Relationship of eGFR and Albuminuria to Concurrent Laboratory Abnormalities: An Individual Participant Data Meta-Analysis in a Global Consortium

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ABSTRACT

Rationale & Objective: Chronic kidney disease (CKD) is complicated by abnormalities that reflect disruption in filtration, tubular, and endocrine functions of the kidney. Our aim was to explore the relationship of specific laboratory abnormalities and hypertension with the eGFR and albuminuria CKD staging framework.

Study Design: Cross-sectional individual participant-level analyses in a global consortium

Setting & Study Populations: 17 CKD and 38 general population and high-risk cohorts

Selection Criteria for Studies: Cohorts in the CKD Prognosis Consortium with data on eGFR and albuminuria as well as a measure of hemoglobin, bicarbonate, phosphorous, parathyroid hormone, potassium, or calcium, or hypertension.

Data Extraction: Data were obtained and analyzed between July 2015 and January 2018.

Analytic Approach: We modeled the association of eGFR and albuminuria with hemoglobin, bicarbonate, phosphorous, parathyroid hormone, potassium, and calcium using linear regression; and with hypertension and categorical definitions of each abnormality using logistic regression. Results were pooled using random-effects meta-analyses.

Results: The CKD cohorts (n=254,666 participants) were 27% female and 10% black, with mean age 69 years (SD 12). The general population/high-risk cohorts (n=1,758,334) were 50% female and 2% black, with mean age 50 years (SD 16). There was a strong, graded association between lower eGFR and all laboratory abnormalities (odds ratios ranging from 3.27 (95% CI: 2.68-3.97) to 8.91 (95% CI: 7.22-10.99) comparing eGFR 15-29 to eGFR 45-59 ml/min/1.73m^2); whereas albuminuria had equivocal or weak associations with abnormalities (odds ratios ranging from 0.77; 95% CI: 0.60-0.99) to 1.92 (95% CI:1.65-2.24) comparing urine albumin to creatinine ratio (ACR) >300 vs ACR <30 mg/g).

Limitations: Variation in study era, health care delivery system, typical diet, and laboratory assays.

Conclusions: Lower eGFR was strongly associated with higher odds of multiple laboratory abnormalities. Knowledge of risk associations might help guide management in the heterogeneous group of patients with CKD.

Key words: chronic kidney disease, glomerular filtration rate, albuminuria, staging system, laboratory tests

Nontechnical summary

The kidney performs many functions in addition to filtering blood and excreting waste. People with poorly functioning kidneys can develop high blood pressure, anemia, and altered bone and mineral metabolism, which often require treatment. In this study of more than 50 cohorts and approximately 2 million people, we assess the risk of these conditions by level of kidney function (measured by the glomerular filtration rate) and kidney damage (measured by the

amount of albumin in a person’s urine). We found that, in general, people with lower levels of kidney function, but not higher levels of kidney damage, had higher blood pressure, anemia, and altered bone and mineral metabolism. This information will help doctors make individualized action plans for their patients.

INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem with high risk of kidney failure, cardiovascular disease and death. CKD is defined by both decreased glomerular filtration rate (GFR) and presence of kidney damage, most commonly detected by albuminuria, and staged by cause, level of GFR and albuminuria. Across countries, the prevalence of CKD is estimated to be approximately 10-15% among adults, and multiple studies have demonstrated the relationship of both GFR and albuminuria to an increased risk for mortality, cardiovascular disease and kidney failure.[1-5]

In addition to the long-term risk of adverse events, CKD is complicated by the presence of abnormalities that reflect disruption in the excretory, metabolic and endocrine functions of the kidney. These abnormalities include anemia, hyperkalemia, acidosis, hyperparathyroidism, hyperphosphatemia, and hypocalcemia as well as hypertension, and often drive further investigations or treatment decisions. In patients with kidney failure, these are often referred to as uremic manifestations, or complications, of kidney disease and are quite common. Interestingly, these abnormalities do not occur in all patients with earlier stages of CKD. Prior studies in general population and CKD cohorts have documented the risk of abnormalities with the level of estimated GFR (eGFR) or albuminuria,[6-9] but few have looked comprehensively and concomitantly across the new CKD staging system, which classifies the severity of CKD by eGFR (G) and albuminuria (A) stage.[10, 11] In addition, the consistency of risk associations across diverse global cohorts along a wide range of eGFR, albuminuria, age, and diabetes has not been determined.

We utilized the large number of participants in the global Chronic Kidney Disease Prognosis Consortium (CKD-PC), covering general, high cardiovascular risk, and CKD cohorts, to explore the prevalence and risk of specific laboratory abnormalities and hypertension across the 2-dimensional eGFR and albuminuria staging framework. We evaluated whether risk associations were consistent across participant characteristics, such as age, sex, race, and diabetes status, as well as individual cohorts. An appreciation of the expected levels of these laboratory values within eGFR and albuminuria stages gives important clinical information to clinicians, and may provide better guidance to assist in the delivery of individualized and precise care to patients.

Methods

Study design and data sources

In this collaborative, individual-level meta-analysis, we used data from CKD-PC member cohorts, details of which have been previously described.[12] Cohorts with at least 1,000 adult participants (500 in CKD cohorts) and eGFR, albuminuria, and long-term follow-up for mortality or kidney outcomes were invited to participate. For the present study, cohorts were additionally required to have a concurrent measurement of at least one of the following: hemoglobin or hematocrit, serum potassium, serum bicarbonate, serum intact parathyroid hormone, serum phosphorus, serum calcium, or hypertension status information. The CKD and the general population or high cardiovascular risk cohorts (herein referred to as general population/high-risk) were analyzed separately. Three large administrative cohorts (Geisinger, Mt. Sinai BioMe, SCREAM) contributed their entire populations to the general population/high risk analysis and their sub-population with eGFR <60 ml/min/1.73m^2 to the CKD analysis. This study was approved for use of de-identified data by the Institutional Review Board at the Johns Hopkins University Bloomberg School of Public Health (IRB Number: 3324) and the need for informed consent was waived.

Kidney Measures

As previously described, serum creatinine measurements provided by the cohorts were standardized to isotope dilution mass spectrometry traceable values.[13] eGFR was estimated using the Chronic Kidney Disease Epidemiology (CKD-EPI) creatinine equation.[14] Measures of albuminuria included the urine albumin-to-creatinine ratio (ACR), urine albumin excretion rate, urine protein-to-creatinine ratio, or semi-quantitative dipstick protein. These measures were converted to albuminuria stages A1-A3, defined as ACR <30 mg/g, 30-299 mg/g, and ≥300 mg/g, as previously described.[15, 16] In categorical analyses, for comparison purposes, we used a reference of eGFR 50 ml/min/1.73m^2 and albuminuria stage A1 for both general population/high risk and CKD cohorts.

Other Covariates

Age, sex, and race were provided by the individual cohorts. Age was categorized as ≥55 and <55 years so as to approximately classify menopausal status in women. Diabetes was defined as fasting glucose ≥7.0 mmol/L (126 mg/dL), non-fasting glucose ≥11.1 mmol/L (200 mg/dL), hemoglobin A1c ≥6.5%, use of glucose lowering drugs, or self-reported diabetes (**Appendix 1**). A history of CVD included myocardial infarction, coronary revascularization, heart failure, and stroke. Smoking was classified as a binary variable (ever vs. never).

Outcomes

Outcomes included values of hemoglobin, potassium, serum bicarbonate, serum intact parathyroid hormone (PTH), serum phosphorus, and serum calcium, all of which were also categorized as binary variables to define anemia, hyperkalemia, acidosis, hyperparathyroidism, hyperphosphatemia, and hypocalcemia. Anemia was defined as hemoglobin <13 g/L for men and <12 g/L for women (for cohorts with only hematocrit available, <39% for men and <36% for women, per WHO guidelines).[17] Hyperkalemia was defined as potassium >5 mmol/L. Acidosis was defined as a serum bicarbonate level <22 mmol/L. Hyperparathyroidism was defined as serum intact PTH level >65 pg/mL. Hyperphosphatemia was defined as a serum phosphorus >4.5 mg/L. Hypocalcemia was defined as an albumin-corrected serum calcium level <8.5 mg/dL. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, use of antihypertensive medications, or a medical diagnosis of hypertension.

Statistical Analysis

Data were analyzed using a two-stage meta-analysis approach within general/high-risk population and CKD cohorts separately. First, each cohort was analyzed individually. Next, associations were combined using a random effects meta-analysis. Heterogeneity was quantified with the I^2 statistic and Cochran's Q test.

To assess the association between eGFR and continuous laboratory values, linear regression was performed, regressing the laboratory value on the eGFR splines, categorical albuminuria stage, the interaction of the two parameters, and adjusting for demographics, diabetes mellitus status, history of CVD, smoking status, BMI, and systolic blood pressure, centered at the reference point. To assess the association between eGFR and categorical laboratory abnormality, a similar procedure was followed using logistic regression. For analyses of hypertension, the approach was identical except analyses were not adjusted for systolic blood pressure. Random effects meta-analysis was performed on the difference from the reference value to report summary results across the cohorts. Interactions between eGFR and albuminuria stage were quantified using the meta-analyzed interaction term for each eGFR spline piece. Interactions that met a Bonferroni threshold for statistical significance ($p<0.05/14$ for general population/high risk cohorts, reflecting comparisons of A3 vs. A1 and A2 vs. A1 for 7 spline pieces and $p<0.05/6$ for CKD cohorts, reflecting comparisons of A3 vs. A1 and A2 vs. A1 for three spline pieces) were reported in the text. For the purposes of reporting the association between albuminuria and each laboratory abnormality, effect sizes were given at the reference point (80 and 50 ml/min/1.73m^2 for general population/high-risk and CKD cohorts, respectively) since most interactions with eGFR were small and not statistically significant.

The adjusted prevalence of each abnormality at each eGFR and albuminuria stage was computed for general population/high-risk and CKD cohorts separately. We first converted the random-effects weighted, adjusted mean odds at the reference point (eGFR 50 ml/min/1.73 m^2) into a prevalence estimate. We then applied the meta-analyzed odds ratios to obtain prevalence estimates at eGFR 95, 80, 65, 35, and 20 ml/min/1.73 m^2 (in CKD cohorts, 65, 35, and 20 ml/min/1.73m^2) for each stage of albuminuria with and without diabetes, adjusted to 60 years old, half male, non-black, 20% history of CVD, 40% ever smoker, and body-mass index 30 kg/m^2. To demonstrate the variation in prevalence estimates across the cohorts, we show the 25th and 75th percentiles for prevalence estimates.

We performed the following sensitivity analyses. For analysis of hemoglobin and anemia, among CKD cohorts with data on medication use, we excluded users of erythropoietin stimulating agents and iron supplements. Similarly, for analyses of potassium and hyperkalemia, we excluded users of angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, renin inhibitors, potassium-sparing diuretics, loop diuretics, thiazide diuretics, other diuretics, kayexalate, and other anti-hypertensive medications. Next, continuous associations were repeated for pre-defined populations of interest by including the relevant interaction terms with eGFR or albuminuria: age (<55 years or ≥55 years), sex, age and sex (women <55 years or ≥55 years; men <55 years or ≥55 years), race (black or non-black), and diabetes status (presence or absence).

All analyses were performed using Stata/MP 14 software (www.stata.com).

Results

Baseline characteristics of participants

There were 254,666 participants in the 17 CKD cohorts (including the CKD sub-population from three administrative high risk cohorts) and 1,758,334 participants in 38 general population/high-risk cohorts (**Table 1**). **Tables S1-S6** show the proportion with each abnormality and mean value for each laboratory test within individual cohorts. The CKD cohorts were 27% female and 10% black, with mean age 69 years (SD 12), mean eGFR 50 ml/min/1.73 m^2 (SD 17), and 109,143 (44%) had urine albumin-to-creatinine ratio (ACR) >30 mg/g and 156,421 (62%) had diabetes. The general population/high risk cohorts were 50% female and 2% black, with mean age 50 years (SD 16) and mean eGFR 88 ml/min/1.73m^2 (SD 20), 174,914 (10%) had urine ACR >30 mg/g and 286,561 (16%) had diabetes.

Associations between eGFR, albuminuria and laboratory tests

Lower eGFR was associated with lower levels of hemoglobin and bicarbonate, and higher levels of potassium, PTH, and phosphorus in the CKD cohorts, with similar associations in the general population/high risk cohorts (**Figures 1 and 2**). For phosphorus, PTH, and calcium there appeared to be a sharper increase in risk below eGFR 30 ml/min per 1.73m^2. For the general population/high risk cohorts, where the associations were evaluated across the range of eGFR, most of the associations became significant at <60 ml/min per 1.73m^2 (95% confidence intervals do not overlap the x-axis), with the exception of PTH where the threshold was 71 ml/min per 1.73m^2 and of potassium where the association was continuous across the range. For all abnormalities, there was quantitative but not qualitative differences across the individual cohorts (**Figures S1-S6**).

Overall, the association of albuminuria stages with laboratory abnormalities was absent or minimal in both CKD and general population/high risk cohorts (**Figures 1 and 2**). In the CKD cohorts, higher albuminuria was associated with slightly lower values of hemoglobin (-0.24 g/dL, 95% CI: -0.37 to -0.10, for A3 vs. A1) and bicarbonate (-0.46 mmol/L, 95% CI: -0.74 to -0.17, for A3 vs. A1) and slightly higher values of potassium (0.04 mmol/L, 95% CI: 0.01 to 0.07, A3 vs. A1) and phosphorus (0.10 mg/dL, 95% CI: 0.06 to 0.14). For PTH, the magnitude of the association with albuminuria differed substantially at eGFR <30 ml/min/1.73m^2, with larger effect sizes in this range in the CKD cohorts. For calcium, higher levels of albuminuria were associated with higher levels of (albumin-corrected) calcium at higher but not lower levels of eGFR.

In sensitivity analyses in CKD cohorts with available medications, the results for hemoglobin were consistent when participants using iron supplementation and erythropoietin stimulating agents were excluded (**Figure S7**). After excluding medications known to affect potassium, the small difference by level of albuminuria was no longer statistically significant (A3 vs. A1, 0.02 mmol/L, 95% CI: -0.02 to 0.07) (**Figure S8**).

After adjusting for albuminuria, people with diabetes had similar relationships between laboratory abnormalities and eGFR (**Figures S9-S10**), although for the same level of eGFR, participants with diabetes consistently had lower levels of hemoglobin and bicarbonate, and higher levels of potassium and phosphorus. For example, in CKD cohorts, the difference in hemoglobin level by diabetes status was -0.43 g/dL (95% CI: -0.57 to -0.28), which was slightly smaller than the difference in hemoglobin level between eGFR 30 and 50 ml/min/1.73m^2 (-0.81 g/dL, 95% CI: -.91 to -0.72). There were also consistent relationships between eGFR and laboratory abnormalities in participants <55 years old and ≥55 years old (**Figures S11-S12**). Similar relationships were seen by sex (**Figures S13-S14**) and when grouped by age as a proxy for menopausal status (women <55 years old and ≥55 years old; **Figures S15-S16**). However, for the same level of eGFR and other covariates, women had lower levels of hemoglobin and potassium and higher levels of bicarbonate, phosphate and calcium compared to men. Although there were few cohorts with both black and non-black participants, associations between eGFR and laboratory abnormalities were also consistent by race (**Figures S17-S18**).

Associations of eGFR and albuminuria with categorical laboratory abnormalities

Overall, there was an increase in the risk for each laboratory abnormality by category of lower eGFR (**Figure S19**). For example, odds ratios (95% confidence interval) ranged from 3.27 (2.68-3.97) to 8.91 (7.22-10.99) across abnormalities, comparing eGFR 15-29 to eGFR 45-59 ml/min per 1.73m^2. There was a lesser gradient observed for higher albuminuria [odds ratios ranging from 0.91 (0.73-1.13) to 1.80 (1.26-2.58) across abnormalities, comparing A3 to A1]. In both general population/high-risk and CKD cohorts, anemia and hyperparathyroidism were the most common laboratory abnormalities for a given eGFR and albuminuria stage, and hypocalcemia was the least common (**Figure 3 and S20**). In the CKD cohorts, the estimated prevalence of anemia, hyperkalemia, and hyperphosphatemia was higher in persons with diabetes vs. those without diabetes, but lesser or no differences were observed for the other abnormalities. In the general population/high-risk cohorts, differences by diabetes status were generally smaller.

Associations of eGFR and albuminuria with hypertension

For the CKD cohorts, there was no association between eGFR and hypertension, but albuminuria was an independent risk factor (adjusted odds ratio for stage A3 vs. A1, 1.42, 95% CI: 1.12-1.80). At higher levels of eGFR observed in the general population/high risk cohorts, the association between eGFR and hypertension was slightly stronger, as was the association with albuminuria (adjusted odds ratio for stage A3 vs. A1, 2.77, 95% CI: 2.26-3.39) (**Figure 4**). There were quantitative but not qualitative differences across the individual cohorts (**Figure S21**). Results were also similar by predefined populations of interest (**Figures S22-S23**).

Discussion

In this large, individual-level meta-analysis of participants from more than 50 cohorts including more than two million participants, we describe the association of laboratory abnormalities and hypertension with level of eGFR and albuminuria across CKD and general population/high-risk cohorts, geographic regions, and individual characteristics including diabetes, age, sex, race, and a proxy for menopausal status. We found a consistent and graded association of hemoglobin, potassium, bicarbonate, PTH, phosphorous as well as calcium in the lower range of eGFR, which was only modestly affected by level of albuminuria, with the exception of PTH in CKD cohorts. For a given level of eGFR and albuminuria, we observed that the most common laboratory abnormalities were anemia and hyperparathyroidism, particularly among the CKD cohorts. The relationship between eGFR and hypertension was present only in the general population/high risk cohorts, perhaps reflecting the fact that the majority of patients with CKD have a diagnosis of hypertension.

Multiple studies have documented the association of risk of laboratory abnormalities with eGFR,[1, 6-9] but few studies examined associations with albuminuria. In the Modification of Diet in Renal Disease (MDRD) Study, lower levels of eGFR, but not higher levels of urine protein, were strongly associated with anemia, hypoalbuminemia, acidosis, and hyperphosphatemia and hypertension.[11] Similarly, in the National Health and Nutrition Examination Survey (NHANES), a representative population cohort in the United States, lower eGFR was strongly associated with anemia, hypoalbuminemia, acidosis, hypertension, and hyperparathyroidism, but there was minimal association between higher levels of albuminuria and all of these abnormalities.[10] In our study, we expanded upon these studies by using both continuous values of the laboratory tests and categorical assessments of the abnormalities, and demonstration of the consistency of the risk associations across CKD and general population/high risk cohort, geographic regions, and participant characteristics including diabetes, age, sex, race, and a proxy for menopausal status. Although we found the relative risks to be fairly consistent within subgroups and across cohorts, the large number of cohorts allowed us to investigate heterogeneity in adjusted absolute risk. We report that the adjusted prevalence varies by type of cohort (CKD vs. general population/high-risk) as well as between individual cohorts, with as much as 5-fold variation between individual cohorts at the 25th and 75th percentile of adjusted risk.

There are potential public health, clinical, and research implications from this study. First, in the general population/high-risk cohorts, where the associations between laboratory abnormality and eGFR were observed throughout the eGFR range, many abnormalities appeared or worsened at a threshold near 60 ml/min/1.73m^2. In both the general population/high risk cohorts and the CKD cohorts, there was a graded association with abnormalities at lower levels of eGFR, and the results were consistent by key subgroups including diabetes status, sex, age, and race. These data provide further support for the current definition and staging system based on eGFR, with eGFR <60 ml/min/1.73m^2 as the threshold for disease classification and severity of CKD, regardless of subgroups.[1, 6] The absence of strong associations with albuminuria reinforce the KDIGO guideline recommendations for frequency of these laboratory tests based on eGFR stage, but not albuminuria stage.[18] Second, these data may assist clinicians to better characterize the severity of kidney disease and direct intensity of investigation and care, such as range and frequency of testing for abnormalities. For example, for some abnormalities, higher prevalence was observed in persons with diabetes. Third, these data may guide interpretation of the potential etiology of the observed abnormality. For example, even in those with eGFR 15-29 ml/min/1.73m^2, only approximately 25% and 40% of the general population/high risk and CKD populations had anemia. Thus, a finding of anemia in patients with severe reduction of eGFR should not preclude investigations for other causes; similarly, finding of anemia at higher levels of eGFR is less likely to be attributable to kidney disease alone. Finally, the data might improve identification of individuals for entry into studies examining progression of CKD, if the prevalence of laboratory abnormalities provides prognostic information in addition to eGFR and albuminuria values.[19]

Strengths of this study include the large number of cohorts and sample size that allow for description of the association of kidney measures, hypertension, and laboratory abnormalities across a variety of clinical settings. Risk associations were fairly consistent across individual cohorts, and between the general population/high risk and CKD cohorts. Where data were available, we described similar associations between users and non-users of medications that could affect laboratory abnormalities, such as erythropoietin stimulating agents for hemoglobin and medications that affect potassium. Limitations include variation between individual cohorts in study era, health care delivery systems, diet, and laboratory assays, which may explain some of the observed varation in prevalence estimates. Differences in study era and health systems might have led to different patterns of testing, whereas assay differences could affect categorical definitions of the laboratory abnormalities and their association with eGFR or albuminuria stage. In particular, assays for PTH, calcium, and albumin (required for adjustment of the calcium) are known to vary widely. Improvements in assay standardization and precision could reveal stronger associations. Regional variation in diet could have led to between-cohort differences in several of the abnormalities including anemia, hyperkalemia, and acidosis. Information on medications was limited and only included erythropoietin stimulating agents, iron supplementation, renin-angiotensin system inhibitors, and diuretics. Thus, our estimates reflect as-treated eGFR, albuminuria, and abnormalities. Covariates used in adjustment were occasionally missing, requiring imputation, which underestimates their variability. We were able to examine differences in associations by diabetes status, but not by cause of kidney disease. Various primary causes of kidney diseases might affect excretory, metabolic, and endocrine kidney functions differently. Prevalence estimates for each abnormality varied by individual cohort even after taking into account eGFR, albuminuria, and measured participant characteristics, likely reflecting differences in selection into individual cohorts or unmeasured determinants of that abnormality (e.g., variation in anemia might be explained by a higher prevalence of beta thalassemia in certain populations).

This study provides a comprehensive description of level of abnormalities by eGFR and albuminuria level. The results supports the current definition and staging system for all populations and set the stage for further refinements of individualized clinical action plans for patients with CKD. Future studies should address how these abnormalities vary by cause of disease, how they appear in combination with other abnormalities in individual patients, and importantly, how the risk for kidney failure, death, and other adverse events differs based on presence or absence of specific abnormalities and their combination. Finally, previous clinical trials aimed at treating these abnormalities have generally targeted specific solitary thresholds for abnormalities. A better understanding of expected values within specific eGFR categories may allow targeting of different thresholds depending on eGFR. Improved understanding of the complexity of kidney diseases by a more thorough characterization of the different laboratory abnormalities reflecting multiple functions of the kidney may help optimize investigation and care for the heterogeneous group of patients with CKD.

Supplementary Material

Appendix 1. Data analysis overview and analytic notes for some of individual studies

Appendix 2. Acronyms or abbreviations for studies included in the current report and their key references linked to the Web references

Appendix 3. Acknowledgements and funding for collaborating cohorts

Table S1. Proportion with anemia and mean value of hemoglobin and hematocrit, by cohort

Table S2. Proportion with hyperkalemia and hypokalemia and mean value of serum potassium, by cohort

Table S3. Proportion with acidosis and mean value of serum bicarbonate, by cohort

Table S4. Proportion with hyperparathyroidism and mean value of serum parathyroid hormone, by cohort

Table S5. Proportion with hyperphosphatemia and mean value of serum phosphorus, by cohort

Table S6. Proportion with hypocalcemia and hypercalcemia and mean value of albumin-corrected serum calcium, by cohort

Figure S1. Forest plot of mean difference of hemoglobin at (A) eGFR 30 vs. 50 ml/min/1.73 m^2 at stage A1 in CKD cohorts and (B) eGFR 50 vs. 80 ml/min/1.73 m^2 at stage A1 in general population and high risk cohorts

Figure S2. Forest plot of mean difference of serum potassium at (A) eGFR 30 vs. 50 ml/min/1.73 m^2 at stage A1 in CKD cohorts and (B) eGFR 50 vs. 80 ml/min/1.73 m^2 at stage A1 in general population and high risk cohorts

Figure S3. Forest plot of mean difference of serum bicarbonate at (A) eGFR 30 vs. 50 ml/min/1.73 m^2 at stage A1 in CKD cohorts and (B) eGFR 50 vs. 80 ml/min/1.73 m^2 at stage A1 in general population and high risk cohorts

Figure S4. Forest plot of mean difference of serum parathyroid hormone at (A) eGFR 30 vs. 50 ml/min/1.73 m^2 at stage A1 in CKD cohorts and (B) eGFR 50 vs. 80 ml/min/1.73 m^2 at stage A1 in general population and high risk cohorts

Figure S5. Forest plot of mean difference of serum phosphorus at (A) eGFR 30 vs. 50 ml/min/1.73 m^2 at stage A1 in CKD cohorts and (B) eGFR 50 vs. 80 ml/min/1.73 m^2 at stage A1 in general population and high risk cohorts

Figure S6. Forest plot of mean difference of corrected serum calcium at (A) eGFR 30 vs. 50 ml/min/1.73 m^2 at stage A1 in CKD cohorts and (B) eGFR 50 vs. 80 ml/min/1.73 m^2 at stage A1 in general population and high risk cohorts

Figure S7. Association between eGFR and hemoglobin by albuminuria stages in CKD cohorts excluding users of iron supplementation and erythropoietin stimulating agents.

Figure S8. Association between eGFR and serum potassium by albuminuria stages in CKD cohorts excluding users of medications that affect potassium.

Figure S9. Association between eGFR and continuous laboratory measures (A) hemoglobin, (B) potassium, (C) bicarbonate, (D) parathyroid hormone, (E) phosphorus, (F) calcium, by diabetes status in CKD cohorts.

Figure S10. Association between eGFR and continuous laboratory measures (A) hemoglobin, (B) potassium, (C) bicarbonate, (D) parathyroid hormone, (E) phosphorus, (F) calcium, by diabetes status in general population and high risk cohorts.

Figure S11. Association between eGFR and continuous laboratory measures (A) hemoglobin, (B) potassium, (C) bicarbonate, (D) parathyroid hormone, (E) phosphorus, (F) calcium, by age in CKD cohorts.

Figure S12. Association between eGFR and continuous laboratory measures (A) hemoglobin, (B) potassium, (C) bicarbonate, (D) parathyroid hormone, (E) phosphorus, (F) calcium, by age in general population and high risk cohorts.

Figure S13. Association between eGFR and continuous laboratory measures (A) hemoglobin, (B) potassium, (C) bicarbonate, (D) parathyroid hormone, (E) phosphorus, (F) calcium, by sex in CKD cohorts.

Figure S14. Association between eGFR and continuous laboratory measures (A) hemoglobin, (B) potassium, (C) bicarbonate, (D) parathyroid hormone, (E) phosphorus, (F) calcium, by sex in general population and high risk cohorts.

Figure S15. Association between eGFR and continuous laboratory measures (A) hemoglobin, (B) potassium, (C) bicarbonate, (D) parathyroid hormone, (E) phosphorus, (F) calcium, by age and sex in CKD cohorts.

Figure S16. Association between eGFR and continuous laboratory measures (A) hemoglobin, (B) potassium, (C) bicarbonate, (D) parathyroid hormone, (E) phosphorus, (F) calcium, by age and sex in general population and high risk cohorts

Figure S17. Association between eGFR and continuous laboratory measures (A) hemoglobin, (B) potassium, (C) bicarbonate, (D) parathyroid hormone, (E) phosphorus, (F) calcium, by race in CKD cohorts

Figure S18. Association between eGFR and continuous laboratory measures (A) hemoglobin, (B) potassium, (C) bicarbonate, (D) parathyroid hormone, (E) phosphorus, (F) calcium, by race in general population and high risk cohorts

Figure S19. Odds ratios of laboratory abnormalities in CKD (top panels) and general population and high risk cohorts (bottom panels)

Figure S20. Meta-analyzed adjusted prevalence (25th and 75th percentile cohort) of abnormalities (categorical laboratory measures) in general population and high risk cohorts by diabetes status

Figure S21. Forest plot of adjusted odds ratio of hypertension at (A) eGFR 30 vs. 50 ml/min/1.73 m2 at stage A1 in CKD cohorts and (B) eGFR 50 vs. 80 ml/min/1.73 m2 at stage A1 in general population and high risk cohorts

Figure S22. Association between eGFR and hypertension by (A) diabetes, (B) age, (C) sex, (D) age and sex, and (E) race in CKD cohorts Figure S23. Association between eGFR and hypertension by (A) diabetes, (B) age, (C) sex, (D) age and sex, and (E) race in general population and high risk cohorts

References

Authors' Contributions:

Study concept and design: LAI, MEG, ASL, JC, RTG, SIH, CPK, MW, AL; data acquisition: MEG, JC; data interpretation: all authors; funding acquisition for CKD-PC: JC. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Table 1. Demographic characteristics and number of participants with available data on each of the laboratory abnormalities.

Study	**Region**	**Clinical Characteristics**							**N with available laboratory data**						
		N	Age, mean (SD)	% Female	% Blacks	% DM	eGFR, mean (SD)	% albuminuria /proteinuria‡	Hgb	K	Bicarb	PTH	Phos	Ca	HTN
CKD Cohorts															
AASK	USA	1094	55 (11)	39%	100%	0%	46 (15)	55%		1066	984		1093	984	1094
BC CKD	Canada	11880	71 (13)	46%	0%	50%	33 (16)	72%	11655	11785	11162	10075	11237	10966	11880
CanPREDDICT	Canada	2061	68 (13)	38%	2%	50%	27 (9)	74%	2045	2052	1822	1900	1978	1956	2061
CARE FOR HOMe	Germany	369	66 (13)	43%	0%	89%	49 (17)	46%	371			371	371	370	369
CCF	USA	19249	72 (12)	55%	14%	34%	47 (14)	29%	12696	17498	16218	1758	3030	12923	19249
CKD-JAC	Japan	2679	61 (12)	38%	0%	32%	37 (17)	88%	2639	2640		2670	2379	2413	2679
CRIB	UK	375	62 (14)	35%	5%	17%	22 (11)	84%	364	373	324	316	360	374	375
GCKD	Germany	5159	61 (12)	40%	0%	36%	49 (18)	57%	5127			5030	5160	5159	5159
Geisinger CKD†	USA	24611	71 (12)	56%	1%	64%	46 (12)	43%	19008	24417	24358	7803	12879	1778	24611
Gonryo	Japan	3009	63 (15)	47%	0%	46%	71 (32)	52%	3044				2278	2042	3009
MASTERPLAN	Netherlands	670	60 (13)	31%	0%	24%	36 (15)	72%	670	670	668	638	670	669	670
MDRD	USA	1736	51 (13)	40%	12%	6%	41 (21)	74%	1719	830	1725		1735	1725	1736
MMKD	Multi§	202	47 (12)	34%	0%	0%	47 (30)	92%	202			201	202	202	202
Mt Sinai BioMe CKD†	USA	3521	63 (13)	56%	31%	58%	43 (13)	50%	1931	3518	3520	1538	1904	3112	3521
PSP-CKD	UK	9434	76 (11)	59%	2%	36%	50 (14)	27%	2223	9405	228		895	1462	9434
RCAV	USA	127812	69 (10)	3%	16%	82%	55 (15)	44%	108044	124843	119959		25507	98308	127812
RENAAL	Multi¶	1512	60 (7)	37%	15%	100%	39 (13)	100%	1510	1513			1510	1509	1512
SCREAM CKD†	Sweden	33232	65 (12)	55%	0%	26%	47 (12)	31%	30209	29383	7011	6850	9517	15330	33232
SRR-CKD	Sweden	3051	68 (15)	33%	0%	38%	25 (12)	79%	3032	2591	1613	2420	2975	2833	3051
Sunnybrook	Canada	3010	61 (18)	47%	0%	47%	56 (31)	59%	2822	2965	2748	1415	2389	2426	3010
Subtotal		**254666**	**69 (12)**	**27%**	**10%**	**62%**	**50 (17)**	**44%**	**209311**	**235549**	**192340**	**42985**	**88069**	**184328**	**254666**

General Population Cohorts															
Aichi	Japan	4987	49 (7)	20%	0%	9%	100 (13)	3%	4987						4987
ARIC*	USA	11889	64 (6)	56%	23%	18%	86 (17)	9%							11889
AusDiab*	Australia	11198	52 (14)	55%	0%	8%	86 (17)	7%							11198
Beijing	China	1533	60 (10)	50%	0%	29%	83 (14)	6%		1530					1533
BIS	Germany	2055	80 (7)	53%	0%	26%	65 (17)	26%	1995				2048	2052	2055
ChinaNS*	China	46810	47 (15)	57%	0%	8%	101 (18)	12%							46810
CHS*	USA	2984	78 (5)	59%	17%	18%	66 (16)	20%							2984
CIRCS	Japan	11916	54 (9)	61%	0%	3%	89 (15)	3%	11475	8034					11916
ESTHER*	Germany	9744	62 (7)	55%	0%	19%	87 (20)	12%							9744
Framingham*	USA	2956	59 (10)	53%	0%	8%	88 (19)	12%							2956
Gubbio	Italy	1684	54 (6)	55%	0%	5%	84 (12)	4%	1684	1684			1684		1684
IPHS	Japan	97769	59 (10)	66%	0%	3%	86 (14)	2%	97740						97769
JMS	Japan	5124	54 (11)	64%	0%	55%	98 (15)	2%	5091						5124
KHS	Korean	243779	44 (10)	33%	0%	5%	88 (14)	14%	243716	108185			152742	224193	243779
MESA*	USA	6796	62 (10)	53%	28%	13%	83 (16)	10%							6796
MRC	UK	12367	81 (5)	61%	0%	8%	57 (15)	7%	12101	11840			11334	12026	12367
NHANES	USA	56017	47 (19)	52%	22%	12%	97 (25)	12%	51434	57208	41359	9774	57208	41405	56017
NIPPON DATA80*	Japan	10382	50 (13)	56%	0%	3%	84 (17)	3%							10382
NIPPON DATA90	Japan	7612	53 (14)	58%	0%	5%	94 (17)	3%	7612						7612
NIPPON DATA2010	Japan	2749	59 (16)	57%	0%	13%	97 (17)	3%	2730						2749
Ohasama	Japan	3300	60 (11)	59%	0%	9%	97 (13)	6%	1926						3300
PREVEND	Netherlands	8060	50 (13)	50%	1%	4%	96 (16)	11%		7319		7314	7319	7313	8060
Rancho Bernardo	USA	1484	71 (12)	60%	0%	14%	66 (16)	15%		1484			1484	1484	1484
REGARDS	USA	27727	65 (9)	54%	40%	21%	85 (20)	15%	19070			2700	1960	1347	27727
RSIII	Netherlands	3519	57 (7)	57%	1%	13%	86 (14)	6%	3525				3375		3519
SEED*	Singapore	7028	58 (10)	49%	0%	29%	86 (19)	24%							7028

Taiwan MJ	Taiwan	501704	41 (14)	51%	0%	5%	89 (18)	2%	501646	159268			369932	369833	501704
Takahata	Japan	3524	63 (10)	55%	0%	8%	98 (13)	15%	3523	1923			1923	1923	3524
ULSAM	Sweden	1123	71 (1)	0%	0%	13%	76 (11)	16%				894	1104	1089	1123
Subtotal		**1107820**	**47 (15)**	**49%**	**3%**	**7%**	**89 (18)**	**7%**	**970255**	**358475**	**41359**	**20682**	**612113**	**662665**	**1107820**
High Risk Cohorts															
ADVANCE	Multi**	11033	66 (6)	43%	0%	100%	78 (17)	31%		11033					11033
Geisinger	USA	65051	61 (15)	52%	2%	62%	80 (27)	30%	46072	64503	64341			51372	65051
Maccabi	Israel	264255	57 (14)	49%	0%	34%	86 (21)	16%	253333	246712		19967	71310	153794	264255
Mt Sinai BioMe	USA	8109	56 (14)	57%	33%	51%	73 (28)	35%	4346	8044	8047			7240	8109
NZDCS*	New Zealand	31622	61 (14)	50%	0%	100%	76 (23)	9%							31622
Pima	USA	5074	33 (14)	56%	0%	27%	120 (19)	20%	5058						5074
SCREAM	Sweden	260047	48 (18)	54%	0%	12%	93 (24)	11%	232861	208611	12001			83703	260047
SMART	Netherlands	3691	58 (13)	29%	0%	25%	77 (21)	33%	3684						3691
ZODIAC	Netherlands	1632	67 (12)	56%	0%	100%	68 (17)	8%		1153		1203	1154	1153	1632
Subtotal		**650514**	**54 (17)**	**51%**	**1%**	**33%**	**88 (24)**	**15%**	**545354**	**540056**	**84389**	**21170**	**72464**	**297262**	**650514**
SUBTOTAL General Population/High Risk		**1758334**	**50 (16)**	**50%**	**2%**	**16%**	**88 (20)**	**10%**	**1515609**	**898531**	**125748**	**41852**	**684577**	**959927**	**1758334**
Total†		**1951875**							**1673772**	**1076762**	**283199**	**84837**	**772646**	**1122573**	**1951875**

DM: diabetes mellitus; HTN: hypertension; Hgb: hemoglobin; K: potassium; PTH: parathyroid hormone; Phos: phosphorous; Ca: corrected calcium

* Studies with only hypertension

† CKD population from three administrative high risk cohorts, not included in the total N

‡ Defined as urine albumin-to-creatinine ratio ≥30 mg/g OR protein-creatinine ratio ≥50 mg/g or dipstick protein ≥1+.

§ Participants are from Austria, Germany, and Italy

¶ Participants are from Argentina, Austria, Brazil, Canada, Chile, China, Costa Rica, Czech Republic, Denmark, France, Germany, Hungary, Israel, Italy, Japan, Malaysia, Mexico, Netherlands, New Zealand, Peru, Portugal, Russia, Singapore, Slovakia, Spain, United Kingdom, United States of America, Venezuela

** Participants are from Australia, Canada, China, Czech Republic, Estonia, France, Germany, Hungary, India, Ireland, Italy, Lithuania, Malaysia, Netherlands, New Zealand, Philippines, Poland, Russia, Slovakia, United Kingdom

Legends

Figure 1. Associations between eGFR and continuous laboratory measures by albuminuria stages in CKD cohorts: A) Hemoglobin B) Potassium C) Bicarbonate D) Parathyroid hormone E) Phosphorus F) Calcium.

Y axis depicts the meta-analyzed difference from the mean adjusted value at eGFR 50 ml/min/1.73m^2 and albuminuria <30 mg/g. eGFR was modeled as a 3-piece linear spline with knots at 30 and 45 ml/min/1.73 m^2; the reference point in continuous analysis was set at 50 ml/min/1.73m^2.

Figure 2. Association between eGFR and continuous laboratory measures by albuminuria stages in general population and high risk cohorts: A) Hemoglobin B) Potassium C) Bicarbonate D) Parathyroid hormone E) Phosphorus F) Calcium

Y axis depicts the meta-analyzed difference from the mean adjusted value at eGFR 80 ml/min/1.73m^2 and albuminuria <30 mg/g. eGFR was modeled as a 7-piece linear spline with knots at 30, 45, 60, 75, 90, 105 ml/min/1.73 m^2; the reference point in continuous analysis was set at 80 ml/min/1.73m^2.

Figure 3. Meta-analyzed adjusted prevalence (25th and 75th percentile cohort) of abnormalities (categorical laboratory measures) in CKD by diabetes status

The adjusted prevalence of each abnormality at each eGFR and albuminuria stage was computed as follows: first, we converted the random-effects weighted adjusted mean odds at the reference point (eGFR 50 ml/min/1.73 m^2) into a prevalence estimate. To the reference estimate, we applied the meta-analyzed odds ratios to obtain prevalence estimates at eGFR 95, 80, 65, 35, and 20 ml/min/1.73 m^2 for each stage of albuminuria with and without diabetes. The prevalence estimates were adjusted to 60 years old, half male, non-black, 20% history of CVD, 40% ever smoker, and body-mass index 30 kg/m^2. The 25th and 75th percentiles for predicted prevalence were the estimates from individual cohorts in the corresponding percentiles of the random-effects weighted distribution of adjusted odds. This was done separately for each abnormality.

Note that the cohorts included in the analyses of each abnormality may differ based on data availability. For example, the cohort in the 25th percentile of anemia may not be the same as the cohort in the 25th percentile of hyperparathyroidism.

Color coding is based on odds ratio quartile within each abnormality. Bold red font indicates the reference cell.

Definitions of each abnormality are as follows: Anemia: Hgb: male<13 g/dL, female<12 g/dL; Hct: male<39%, female<36%. Hyperkalemia: potassium >5 mmol/L. Acidosis: bicarbonate <22 mmol/L. Hyperparathyroidism: intact PTH >65 pg/mL. Hyperphosphatemia: phosphorus >4.5 mg/dL. Hypocalcemia: corrected calcium <8.5 mg/dL.

Figure 4. Association between eGFR and hypertension by albuminuria stages in CKD cohorts (A) and general population and high risk cohorts (B)

Abbreviations: A1, A2, A3 refer to albuminuria stages: A1, <30 mg/g; A2, 30-299 mg/g; and A3, 300+ mg/g. Y-axis refers to the meta-analyzed adjusted odds ratio and 95% confidence interval compared to a reference of eGFR 50 (80 in the right graph) ml/min/1.73m^2 in A1 (black diamond). In analyses of the general population/high risk cohorts, eGFR was modeled as a 7-piece linear spline with knots at 30, 45, 60, 75, 90, 105 ml/min/1.73m^2; the reference point in continuous analysis was set at 80 ml/min/1.73m^2. In analyses of CKD populations, eGFR was modeled as a 3-piece linear spline with knots at 30 and 45 ml/min/1.73m^2; the reference point in continuous analysis was set at 50 ml/min/1.73m^2.

Figure 1. Associations between eGFR and continuous laboratory measures by albuminuria stages in CKD cohorts: A) Hemoglobin B) Potassium C) Bicarbonate D) Parathyroid hormone E) Phosphorus F) Calcium.

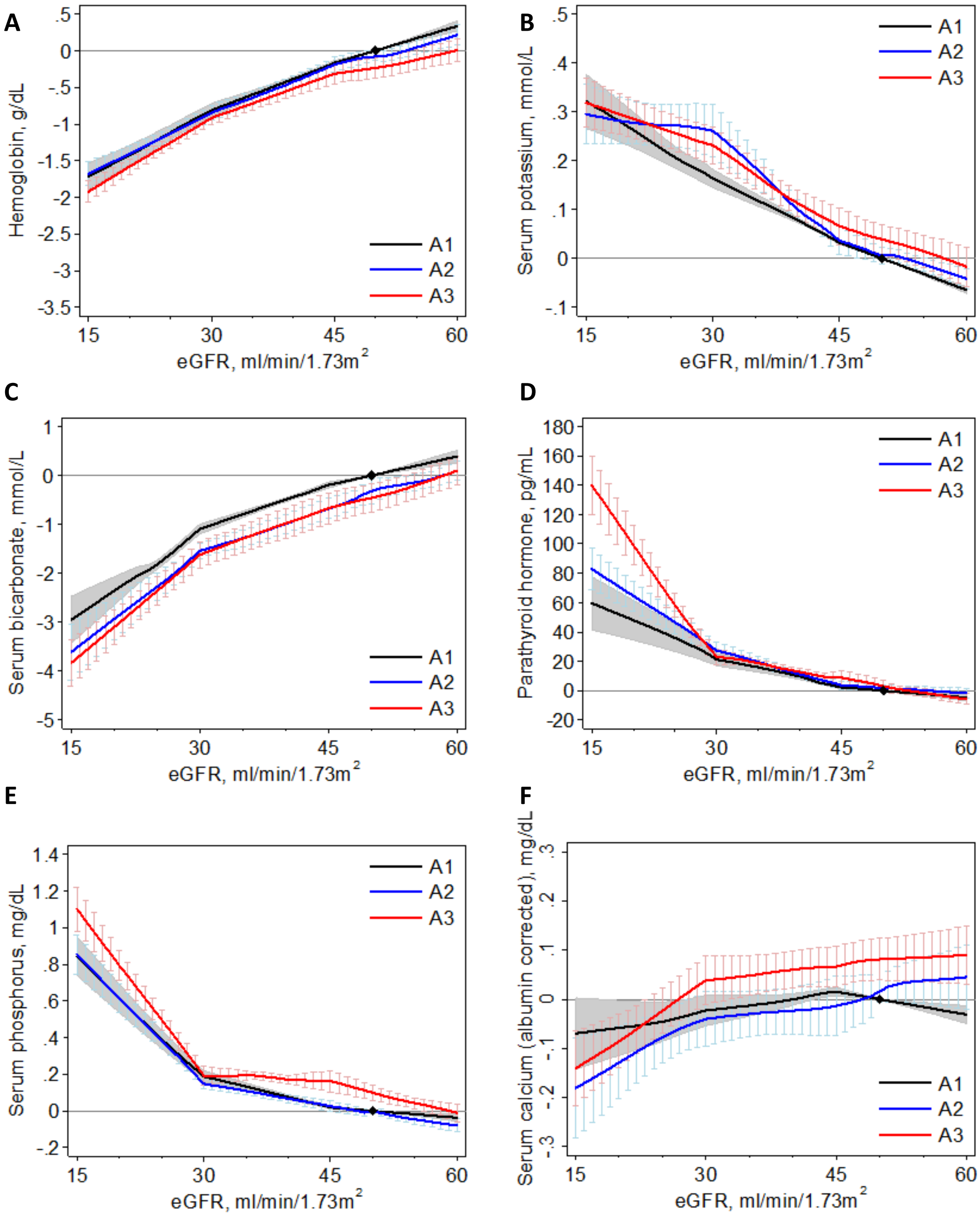

Figure 2. Association between eGFR and continuous laboratory measures by albuminuria stages in general population and high risk cohorts: A) Hemoglobin B) Potassium C) Bicarbonate D) Parathyroid hormone E) Phosphorus F) Calcium.

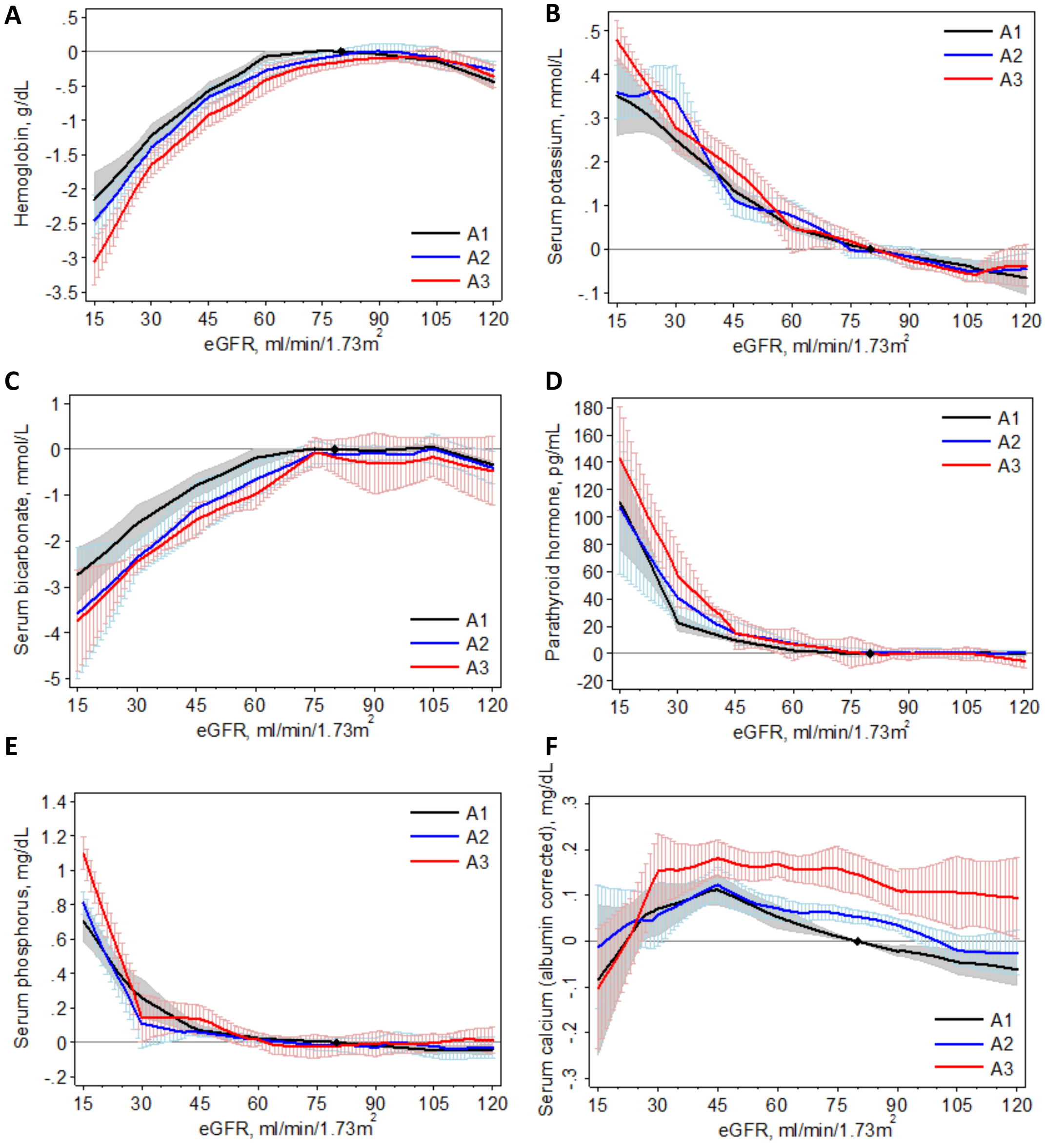

Figure 3. Meta-analyzed adjusted prevalence (25th and 75th percentile cohort) of abnormalities (categorical laboratory measures) in CKD by diabetes status

No Diabetes

Anemia

eGFR	A1	A2	A3
>90			
75-89			
60-74	14.9% (11.8, 18.6)	23.1% (18.7, 28.2)	23.4% (18.9, 28.5)
45-59	**22.1% (17.7, 26.9)**	24.9% (20.2, 30.2)	29.1% (23.9, 34.9)
30-44	39.2% (33.0, 45.7)	36.9% (30.8, 43.2)	40.8% (34.4, 47.3)
15-29	60.6% (54.0, 66.7)	60.7% (54.1, 66.8)	64.2% (57.7, 70.0)

Hyperkalemia

eGFR	A1	A2	A3
>90			
75-89			
60-74	3.9% (2.0, 5.0)	5.0% (2.6, 6.3)	5.8% (3.0, 7.2)
45-59	**6.3% (3.3, 7.8)**	6.8% (3.6, 8.5)	7.7% (4.1, 9.6)
30-44	11.8% (6.4, 14.6)	13.6% (7.4, 16.7)	13.9% (7.6, 17.1)
15-29	21.7% (12.3, 26.1)	20.8% (11.8, 25.1)	22.3% (12.7, 26.7)

Acidosis

eGFR	A1	A2	A3
>90			
75-89			
60-74	4.4% (3.2, 5.9)	7.8% (5.7, 10.2)	6.1% (4.4, 8.1)
45-59	**5.5% (4.0, 7.3)**	9.2% (6.7, 12.1)	9.0% (6.6, 11.8)
30-44	12.2% (9.0, 15.8)	17.9% (13.4, 22.7)	15.5% (11.6, 19.9)
15-29	26.9% (20.7, 33.1)	36.6% (29.1, 43.7)	36.2% (28.8, 43.3)

Hyperparathyroidism

eGFR	A1	A2	A3
>90			
75-89			
60-74	29.5% (24.2, 36.7)	31.4% (25.9, 38.8)	28.7% (23.5, 35.7)
45-59	**37.6% (31.5, 45.4)**	39.0% (32.8, 46.9)	42.2% (35.8, 50.2)
30-44	59.2% (52.5, 66.7)	61.3% (54.7, 68.6)	66.3% (60.0, 73.1)
15-29	72.0% (66.3, 78.0)	78.9% (74.1, 83.8)	85.3% (81.5, 88.9)

Hyperphosphatemia

eGFR	A1	A2	A3
>90			
75-89			
60-74	2.9% (1.7, 5.2)	3.4% (2.0, 6.1)	5.7% (3.3, 10.0)
45-59	**3.3% (1.9, 5.8)**	3.5% (2.0, 6.2)	7.3% (4.2, 12.5)
30-44	5.6% (3.2, 9.8)	6.2% (3.6, 10.6)	9.4% (5.5, 15.8)
15-29	28.0% (17.9, 41.4)	26.2% (16.6, 39.2)	34.2% (22.6, 48.5)

Hypocalcemia

eGFR	A1	A2	A3
>90			
75-89			
60-74	2.3% (1.1, 5.9)	2.6% (1.3, 6.7)	1.3% (0.6, 3.4)
45-59	**2.4% (1.2, 6.2)**	2.7% (1.3, 6.9)	2.2% (1.1, 5.7)
30-44	3.8% (1.8, 9.4)	3.1% (1.5, 7.9)	3.1% (1.5, 7.8)
15-29	7.8% (3.8, 18.4)	8.1% (4.0, 19.0)	7.2% (3.5, 17.1)

Diabetes

Anemia

eGFR	A1	A2	A3
>90			
75-89			
60-74	23.7% (19.2, 28.8)	27.9% (22.7, 33.5)	33.9% (28.1, 40.1)
45-59	**32.1% (26.4, 38.1)**	34.8% (28.9, 41.0)	40.1% (33.8, 46.6)
30-44	47.2% (40.5, 53.8)	48.3% (41.6, 54.9)	53.3% (46.5, 59.8)
15-29	66.1% (59.8, 71.8)	66.5% (60.2, 72.1)	74.5% (69.0, 79.2)

Hyperkalemia

eGFR	A1	A2	A3
>90			
75-89			
60-74	6.9% (3.6, 8.7)	9.2% (4.9, 11.4)	10.5% (5.6, 12.9)
45-59	**10.8% (5.8, 13.4)**	11.0% (5.9, 13.7)	13.4% (7.3, 16.4)
30-44	16.0% (8.8, 19.5)	19.8% (11.1, 23.9)	21.1% (11.9, 25.4)
15-29	25.6% (14.9, 30.5)	25.2% (14.6, 30.0)	27.3% (16.0, 32.3)

Acidosis

eGFR	A1	A2	A3
>90			
75-89			
60-74	6.0% (4.3, 7.9)	7.4% (5.4, 9.7)	9.4% (6.9, 12.3)
45-59	**7.7% (5.6, 10.1)**	9.7% (7.1, 12.7)	12.2% (9.0, 15.8)
30-44	13.8% (10.2, 17.7)	17.5% (13.1, 22.2)	19.5% (14.7, 24.6)
15-29	27.1% (20.9, 33.3)	32.5% (25.5, 39.4)	37.7% (30.1, 44.9)

Hyperparathyroidism

eGFR	A1	A2	A3
>90			
75-89			
60-74	24.9% (20.2, 31.4)	37.4% (31.4, 45.2)	25.4% (20.6, 32.0)
45-59	**38.2% (32.0, 46.0)**	42.6% (36.2, 50.6)	40.3% (34.0, 48.2)
30-44	57.8% (51.1, 65.4)	62.1% (55.6, 69.3)	65.6% (59.2, 72.4)
15-29	70.0% (64.0, 76.3)	77.6% (72.6, 82.7)	84.6% (80.8, 88.4)

Hyperphosphatemia

eGFR	A1	A2	A3
>90			
75-89			
60-74	4.7% (2.7, 8.2)	8.2% (4.8, 13.9)	8.9% (5.2, 15.1)
45-59	**6.0% (3.5, 10.4)**	6.0% (3.4, 10.3)	10.0% (5.8, 16.7)
30-44	9.3% (5.4, 15.7)	10.4% (6.1, 17.4)	15.0% (9.0, 24.3)
15-29	32.1% (21.0, 46.2)	35.8% (23.8, 50.3)	45.0% (31.5, 59.8)

Hypocalcemia

eGFR	A1	A2	A3
>90			
75-89			
60-74	2.0% (1.0, 5.1)	2.2% (1.1, 5.7)	1.9% (0.9, 4.8)
45-59	**2.8% (1.3, 7.1)**	2.9% (1.4, 7.3)	1.8% (0.9, 4.7)
30-44	3.1% (1.5, 7.8)	3.6% (1.7, 9.1)	2.5% (1.2, 6.4)
15-29	7.1% (3.5, 16.8)	10.4% (5.2, 23.6)	8.0% (3.9, 18.7)

Figure 4. Association between eGFR and hypertension by albuminuria stages in CKD cohorts (A) and general population and high risk cohorts (B)