditions affecting the non-glomerular filtration rate (GFR) determinants of low molecular weight serum proteins, β -trace protein (BTP), β_2 -microglobulin (B2M) and cystatin C, are not well characterized.

Study Design—Pooled cross-sectional analysis of three studies.

Setting & Participants—3156 persons with chronic kidney disease (CKD) from the MDRD (Modification of Diet in Renal Disease) Study, AASK (African American Study of Kidney Disease and Hypertension) and the CRIC (Chronic Renal Insufficiency Cohort) Study.

Predictors—Demographic and clinical factors hypothesized to be associated with non-GFR determinants of the filtration markers, selected from literature review and physiological and clinical considerations.

Outcomes—Serum levels of creatinine, BTP, B2M and cystatin C.

Results—In multivariable-adjusted errors-in-variables regression models that included adjustment for measured GFR (mGFR) and mGFR measurement error, creatinine had stronger associations with male sex, black race and higher urine creatinine than the other filtration markers. BTP was associated less strongly with age, similar in direction with sex, and opposite in direction with race than creatinine. Like cystatin C, B2M was associated less strongly with age, sex and race than creatinine. BTP, B2M and cystatin C were associated more strongly than creatinine with other factors, including urine protein and weight for BTP, smoking and urine protein for B2M and smoking for cystatin C.

Limitations—Findings may not be generalizable to populations without CKD, and residual confounding with GFR due to incomplete adjustment for GFR measurement error.

Conclusions—Like creatinine, serum levels of low molecular weight proteins are affected by conditions other than GFR. Knowledge of these conditions can aid the interpretation of GFR estimates and risk using these markers and guide the use of these filtration markers in developing GFR estimating equations.

Keywords

glomerular filtration rate (GFR); creatinine; cystatin C; beta trace protein (BTP); beta-2 microglobulin (B2M); determinants of kidney function; biomarker; filtration marker; kidney disease; estimation of kidney function

Estimated glomerular filtration rate (eGFR) is reported each time serum creatinine is measured by more than 90% of US clinical laboratories,¹ and plays an important role in detecting, evaluating, and managing chronic kidney disease (CKD).² However, the accuracy of creatinine-based eGFR (eGFR_{cr}) compared to measured GFR (mGFR) is limited due to physiological processes other than GFR that affect serum creatinine concentration, including

the generation, renal tubular secretion and reabsorption, and extrarenal elimination of creatinine, together known as non-GFR determinants. Estimating equations for GFR incorporate age, sex and race as surrogates for the production of creatinine by muscle, but the coefficients for these factors represent average values for their relationship with this physiologic process, resulting in bias (systematic error compared to mGFR) in some subgroups and imprecision (random error compared to mGFR) in all.^{3;4}

Low molecular weight (LMW) serum proteins, including β -trace protein (BTP), β_2 -microglobulin (B2M) and cystatin C are candidate endogenous filtration markers that may be less affected than creatinine by non-GFR determinants. Some recent studies show that serum concentrations of BTP, B2M and cystatin C are more strongly correlated with mGFR and less strongly associated with age, sex and race than creatinine, but the GFR estimates based on single markers (eGFR_{BTP}, eGFR_{B2M} or eGFR_{cys}, respectively) are not more accurate than eGFR_{Cr}.^{5;6} These findings suggest that the non-GFR determinants of these markers are affected by conditions other than age, sex and race. In addition, prior work suggests that serum concentrations of BTP, B2M and cystatin C are more strongly associated than creatinine with adverse outcomes of CKD, such as kidney failure,^{7–11} cardiovascular disease^{9;11} and mortality,^{8–12} suggesting that conditions affecting their non-GFR determinants have differential associations with these outcomes. Knowledge of conditions that affect the non-GFR determinants of these markers may enable more accurate interpretation of GFR estimates using these markers and their associations with adverse outcomes.

Unlike creatinine, LMW serum proteins are reabsorbed and catabolized after filtration, with small amounts lost in the urine, so it is difficult to measure their non-GFR determinants directly. Prior investigations in the MDRD (Modification of Diet in Renal Disease) Study, AASK (African American Study of Kidney Disease and Hypertension), and the CRIC (Chronic Renal Insufficiency Cohort) Study have described demographic and clinical factors other than GFR that are associated with creatinine and cystatin C.^{13;14} In this study, we evaluate associations of factors other than GFR with serum levels of BTP and B2M in these studies and compare them with associations observed with cystatin C and creatinine, in order to identify conditions that may affect their non-GFR determinants in CKD.

Methods

Study Population

We included 3156 participants from the MDRD Study randomized cohort (N=679), the AASK baseline cohort (G1 visit; N=1208), and the CRIC Study (N=1269) with mGFR assessment, cystatin C, BTP, and B2M measured in stored samples, and non-missing data on factors hypothesized to be associated with their non-GFR determinants (Figure S1, available as online supplementary material). Baseline characteristics of included and excluded participants are in Table S1.

Predictor Variable Assessment

Demographic and clinical factors were considered predictor variables and were selected based on literature review and physiological and clinical considerations. Predictors of interest included measures of body composition (age, sex, race, height, weight, body mass index, body surface area, urine creatinine), cardiovascular disease risk factors (diabetes, smoking, systolic blood pressure, diastolic blood pressure, glucose, total cholesterol, high density lipoprotein [HDL] cholesterol, cardiovascular disease), measures related to severity of kidney disease (hemoglobin, urine protein), measures of inflammation (albumin, C-reactive protein [CRP]) and measures of dietary intake (serum sodium, urine urea nitrogen). Measurement methods and definitions of the aforementioned variables have been described previously.^{15–17}

GFR and Filtration Marker Assessment

The GFR was measured in the MDRD Study, AASK, and the CRIC Study as three-or four-period urinary clearances of iothalamate.^{14;16;18} Serum BTP, B2M and creatinine were assayed at the University of Minnesota.⁶ Serum cystatin-C was measured at the Cleveland Clinic Research Laboratory used for the MDRD Study and AASK and at the University of Pennsylvania for the CRIC study.^{13;14} Additional information for these assays are presented in Item S1.

Statistical Analyses

Analyses were performed pooled across the three studies. Filtration markers were log transformed to replicate the multiplicative relationship between predictors and endogenous filtration markers. We evaluated correlations among filtration markers using Pearson correlation and partial Pearson correlation coefficients after adjustment for log transformed mGFR. We evaluated the unadjusted association of each predictor variable with each separate filtration marker using linear regression. In order to identify factors that are associated with the non-GFR determinants of the filtration markers rather than GFR, we modeled each filtration marker as a function of candidate factors with adjustment for mGFR and correcting for attenuation by mGFR measurement error using errors-in-variables regression. Consistent with earlier work, we used 0.015 as an estimate for the mGFR measurement error variance on the log scale estimated using data from the MDRD Study and AASK.^{13;19} Interactions with study cohort were evaluated in pooled models adjusted for mGFR and mGFR measurement error, with a Bonferroni correction for the p-value significance threshold to account for multiple testing. Errors-in-variables regression models were further adjusted for age, sex and race. Models adjusted for mGFR, mGFR measurement error, and study and further adjusted for age, sex and race incorporated one candidate factor at a time as the predictor of interest. Finally, we constructed multivariable errors-in-variables regression models for each filtration marker using a set of selected demographic and clinical characteristics with adjustment for mGFR, mGFR measurement error, and study.

Parameter estimates for all models were transformed as $100 \times (e^{\text{coefficient}} - 1)$ such that values can be interpreted as the geometric mean percent difference in the filtration marker for a interquartile range (IQR) difference in continuous predictors (a difference from the 25th to

75th percentile of a continuous variable) or for the presence of categorical predictors. We selected an IQR as the standardized unit for continuous variables to allow for a more direct comparison of strength of association for continuous and binary predictors. Strengths of associations were classified as strong, intermediate, and weak (absolute percent differences of >10%, 5%–10%, and <5%, respectively). The cut-points for these ranges were author-defined for the purposes of comparisons within this study. Additional details on the statistical analyses are presented in Item S1. Analyses were computed using R statistical software version 3.1.0 (R Foundation for Statistical Computing) and SAS version 9.4 (SAS Institute Inc, Cary, NC).

Results

Participant Characteristics

In the pooled study sample, mean age was 54.2 years, 60.1% were male, 54.6% were black, and 22.5% had diabetes (Table 1). Mean mGFR was 47 ml/min/1.73 m²; mean serum concentrations of BTP, B2M, cystatin C and creatinine were 1.3 mg/L, 4.3 mg/L, 1.9 mg/L and 1.7 mg/dL, respectively. Characteristics by study cohort are shown in Table S2.

Correlations Among Filtration Markers

Strong inverse correlations were observed between log-transformed serum concentrations of the filtration markers with mGFR (ranging from −0.80 for creatinine to −0.88 for cystatin C; Table S3). Correlations among the serum concentrations of the markers ranged from 0.90 (B2M and cystatin C) to 0.75 (BTP and creatinine). After adjusting for mGFR, partial correlations among markers ranged from 0.62 (B2M and cystatin C) to 0.30 (BTP and creatinine).

Associations of Factors With Filtration Markers

Associations of factors with filtration markers with and without adjustment for mGFR, mGFR measurement error and study cohort are shown in Figure 1 and Table S4, respectively. When comparing associations of factors with BTP, B2M, and cystatin C with their associations with creatinine (Figure S2), we observed that creatinine had stronger associations with male sex, black race, larger body surface area, greater height and higher urine creatinine than the other filtration markers. Both BTP and creatinine had strong positive associations with male sex and urine protein, but their associations with black race were of similar magnitude but in opposite directions. B2M and creatinine had strong associations in common only with urine protein. Cystatin C and creatinine had no strong associations in common. Both B2M and cystatin, but not creatinine, had intermediate associations with smoking.

In general, adjustment for age, sex and race affected associations of BTP, B2M and cystatin C less than associations with creatinine (Figure 2). Associations were attenuated for many factors in multivariable adjusted models (Figure 3). Higher BTP retained strong associations with male sex and higher urine protein, and intermediate associations with non-black race and lower weight. Higher B2M retained intermediate associations with non-black race, smoking and higher urine protein. Higher serum cystatin C retained intermediate

associations with male sex and smoking. Higher serum creatinine retained strong associations with male sex and black race, and intermediate associations with younger age and higher urine creatinine.

Patterns of Associations Across Filtration Markers

When examining patterns of strength of associations for each factor across the filtration markers (Figure S3), we observed no concordant patterns with strong or intermediate associations among all four filtration markers, suggesting no consistent biases due to residual confounding with mGFR. Patterns were discordant for age, sex, race, weight, smoking, urine creatinine and urine protein, suggesting differing effects of these conditions across markers. Patterns of association persisted with slight attenuation with sequential model adjustment. Creatinine retained stronger associations with male sex, black race and higher urine creatinine than the other filtration markers.

Discussion

In principle, serum concentrations of every endogenous filtration marker are affected by non-GFR determinants, which cause bias and imprecision (representing systematic and random error, respectively) in GFR estimates compared to mGFR and potentially confound risk associations in persons with decreased GFR. We found differential associations of demographic and clinical factors with filtration markers after adjustment for mGFR and GFR measurement error that persisted after multivariable adjustment, which imply differential effects of associated conditions on non-GFR determinants across markers. After multivariable adjustment, creatinine had stronger associations with male sex, black race and higher urine creatinine than the other filtration markers. We determined that BTP was affected less by age, similarly by sex, and oppositely by race than creatinine, and that B2M, like cystatin C, was affected less by age, sex and race than creatinine. In addition, BTP, B2M, and cystatin C were affected more strongly than creatinine by factors other than age, sex and race, including urine protein and weight for BTP, smoking and urine protein for B2M, and smoking for cystatin C. Our results substantially extend the work of prior studies examining the associations with BTP, and B2M and cystatin C, and may have implications for their use in clinical research and practice.

Knowledge of factors affecting the non-GFR determinants of filtration markers is important for clinical interpretation of eGFR, but studies without mGFR are limited by the inability to distinguish factors that are associated with filtration marker concentrations by GFR versus non-GFR mechanisms. The non-GFR determinants of creatinine such as generation by muscle, tubular reabsorption and secretion, and extrarenal clearance, are well-known because they can be inferred using measurements of urinary creatinine excretion. In GFR estimating equations, age, sex and race are included as surrogates of creatinine generation by muscle. Consequently, a creatinine-based estimating equation will not be accurate in patients with conditions affecting muscle mass (for example, malnutrition, neuromuscular disorders, limb amputation, and extremes of body size) since age, sex and race cannot account for the muscle creatinine generation in these conditions. In contrast to creatinine, only small amounts of LMW serum proteins are lost in the urine. Thus their non-GFR determinants

cannot be measured without invasive procedures, and instead must be inferred from associations with demographic and clinical factors.

Cystatin C is a 120 amino acid protein (molecular mass, 13 kDa) cysteine protease inhibitor with multiple biologic functions; it modulates the immune system, has antibacterial and antiviral activities, and modifies the response to brain injury. It is thought to be generated in all nucleated cells.²⁰ The serum concentration of cystatin C is consistently more strongly associated than creatinine with risk of cardiovascular disease and mortality in population-based cohorts and clinical populations with CKD.^{7–12} Prior studies have identified several factors that may be associated with non-GFR determinants of cystatin C.^{13;21–24} In these studies higher values for measures of body size and composition (for example, weight, height, body mass index, lean mass) and inflammation (C-reactive protein) are consistently shown to be associated with lower eGFR_{cys} (higher cystatin C). Current smoking and male sex have been shown to be associated with lower eGFR_{cys} in some,^{13;22;23} but not all,²⁴ studies. Our study confirms intermediate associations with male sex and smoking that are independent of mGFR. These associations may reflect higher metabolic rate in men compared to women and in smokers compared to non-smokers, which may contribute in part to the stronger associations of lower eGFR_{cys} than lower eGFR_{cr} with cardiovascular disease and mortality in prior work, even with adjustment for sex and smoking.⁹ Studies of the mechanisms underlying these associations are necessary. Unlike some prior studies, we detected only a weak association between cystatin C and measures of body size and CRP. However, we did not have measures of fat mass or other inflammatory markers, which would be important for further studies.

BTP is a 168 amino acid (molecular mass, 23–29 kDa) glycoprotein enzyme produced in the central nervous system that promotes the conversion of prostaglandin H₂ to prostaglandin D, and is used clinically as a marker for leakage of cerebrospinal fluid into nasal secretions.²⁵ B2M is a 100 amino acid protein (molecular mass, 12 kDa) component of class I major histocompatibility molecules and is found on nucleated cells, and is used clinically as a marker for tumor burden in some lymphoproliferative and plasma cell disorders.^{26;27} The serum concentrations of BTP and B2M are generally more strongly associated than creatinine with cardiovascular disease and mortality in general population and CKD studies,^{8;9;12} and in some studies they are more strongly associated with progression to end-stage renal disease.⁷ Few studies have evaluated factors associated with BTP and B2M, in particular in populations with mGFR. In a study of kidney transplant recipients with mGFRs, male sex and higher serum albumin were associated with higher BTP.²⁸ In adults from the NHANES (National Health and Nutrition Examination Survey), a population based study without GFR measurements, factors associated with elevated BTP in unadjusted analyses included older age, male sex, non-Hispanic white race/ethnicity, hypertension, higher CRP, lower HDL cholesterol, and having <12 years of education.²⁹ Factors associated with elevated B2M in NHANES included older age, higher body mass index, hypertension, higher CRP, lower HDL cholesterol, and having <12 years of education. Our study confirms associations of male sex and non-black race with higher BTP independent of mGFR. The observed associations of higher BTP with lower weight and higher urine protein and of higher B2M with non-black race, smoking and higher urine protein, independent of mGFR, appear to be novel. The pattern of associations of these factors is not consistent across all

filtration markers, suggesting these factors are associated with non-GFR determinants of the filtration markers rather than with GFR. Furthermore, these associations could contribute to the stronger associations of BTP or B2M than $eGFR_{cr}$ with end-stage renal disease, cardiovascular disease and mortality observed in other studies.^{7–12} The moderately strong associations of BTP and B2M with urine protein may reflect confounding by severity of kidney disease that is not reflected by mGFR. Again, studies of the mechanisms for these associations would be enlightening.

Our findings have implications for the use of estimating equations in clinical practice and research. First, current guidelines recommend use of $eGFR_{cr-cys}$ or $eGFR_{cys}$ to confirm decreased $eGFR_{cr}$.³⁰ The finding that cystatin C may be affected by smoking may account, in part, for the improved performance of $eGFR_{cr-cys}$ over $eGFR_{cys}$ compared to mGFR in earlier studies.^{5;31;32} Based on this, we would suggest preferential use of $eGFR_{cr-cys}$ over $eGFR_{cys}$ to confirm decreased $eGFR_{cr}$ unless there are conditions present when $eGFR_{cr}$ is known to be biased (see examples discussed in earlier paragraph) or in racial-ethnic groups in which $eGFR_{cr}$ using equations developed in North American and European populations is known to be less accurate. In a cohort of 232 multi-ethnic Asian CKD patients, $eGFR_{cr-cys}$ was shown to be more accurate than $eGFR_{cys}$,³³ further study is warranted in larger study samples and in other racial-ethnic populations. Cystatin C is now widely available in clinical laboratories, however, traceability of assays to the standardized reference material is not yet optimal³⁴. As assays improve, we suggest more frequent use of cystatin C for these purposes.

Second, the patterns of associations of BTP and B2M with demographic and clinical factors suggest indications for future use as filtration markers. The concordant pattern between B2M and cystatin C gives rise to high correlations between them, even after adjustment for their correlation with mGFR, suggesting that B2M might have application as a replacement for cystatin C if cystatin C is not available. For example, in the absence of lymphoproliferative or plasma cell disorders, $eGFR_{B2M}$ could be considered as a confirmatory test for decreased $eGFR_{cr}$ or for use in other racial-ethnic groups, although this has not been studied. By contrast, the discordant pattern between BTP and creatinine gives rise to lower correlations between them after adjustment for their correlation with mGFR, suggesting that BTP may be a useful addition to a multiple marker GFR estimation equation with creatinine in CKD. Work by Inker and colleagues in the same three study cohorts showed that $eGFR_{BTP}$ and $eGFR_{B2M}$ were not as accurate as $eGFR_{cr}$ or $eGFR_{cys}$ and a multiple marker equation including all four markers was not more accurate than $eGFR_{cr-cys}$, however further evaluation is necessary in a more diverse dataset.⁶ At present, BTP is available only for research; although B2M is readily available in clinical laboratories, there is no standardized reference material. Standardization of laboratory measurement procedures will be required for comparisons among studies of these filtration markers.

Third, our results may help to interpret differences among filtration markers in their risk associations with adverse events observed in past studies. We suggest that confounding by conditions associated with non-GFR determinants likely accounts for the stronger associations with adverse events with LMW serum proteins than with creatinine observed in these studies.^{7–12} For example, lower $eGFR_{BTP}$, $eGFR_{B2M}$ and $eGFR_{cys}$ due to smoking or

higher urine protein would be associated with higher risk, whereas lower $eGFR_{cr}$ due to higher muscle mass would be associated with lower risk.

Strengths of the study include our large, diverse, and well-characterized study sample of persons with CKD and the uniform methods for mGFR and filtration marker assays, enabling comparison of the strength of associations across all four markers for a wide range of demographic and clinical characteristics. Our study also has limitations. There is potential for both residual confounding and confounding due to unmeasured or unknown factors in our effect estimates. Our findings may not be generalizable to populations without CKD or populations consisting of racial-ethnic groups other than US whites and blacks. Our study sample was also limited to participants with available data for all covariates of interest, which may introduce selection bias. We evaluated demographic and clinical characteristics collected as part of these cohort studies; in future prospective studies it would be of interest to collect data on additional potential surrogates for non-GFR determinants, such as dietary factors, medication use, thyroid function and proliferative hematological or cerebral disorders. There is potential for exposure misclassification within each cohort. Measurement error in mGFR was estimated in two (MDRD Study and AASK) of the three cohorts included in the pooled analysis, and we cannot rule out residual confounding due to incomplete adjustment for this measurement error. This residual confounding, in particular, could account for the weak associations observed among filtration markers, which is, in part, why we have focused on associations of greater magnitude in the current study. We observed some statistically significant interactions by study, indicating that there is some variation in the magnitude of associations across cohorts. This may be explained by differences in the study cohorts by design (for example, AASK includes only African American participants who are free of diabetes) or differences in clinical assessment. There are some differences in strength of associations with age, sex and race with BTP, B2M and cystatin C compared to the recently described CKD-EPI (CKD Epidemiology Collaboration) estimating equations using these markers ($eGFR_{BTP}$, $eGFR_{B2M}$, and $eGFR_{cys}$). These differences may reflect that the analyses for derivation of estimating equations were conducted using different statistical models that were not adjusted for other factors and that final decisions of whether to include age, sex and race in estimating equations were based on analysis of equation performance rather than statistical significance of the coefficients.

In conclusion, like creatinine, LMW serum protein filtration markers (BTP, B2M and cystatin C) are associated with factors other than GFR, reflecting conditions affecting their non-GFR determinants. Knowledge of these associations can facilitate the interpretation of $eGFR$ based on these markers. The differences in patterns of non-GFR determinants across filtration markers suggest that the inclusion of multiple markers into a panel can potentially improve the accuracy of GFR estimates. To increase understanding of the non-GFR determinants of LMW serum protein filtration markers across more generalized populations and to guide the use of the combinations of these markers in GFR estimates, additional research is required.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Factor of Interest	IQR	Geometric Mean Percent Difference in Filtration Marker (95% Confidence Interval)			
		β -Trace Protein	β_2 -Microglobulin	Cystatin C	Creatinine
Log mGFR (mL/min/1.73 m ²)§	0.6	-46 (-47, -44.9)	-45.8 (-46.7, -44.9)	-37.7 (-38.4, -37)	-39.2 (-40.1, -38.3)*
Age (y)	17.1	-5.6 (-7.1, -4.1)	-1.7 (-3, -0.5)*	-1.7 (-2.6, -0.8)*	-8.7 (-9.7, -7.6)
Male (vs female)	-	12.6 (10.1, 15.2)	3.3 (1.4, 5.3)*	6.6 (5.2, 7.9)	31.3 (29.4, 33.2)
Black (vs not black)	-	-10.3 (-13.2, -7.3)	-3.4 (-6.2, -0.6)	0.2 (-1.7, 2.2)	10.4 (7.4, 13.4)
Height (cm)	15.2	4.1 (2.4, 6)	1.8 (0.3, 3.3)	3.4 (2.4, 4.4)	17.9 (16.5, 19.3)
Weight (kg)	26.3	-3.3 (-4.8, -1.7)	3.6 (2.4, 4.8)	4.4 (3.5, 5.3)	7 (5.8, 8.1)*
Body surface area (m ²)	0.34	-1.7 (-3.3, -0.2)	3.4 (2.2, 4.7)	4.7 (3.8, 5.6)	10.7 (9.6, 11.9)*
Body mass index (kg/m ²)	8.1	-5.2 (-6.6, -3.7)	3.2 (2, 4.4)	3.1 (2.3, 4)	-0.7 (-1.7, 0.4)
Diabetes (yes vs no)	-	2.4 (-0.7, 5.7)	4.7 (2.2, 7.3)	3.3 (1.5, 5.2)	-3.8 (-6, -1.4)
Smoking (current vs not current)	-	2 (-1.2, 5.3)	6.7 (4, 9.4)	7 (5.2, 8.8)	1 (-1.2, 3.2)
Cardiovascular disease (yes vs no)	-	1.4 (-1.3, 4)	2.2 (0.1, 4.2)	3.7 (2.2, 5.1)	0.1 (-1.8, 1.9)
Systolic BP (mm Hg)	30	2.9 (1.3, 4.5)	1 (-0.2, 2.3)	0.7 (-0.2, 1.6)	-0.9 (-2.1, 0.2)
Diastolic BP (mm Hg)	23.7	3.2 (1, 5.3)	0.5 (-1.1, 2.2)	1.1 (-0.1, 2.2)	6.8 (5.2, 8.4)
Serum glucose (mg/dL)	22	0.4 (-0.3, 1.1)	0.6 (0.1, 1.2)	0.5 (0.1, 0.9)	-0.2 (-0.7, 0.4)
Hemoglobin (g/dL)	2.3	0.5 (-1.2, 2.2)	-1.2 (-2.6, 0.2)	2.5 (1.6, 3.5)*	7.7 (6.4, 9)
Serum albumin (g/dL)	0.6	-6.5 (-8.1, -4.8)	-5.4 (-6.8, -4)	-1.2 (-2.3, -0.1)	3.2 (1.8, 4.7)
Serum total cholesterol (mg/dL)	65	-3.8 (-5.4, -2.2)	-3.9 (-5.2, -2.7)	-1.2 (-2, -0.3)	-2.9 (-4.1, -1.8)
Serum HDL cholesterol (mg/dL)	18	-1.4 (-2.7, -0.1)	-3.5 (-4.6, -2.4)*	-3.4 (-4.1, -2.7)	-5.8 (-6.7, -4.9)
log C-reactive protein (mg/L)	1.7	-2.9 (-4.4, -1.4)	4.2 (2.7, 5.7)*	3.4 (2.4, 4.3)	-3.6 (-4.7, -2.4)
Serum sodium (mEq/L)	4	-1.9 (-3.4, -0.4)	-1.5 (-2.7, -0.2)	0.5 (-0.3, 1.4)	1.5 (0.4, 2.7)
Urine creatinine (mg/kg/d)	7.3	5.2 (3.5, 6.9)	-1.6 (-2.8, -0.4)	0.4 (-0.5, 1.3)	13.9 (12.6, 15.3)
Urine urea nitrogen (mg/kg/d)	52.8	2.9 (1.4, 4.4)	-1.5 (-2.6, -0.4)	0.1 (-0.7, 0.9)	3.1 (2, 4.3)*
Log urine protein (mg/d)	2.8	17.9 (15.5, 20.4)	9.6 (7.7, 11.5)	6.2 (4.9, 7.5)	10.7 (8.9, 12.5)

Figure 1.

Percent difference in level of filtration markers, adjusted for mGFR, mGFR measurement error and study (N=3156) Conversion factor for units: serum creatinine in mg/dL to μ mol/L, $\times 88.4$; serum glucose in mg/dL to mmol/L, $\times 0.05551$; cholesterol in mg/dL to mmol/L, $\times 0.02586$. Percent difference in level of filtration markers for one interquartile range [IQR] higher level in continuous variables, defined as the difference between the 25th and 75th percentiles; mGFR, measured glomerular filtration rate; HDL, high density lipoprotein. Strength of association is indicated by color: Red, strong (absolute change >10%); orange, intermediate (absolute change between 5–10% inclusive); and yellow, weak (absolute change <5%). Models incorporated one candidate factor at a time as the predictor of interest for each separate filtration marker outcome. § Adjusted for mGFR measurement error and study. *In separate models with an interaction term included for the factor of interest and study cohort, the p-value for interaction term is <0.002 (Bonferroni correction applied to P-value threshold [0.05/23=0.0022] to account for multiple testing).

Factor of Interest	IQR	Geometric Mean Percent Difference in Filtration Marker (95% Confidence Interval)			
		β -Trace Protein	β_2 -Microglobulin	Cystatin C	Creatinine
Log mGFR (mL/min/1.73 m ²)§	0.6	-46.4 (-47.4, -45.4)	-45.9 (-46.8, -45)	-38 (-38.7, -37.3)	-40.4 (-41.1, -39.6)
Age (y)*	17.1	-5.6 (-7.1, -4.1)	-1.7 (-3, -0.5)	-1.7 (-2.6, -0.8)	-8.6 (-9.5, -7.7)
Male (vs female)*	-	12.3 (9.9, 14.8)	3.2 (1.3, 5.2)	6.6 (5.2, 7.9)	31.6 (29.8, 33.4)
Black (vs not black)*	-	-9.8 (-12.6, -6.8)	-3.3 (-6, -0.4)	0.5 (-1.4, 2.5)	11.9 (9.3, 14.5)
Height (cm)	15.2	-4.1 (-6.3, -1.9)	0.1 (-1.8, 2)	-0.1 (-1.4, 1.1)	2.6 (1.2, 4.1)
Weight (kg)	26.3	-5.5 (-7.1, -4)	3.4 (2.1, 4.8)	3.4 (2.5, 4.4)	0.6 (-0.3, 1.6)
Body surface area (m ²)	0.34	-6.1 (-7.8, -4.5)	3.3 (1.9, 4.7)	3.3 (2.3, 4.3)	1 (0, 2.1)
Body mass index (kg/m ²)	8.1	-4.2 (-5.6, -2.7)	3.6 (2.4, 4.9)	3.5 (2.6, 4.3)	0 (-0.9, 0.9)
Diabetes (yes vs no)	-	4.4 (1.2, 7.6)	5.5 (2.9, 8.1)	3.6 (1.8, 5.5)	-3 (-4.8, -1.1)
Smoking (current vs not current)	-	1.5 (-1.6, 4.7)	6.6 (4, 9.3)	6.6 (4.8, 8.4)	-1.4 (-3.2, 0.4)
Cardiovascular disease (yes vs no)	-	1.4 (-1.2, 4)	2.3 (0.2, 4.4)	3.4 (1.9, 4.8)	-1.4 (-2.9, 0.1)
Systolic BP (mm Hg)	30	4 (2.5, 5.6)	1.4 (0.1, 2.6)	0.8 (-0.1, 1.7)	-0.7 (-1.6, 0.3)
Diastolic BP (mm Hg)	23.7	0.8 (-1.3, 3)	-0.2 (-1.8, 1.5)	-0.2 (-1.4, 1.1)	0.4 (-0.8, 1.7)
Serum glucose (mg/dL)	22	0.6 (-0.1, 1.2)	0.7 (0.1, 1.2)	0.5 (0.1, 0.9)	-0.1 (-0.6, 0.3)
Hemoglobin (g/dL)	2.3	-3.6 (-5.3, -1.9)	-2.6 (-4, -1.1)	1 (0, 2.1)	1 (0, 2.1)
Serum albumin (g/dL)	0.6	-6.8 (-8.3, -5.3)	-5.6 (-6.9, -4.1)	-1.4 (-2.4, -0.3)	2.8 (1.7, 3.9)
Serum total cholesterol (mg/dL)	65	-2.3 (-3.9, -0.7)	-3.6 (-4.9, -2.3)	-0.4 (-1.3, 0.4)	-0.1 (-1.1, 0.9)
Serum HDL cholesterol (mg/dL)	18	1.6 (0.2, 3)	-3.2 (-4.3, -2)	-2.4 (-3.2, -1.6)	-0.5 (-1.3, 0.4)
log C-reactive protein (mg/L)	1.7	-1.1 (-2.6, 0.4)	4.9 (3.4, 6.5)	4.2 (3.2, 5.1)	-1.2 (-2.2, -0.3)
Serum sodium (mEq/L)	4	-1.6 (-3, -0.1)	-1.4 (-2.6, -0.1)	0.3 (-0.5, 1.2)	0.6 (-0.3, 1.5)
Urine creatinine (mg/kg/d)	7.3	1.7 (0, 3.5)	-3 (-4.3, -1.8)	-1.7 (-2.6, -0.7)	6.1 (5, 7.1)
Urine urea nitrogen (mg/kg/d)	52.8	1.4 (-0.1, 2.8)	-2.1 (-3.2, -0.9)	-0.3 (-1.1, 0.5)	2.2 (1.3, 3.1)
Log urine protein (mg/d)	2.8	15.5 (13, 18.1)	9.6 (7.5, 11.6)	5 (3.6, 6.3)	2.5 (0.9, 4)

Figure 2.

Percent difference in level of filtration markers, adjusted for mGFR, mGFR measurement error, study, age, sex, and race (N=3156) Conversion factor for units: serum creatinine in mg/dL to μ mol/L, $\times 88.4$; serum glucose in mg/dL to mmol/L, $\times 0.05551$; cholesterol in mg/dL to mmol/L, $\times 0.02586$. Percent difference in level of filtration markers for an interquartile range [IQR] increase in continuous variables, defined as the difference between the 25th and 75th percentiles; mGFR, measured glomerular filtration rate; HDL, high density lipoprotein. Strengths of association is indicated by color: Red, strong (absolute change >10%); orange, intermediate (absolute change between 5–10% inclusive); and yellow, weak (absolute change <5%). Models incorporated one candidate factor at a time as the predictor of interest for each separate filtration marker outcome. § Adjusted for mGFR measurement error, study, age, sex, and race. * Age parameter estimates adjusted for mGFR, mGFR measurement error, study, sex, and race; sex parameter estimates adjusted for mGFR, mGFR measurement error, study, age, and race; race parameter estimates adjusted for mGFR, mGFR measurement error, study, age, and sex.

Factor of Interest	IQR	Geometric Mean Percent Difference in Filtration Marker (95% Confidence Interval)			
		β -Trace Protein	β_2 -Microglobulin	Cystatin C	Creatinine
Log mGFR (mL/min/1.73 m ²)	0.6	-42.6 (-43.8, -41.3)	-43.4(-44.5,-42.2)	-36.8 (-37.6, -35.9)	-40.8 (-41.7, -39.9)
Age (y)	17.1	-3.2 (-4.7, -1.6)	-0.5 (-1.8, 0.9)	-1 (-2, -0.1)	-6.6 (-7.5, -5.6)
Male (vs female)	-	12.6 (9.3, 16)	2.7 (0.1, 5.2)	6.3 (4.6, 8.1)	23.1 (20.8, 25.5)
Black (vs not black)	-	-9.2 (-11.9, -6.4)	-5.8 (-8.6, -3)	-1.3 (-3.1, 0.6)	10.3 (7.6, 13)
Height (cm)	15.2	0.6 (-1.8, 3)	-0.1 (-2.1, 2)	-1.3 (-2.6, 0)	1.3 (-0.3, 2.8)
Weight (kg)	26.3	-7.4 (-9.1, -5.7)	1.2 (-0.3, 2.7)	2.9 (1.9, 4)	2.3 (1.1, 3.4)
Diabetes (yes vs no)	-	2.2 (-0.8, 5.3)	2.1 (-0.3, 4.7)	1.7 (0, 3.5)	-1.9 (-3.8, 0)
Smoking (current vs not current)	-	-0.5 (-3.4, 2.5)	6.2 (3.6, 8.8)	7.1 (5.3, 8.9)	-0.6 (-2.4, 1.2)
Serum albumin (g/dL)	0.6	-4.0 (-5.6, -2.4)	-2.5 (-4, -0.9)	1 (-0.1, 2.1)	3.3 (2.2, 4.5)
Log C-Reactive Protein (mg/L)	1.7	0.3 (-1.1, 1.8)	3.4 (1.8, 5.1)	2.8 (1.9, 3.9)	-1 (-2, 0)
Urine creatinine (mg/kg/d)	7.3	0.6 (-1.4, 2.6)	-1.2 (-2.7, 0.4)	-1 (-2.2, 0.1)	6.8 (5.4, 8.1)
Urine urea nitrogen (mg/kg/d)	52.8	-0.9 (-2.5, 0.8)	-1 (-2.3, 0.3)	0.9 (-0.1, 1.9)	-1.1 (-2.1, 0)
Log urine protein (mg/d)	2.8	14.4 (11.7, 17.1)	7.6 (5.5, 9.8)	4.4 (3, 5.8)	4.1 (2.4, 5.8)

Figure 3.

Percent difference in level of filtration markers, adjusted for mGFR, mGFR measurement error, study, and full multivariable* adjustment (N=3156) Conversion factor for units: serum creatinine in mg/dL to μ mol/L, $\times 88.4$; serum glucose in mg/dL to mmol/L, $\times 0.05551$; cholesterol in mg/dL to mmol/L, $\times 0.02586$. Percent difference in level of filtration markers for an interquartile range [IQR] increase in continuous variables, defined as the difference between the 25th and 75th percentiles; GFR, measured glomerular filtration rate. Strength of association is indicated by color: Red, strong (absolute change >10%); orange, intermediate (absolute change between 5–10% inclusive); and yellow, weak (absolute change <5%). *All predictors listed in the first column are included as part of the multivariable adjusted model.

Table 1

Subject Characteristics in Pooled Dataset.

Characteristic	Value
No. of participants	3156
mGFR (mL/min/1.73 m ²) *	47 ±21
Age (y)	54.2 ±11.6
Male sex	60.1
Black race	54.6
Height (cm)	170 ±10
Weight (kg)	87.6 ±20.1
Body surface area (m ²)	2 ±0.25
Body mass index (kg/m ²)	30.2 ±6.4
Diabetes	22.5
Current Smoker	17.2
History of cardiovascular disease	31.7
Systolic blood pressure (mmHg)	137.5 ±24
Diastolic blood pressure (mmHg)	83 ±16
Serum glucose (mg/dL)	101.7 ±36.4
Hemoglobin (g/dL)	12.9 ±1.8
Serum albumin (g/dL)	4.1 ±0.4
Serum total cholesterol (mg/dL)	201.5 ±48.3
Serum HDL cholesterol (mg/dL)	45.9 ±15.8
Serum CRP (mg/L)	0.3 [0.1–0.7]
Serum sodium (mEq/l)	138.9 ±3
Urine creatinine (mg/kg/day)	17.2 ±5.6
Urine urea nitrogen (g/kg/day)	104.1 ±43.1
Urine protein (mg/day)	160 [55–901]
Serum BTP (mg/L)	1.3 ±0.7
Serum B2M (mg/L)	4.3 ±2.4
Serum cystatin C (mg/L)	1.7 ±0.6
Serum creatinine (mg/dL)	1.9 ±0.9

Note: Unless otherwise noted, values for categorical variables are given as percentage; values for continuous variables, as mean ± standard deviation or median [interquartile range].

Conversion factor for units: serum creatinine in mg/dL to $\mu\text{mol/L}$, $\times 88.4$; serum glucose in mg/dL to mmol/L, $\times 0.05551$; cholesterol in mg/dL to mmol/L, $\times 0.02586$.

B2M, β_2 -microglobulin; BTP, β -trace protein; CRP, C-reactive protein; HDL, high-density lipoprotein; mGFR, measured glomerular filtration rate

* Median [IQR] for mGFR: 45 [31–60] mL/min/1.73 m²