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"Advances in Chronic Kidney Disease (Hypertension Issue)" The impact of *APOL1* on chronic kidney disease and hypertension

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Abstract

Essential hypertension is a clinical diagnosis based upon the presence of an elevated systemic blood pressure on physical examination without a clear inciting cause. It has multiple etiologies and is not a homogeneous disorder. Hypertension contributes to the development and progression of atherosclerotic cardiovascular disease and anti-hypertensive treatment reduces the risk of fatal and non-fatal myocardial infarction, stroke and congestive heart failure. Although hypertension is frequently present in non-diabetic individuals with low levels of proteinuria and chronic kidney disease, reducing blood pressures in this population does not reliably slow nephropathy progression. Many of these patients with recent African ancestry have the primary kidney disease "solidified glomerulosclerosis" that is strongly associated with apolipoprotein L1 gene (*APOL1*) renal-risk variants. This kidney disease contributes to secondarily elevated blood pressures. The *APOL1*-associated spectrum of non-diabetic nephropathy also includes proteinuric kidney diseases idiopathic focal segmental glomerulosclerosis (FSGS), collapsing glomerulopathy, severe lupus nephritis and sickle cell nephropathy. This article reviews relationships between mild-to-moderate essential hypertension and chronic kidney disease with a focus on the role of *APOL1* in development of hypertension. Available evidence strongly supports that *APOL1* renal-risk variants associate with glomerulosclerosis in African Americans which then causes secondary hypertension, not with essential hypertension *per se*.

Keywords

African Americans; *APOL1*; chronic kidney disease; FSGS; genetics; hypertension

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Conflict of interest: Wake Forest University Health Sciences and Barry Freedman have rights to an issued United States patent related to *APOL1* genetic testing (www.apol1genetest.com). Dr. Freedman is a consultant for Ionis and AstraZeneca Pharmaceuticals. Dr. Todd Robinson has no disclosures to report.

Introduction

Querying PubMed for the key words “hypertension and chronic kidney disease” in August 2018 returned more than 22,000 publications. Many describe distinct pathophysiologic processes that can produce chronic kidney disease (CKD) and/or elevate the systemic blood pressure. In contrast, others present “hypertension-attributed nephropathy” and “essential hypertension” as homogeneous clinical syndromes. This is an inaccurate assessment; a multitude of genetic factors, environmental exposures and co-existing diseases acting in concert contribute to alterations in kidney function, systolic (SBP) and diastolic blood pressure (DBP).[1,2]

A continuum of blood pressure exists in the general population. Graded increases in risk of adverse cardiovascular disease (CVD) outcomes and death occur in those with higher systemic pressures.[3] Mortality rates are also increased in those with very low blood pressures, likely reflecting comorbid conditions. An equally high blood pressure in two individuals of the same age and ancestral background does not guarantee that they have similar pathophysiologic processes underlying their disorders or that they will respond equally to a given class of anti-hypertensive medications. These individuals likely face different risks for development of kidney, CVD and cerebrovascular disease. The disease process referred to as “essential hypertension” is a physical exam finding reflecting a high SBP and/or DBP without obvious cause. The term essential is synonymous with idiopathic. If a pathophysiologic cause were evident, patients would have secondary hypertension.

Hypertension is reportedly the primary etiology of end-stage renal disease (ESRD) in 24.6% of incident European American and 37.9% of incident African American patients initiating chronic dialysis.[4] Accelerated and malignant forms of hypertension, atheroembolic kidney disease and renovascular hypertension are clearly documented causes of CKD that develop in hypertensive individuals. Kidney function can decline rapidly in these disorders. However, the concept that mild-to-moderate essential hypertension is a common initiator of CKD is tenuous at best.[5,6] The discovery of association between the apolipoprotein L1 gene (*APOL1*) and non-diabetic nephropathy in populations with recent African ancestry supports that CKD typically develops first and is followed by elevations in systemic blood pressures.[7,8] This manuscript reviews the studies that have assessed association between *APOL1* renal-risk variants (RRVs) with hypertension and CKD and support this conclusion.

Effects of blood pressure reductions on renal and cardiovascular disease outcomes

The landmark National Institutes of Health-sponsored Systolic Blood Pressure Intervention Trial (SPRINT) and African American Study of Kidney Disease and Hypertension Trial (AASK) prospectively evaluated the effects of blood pressure reduction on risk of development and progression of CKD, as well as effects on CVD and mortality.[9–11] Effects of *APOL1* RRVs on outcome were also retrospectively assessed in these trials.

Reducing SBP to a target below 120 mm Hg (intensive treatment) versus to below 140 mm Hg (standard treatment) was assessed in SPRINT. In all, 9,361 non-diabetic participants

aged >50 years with a SBP >130–180 mm Hg and at high risk for CVD were randomly assigned to the two treatment arms. To study individuals at increased risk for CVD, the trial was enriched for participants ≥75 years of age, those with prior CVD events (excluding stroke), 10-year risk of CVD ≥15% based on the Framingham risk score, or CKD defined as an estimated glomerular filtration rate (eGFR) 20 to <60 ml/min/1.73m^2 with <1 gram proteinuria per day (patients with polycystic kidney disease were excluded). SPRINT results underscore that intensive blood pressure treatment significantly reduces the frequency of major fatal and non-fatal CVD events, as well as death from all causes in high-risk patients with hypertension.

In contrast, renal outcomes in the intensively treated arm of SPRINT were less favorable than outcomes for CVD and mortality.[12,13] SPRINT employed a “composite renal outcome” to evaluate the 2,646 participants with CKD at baseline. This was defined as first occurrence of a reduction in eGFR ≥50%, need for chronic dialysis (defined as ≥90 days) or kidney transplantation. The CKD subgroup consisted of 1,330 SPRINT participants randomized to intensive and 1,316 randomized to standard anti-hypertensive treatment. The outcome for the composite renal outcome in the intensive versus the standard treatment arm was not significantly different (hazard ratio [HR] 0.89, 95% confidence interval [CI] 0.4–1.87; p=0.76). In isolation, neither a ≥50% reduction in eGFR (HR 0.87, 95% CI 0.36–2.07; p=0.75) or initiation of long-term dialysis (HR 0.57, 95% CI 0.19–1.54; p=0.27) was significantly impacted by intensive blood pressure lowering and no participant received a kidney transplant. In the 6,677 SPRINT participants without CKD at baseline (3,332 intensive treatment and 3,345 standard treatment), significantly higher rates of incident ≥30% declines in eGFR to <60 ml/min/1.73 m^2 were seen with intensive blood pressure lowering (HR 3.49, 95% CI 2.44–5.10; p<0.001). Incident albuminuria, defined as a doubling of the urine albumin:creatinine ratio from <10 mg/g to >10 mg/g, showed non-significant trends towards better outcome in the intensive treatment arm for participants with and without CKD at baseline (HR 0.72, 95% CI 0.48–1.07; p=0.11 and HR 0.81, 95% CI 0.63–1.04; p=0.10, respectively).

Hypertensive and non-diabetic SPRINT participants with Stage 3 CKD and <1 gm proteinuria per day appeared to derive no renal benefit from intensive blood pressure control. These patients, many labelled with “hypertensive nephrosclerosis” in the medical record, are unlikely to be offered a kidney biopsy due to low levels of proteinuria. Their risk of developing a ≥50% decrement in eGFR or starting dialysis were no different with SBP targets <120 mm Hg or <140 mm Hg. Albuminuria tended to be lower in the group targeting intensive blood pressure control and this may reflect more frequent use (or higher doses) of renin-angiotensin-aldosterone system (RAAS) blocking agents. Incident CKD developed more often in SPRINT participants without nephropathy at baseline targeted for intensive lowering of blood pressure. In those without CKD at baseline, the differences in adjusted mean eGFR between the intensive and standard treatment groups, respectively, were −3.32 ml/min/1.73 m^2 at 6 months and 4.50 ml/min/1.73 m^2 at 18 months; this difference remained stable for the remainder of follow-up. At 3 years, an incident CKD event developed in 3.7% of intensively treated participants versus 1.0% in the standard treatment arm (HR 3.54, 95% CI 2.50–5.02). However, even with the higher rates of incident CKD, SPRINT showed significant reductions in CVD events and mortality with intensive blood pressure treatment.

Intensive blood pressure control clearly reduces CVD events and saves lives in high risk non-diabetic individuals with hypertension. However, SPRINT demonstrated that intensive blood pressure control fails to slow the progression of established nephropathy in non-diabetic individuals with low levels of proteinuria. In addition, more hypertensive participants without CKD developed nephropathy with a target SBP <120 mm Hg.[13] This was not likely a purely hemodynamic effect because it persisted throughout the trial. The SPRINT Alzheimer's, Seniors and Kidney Study (SPRINT ASK) will be performing an additional assessment of kidney function one year after the final study visit, results are expected soon.

SPRINT included 2,571 African Americans who provided DNA and consented to genetic testing.[14,15] Similar to the 13% frequency of *APOL1* high-risk for CKD genotypes (G1G1, G2G2, or G1G2) in the general African American population, approximately 14% of African Americans in SPRINT had two *APOL1* RRVs. These high-risk genotypes were associated with prevalent CKD and albuminuria at baseline in African Americans in SPRINT, but not with CVD. After median 39-month follow-up, no association was observed between the composite CVD outcome (or its' components) with *APOL1* renal-risk genotypes. A non-significant trend (p=0.11) toward *APOL1* association with incident CKD was observed, reflecting a sustained 30% decrease in eGFR to <60 ml/min/1.73 m^2.

SPRINT broke new ground in understanding the relationships between initiation and progression of CKD based on anti-hypertensive treatment targets. Results were consistent with findings in the AASK Trial and the subsequent AASK Cohort Study.[10,11] In contrast to SPRINT, AASK specifically enrolled African Americans who were thought to have kidney disease related to the effects of high blood pressure. The hypothesis was that by aggressively lowering blood pressures and using high dose RAAS blocking agents, specifically angiotensin-converting enzyme inhibitors, the progression of presumed hypertensive kidney disease in AASK participants could be slowed. Despite impressive reductions in blood pressure, nearly 60% of AASK participants developed a primary study outcome within 10 years; this included a doubling of the serum creatinine concentration, initiation of dialysis or death. In fact, few AASK participants died; most who met the primary study outcome had a renal event. AASK demonstrated that aggressive blood pressure control was ineffective in slowing the progression of established nephropathy attributed to the effects of hypertension in African Americans; it included different classes of anti-hypertensive medications and prescription of high dose RAAS blockade. Genetic analyses in AASK revealed that participants were enriched for *APOL1* renal-risk genotypes and these were the major predictor of risk for progression of nephropathy.

APOL1 renal-risk genotypes are known to be associated with a spectrum of diseases related to focal segmental glomerulosclerosis (FSGS); these include solidified glomerulosclerosis with minimal to absent proteinuria (the disorder often erroneously attributed to hypertension), collapsing glomerulopathy, severe lupus nephritis, sickle cell nephropathy, and more rapid failure of renal allografts based on the kidney donors' genotype.[6,16] It is apparent that many African American AASK participants who had progressive CKD had a primary kidney disease and not nephropathy related to hypertension.[17,18] Many cases with

minimal or no proteinuria appear to have been caused by *APOL1*, including solidified glomerulosclerosis and FSGS as reported in an AASK kidney biopsy study.[6,19]

Effects of *APOL1* on systemic blood pressure: BioMe, AASK and SPRINT

Secondary hypertension is a well-established manifestation of longstanding CKD from glomerular, tubulo-interstitial and vascular etiologies. Nonetheless, many patients continue to be mislabeled as having CKD or ESRD thought due to mild-to-moderate essential hypertension based on their clinical presentation and compounded by lack of knowledge of *APOL1* genotypes.

The Mount Sinai BioMe bio-bank repository was analyzed to assess blood pressures in African Americans based on *APOL1*.[20] A total of 5,200 African American bio-bank participants were included in this study and replication cohorts consisted of an additional 1,623 BioMe participants, 1,809 Vanderbilt BioVU participants, and 567 Northwestern NuGene bio-bank participants. Blood pressure and *APOL1* RRV associations were evaluated in the discovery and replications cohorts and in a model adjusted for age, sex, body mass index (BMI), and eGFR. These investigators found that in the 14–16% of African American patients with two *APOL1* RRVs, there was an additive effect on SBP and age at diagnosis of hypertension. Individuals with two *APOL1* RRVs were diagnosed with hypertension two to five years earlier than those with zero or one RRV.

In the fully-adjusted analysis, BioMe participants aged 20 to 29 years had an increase in SBP of 0.94 mmHg per copy of an *APOL1* RRV. Additionally, the individuals in this age group developed declines in eGFR approximately 10 years later, which became evident in the 30 to 39 year age range. This suggested that hypertension pre-dated, and may have led to, declining eGFR. As such, the authors proposed that the earliest effect of *APOL1* might be on hypertension and not CKD. The BioMe analysis, including samples and data from a bio-bank and electronic medical record in prevalent patients, is the sole report of *APOL1* association primarily with hypertension. Table 1 summarizes results from 13 other population-based, clinical and research cohorts that assessed *APOL1* associations with blood pressure, hypertension and CKD. Nearly all support primary association between *APOL1* and kidney disease and/or reduced eGFR.

Relationships between *APOL1* and blood pressure were examined in two small African American cohorts with detailed phenotypes: hypertensive children and living kidney donors. *APOL1* genotype, hypertension and family history of ESRD were analyzed in 93 pediatric and young adult African Americans with severe hypertension or FSGS.[21] *APOL1* high-risk genotypes were significantly associated with CKD and with family history of ESRD in these young individuals. In all, 66% of those with a family history of ESRD had two *APOL1* RRVs, as did 83% of pediatric cases previously diagnosed as having “hypertension-attributed CKD”. In contrast, hypertensive African American children with a normal eGFR, no proteinuria and without a family history of ESRD universally lacked two *APOL1* RRVs. The cohort of African American living kidney donors also showed similar pre- and post-donation blood pressures and frequencies of hypertension, irrespective of *APOL1* genotype.[22] Significantly lower pre- and post-donation eGFRs were present in the donors with

APOL1 renal-risk genotypes. Both cohort studies support the hypothesis that hypertension was primarily a manifestation of underlying CKD and did not initiate nephropathy.

The previously discussed AASK[10] and SPRINT trials[9] had intervention arms that randomized hypertensive participants with non-diabetic CKD to intensive pharmacologic control of blood pressure. In AASK participants randomized to the aggressive blood pressure control arm (mean arterial blood pressure [MABP] ≤92 mmHg), there was no observed benefit in slowing the rate of progression of kidney failure compared to those randomized to MABP 102–107 mmHg. A subset of 675 AASK participants with clinically diagnosed "hypertensive nephropathy" had *APOL1* genotyping. All had baseline CKD defined as an iothalamate GFR 20–65 ml/min/1.73m^2 and sub-nephrotic or absent proteinuria.[17] The investigators, along with an accompanying editorial,[23] concluded that the progression of kidney disease in AASK participants with non-diabetic CKD was strongly associated with *APOL1* and systemic blood pressures had no effect. There were also no significant differences in SBP, DBP or MABP one year after randomization based on the presence of two *APOL1* RRVs, versus zero or one.

In the contemporary SPRINT, a post hoc analysis of 2,568 African American participants focused on *APOL1* genotype and incident CVD events.[14] SPRINT participants were all hypertensive and uniformly lacked diabetes mellitus. CVD events assessed included a composite of myocardial infarction, acute coronary syndrome and stroke, as well as heart failure and CVD-related death. Results were adjusted for demographic characteristics and to which blood pressure intervention group participants were randomized. In African Americans with *APOL1* renal-risk genotypes, baseline SBP and DBP were similar to those who had zero or one *APOL1* RRV. As expected, those with two *APOL1* RRVs had a lower baseline eGFR and significantly more proteinuria. No significant relationship was observed between *APOL1* RRVs and the composite primary CVD end-point.

APOL1 and blood pressure in population-based, primary prevention, community-based and diabetes-affected cohorts

Several large cardiovascular and diabetes-complication studies recorded blood pressures and performed *APOL1* genotyping in African Americans. The Cardiovascular Health Study (CHS) assessed a population-based cohort of Americans older than 65 years and a sub-group was genotyped for *APOL1.*[24] Genotypes were assessed for association with subclinical atherosclerosis, incident CVD, mortality and kidney disease after more than 13 years of follow-up. In CHS, 91 African Americans had two *APOL1* RRVs. Their outcomes were compared with 707 other African Americans with zero or one RRV and approximately 5,000 European Americans (presumably lacking *APOL1* RRVs). African Americans in the *APOL1* renal-risk genotype group had more albuminuria and a strong association with reduced eGFR. Moreover, higher mortality was observed in the *APOL1* high-risk genotype group, with higher rates of myocardial infarction. Albuminuria and risk for myocardial infarction and mortality were similar between African Americans with zero or one *APOL1* RRV and European Americans. Although the CHS analysis was an older sample with few African

Americans having two *APOL1* RRVs, no associations between *APOL1* genotype and hypertension or blood pressure were evident.

In contrast to CHS, the Coronary Artery Risk Development in Young Adults (CARDIA) study enrolled 1,330 younger African Americans.[25] As in the general population, 13% had two *APOL1* RRVs. The mean age at recruitment was 24 years. After 25 year follow-up, assessment of changes in blood pressure, adjusted for demographic, socioeconomic and hypertension risk factors, medications and kidney function were performed. From young adulthood to mid-life, African Americans had greater increases in blood pressure than their European American counterparts, but the difference was not associated with *APOL1* genotype. In CARDIA, *APOL1* genotypes were not associated with eGFR computed with cystatin-c; however, there was a significantly higher baseline urine albumin-to-creatinine ratio in African Americans with two *APOL1* RRVs compared to African Americans with zero or one RRV.

Community-based studies are reviewed next. The observational Jackson Heart study (JHS) recruited participants from urban and rural communities in the proximity of Jackson, Mississippi.[26] Replication was performed in the Women's Health Initiative (WHI) cohort. In a subgroup analysis of JHS, *APOL1* was genotyped in 1,959 randomly selected African American participants and associations between *APOL1* and renal and CVD phenotypes were performed. CKD was more often present in the *APOL1* high-risk genotype group. There were no significant differences in the baseline distributions of age, gender, type 2 diabetes mellitus, and presence of hypertension among JHS participants with or without *APOL1* renal-risk genotypes. JHS participants with two *APOL1* RRVs had an increased risk of CVD, which persisted after adjustment for CVD and CKD risk factors. *APOL1* renal-risk genotypes were associated with both low eGFR and hypertension in the WHI, suggesting the potential for confounding between these end-points.[26] *APOL1* genotypes were associated with declines in eGFR, without concurrent association with high blood pressure in the Atherosclerosis Risk In Communities (ARIC) cohort.[27] ARIC prospectively evaluated 15,140 individuals and had 25 year follow-up. In sub-group analyses, investigators assessed *APOL1* association with eGFR in the context of clinical events such as acute kidney injury (AKI), hypertension, diabetes, hospitalizations and mortality. Although the majority of ARIC participants were European American, approximately 20% were African American. There were no statistically significant differences in baseline SBP or prevalence of hypertension in African Americans with or without *APOL1* high-risk genotypes. However, African Americans with two (and one) *APOL1* RRVs had a higher risk of total and pre-ESRD hospitalizations, AKI, ESRD, hypertension, diabetes mellitus, CVD, and all-cause mortality compared with European Americans. In the fully-adjusted analyses (irrespective of *APOL1* genotype), African Americans had higher risk of incident hypertension, diabetes and ESRD than European Americans, but lower risk of total hospitalizations and incident CVD.

The Multi-Ethnic Study of Atherosclerosis (MESA) primary prevention cohort enrolled individuals without prevalent CVD and 1,746 of 6,814 African American participants had *APOL1* genotyping.[28] MESA found no association between *APOL1* RRVs and sub-clinical CVD. While there was a higher risk of incident heart failure in the *APOL1* high-risk genotype group, no evidence of association was seen with incident myocardial infarction,

coronary heart disease or stroke. There was also no association between *APOL1* genotype and blood pressure or eGFR. Mean baseline SBP and DBP were similar in the 1,533 *APOL1* low-genetic risk participants (average blood pressure 132/74 mm Hg) and 213 *APOL1* high-genetic risk participants (average baseline blood pressure 131/75 mm Hg). This primary prevention study is important because baseline blood pressure readings were unlikely to be confounded by disease.

APOL1 genotypes were also available in 2,010 African American Reasons for Geographic and Racial Differences in Stroke (REGARDS) study participants. In an analysis assessing lipoprotein subfraction measurements and associations with clinical CVD, the risk of ESRD was significantly higher in those with two *APOL1* RRVs, compared to those with zero or one.[29] There were no significant difference in blood pressure based on the number of *APOL1* RRVs; 73% with two *APOL1* RRVs had hypertension at baseline, compared to 76% with zero and 77% with one *APOL1* RRV. The effect translated to a one to two mm Hg difference in SBP between groups.

Finally, relationships between *APOL1* and hypertension were assessed in patients with type 2 diabetes mellitus. The importance of these reports lie in their ability to test *APOL1* association with hypertension without the potential for confounding by *APOL1* association with diabetic kidney disease. Among 717 African American-Diabetes Heart Study (AA-DHS) participants, the proportions of participants with zero, one or two *APOL1* RRVs was similar to that in the general population.[30] Adjusting for demographic and renal disease-risk factors in this diabetes-affected cohort, *APOL1* RRVs were not significantly associated with albuminuria or eGFR. There was also no difference in the percentage of individuals with hypertension based on *APOL1* genotype. The proportion of AA-DHS participants with hypertension was 83.3%, 84.2% and 80.7%, respectively, for zero, one and two *APOL1* RRVs (intergroup p-value=0.72). There was also no association between *APOL1* genotype and hypertension in the AA-DHS MIND cohort.[31]

Conclusions

Discovery of the powerful association between *APOL1* and CKD in populations with recent African ancestry demonstrates that non-diabetic nephropathy with low level proteinuria is frequently an inherited disorder in this population and produces secondarily elevated blood pressure. A multitude of studies in populations with different ages, various kidney and systemic diseases, and in population-based cohorts support this conclusion. It remains important to recognize that intensive blood pressure control, including with high-dose RAAS blockade, does not slow the progression of or prevent declines in eGFR in hypertensive individuals with CKD and sub-nephrotic proteinuria. The effects of APOL1 RRV proteins on kidney cells need to be blocked to cure APOL1-associated kidney diseases, intensive blood pressure control has not produced favorable effects.

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Clinical Summary

- Despite weak evidence supporting the role of mild-to-moderate essential hypertension as an initiator of chronic kidney disease, the 2017 United States Renal Data System Annual Data Report lists hypertension as the primary cause of end-stage renal disease in 24.6% of incident European American and 37.9% of incident African American patients.
- Two renal histologic patterns predominate in non-diabetic patients with chronic kidney disease, hypertension and low level proteinuria: (a) arteriolar nephrosclerosis with intima-medial proliferation of cells and collagen deposition in the pre-glomerular arterioles ultimately resulting in glomerular ischemia and obsolescent glomerulosclerosis, and (b) solidified glomerulosclerosis associated with the apolipoprotein L1 gene (*APOL1*) in patients with recent African ancestry.
- Although a kidney biopsy or *APOL1* genotyping is required to establish whether arteriolar nephrosclerosis or *APOL1*-associated solidified glomerulosclerosis is present, aggressive blood pressure control with renin-angiotensin-aldosterone system blockade fails to slow progression of either kidney disease in hypertensive patients.
- The preponderance of evidence supports a major role for *APOL1* renal-risk variants in the development and progression of glomerulosclerosis and other primary kidney diseases, not with hypertension *per se*.

Table 1.

Studies reporting hypertension and CKD phenotypes, based on *APOL1* renal-risk genotypes

Sample/Cohort	***APOL1* association with hypertension/blood pressure**	***APOL1* association with ↓eGFR/CKD**	**Ref.**
Pediatric Nephrology Clinic; St. Louis, MO	No	Yes	21
African American Study of Kidney Disease and Hypertension, AASK	No	Yes	17,18
Cardiovascular Health Study, CHS	No	Yes	24
Jackson Heart Study, JHS	No	Yes	26
African American-Diabetes Heart Study, AA-DHS[a]	No	No	30
AA-DHS Memory in Diabetes, AA-DHS MIND[a]	No	Yes	31
Atherosclerosis Risk In Communities, ARIC	No	Yes	27
Coronary Artery Risk Development in Young Adults, CARDIA	No	Yes[b]	25
Systolic Blood Pressure Intervention Trial, SPRINT	No	Yes	9
Multi-Ethnic Study of Atherosclerosis, MESA	No	No	28
Reasons for Geographic and Racial Differences in Stroke, REGARDS	No	No	29
Living Kidney Donors; Detroit, MI	No	Yes	22
Women's Health Initiative, WHI	Yes[c]	Yes	26
BioMe Biobank; New York, NY	Yes[d]	Yes	20

[a] all participants had type 2 diabetes mellitus

[b] association with albuminuria (not eGFR)

[c] blood pressure association confounded by ↓eGFR

[d] blood pressures rose prior to the fall in eGFR