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

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**ABSTRACT**

**Background:** Chronic kidney disease (CKD) is complicated by abnormalities that reflect disruption in filtration, tubular and endocrine functions of the kidney. We describe the magnitude of risk associations across glomerular filtration rate (GFR) and albuminuria stages with specific laboratory abnormalities and hypertension, and their consistency across diverse global cohorts.

**Methods**: Using 17 CKD and 38 general population and high-risk cohorts, we evaluated the association between eGFR and anemia, acidosis, hyperphosphatemia, hyperparathyroidism, hyperkalemia, and hypocalcemia, pooling results using random-effects meta-analyses. Variation in associations was assessed by albuminuria and participant characteristics.

**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 49% female and 3% black, with mean age 51 years (SD 16). There was a strong, graded association between lower eGFR and all laboratory abnormalities (odds ratios ranging from 2.31 (95% CI: 1.37-3.92) to 8.46 (95% CI: 6.83-10.49) comparing GFR 15-29 to GFR 45-59 ml/min/1.73m2) whereas albuminuria had weaker 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). There was little difference in associations with eGFR by age, race, sex, or diabetes status.

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

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**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 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% amongst 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](#_ENREF_1)

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. Interestingly, these abnormalities do not occur in all patients with CKD. Prior studies in general population and CKD cohorts have documented the risk of abnormalities individually by level of estimated GFR or albuminuria,[6-9](#_ENREF_6) but few have looked comprehensively and concomitantly across the new CKD staging system, which classifies CKD by eGFR (G) and albuminuria (A) stage.[10](#_ENREF_10),[11](#_ENREF_11) In addition, the consistency of risk associations across diverse global cohorts along a wide range of GFR, 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 risk and CKD cohorts to explore the risk of specific laboratory abnormalities and hypertension within the 2-dimensional GFR and albuminuria staging framework. We evaluated whether risk associations were consistent across patient 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 GFR 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, as well as direct further investigation and interventions.

**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](#_ENREF_12) Cohorts from around the world with at least 1,000 adult participants (or at least 500 participants in CKD cohorts) and information regarding serum creatinine for 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, which resulted in a slightly smaller sample size for some cohorts. The present study included 17 CKD cohorts and 38 general population or high cardiovascular risk cohorts. To ensure adequate overlap of underlying kidney function, the CKD and the general population/high risk cohorts were analyzed separately, with the exception of three large administrative cohorts (Geisinger, Mt. Sinai BioMe, SCREAM), where the entire population contributed data to the general population and high-risk cohort analysis and the sub-population with eGFR <60 ml/min/1.73 m2 contributed data to the CKD analysis.

*Kidney Measures*

Using serum creatinine provided by the cohorts, eGFR was estimated using the Chronic Kidney Disease Epidemiology (CKD-EPI) creatinine equation.[13](#_ENREF_13) If creatinine was not standardized to isotope dilution mass spectrometry, values were multiplied by 0.95 prior to incorporation in the estimating equation. 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/1.73 m2; the reference point in continuous analysis was set at 80 ml/min/1.73 m2, consistent with previous analyses.[14-16](#_ENREF_14) In analyses of CKD populations, eGFR was modeled as a 3-piece linear spline with knots at 30 and 45 ml/min/1.73 m2; the reference point in continuous analysis was set at 50 ml/min/1.73 m2. 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.[17](#_ENREF_17),[18](#_ENREF_18) In categorical analyses, for comparison purposes, we used a reference of eGFR 50 ml/min/1.73 m2 and albuminuria stageA1 for both general population and CKD cohorts.

*Other Covariates*

Age, sex, and race were provided by the individual cohorts. 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. A history of CVD included myocardial infarction, coronary revascularization, heart failure, and stroke. Smoking was classified as a binary variable (ever vs. never). Body-mass index was reported as weight in kilograms divided by height in meters-squared. Systolic blood pressure was recorded in mmHg.

*Outcomes*

Outcomes included values of hemoglobin, potassium, serum bicarbonate, serum intact parathyroid hormone, 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).[19](#_ENREF_19) 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 parathyroid hormone 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 mmol/L. 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. Covariates that were missing <50% of the time were imputed using the cohort-specific mean; covariates missing ≥50% were not included in the adjustment (**Appendix 1**). Demographic variables, kidney measures, medication use, and laboratory abnormalities were not imputed. Next, associations were combined using a random effects meta-analysis. Heterogeneity was assessed at the reference point (e.g., the adjusted variation in underlying values or odds) as well as for the relative association (e.g., the adjusted variation in odds ratios) and 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. 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. Statistical significance for each point outside the reference was determined using meta-analyzed beta coefficients and standard errors. Interactions between eGFR and albuminuria stage were quantified using the meta-analyzed interaction term for each 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/1.73 m2 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 as follows: first, we converted the random-effects weighted, adjusted mean odds at the reference point (eGFR 50 ml/min/1.73 m2) into a prevalence estimate. To the reference estimate, we applied the meta-analyzed odds ratios to obtain prevalence estimates at eGFR 95, 65, 50, 35, and 20 ml/min/1.73 m2 for each stage of albuminuria. The prevalence estimates were adjusted to 60 years old, half male, non-black, 30% diabetes, 20% history of CVD, 40% ever smoker, and body-mass index 30 kg/m2. To demonstrate the variation in prevalence estimates across the cohorts, we show the 25th and 75th percentiles for prevalence estimates, which are the estimates from the individual cohorts in the corresponding percentiles of the random-effects weighted distribution of adjusted odds.  This was done separately for each abnormality and cohort type (CKD and general population/high risk).

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](http://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 or high cardiovascular risk cohorts (**Table 1**). **eTables 1-6** 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 m2 (SD 17), and 109,143 (44%) had urine 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/1.73 m2 (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 1.73m2. For the general population/high risk cohorts, where the associations were evaluated across the range of GFR, most of the associations became significant at < 60 ml/min per 1.73 m2 (95% confidence intervals do not overlap the x-axis), with the exception of PTH where the threshold was 71 ml/min per 1.73 m2 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 (**eFigure 1-6**).

Overall, the association of albuminuria stages with laboratory abnormalities was absent or minimal in both CKD and general population/high risk populations (**Figures 1 and 2**). In the CKD cohorts, higher albuminuria was associated with slightly lower values of hemoglobin (-0.24, 95% CI: -0.37 to -0.10, for A3 vs. A1) and bicarbonate (-0.46, 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 (0.11 mg/dL, 95% CI: 0.06 to 0.16). For PTH, the magnitude of the association with albuminuria differed substantially at GFR <30 ml/min/1.73 m2, with larger effect sizes in this range in the CKD cohorts.

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 (**eFigure 7**). 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) (**eFigure 8**).

In the analyses of the predefined populations of interest, after adjusting for albuminuria, people with diabetes had similar relationships between laboratory abnormalities and eGFR (**eFigure 9-10**). Independent of eGFR and other covariates, patients with diabetes had slightly lower levels of hemoglobin, bicarbonate and phosphorous and higher levels of potassium. There were also consistent relationships between eGFR and laboratory abnormalities in participants <55 years old and ≥55 years old (**eFigure 11-12**). Similar relationships were seen by sex (**eFigure 13-14**) and when grouped by age as a proxy for menopausal status (women <55 years old and ≥55 years old; **eFigure 15-16**). Although there were few cohorts with both black and non-black participants, associations between eGFR and laboratory abnormalities were also consistent by race (**eFigure 17-18**).

Associations of eGFR and albuminuria with categorical laboratory abnormalities

**Figure 3** shows the associations of each laboratory abnormality with category of eGFR and ACR within the CKD and general population/high-risk cohorts. Overall, there was an increase in the risk for each laboratory abnormality with lower eGFR [odds ratios (95% confidence interval) ranging from 2.31 (1.37-3.92) to 8.46 (6.83-10.49) across abnormalities, comparing GFR 15-29 to GFR 45-59 ml/min per 1.73 m2] with a lesser gradient observed for higher albuminuria [odds ratios ranging from (0.77 (0.60-0.99) to 1.92 (1.65-2.24) across abnormalities, comparing A3 to A1]. Odds ratios were mostly similar in the general population/high risk and CKD cohorts, although for anemia and hyperparathyroidism there was greater risk with higher levels of albuminuria in the general population and high-risk cohorts compared to the CKD cohorts. For all abnormalities, there was little qualitative difference in odds ratios across the individual cohorts.

On the other hand, adjusted absolute risks varied both by type of cohort and between individual cohorts. Compared to the CKD cohorts, general population cohorts had lower adjusted prevalence (25th-75th percentile cohort) of anemia [10.4% (7.2%-12.7%) vs. 24.0% (19.1%-29.7%)] and hyperparathyroidism [15.9% (13.7%-21.0%) vs. 34.6% (30.7%-45.0%)] and higher prevalence of hypocalcemia [4.6% (2.6%-12.4%) vs. 2.4% (1.3%-5.9%)]; the adjusted prevalence of other abnormalities was more similar (**eFigure 19**).

Associations of eGFR and albuminuria with hypertension

For the CKD cohorts, the association between eGFR and hypertension was relatively flat, 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 (**eFigure 20**). Results were also similar by predefined populations of interest (**eFigures 21-22**).

**Discussion**

In this large, individual-level meta-analysis of patients from more than 50 general population, high-risk, and CKD cohorts including more than two million participants, we describe the association of laboratory abnormalities with level of eGFR and albuminuria. We found a 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](#_ENREF_1),[6-9](#_ENREF_6), 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. 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. 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 patient 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 were observed to appear or worsen at a threshold near 60 ml/min per 1.73 m2. In both the general population/high risk cohorts and the CKD cohorts, there was a graded association with abnormalities at lower levels of eGFR. These data provide further support for the current staging system based on eGFR, with eGFR < 60 ml/min per 1.73 m2 the GFR threshold for disease classification.[1](#_ENREF_1),[6](#_ENREF_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.[20](#_ENREF_20) Second, these data may assist clinicians to better characterize the severity of kidney disease. Knowledge of the expected prevalence for each abnormality for a given level of eGFR may help direct intensity of investigation and care by nephrologists, primary care physicians, or other providers, such as guidance of the range and frequency of testing for abnormalities. 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 per 1.73 m2, 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 is demonstrated to provide prognostic information in addition to eGFR and albuminuria values.[21](#_ENREF_21)

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, 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 GFR or albuminuria stage. In particular, assays for PTH, calcium, and albumin (required for adjustment of the calcium) are known to vary widely. Information on medications was limited and only included erythropoietin stimulating agents, iron supplementation, renin-angiotensin system inhibitors, and diuretics. 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, and therefore would be of interest when implementing these data in clinical practice. Prevalence estimates for each abnormality varied by individual cohort even after taking into account eGFR, albuminuria, and measured patient 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 and sets 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 GFR. 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.

**Contributors:**

LAI, ASL, MEG, JC, RTG, SIH, CPK, MW, AL conceived of the study concept and design. MEG, JC, and the CKD-PC investigators/collaborators listed below acquired the data. Yingying Sang and the Data Coordinating Center members listed below analyzed the data. All authors took part in the interpretation of the data. LAI, MEG, and AL drafted the manuscript, and all authors provided critical revisions of the manuscript for important intellectual content. All collaborators shared data and were given the opportunity to comment on the manuscript. JC obtained funding for CKD-PC and individual cohort and collaborator support is listed in appendix 3 in the Supplement.

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**CKD-PC investigators/collaborators** (study acronyms/abbreviations are listed in appendix 2 in the Supplement)**:**

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

|  |  |  |  |
| --- | --- | --- | --- |
| **Study** | **Region**  | **Clinical Characteristics** | **Available 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% |  | 9405 | 228 |  |  |  | 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%** | **207088** | **235549** | **192340** | **42985** | **87174** | **182866** | **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) | 71% | 2730 |  |  |  | 2749 |  | 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** | **614862** | **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** | **687326** | **959927** | **1758334** |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Total†** |  | **1951875** |  |  |  |  |  |  | **1671549** | **1076762** | **283199** | **84837** | **774500** | **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+. |

**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 difference from meta-analyzed adjusted value at eGFR 80 ml/min/1.73 m2 and albuminuria <30 mg/g.**

**B**

**A**

     

**D**

**F**

**E**

**C**

**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 difference from meta-analyzed adjusted value at eGFR 50 ml/min/1.73 m2 and albuminuria <30 mg/g.**

**B**

**A**



**E**

**F**

**C**

**D**

**Figure 3. Odds ratios of laboratory abnormalities in CKD (top panels) and general population and high risk cohorts (bottom panels)**



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



**B**

**A**