Published in final edited form as:

Am J Kidney Dis. 2015 January ; 65(1): 58–66. doi:10.1053/j.ajkd.2014.06.025.

Association of Kidney Function and Albuminuria With Prevalent and Incident Hypertension: The Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Background—Decreased kidney function and kidney damage may predate hypertension, but only a few studies have investigated both types of markers simultaneously, and these studies have obtained conflicting results.

Study Design—Cross-sectional for prevalent and prospective observational study for incident hypertension.

Setting & Participants—9,593 participants from the Atherosclerosis Risk in Communities (ARIC) Study, aged 53–75 years during 1996–1998.

Predictors—Several markers of kidney function (estimated glomerular filtration rate [eGFR] using serum creatinine and/or cystatin C and two novel markers [β -trace protein and β_2 -microglobulin]) and one marker of kidney damage (urinary albumin-creatinine ratio [ACR]). Every kidney marker was categorized by its quintiles (top quintile as a reference for eGFRs and bottom quintile for the rest).

Outcomes—Prevalent and incident hypertension.

Measurements—Prevalence and HRs of hypertension based on modified Poisson regression and Cox proportional hazards models, respectively.

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Contributions: Research idea and study design: KM; data acquisition: KM, JC; data analysis/interpretation: MH, KM, YS, SHB, BCA, JC; statistical analysis: MH, YS; supervision or mentorship: KM. 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. KM takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Financial Disclosure: The authors declare that they have no other relevant financial interests.

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

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Results—There were 4,378 participants (45.6%) with prevalent hypertension at baseline and 2,175 incident hypertension cases during a median follow-up of 9.8 years. While all five kidney function markers were significantly associated with prevalent hypertension, prevalent hypertension was most notably associated with higher ACR (adjusted prevalence ratio, 1.60 [95% CI, 1.50-1.71] for the highest vs lowest ACR quintile). Similarly, ACR was consistently associated with incident hypertension in all models tested (adjusted HR, 1.28 [95% CI, 1.10-1.49] for top quintile), while kidney function markers demonstrated significant associations in some, but not all, models. Even mildly increased ACR (9.14-14.0 mg/g) was significantly associated with incident hypertension.

Limitations—Self-reported use of antihypertensive medication for defining incident hypertension, single assessment of kidney markers, and relatively narrow age range.

Conclusions—Although all kidney markers were associated with prevalent hypertension, only elevated albuminuria was consistently associated with incident hypertension, suggesting that kidney damage is more closely related to hypertension than moderate reduction in overall kidney function.

Index words

incident hypertension; prevalent hypertension; kidney filtration markers; albuminuria; kidney damage; decreased kidney function; renal impairment; cohort study

Hypertension is a chronic cardiovascular condition characterized by elevated arterial blood pressure and affects 78 million US adults older than 20 years, which represents 33.0% of the entire US population ¹. Hypertension causes a series of complications including kidney and cardiovascular disease ². More than 90% of all hypertension cases are considered as primary or essential hypertension ³, and it is a result of complex interaction among genetic variants, lifestyles, and environmental factors ². Other cases that are caused by identifiable reasons, e.g., endocrinological disorders, are categorized as secondary hypertension ².

Although hypertension is an established risk factor for decreased kidney function ⁴, some evidence supports reverse association as well. Basic research studies have shown that subtle kidney injuries may predict elevated blood pressure in rats. The number of nephrons is lower in some animal models with hypertension as compared to those without hypertension ⁵⁻⁸. Similar results were observed in humans using data from casualties of traffic accidents or in the context of premature infants ⁹⁻¹¹. Several epidemiologic studies have investigated the association of kidney function and damage with risk for hypertension ¹²⁻¹⁸. Most of those studies focused on albuminuria, a marker of kidney damage ¹²⁻¹⁶. To our knowledge, only two studies investigated markers for both kidney function and damage and obtained conflicting results. One reported a stronger association with albuminuria than kidney function ¹⁴, while the other showed a closer association with kidney function ¹².

The primary objective of this study was to investigate the relationship of kidney function and damage markers to incident hypertension in the Atherosclerosis Risk in Communities (ARIC) Study. Given more limited evidence for kidney function in this context, we tested various kidney function markers including glomerular filtration rate (GFR) estimated by three equations based on serum creatinine and/or cystatin C shown to have better accuracy

than conventional equations^{18;19} and two novel markers (β -trace protein [BTP] and β_2 -microglobulin [B2M])²⁰⁻²². Recognizing potential bidirectional association, we also assessed their associations with prevalent hypertension at baseline.

Methods

Participants

The ARIC Study is a prospective cohort study enrolling 15,792 participants aged 45-64 years from four US communities (Forsyth County, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland) during the baseline examination (1987-1989). Details of the ARIC study have been previously described elsewhere²³. For this investigation, a total of 10,890 out of 11,656 participants who attended visit 4 (1996-1998) had all the data for the present study including estimated glomerular filtration rate (eGFR) and albuminuria (Figure 1). We excluded participants with prevalent coronary heart disease (CHD) and heart failure (HF) because they may have received drugs with an antihypertensive effect for treatment of these conditions (β blockers or renin angiotensin system inhibitors) but not for hypertension. Prevalent CHD at visit 4 was defined as self-reported history of CHD at visit 1 or adjudicated CHD cases between visits 1 and 4. Prevalent HF was defined as Gothenburg criteria^{24;25} stage 3 at visit 1 or incident HF hospitalization between visits 1 and 4. Due to a small number of participants (n=29), we further excluded participants whose race was not black or white (i.e. Asian or Native American), leaving a final sample of 9,593 participants. The analysis for BTP and B2M was restricted to 8,982 participants, in whom these novel filtration markers were measured using stored samples.

Measurements

Participant characteristics were recorded at visit 4, unless otherwise specified. Alcohol consumption and smoking status were determined by self-report and were categorized as current vs. former/never. Height and weight were measured with the participant in light clothing without shoes. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Diabetes was diagnosed as a fasting plasma glucose level ≥ 126 mg/dL (7.0 mmol/L), non-fasting glucose of ≥ 200 mg/dL (11.1 mmol/L), self-reported physician diagnosis of diabetes, or use of antidiabetic medications. Stroke history refers to prevalent stroke status at visit 1 and any adjudicated cases between visits 1 and 4. Total cholesterol was measured using enzymatic methods. Physical activity level was recorded at visit 3 (1993-1995), and we used a sport index score ranging from 1 to 5 (1, lowest level of activity; 5, highest level of activity), based on self-reported frequency of exercise and sweating, exercise intensity and a subjective assessment of physical activity compared to peers with similar age. Information about completed years of education was obtained at visit 1 and was grouped into three categories: no/basic (less than high school), intermediate (high school graduate or vocational school), and advanced (college, graduate school, or professional school).

Kidney Function and Damage Markers

For eGFR, we used the best available equations based on serum creatinine and/or cystatin C along with demographic variables such as age, gender, and race (eGFR_{cr-cys}, eGFR_{cr}, and eGFR_{cys} [race not included in this equation])^{18,19}. Our primary kidney function measure was eGFR_{cr-cys}, since this is the best available estimate of measured GFR¹⁸. A modified kinetic Jaffé method was adapted to measure serum creatinine level, and it was standardized to isotope-dilution mass spectrometry–traceable measurements in ARIC visit 4²⁶. Serum cystatin C was measured by a particle-enhanced immunonephelometric assay using a BNII nephelometer (Siemens Healthcare Diagnostics). Additionally, serum BTP and B2M were also measured by the same nephelometer and were investigated as additional kidney function markers. The reliability coefficients for these novel kidney function markers were >0.94²². As recommended in the clinical guidelines²⁷, urinary albumin-creatinine ratio (ACR) was used as a measure of kidney damage. Concentrations of urinary albumin and creatinine were determined separately by nephelometry and the Jaffé method, respectively, using spot urine samples.

Definition of Hypertension

Certified technicians measured sitting blood pressure twice 5 minutes apart after a rest using a random-zero sphygmomanometer. The average of the two readings was recorded. Prevalent hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg, or diastolic blood pressure (DBP) ≥ 90 mmHg, or taking any antihypertensive medications at baseline and was used as the outcome variable for cross-sectional analysis. Participants were requested to bring medication containers at baseline and were specifically asked whether they were taking medications for high blood pressure. Among those without prevalent hypertension at baseline, incident hypertension was defined as self-reported use of antihypertensive medication from annual follow-up phone call interviews after baseline and was used as the outcome variable for prospective analysis.

Statistical Analysis

We used ANOVA and chi-square test to compare any differences in baseline characteristics across ACR quintiles, since ACR was most consistently associated with prevalent and incident hypertension among kidney markers tested, as subsequently demonstrated. Subsequently, Spearman's correlation coefficients between the six kidney markers were evaluated.

To compare the strength of associations of six kidney markers with prevalent and incident hypertension in the same conditions, we assessed their quintiles (top quintile as a reference for eGFRs and bottom quintile for the rest of kidney markers). For eGFR and ACR, we also tested cut points used in clinical guidelines²⁸. We conducted modified Poisson regression model with a robust error variance to investigate the association of those kidney markers with prevalent hypertension at baseline. We developed four models for the adjustment for potential confounders in the analysis of prevalent hypertension: model 1 was unadjusted; model 2 adjusted for major demographic variables (i.e., age, gender, and race); model 3 further adjusted for conventional confounders (BMI, alcohol consumption, smoking, diabetes, prevalent stroke, total cholesterol, education level, and physical activity); and

model 4 additionally included the opponent kidney measure (namely, log-ACR for analysis of kidney function marker and $eGFR_{cr-cys}$ for analysis of ACR).

For the analysis of incident hypertension, we first illustrated the cumulative probabilities of hypertension during follow-up across quintiles of every kidney marker using Kaplan-Meier estimates. Participants were followed up since visit 4 until they developed hypertension or were censored at the end of follow-up, with a median duration of 9.8 years (up to April 2009). The difference across quintiles was evaluated by log-rank test. We then used Cox proportional hazards models to quantify the adjusted associations between the kidney measures and future hypertension. We incorporated the same four models as done in the analysis for prevalent hypertension but also tested model 5 with measured SBP and DBP at baseline in addition to model 4 variables. We also repeated the analysis after stratifying the participants by age (< and ≥ 65 years), gender, race, diabetes, smoking, alcohol consumption status, and baseline blood pressure (normal: SBP <120 mmHg and DBP <80 mmHg; prehypertension: SBP 120-139 mmHg or DBP 80-89 mmHg²⁹). Potential effect modification was tested by likelihood ratio test.

Results

Baseline Characteristics

The average age was 62.6 years, and 5,578 (58.1%) were women. The majority of the population were white ($n=7,488$ [78.1%]). The baseline characteristics of the participants were compared across ACR quintiles (Table 1). As compared to those with lower ACR values (quintiles 1-3 [Q1-3]), participants with higher ACR values (Q 4-5) were more likely to be older, female, and smokers and to have diabetes, history of stroke, and higher BMI. These individuals were less likely to be highly educated or current drinkers. As anticipated, three $eGFR$ s had moderate to strong correlations with each other ($r > 0.55$) (Table S1, available as online supplementary material). The markers BTP and B2M also demonstrated relatively strong correlations with each other and $eGFR$ s ($|r|$ range, 0.36-0.69). In contrast, ACR was weakly correlated with the five kidney function markers ($|r|$ range, 0.10-0.20).

Associations of Kidney Markers With Prevalent Hypertension

There were 4,378 participants (45.6%) with prevalent hypertension at baseline, and prevalence ratios of hypertension at baseline by quintiles of kidney markers are shown in Table 2. The lowest quintile (Q5) of $eGFR$ was significantly associated with prevalent hypertension in every model (prevalence ratio range, 1.13-1.48), regardless of equations used. Similarly, the highest quintile (Q5) of BTP and B2M were associated with higher prevalence of hypertension compared to the corresponding lowest quintile. Among kidney function markers, in model 4, the prevalence ratio was highest for Q5 of B2M (1.16 [95% confidence interval, 1.08-1.25] vs. 1.15 for other function markers), and significant association was observed even in Q4 for B2M regardless of the adjustment. Of note, the prevalence ratio for the highest quintile (Q5) of ACR was consistently higher than that for Q5 of every kidney filtration marker (1.60 [95% CI, 1.50-1.71] for Q5 vs. Q1 in model 4). Moreover, a significant association with prevalent hypertension was observed even at Q2 of ACR (borderline significance for Q3).

Associations of Kidney Markers With Incident Hypertension

Out of 5,215 participants without prevalent hypertension at baseline, 2,175 individuals developed hypertension during a median follow-up of 9.8 years. Figure S1 illustrates cumulative probabilities of hypertension by quintiles of kidney markers. Consistent with the results for prevalent hypertension, the higher cumulative probabilities of hypertension was most evident for Q5 of ACR ($P < 0.001$) as compared to the kidney function markers (P -values for log-rank test ranged from 0.004 to 0.9). The association between ACR and incident hypertension remained significant in Q5 across all five models (hazard ratio range, 1.28-1.53) (Table 3). The results were not altered when we excluded those with macroalbuminuria (ACR ≥ 300 mg/g) (Table S2).

In contrast, significant associations with incident hypertension were not consistently observed for any of kidney function markers in the five models. Specifically, significant associations were observed for Q5 of eGFR_{cys} and B2M in models 1 and 2 and only for Q5 of B2M in model 5, whereas none of the kidney function markers was significant in models 3 and 4. When we subdivided Q5 for every kidney marker into three categories, the highest category (Q5.3) was significantly associated with incident hypertension for eGFR_{cr-cys} and B2M in model 5 but not necessarily in other models (Table S3).

In contrast, all three categories in the top quintile of ACR were significantly associated with incident hypertension across all models. Of note, the significant association was observed even among those with an ACR of 9.14-14.0 mg/g. As a U-shaped association was observed for eGFR incorporating serum creatinine, we repeated the analysis with Q3 as a reference (Table S4). In this analysis, hazard ratios for Q5 of eGFR_{cr-cys}, eGFR_{cr}, and B2M were significant in model 5 but not necessarily in other Models.

When quintiles of serum creatinine and cystatin C were assessed, serum creatinine, but not cystatin C, showed consistently significant association (Table S5). When eGFR and ACR were categorized by clinical cutpoints, eGFR_{cr-cys}, but not eGFR_{cr} or eGFR_{cys}, of 45-59 ml/min/1.73m² was significantly associated with incident hypertension compared to eGFR ≥ 90 ml/min/1.73 m² in model 5 but not in other models (Table S6). In contrast, all higher ACR categories, i.e., 10-29, 30-299, and ≥ 300 mg/g, were significantly associated with hypertension risk compared to ACR < 10 mg/g. Figure S2 shows a summary of hazard ratios for incident hypertension for combined clinical cutpoints of eGFR_{cr-cys} and ACR.

Subgroup Analysis

Given the more consistent association of incident hypertension with ACR as compared to the kidney function markers, we assessed the top quintile versus the lowest quintile of ACR in various subgroups according to age, gender, race, hypertension status, diabetes, smoking and alcohol consumption status, and eGFR levels (Table 4). Although there was some quantitative heterogeneity, we observed a positive association between high ACR and incident hypertension in all subgroups, without any statistically significant interaction. Of note, the association for ACR was insignificant among those with normal blood pressure ($< 120/80$ mmHg) at baseline. Similarly, the association for B2M remained significant when

the analysis was restricted to those with normal blood pressure at baseline in model 5 (Table S7).

Discussion

Although we observed significantly independent association of every kidney marker with prevalent hypertension, the independent association with incident hypertension was consistently significant for ACR but not necessarily for kidney function markers. Among kidney function markers, B2M appeared to be most strongly associated with incident hypertension, although the association was significant in some, but not all, models. The association between high ACR and incident hypertension was largely consistent across demographic and clinical subgroups. Of note, the association was significant even at the high-normal range of ACR (9-14 mg/g) and was consistent between those with normal (<120/80 mmHg) and high-normal (120/80) blood pressure at baseline. These results suggest that kidney damage, represented by high albuminuria, plays a more important role than reduced kidney function in the development of hypertension in the general population.

The more evident associations of ACR over kidney function markers with risk of future hypertension are largely consistent with a report from Brantsma and colleagues using data from Dutch general population¹⁴. Also, our results are in line with more abundant reports for ACR compared to measures of kidney function in the context of their contributions to the development of hypertension¹²⁻¹⁶. There are several potential pathophysiological mechanisms linking high ACR to incident hypertension. Excess urinary protein can activate nuclear factor κ B (NF κ B) and suppress inhibitor of NF κ B levels in proximal tubular epithelial cells and thus stimulate inflammatory signals and reactive oxygen species formation^{30;31}, conditions linked to the development of hypertension³². A study also reported that the production of kidney endothelin 1, a molecule with prohypertensive actions, increases if the kidney is damaged³³. It has also been pointed out that albuminuria reflects systemic endothelial dysfunction, which has been shown to precede hypertension development^{34;35}.

The results for ACR in our study may have some clinical and public health implications. First our results support more attention on albuminuria in addition to low GFR for the assessment of clinical risk related to chronic kidney disease²⁸. Also, albuminuria may be useful as a risk marker for developing hypertension. Whether screening for hypertension risk by albuminuria is effective or not cannot be answered by our observational study. Nevertheless, albuminuria may be used to encourage those at high risk for hypertension to modify their lifestyle (eg, suggesting a reduction in salt intake or an increase in physical activity). For those with high albuminuria, closer monitoring of blood pressure in the clinic or home may be another approach³⁶. Although a broader range of considerations is required to assess the usefulness of pharmacological therapy, given that some investigators have tested antihypertensive medication to prevent progression from prehypertension to hypertension³⁷, albuminuria may be useful to refine the target population, if this approach is established. In terms of cost, dipstick has the advantage over ACR and may warrant future investigations in its association with risk of hypertension.

The inconsistent associations of low kidney function and future risk of hypertension in our study corresponds to the limited number of epidemiological studies reporting the association of decreased kidney function with future hypertension^{12;17}, despite plenty of studies adjusted for reduced kidney function when reporting the association for albuminuria¹²⁻¹⁶. The five measures of kidney function, including $eGFR_{cr-cys}$ based on the best available equation incorporating both serum creatinine and cystatin C,¹⁸ demonstrated consistently weaker associations with incident hypertension compared to ACR. Nevertheless, there were significant associations in some models for incident hypertension (Table 3 and Tables S3-S7) and in all models for prevalent hypertension (Table 2). Thus, our results do not entirely deny the involvement of decreased kidney function in the development of hypertension. Reduced kidney function may be an important promoter of further blood pressure elevation among those with prehypertension, contributing to a vicious cycle. Also, it is well known that decreased kidney function complicates blood pressure control among those with hypertension³⁸. However, our results suggest that it may be unlikely that mildly decreased kidney function is a major predictor of incident hypertension in the general population.

The U-shaped relationship observed for $eGFR_{cr}$ is consistent with what has been shown for other outcomes such as mortality. The paradoxically higher clinical risk at higher $eGFR$ range is considered to be due to confounding by lower muscle mass resulting from poor health condition. This explanation may be applied to hypertension risk as well. Indeed, several studies have reported the inverse relationship between muscle mass and blood pressure³⁹⁻⁴². Reduced peripheral resistance along with skeletal muscular growth and endurance after resistance exercise is a potential underlying mechanism^{39;43}. However, the association of muscle mass and exercise regimens with blood pressure is still controversial and requires further investigation^{43;44}.

Among kidney function markers, the associations with prevalent and incident hypertension were overall most consistent for B2M. A component of MHC class I molecule and present in all nucleated cells, B2M is considered a good marker of kidney function. Although it is not entirely clear why the association with hypertension for this molecule was stronger than for other kidney function markers, some investigators report that B2M may contribute to amyloid formation in the vascular wall and may directly damage blood vessels⁴⁵. Given that a few studies demonstrate that B2M may be more strongly associated with adverse outcomes than cystatin C⁴⁶, the aspects of B2M beyond kidney function warrant further investigations.

There are several limitations in our study. First, we relied on self-reported use of antihypertensive drugs to define incident hypertension⁴⁷, which should be more specific but not that sensitive. However, in a subsample of ARIC participants ($n \approx 2,000$) who participated in the magnetic resonance imaging assessment of the carotid arteries in 2005-2006, this self-reported use of antihypertensive drugs yielded sensitivity of 74.3% and specificity of 97.8% with measured blood pressure and antihypertensive medication use verified by checking medication bottles as the gold standard. Although our estimates could have been biased if kidney markers themselves influenced the decision regarding initiation of antihypertensive drugs, it is unlikely that high ACR within normal range, which was associated with future hypertension in our study, affected clinical decision-making. Second,

we only had a single measurement of kidney markers, making our analysis prone to some degree of misclassification. Nevertheless, this type of misclassification generally biases the results toward the null. Third, our study participants were aged 52-75 years at baseline. Thus, our results may not be generalizable to individuals outside of this age range. Fourth, because we only investigated whites and blacks, the results may not be generalized to other racial/ethnic groups. Finally, inherent to any observational study, we cannot rule out the possibility of residual confounding even with rigorous adjustment for various potential confounders at baseline.

In conclusion, this prospective cohort study demonstrated that ACR was independently associated with incident hypertension, even at the range currently considered normal and in people with normal blood pressure at baseline. This association was consistent across demographic and clinical subgroups. In contrast, the associations for kidney function markers were not consistent or robust. These findings suggest that kidney damage plays a more important role in the development of hypertension than mild reduction in kidney function in the general population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank the staff and participants of the ARIC Study for their important contributions.

Support: The ARIC Study is carried out as a collaborative study supported by National Heart, Lung and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, HHSN268201100012C). The funder of this study had no role in study design; the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the report for publication.

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Figure 1.
Flow chart of the selection of study participants.

Table 1
Baseline characteristics of participants according to ACR quintiles

	Overall (n=9,593)	Q1: <1.36 (n=1,897)	Q2: 1.36-<2.78 (n=1,923)	Q3: 2.78-<4.76 (n=2,009)	Q4: 4.76-<9.14 (n=1,844)	Q 5: 9.14 (n=1,920)	P-value
Age at visit 4 (y)	62.6 ±5.6	61.8 ±5.4	62.1 ±5.5	62.3 ±5.5	63.0 ±5.7	63.7 ±5.1	<0.001
Male sex	4,015 (41.9)	1,027 (54.1)	860 (44.7)	791 (39.4)	590 (32.0)	747 (38.9)	<0.001
BMI (kg/m ²)	28.6 ±5.5	29.8 ±5.5	28.3 ±5.1	28.2 ±5.1	28.0 ±5.5	28.9 ±5.9	<0.001
White race	7,488 (78.1)	1,141 (60.2)	1,565 (81.4)	1,744 (86.8)	1,591 (86.3)	1,447 (75.4)	<0.001
Current drinker	4,863 (50.9)	895 (47.6)	1,031 (53.8)	1,079 (53.8)	971 (52.8)	887 (46.5)	<0.001
Current smoker	1,422 (14.9)	313 (16.6)	246 (12.9)	235 (11.7)	279 (15.2)	349 (18.3)	<0.001
Diabetes	1,407 (14.7)	308 (16.3)	196 (10.2)	175 (8.7)	215 (11.7)	513 (26.9)	<0.001
Prevalent stroke	164 (1.7)	29 (1.5)	33 (1.7)	21 (1.1)	17 (0.9)	64 (3.3)	<0.001
Total cholesterol (mg/dL)	5.2 ±0.9	5.2 ±1.0	5.2 ±0.9	5.2 ±0.9	5.3 ±0.9	5.2 ±1.0	0.002
Antihypertensive medications	3,225 (33.7)	605 (31.9)	560 (29.1)	545 (27.1)	613 (33.3)	902 (47.2)	<0.001
Systolic blood pressure (mm Hg)	127.4 ±18.9	124.2 ±16.9	123.9 ±17.1	124.7 ±17.3	128.0 ±18.8	136.1 ±21.5	<0.001
Diastolic blood pressure (mm Hg)	71.2 ±10.2	71.1 ±9.7	70.3 ±9.6	70.1 ±9.6	71.1 ±10.3	73.5 ±11.6	<0.001
Education							<0.001
No or basic	1,735 (18.1)	420 (22.2)	306 (15.9)	298 (14.9)	290 (15.7)	421 (22.0)	
Intermediate	4,038 (42.2)	730 (38.5)	834 (43.4)	882 (44.0)	833 (45.2)	759 (39.7)	
Advanced	3,806 (39.7)	746 (39.4)	781 (40.7)	827 (41.2)	720 (39.1)	732 (38.3)	
Physical activity*	2.6 ±0.8	2.5 ±0.8	2.6 ±0.8	2.6 ±0.8	2.6 ±0.8	2.5 ±0.8	<0.001

Note: Quintiles are of ACR expressed as mg/g. Values for categorical variables are given as number (percentage); values for continuous variables, as mean ± standard deviation. Conversion factor for cholesterol in mg/dL to mmol/L, $\times 0.02586$.

ACR, albumin-creatinine ratio; Q, quintile

* Physical activity expressed as sport index score (1, lowest level of activity; 5, highest level of activity)

Table 2
Prevalence ratios for prevalent hypertension among quintiles of kidney function and damage markers

	Q1	Q2	Q3	Q4	Q5
eGFR _{cr-ys} (ml/min/1.73 m ²)	105.01	97.52 to <105.01	89.97 to <97.52	79.70 to <89.97	<79.70
Model 1	Referent	0.89 (0.83, 0.96)	0.96 (0.90, 1.04)	1.00 (0.93, 1.07)	1.32 (1.24, 2.41)
Model 2	Referent	0.95 (0.88, 1.02)	1.01 (0.94, 1.08)	1.03 (0.95, 1.10)	1.29 (1.21, 1.38)
Model 3	Referent	0.93 (0.86, 1.00)	0.96 (0.89, 1.04)	0.98 (0.90, 1.05)	1.17 (1.09, 1.26)
Model 4	Referent	0.94 (0.87, 1.01)	0.97 (0.90, 1.04)	0.98 (0.91, 1.06)	1.13 (1.05, 1.21)
eGFR _{cr} (ml/min/1.73 m ²)	97.00	89.78 to <97.00	82.35 to <89.78	72.45 to <82.35	<72.45
Model 1	Referent	0.85 (0.79, 0.92)	0.92 (0.86, 0.99)	0.90 (0.84, 0.96)	1.19 (1.12, 1.27)
Model 2	Referent	0.94 (0.88, 1.02)	0.95 (0.89, 1.02)	0.95 (0.89, 1.02)	1.16 (1.09, 1.24)
Model 3	Referent	0.97 (0.90, 1.05)	0.96 (0.89, 1.03)	0.98 (0.91, 1.05)	1.16 (1.08, 1.24)
Model 4	Referent	0.97 (0.91, 1.05)	0.97 (0.90, 1.05)	0.99 (0.92, 1.07)	1.13 (1.05, 1.21)
eGFR _{ys} (ml/min/1.73 m ²)	109.11	103.06 to <109.10	95.90 to <103.06	82.69 to <95.90	<82.69
Model 1	Referent	1.00 (0.92, 1.08)	1.11 (1.03, 1.20)	1.19 (1.11, 1.28)	1.48 (1.39, 1.59)
Model 2	Referent	1.00 (0.93, 1.08)	1.08 (0.99, 1.16)	1.15 (1.07, 1.24)	1.39 (1.29, 1.49)
Model 3	Referent	0.99 (0.91, 1.07)	1.02 (0.94, 1.10)	1.05 (0.97, 1.14)	1.21 (1.12, 1.31)
Model 4	Referent	1.00 (0.92, 1.08)	1.02 (0.94, 1.10)	1.05 (0.97, 1.14)	1.15 (1.07, 1.25)
BTP (mg/dL)	<0.56	0.56 to <0.63	0.63 to <0.70	0.70 to <0.79	0.79
Model 1	Referent	0.85 (0.80, 0.92)	0.83 (0.78, 0.90)	0.84 (0.78, 0.91)	1.08 (1.02, 1.16)
Model 2	Referent	0.91 (0.85, 0.98)	0.93 (0.86, 0.99)	0.94 (0.87, 1.01)	1.17 (1.09, 1.25)
Model 3	Referent	0.94 (0.88, 1.01)	0.95 (0.88, 1.03)	0.94 (0.87, 1.02)	1.14 (1.06, 1.22)
Model 4	Referent	0.94 (0.87, 1.00)	0.94 (0.88, 1.02)	0.92 (0.85, 0.99)	1.05 (0.98, 1.13)
B2M (mg/dL)	<0.16	0.16 to <0.18	0.18 to <0.20	0.20 to <0.23	0.23
Model 1	Referent	0.98 (0.91, 1.07)	1.04 (0.96, 1.12)	1.19 (1.10, 1.28)	1.43 (1.34, 1.53)
Model 2	Referent	1.03 (0.95, 1.11)	1.09 (1.01, 1.18)	1.22 (1.13, 1.31)	1.40 (1.31, 1.50)
Model 3	Referent	1.01 (0.93, 1.09)	1.03 (0.95, 1.11)	1.12 (1.03, 1.20)	1.24 (1.15, 1.33)
Model 4	Referent	1.01 (0.93, 1.09)	1.02 (0.95, 1.11)	1.11 (1.03, 1.20)	1.16 (1.08, 1.25)
ACR (mg/g)	<1.36	1.36 to <2.78	2.78 to <4.76	4.76 to <9.14	9.14

	Q1	Q2	Q3	Q4	Q5
Model 1	Referent	0.95 (0.88, 1.03)	0.90 (0.83, 0.97)	1.14 (1.06, 1.23)	1.59 (1.49, 1.70)
Model 2	Referent	1.06 (0.98, 1.15)	1.03 (0.95, 1.12)	1.27 (1.18, 1.37)	1.63 (1.53, 1.74)
Model 3	Referent	1.10 (1.01, 1.18)	1.07 (0.99, 1.16)	1.33 (1.24, 1.43)	1.62 (1.51, 1.73)
Model 4	Referent	1.09 (1.01, 1.18)	1.08 (0.99, 1.16)	1.34 (1.24, 1.44)	1.60 (1.50, 1.71)

Note: Except where indicated, values are given as prevalence ratio (95% confidence interval). Significant associations are shown in bold. Model 1 was unadjusted; Model 2 was adjusted for age, gender, and race; Model 3 was adjusted for covariates in Model 2 plus BMI, alcohol consumption, smoking, diabetes, prevalent stroke, total cholesterol, education level, and physical activity; Model 4 was adjusted for Model 3 covariates plus log-ACR and eGFR_{cr-cys}.

BMI, body mass index; eGFR: estimated glomerular filtration rate; eGFR_{cr}, creatinine-based eGFR; eGFR_{cys}, cystatin C–based eGFR; eGFR_{cr-cys}, creatinine and cystatin C-based eGFR; BTP: β trace protein, B2M: β 2-microglobulin, ACR: albumin-creatinine ratio. Q, quintile

Table 3
Hazard ratios of incident hypertension among quintiles of kidney function and damage markers

	Q1	Q2	Q3	Q4	Q5
eGFR _{cr-ys} (ml/min/1.73 m ²)	105.01	97.52 to <105.01	89.97 to <97.52	79.70 to <89.97	<79.70
Model 1	Referent	0.98 (0.86, 1.12)	0.87 (0.76, 0.99)	1.04 (0.92, 1.19)	1.08 (0.94, 1.24)
Model 2	Referent	1.03 (0.90, 1.17)	0.91 (0.79, 1.05)	1.09 (0.95, 1.24)	1.12 (0.96, 1.30)
Model 3	Referent	0.99 (0.87, 1.14)	0.89 (0.77, 1.03)	1.00 (0.86, 1.15)	1.00 (0.86, 1.17)
Model 4	Referent	1.01 (0.88, 1.15)	0.91 (0.79, 1.05)	1.02 (0.89, 1.18)	1.01 (0.87, 1.18)
Model 5	Referent	0.95 (0.83, 1.08)	0.87 (0.75, 1.00)	1.03 (0.89, 1.19)	1.11 (0.94, 1.30)
eGFR _{cr} (ml/min/1.73 m ²)	97.00	89.78 to <97.00	82.35 to <89.78	72.45 to <82.35	<72.45
Model 1	Referent	0.85 (0.75, 0.97)	0.84 (0.74, 0.96)	0.80 (0.70, 0.91)	0.94 (0.82, 1.08)
Model 2	Referent	0.88 (0.77, 1.01)	0.85 (0.74, 0.98)	0.82 (0.71, 0.94)	0.94 (0.81, 1.09)
Model 3	Referent	0.90 (0.78, 1.04)	0.88 (0.76, 1.01)	0.85 (0.74, 0.99)	0.99 (0.85, 1.16)
Model 4	Referent	0.93 (0.80, 1.06)	0.90 (0.78, 1.04)	0.88 (0.77, 1.02)	1.03 (0.88, 1.20)
Model 5	Referent	0.91 (0.79, 1.04)	0.86 (0.75, 1.00)	0.89 (0.77, 1.02)	1.07 (0.92, 1.25)
eGFR _{ys} (ml/min/1.73 m ²)	109.11	103.06 to <109.10	95.90 to <103.06	82.69 to <95.90	<82.69
Model 1	Referent	1.02 (0.90, 1.16)	1.03 (0.91, 1.18)	1.18 (1.04, 1.34)	1.19 (1.04, 1.37)
Model 2	Referent	1.05 (0.92, 1.19)	1.07 (0.93, 1.23)	1.23 (1.07, 1.41)	1.24 (1.06, 1.44)
Model 3	Referent	1.01 (0.89, 1.16)	0.97 (0.84, 1.13)	1.06 (0.91, 1.22)	1.00 (0.85, 1.18)
Model 4	Referent	1.03 (0.90, 1.18)	0.99 (0.86, 1.15)	1.08 (0.94, 1.25)	1.01 (0.86, 1.19)
Model 5	Referent	0.95 (0.83, 1.09)	0.96 (0.83, 1.11)	1.07 (0.92, 1.23)	1.09 (0.92, 1.28)
BTP (mg/dL)	<0.56	0.56 to <0.63	0.63 to <0.70	0.70 to <0.79	0.79
Model 1	Referent	0.97 (0.85, 1.12)	1.00 (0.87, 1.14)	0.94 (0.82, 1.08)	0.96 (0.83, 1.11)
Model 2	Referent	1.02 (0.88, 1.17)	1.06 (0.92, 1.22)	1.01 (0.88, 1.17)	1.03 (0.88, 1.20)
Model 3	Referent	1.04 (0.91, 1.20)	1.07 (0.93, 1.23)	1.00 (0.87, 1.16)	1.06 (0.90, 1.24)
Model 4	Referent	1.04 (0.91, 1.20)	1.08 (0.94, 1.24)	1.00 (0.87, 1.16)	1.04 (0.89, 1.23)
Model 5	Referent	1.08 (0.94, 1.25)	1.11 (0.96, 1.28)	1.05 (0.90, 1.22)	1.10 (0.93, 1.29)
B2M (mg/dL)	<0.16	0.16 to <0.18	0.18 to <0.20	0.20 to <0.23	0.23
Model 1	Referent	1.09 (0.95, 1.24)	1.02 (0.89, 1.16)	1.13 (0.99, 1.30)	1.26 (1.09, 1.45)

	Q1	Q2	Q3	Q4	Q5
Model 2	Referent	1.12 (0.98, 1.28)	1.06 (0.93, 1.22)	1.18 (1.03, 1.36)	1.29 (1.12, 1.50)
Model 3	Referent	1.11 (0.97, 1.27)	1.03 (0.89, 1.18)	1.08 (0.94, 1.26)	1.13 (0.97, 1.33)
Model 4	Referent	1.11 (0.97, 1.28)	1.05 (0.91, 1.20)	1.12 (0.96, 1.29)	1.14 (0.98, 1.34)
Model 5	Referent	1.11 (0.97, 1.27)	1.07 (0.93, 1.23)	1.13 (0.98, 1.31)	1.25 (1.07, 1.46)
ACR (mg/g)	<1.36	1.36 to <2.78	2.78 to <4.76	4.76 to <9.14	9.14
Model 1	Referent	0.86 (0.76, 0.98)	1.01 (0.89, 1.14)	0.93 (0.81, 1.06)	1.41 (1.23, 1.63)
Model 2	Referent	0.92 (0.81, 1.06)	1.10 (0.96, 1.25)	1.01 (0.88, 1.16)	1.51 (1.31, 1.75)
Model 3	Referent	0.99 (0.87, 1.14)	1.17 (1.02, 1.33)	1.11 (0.96, 1.28)	1.53 (1.32, 1.77)
Model 4	Referent	0.99 (0.87, 1.14)	1.17 (1.02, 1.33)	1.11 (0.96, 1.28)	1.53 (1.32, 1.77)
Model 5	Referent	0.94 (0.82, 1.07)	1.05 (0.92, 1.20)	0.99 (0.86, 1.14)	1.28 (1.10, 1.49)

Note: Values are given as hazard ratio (95% confidence interval). Significant associations are shown in bold. Model 1 was unadjusted; Model 2 was adjusted for age, gender, and race; Model 3 was adjusted for covariates in Model 2 plus BMI, alcohol consumption, smoking, diabetes, prevalent stroke, total cholesterol, education level, and physical activity; Model 4 was adjusted for Model 3 covariates plus log-ACR and eGFR_{cr-cys}. Model 5 was adjusted for Model 4 variables plus measured blood pressure.

BMI: body mass index; eGFR: estimated glomerular filtration rate; eGFR_{cr}: creatinine-based eGFR; eGFR_{cys}: cystatin C–based eGFR; eGFR_{cr-cys}: creatinine and cystatin C-based eGFR; BTP: β trace protein, B2M: β 2-microglobulin, ACR: albumin-creatinine ratio. Q: quintile

Table 4
Hazard ratios of incident hypertension for those in top quintile of ACR in subgroups

	ACR-Q5	P-value
Age		0.07
<65 y	1.37 (1.13, 1.64)	
65 y	1.13 (0.88, 1.46)	
Sex		0.04
Male	1.57 (1.25, 1.98)	
Female	1.11 (0.91, 1.36)	
Race		0.7
White	1.21 (0.85, 1.74)	
Black	1.28 (1.08, 1.52)	
Baseline BP		0.6
<120/80 mm Hg	1.32 (1.03, 1.69)	
120/80 mm Hg	1.27 (1.05, 1.53)	
Diabetes		0.6
Yes	1.32 (0.95, 1.83)	
No	1.21 (1.02, 1.44)	
Smoking		0.8
Yes	1.24 (0.86, 1.79)	
No	1.29 (1.09, 1.52)	
Alcohol consumption		0.9
Yes	1.23 (1.00, 1.51)	
No	1.33 (1.07, 1.65)	

Note: Values given as hazard ratio (95% confidence interval). ACR quintile1 was the referent. Covariates included: systolic BP, diastolic BP, eGFR_{cr-cys}, age, gender, body mass index, race, alcohol consumption status, smoking status, diabetes, prevalent stroke, total cholesterol level, education, and physical activity level.

BP, blood pressure; ACR, albumin-creatinine ratio; Q, quintile