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Endothelial Dysfunction Biomarkers and CKD Incidence in the REGARDS Cohort

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Introduction: Chronic kidney disease (CKD) is only partly caused by traditional risk factors. Endothelial dysfunction is common in CKD and may contribute to CKD incidence. We studied the association of circulating biomarkers reflecting endothelial dysfunction with incident CKD.

Methods: The Reasons for Geographical and Racial Differences in Stroke (REGARDS) study is a prospective cohort of 30,239 Black or White adults aged ≥45 years. Baseline levels of intercellular cellular adhesion molecule 1 (ICAM-1), vascular cellular adhesion molecule 1 (VCAM-1), factor VIII (FVIII), and E-selectin were measured in 3300 participants without baseline CKD or albuminuria who attended a second visit 9.4 years later. Kidney outcomes were incident CKD (estimated glomerular filtration rate [eGFR] <60 ml/min per 1.73 m^2 and ≥40% decline or onset of new end-stage kidney disease), incident ≥30% eGFR decline, and incident albuminuria (albumin-to-creatinine ratio [ACR] ≥30 mg/g). Sequentially adjusted logistic regression models assessed the association of biomarkers with kidney outcomes.

Results: Median age of participants was 62 years, 49% were women, and 46% identified as Black. Of the participants, 228 (6.9%) developed CKD, 613 (18.9%) experienced ≥30% decline in eGFR, and 356 (11.4%) developed albuminuria. The adjusted odds ratios (ORs) for incident CKD per 1 SD increment biomarker was 1.12 for ICAM-1 (95% confidence interval [CI]: 1.02–1.22), 1.10 for VCAM-1 (95% CI: 1.01–1.20), 1.15 for FVIII (95% CI: 1.06–1.24), and 1.10 for E-selectin (95% CI: 1.01–1.20). Results were similar for incident ≥30% eGFR decline but not albuminuria, where only higher FVIII was positively associated.

Conclusion: Higher concentration of ICAM-1, VCAM-1, FVIII, and E-selectin were associated with incident CKD and ≥30% eGFR decline in a large cohort study. Higher FVIII was also associated with incident albuminuria.

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Despite improved screening, more than half of US adults are projected to develop CKD in their lifetime.[1] Medicare spending on CKD (excluding kidney failure) exceeds $80 billion annually because CKD is highly associated with cardiovascular disease and hospitalization.[2] Although hypertension and diabetes are strong risk factors for CKD, only 54% of CKD risk is attributable to these diseases and not all of CKD risk is accounted for by known risk factors.[3] Therefore, the identification of new and modifiable risk markers of CKD could help improve understanding of CKD pathogenesis and reduce burden, costs, and related diseases.

Once considered a passive tissue,[4] we now know that the vascular endothelium is a major determinant of cardiovascular outcomes.[5]Endothelial dysfunction-which encompasses atherosclerotic changes and dysregulation of hemostasis, vascular tone, and inflammatory response-is important to coronary artery disease, stroke, peripheral vascular disease, and

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diabetic vascular complications,[6-9] among other cardiovascular diseases. Further, endothelial dysfunction is prevalent in individuals with CKD and is a mechanism by which CKD leads to adverse cardiovascular outcomes.[10,11]

However, the observed coexistence of CKD and endothelial dysfunction remains incompletely characterized. It is hypothesized that endothelial dysfunction in CKD relates to common risk factors and/or CKD itself; however, the previous literature on established biomarkers of endothelial dysfunction and CKD is primarily cross-sectional; higher concentrations of biomarkers of inflammation and coagulation activation are correlated with lower eGFR and higher albuminuria.[12-14] This was also observed in a smaller case-control study examining additional biomarkers of endothelial dysfunction.[15] Available prospective studies are limited by reporting end points without clear meaning in isolation (i.e., incident eGFR <60 ml/min per 1.73 m^2 or eGFR decline)[16-18] or by considering a composite outcome of incident CKD or CKD progression.[19] Thus, it remains unclear whether endothelial dysfunction is simply coexistent with CKD or is a risk factor for the development of CKD.

To address this gap, we studied the association of 4 established circulating biomarkers of endothelial dysfunction with incident CKD and albuminuria in a prospective cohort study. The biomarkers assessed here included ICAM-1, VCAM-1, FVIII, and E-selectin. Each are considered markers of endothelial dysfunction; FVIII is a coagulation factor but is released from the subendothelium upon endothelial activation, so FVIII is considered a marker of endothelial dysfunction. We hypothesized that higher circulating levels of these markers would be positively associated with incidence of CKD and albuminuria.

METHODS

Study Population

The REGARDS study is a prospective, population-based cohort of 30,239 Black and White American adults aged ≥45 years, enrolled in 2003 to 2007. The primary objective of this study was to evaluate racial and regional differences in stroke risk and cognitive impairment. A detailed description of the study design has been previously described.[20] In brief, participants completed extensive baseline testing, including blood and urine sampling, and were followed-up with prospectively by phone contact for monitoring of health status. REGARDS did not ascertain longitudinal data relating to interval clinical diagnosis of CKD, but 16,150 participants (53.4%) completed a second study visit approximately 10 years after enrollment, which included additional blood and urine sampling to test kidney function. Study methods were approved by institutional review boards at each participating site and each participant provided written informed consent.

To efficiently test hypotheses related to biomarkers of cardiovascular risk, REGARDS investigators established the Biomarker Mediators of Racial Disparities in Risk factors nested cohort. The Biomarker Mediators of Racial Disparities in Risk factors cohort consists of 4400 participants who completed the second study visit, evenly distributed by race and gender (25% each White men, White women, Black men, and Black women).[21] We chose to study this subcohort because all had measures of kidney function at baseline and follow-up to determine incident kidney outcomes.

For this study, among the Biomarker Mediators of Racial Disparities in Risk factors cohort participants, we excluded those with missing measures of kidney function or evidence of CKD at baseline, defined as eGFR <60 ml/min per 1.73 m^2 or urine ACR ≥30 mg/g. eGFR was calculated using the 2021 CKD Epidemiology Collaboration equation, including both serum creatinine and cystatin C, but not race.[22]

Measurements and Definitions

Participant race was by self-identification; REGARDS included only individuals who self-identified as White, Black, or African American.[20] Geographic region of residence was defined as stroke buckle, nonbuckle stroke belt, or other US region.[23,24] Hypertension was defined as self-reported use of antihypertensive medication, systolic blood pressure ≥140 mm Hg, or diastolic pressure ≥90 mm Hg. Diabetes mellitus was defined by self-reported use of antidiabetic medication, fasting blood glucose ≥126 mg/dl, or nonfasting glucose ≥200 mg/dl among participants who failed to fast. Body mass index (BMI) was calculated using study-staff- measured weight and height. Dyslipidemia was defined as self-reported use of antihyperlipidemic medication, total cholesterol ≥240 mg/dl, low-density lipoprotein ≥160 mg/dl, or high-density lipoprotein ≤40 mg/dl. Coronary artery disease was defined as self-reported physician diagnosis of a myocardial infarction, bypass, percutaneous coronary intervention, or based on electrocardiogram detection.

The primary prespecified outcome was incident CKD, defined as ≥40% decrease in eGFR from baseline to the second visit and eGFR <60 ml/min per 1.73 m^2 at the second study visit in those with an eGFR ≥ 60 ml/min per 1.73 m^2 at the baseline visit, or initiation of kidney replacement therapy as ascertained via United States Renal Data System linkage. Secondary prespecified outcomes were the following: (i) ≥30% decrease in

eGFR from baseline at the second visit and (ii) incident albuminuria (ACR ≥30 mg/g at the second visit in those with an ACR <30 mg/g at the baseline visit).

Laboratory Methods

Blood and urine samples were obtained using standardized methods. Blood was centrifuged within 120 minutes of sampling. Samples were shipped overnight on ice to a central biorepository and stored at −80 °C until batch analysis.[25]

Four previously validated[26,27] plasma markers of endothelial dysfunction (ICAM-1, VCAM-1, FVIII, and E-selectin) were selected for measurement based on previous cross-sectional studies supporting correlations with CKD.[21] Each biomarker was measured using commercially available enzyme-linked immunoassays: FVIII antigen by Affinity Biologicals (F8C-Elisa; Hamilton, Ontario, Canada) and the remainder by R&D Systems (ICAM-1 by CDIM00, VCAM-1 by DVC00, and E-selectin by PDSLE00; Minneapolis, MN). Laboratory analytical coefficients of variation for each assay were: ICAM-1, 9.2% to 11.6%; VCAM-1, 9.9% to 11.7%; FVIII, 3.3% to 11.5%; E-selectin, 10.0% to 14.3%. Serum creatinine was measured and calibrated via isotope dilution mass spectrometry.[28] Cystatin C was measured by particle-enhanced immunonephelometry (N Latex Cystatin C on the BNII, Siemens AG, Munich, Germany).[29] Serum creatinine and cystatin C measurements were calibrated for drift by reassaying samples from 50 randomly-selected participants who had available baseline and follow-up samples. Urine albumin was measured using nephelometry (BNII ProSpec, Siemens AG, Munich, Germany). Urine creatinine was measured by the Jaffe method (Modular-P Chemistry Analyzer, Roche/Hitachi, Basel, Switzerland).[30]

Due to lack of plasma samples, biomarker data was missing for 31 for ICAM-1 (1.0%), 42 for VCAM-1(1.3%), 32 for FVIII (1.0%), and 29 for E-selectin (0.9%).

Statistical Methods

Baseline characteristics were presented as percent or median (interquartile range [IQR]) by highest and lowest biomarker quartiles. Correlations of markers with each other marker and eGFR were plotted and Spearman rank correlation coefficients calculated. Given that the distributions of ICAM-1, VCAM-1, FVIII, and E-selectin were skewed, natural log transformation was performed on these markers for continuous analyses.

The association of each marker with each prespecified kidney outcome was assessed via sequential logistic regression models. We could not perform Cox analyses because kidney function was assessed at 2 time points: baseline and the second visit. Model 1 was unadjusted. Model 2 was adjusted for age, gender, race, and geographic region of residence. Model 3 was further adjusted for BMI, hypertension, diabetes mellitus, coronary artery disease, smoking status (current, prior, or never), and dyslipidemia. Model 4 was further adjusted for baseline eGFR and urine ACR. All models were weighted to reflect the makeup of the REGARDS cohort from which this nested subcohort was sampled.[21] An exploratory model added all 4 markers as covariates to model 4.

Markers were considered using 3 approaches. First, markers were modeled continuously per 1 log-transformed SD. Second, restricted cubic spline plots were visually inspected to study potential nonlinear relationships, such as threshold effects with odds increasing only with biomarker levels above a certain concentration. Splines utilized 5 knots placed at the 5th, 27.5th, 50th, 72.5th and 95th percentiles, and *P*-values for overall and nonlinear association were computed.[31] The 10th and 90th percentiles were chosen arbitrarily as reference points to describe odds at extreme biomarker concentrations, relative to median. Third, each marker was considered categorically by quartile with the first quartile serving as reference.

All data were <5% missing and missing data were not imputed. Analyses were completed using R (version 4.2.1, R Foundation, Vienna, Austria) with use of the rms package.[31,32]

RESULTS

Cohort Characteristics and Cross-Sectional Correlations

Of the 4400 participants in the Biomarker Mediators of Racial Disparities in Risk factors nested cohort, 3300 (75.0%) were included in analyses for the primary outcome of incident CKD and the secondary outcome of ≥30% decrease in eGFR (Supplementary Figure S1). For the secondary outcome of incident albuminuria, we included 3120 of these participants who also provided urine at the second study visit (Supplementary Figure S2).

In the primary analysis, median age was 62 years (IQR: 57–68), 1606 (48.7%) were women, 1516 (45.9%) self-identified as Black race, 1650 (50.0%) had hypertension, 485 (14.7%) had diabetes, and median eGFR was 92 ml/min per 1.73 m^2 (IQR: 81–103). Median baseline biomarker concentrations were: ICAM-1, 295 ng/ml (IQR 253–343); VCAM-1, 658 ng/ml (IQR: 530–817); FVIII, 100% (IQR: 83–121); and E-selectin, 36 ng/ml (IQR: 26–46). There were no material differences in participant characteristics or baseline

Table 1. Baseline cohort characteristics by biomarkers of endothelial dysfunction

	ICAM-1		VCAM-1		Factor VIII		E-selectin	
Characteristic, *n* (%)	Q1 <253 ng/ml	Q4 ≥343 ng/ml	Q1 <530 ng/ml	Q4 ≥817 ng/ml	Q1 <83%	Q4 ≥121%	Q1 <26 ng/ml	Q4 ≥46 ng/ml
Age, yr – median (IQR)	61 (56–68)	62 (57–68)	60 (55–65)	65 (59–71)	60 (55–65)	64 (58–70)	63 (57–70)	61 (57–66)
Women	401 (49.1%)	412 (50.4%)	423 (51.9%)	371 (45.5%)	384 (47.0%)	425 (52.0%)	438 (53.5%)	360 (44.0%)
Black race	340 (41.6%)	398 (48.7%)	572 (70.2%)	214 (26.3%)	328 (40.1%)	445 (54.5%)	286 (35.0%)	455 (55.6%)
Geographic region of residence								
Stroke buckle	161 (19.7%)	154 (18.8%)	159 (19.5%)	179 (22.0%)	183 (22.4%)	150 (18.4%)	153 (18.7%)	178 (21.8%)
Other stroke belt	292 (35.7%)	271 (33.1%)	267 (32.8%)	292 (35.8%)	285 (34.9%)	297 (36.4%)	271 (33.1%)	256 (31.3%)
Other US region	364 (44.6%)	393 (48.0%)	389 (47.7%)	344 (42.2%)	349 (42.7%)	370 (45.3%)	394 (48.2%)	384 (46.9%)
BMI, kg/m^2 – median (IQR)	27 (25–31)	29 (26–33)	29 (26–32)	28 (25–31)	28 (25–31)	29 (26–33)	27 (24–31)	30 (27–34)
Diabetes mellitus	82 (10.0%)	157 (19.2%)	140 (17.2%)	106 (13.0%)	103 (12.6%)	146 (17.9%)	75 (9.2%)	193 (23.6%)
Hypertension	363 (44.4%)	462 (56.5%)	433 (53.1%)	401 (49.2%)	365 (44.7%)	454 (55.6%)	348 (42.5%)	467 (57.1%)
SBP, mm Hg – median (IQR)	121 (112–131)	126 (118–137)	123 (117–135)	123 (116–133)	122 (115–133)	124 (116–135)	121 (113–131)	126 (119–136)
Coronary artery disease	82 (10.0%)	98 (12.0%)	80 (9.8%)	109 (13.4%)	84 (10.3%)	112 (13.7%)	95 (11.6%)	83 (10.1%)
Dyslipidemia	426 (52.1%)	485 (59.3%)	467 (57.3%)	457 (56.1%)	424 (51.9%)	496 (60.7%)	424 (51.8%)	501 (61.2%)
eGFR, ml/min per 1.73 m^2 – median (IQR)	96 (84–107)	88 (77–99)	97 (87–108)	87 (75–98)	98 (86–108)	87 (76–98)	93 (82–104)	91 (80–101)
Urine ACR, mg/g – median (IQR)	5.4 (3.7–8.5)	6.1 (4.2–10.2)	5.6 (3.9–8.7)	6.0 (4.0–9.7)	5.5 (3.8–8.7)	6.0 (4.2–9.9)	5.5 (3.9–8.7)	6.1 (4.0–10.3)
Smoking status[a]								
Never	445 (54.5%)	325 (39.7%)	364 (44.7%)	433 (53.1%)	409 (50.1%)	387 (47.4%)	414 (50.6%)	379 (46.3%)
Past	326 (39.9%)	322 (39.4%)	326 (40.0%)	329 (40.4%)	313 (38.3%)	348 (42.6%)	329 (40.2%)	324 (39.6%)
Current	43 (5.3%)	168 (20.5%)	122 (15.0%)	50 (6.1%)	95 (11.6%)	79 (9.7%)	73 (8.9%)	113 (13.8%)

ACR, albumin-to-creatinine ratio; BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate by the 2021 CKD-EPI equation with serum creatinine and cystatin C but not race; ICAM-1, intercellular cellular adhesion molecule 1; IQR, interquartile range; SBP, systolic blood pressure; VCAM-1, vascular cellular adhesion molecule 1.
[a]Column percentages may not add to 100% due to missing participant data. All data are <5% missing.
Unweighted participant characteristics are presented here, but logistic regression models were weighted to reflect the entire cohort from which this subcohort was sample.

biomarker levels by urine availability at the second visit (data not shown).

In Table 1, we show the characteristics of participants by highest and lowest quartiles of biomarkers. Participants with higher baseline ICAM-1 tended to have higher BMI, lower eGFR, diabetes, hypertension, dyslipidemia, and current smoking status. Those with higher VCAM-1 tended to be older, male, self-identify as White race, have coronary artery disease, lower eGFR, and were less frequently current smokers. Those with higher FVIII tended to be older, self-identify as Black race, have diabetes, hypertension, dyslipidemia, lower eGFR, and higher ACR. Those with higher E-selectin tended to be male, self-identify as Black race, have higher BMI, diabetes, hypertension, dyslipidemia, higher ACR, and current smoking status. Participant characteristics by all quartiles of biomarkers are shown in Supplementary Tables S1 to S4.

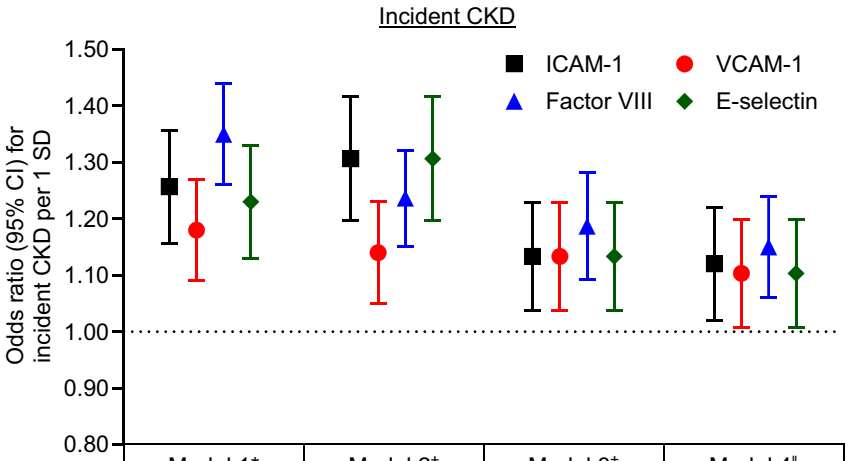
Examining pairwise correlations of biomarkers, only ICAM-1 and E-selectin were moderately correlated (Spearman $\rho = 0.40$; Supplementary Figure S3), whereas the remaining biomarkers had weak or negligible correlations. The correlation of biomarkers with eGFR ranged from −0.05 to −0.24 (Supplementary Figure S4).

Over a median follow-up of 9.4 years (IQR: 8.5–9.8), 228 (6.9%) developed CKD, 613 (18.6%) developed a ≥30% decline in eGFR, and 356 (11.4%) developed albuminuria (Supplementary Figures S1 and S2). Fewer than 11 participants developed end-stage kidney disease. Only 51 participants (1.6%) developed both incident CKD and albuminuria.

Baseline levels of each biomarker were higher in those who developed CKD than in those who did not (median concentrations for cases vs. noncases; ICAM-1, 306 vs. 294 ng/ml; VCAM-1, 675 vs. 656 ng/ml; FVIII, 108% vs. 100%; and E-selectin, 38 vs. 34 ng/ml). Similar findings were observed for participants that developed ≥30% decline in eGFR (median concentrations for cases vs. noncases: ICAM-1, 309 vs. 291 ng/ml; VCAM-1, 665 vs. 657 ng/ml; FVIII, 103% vs. 99%; and E-selectin, 36 vs. 34 ng/ml) and albuminuria (median concentrations for cases vs. noncases: ICAM-1, 301 vs. 294 ng/ml; VCAM-1, 664 vs. 657 ng/ml; FVIII, 105% vs. 100%; and E-selectin, 36 vs. 34 ng/ml).

Associations of Endothelial Dysfunction Biomarkers With Incident CKD

In unadjusted models (model 1), each of the 4 biomarkers had modest associations with incident CKD (Figure 1). Adjustment for demographic factors and geographic region of residence (model 2) attenuated the OR for incident CKD for FVIII and VCAM-1, whereas associations of ICAM-1 and E-selectin with incident CKD were accentuated. Further adjustment for CKD risk factors (model 3) partially attenuated the associations of ICAM-1 and E-selectin, but not VCAM-1 or FVIII. The final adjustment for baseline eGFR and urine ACR (model 4) did not alter interpretation and each



	Model 1*	Model 2†	Model 3‡	Model 4‖
ICAM-1	1.25 (1.16, 1.36)	1.30 (1.20, 1.42)	1.13 (1.04, 1.23)	1.12 (1.02, 1.22)
VCAM-1	1.18 (1.09, 1.27)	1.14 (1.05, 1.23)	1.13 (1.04, 1.23)	1.10 (1.01, 1.20)
Factor VIII	1.35 (1.26, 1.44)	1.24 (1.15, 1.32)	1.19 (1.09, 1.28)	1.15 (1.06, 1.24)
E-selectin	1.23 (1.13, 1.33)	1.30 (1.20, 1.42)	1.13 (1.04, 1.23)	1.10 (1.01, 1.20)

Figure 1. Odds ratios and 95% CIs for incident CKD per 1 SD increment of biomarkers of endothelial dysfunction.
[a]Model 1 was unadjusted.
[b]Model 2 adjusted for age, sex, race, and geographic region of residence.
[c]Model 3 was further adjusted for body mass index, hypertension, diabetes, coronary artery disease, smoking status, and dyslipidemia.
[d]Model 4 was further adjusted for baseline eGFR and ACR.
1 log-transformed SD was, as follows: ICAM-1, 0.25 ln(ng/ml); VCAM-1, 0.36 ln(ng/ml); factor VIII, 0.32 ln (%); E-selectin, 0.46 ln(ng/ml). Regression models were weighted to reflect the entire cohort from which this subcohort was sampled.
ACR, urinary albumin-to-creatinine ratio; CI, confidence interval; CKD, chronic kidney disease defined by eGFR <60 ml/min per 1.73 m^2 plus 40% decline from baseline or new kidney failure; eGFR, estimated glomerular filtration rate by 2021 CKD-EPI equation by serum creatinine and cystatin C; ICAM-1, intercellular cellular adhesion molecule 1.

biomarker remained independently associated with incident CKD. Fully adjusted ORs per 1 SD increment were 1.12 for ICAM-1 (95% CI: 1.02–1.22), 1.10 for VCAM-1 (95% CI: 1.01–1.20), 1.15 for FVIII (95% CI: 1.06–1.24), and 1.10 for E-selectin (95% CI: 1.01–1.20).

Interpretation of associations of categorically classified biomarkers were largely similar to continuous analysis results (Supplementary Table S5). The directionality and strength of ORs for associations for each biomarker closely matched primary analyses, and only the association for 4th versus 1st quartile of ICAM-1 was statistically significant in final models (adjusted OR 1.30, 95% CI: 1.02–1.66).

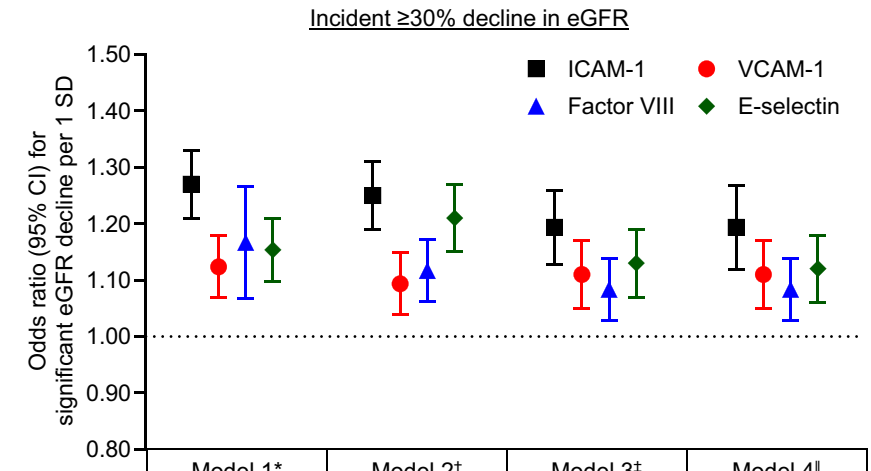
In the exploratory analysis with all 4 biomarkers added to a fully adjusted model 4 (Supplementary Figure S5), associations for FVIII and E-selectin closely matched the results above (adjusted ORs per 1 SD increment: 1.14 for FVIII [95% CI: 1.05–1.24], 1.09 for E-selectin [95% CI: 0.99–1.20]), whereas associations for ICAM-1 and VCAM-1 were attenuated (adjusted ORs per 1 SD increment: 1.03 for ICAM-1 [95% CI: 0.94–1.13], 1.05 for VCAM-1 [95% CI: 0.96–1.15]). In this model, the magnitudes of association for both FVIII and E-selectin were comparable to other risk factors, including female sex, higher BMI, hypertension, lower eGFR (per 10 ml/min per 1.73 m^2) and higher urine ACR (per 1 SD increment).

E-Selectin's Nonlinear Association With Incident CKD

Spline plots revealed a significant nonlinear association of E-selectin and incident CKD (adjusted *P*-value for nonlinear association = 0.01), but not other biomarkers (all other adjusted *P*-values for nonlinear association ≥0.06, plots not shown). For E-selectin, a threshold effect was observed, which persisted following sequential adjustments (Supplementary Figure S6; fully adjusted OR 1.41, 95% CI: 1.10–1.81 for 90th percentile vs. median).

Associations With Incident ≥30% Decline in eGFR

Analyses for the secondary outcome of ≥30% decline in eGFR were similar to the primary outcome (Figure 2, Supplementary Figure S7, Supplementary Table S6).



	Model 1*	Model 2†	Model 3‡	Model 4‖
ICAM-1	1.27 (1.21, 1.33)	1.25 (1.19, 1.31)	1.19 (1.13, 1.26)	1.19 (1.12, 1.27)
VCAM-1	1.12 (1.07, 1.18)	1.09 (1.04, 1.15)	1.11 (1.05, 1.17)	1.11 (1.05, 1.17)
Factor VIII	1.16 (1.07, 1.27)	1.12 (1.06, 1.17)	1.08 (1.03, 1.14)	1.08 (1.03, 1.14)
E-selectin	1.15 (1.10, 1.21)	1.21 (1.15, 1.27)	1.13 (1.07, 1.19)	1.12 (1.06, 1.18)

Figure 2. Odds ratios and 95% CIs for incident ≥ 30% decline in eGFR per 1 SD increment of biomarkers of endothelial dysfunction.
[a]Model 1 was unadjusted.
[b]Model 2 adjusted for age, sex, race, and geographic region of residence.
[c]Model 3 was further adjusted for body mass index, hypertension, diabetes, coronary artery disease, smoking status, and dyslipidemia.
[d]Model 4 was further adjusted for baseline eGFR and ACR.
1 log-transformed SD was, as follows: ICAM-1, 0.25 ln(ng/ml); VCAM-1, 0.36 ln(ng/ml); factor VIII, 0.32 ln(%); E-selectin, 0.46 ln(ng/ml). Regression models were weighted to reflect the entire cohort from which this subcohort was sampled.
ACR, urinary albumin-to-creatinine ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate by 2021 CKD-EPI equation by serum creatinine and cystatin C; ICAM-1, intercellular cellular adhesion molecule 1.

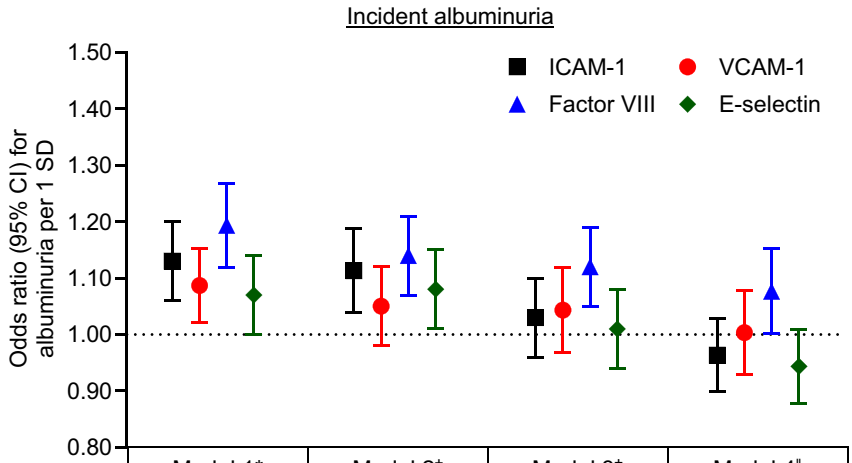
Associations With Incident Albuminuria

Only higher FVIII was independently associated with higher odds of incident albuminuria (Figure 3; adjusted OR 1.08 per 1 SD increment FVIII, 95% CI: 1.00–1.15). Spline plots showed nonlinear association for E-selectin only (adjusted *P*-value to nonlinear association <0.001, $P \geq 0.27$ for all other markers) with an inverse association apparent at only extreme high concentrations (adjusted OR 0.75 [95% CI: 0.60–0.94] for 90th percentile vs. median; Supplementary Figure S8). These patterns of association for FVIII and E-selectin were not confirmed by quartile analyses (Supplementary Table S7).

DISCUSSION

In this biracial cohort of US adults followed-up with for 9.4 years, multiple biomarkers of endothelial dysfunction were associated with incident CKD, but not incident albuminuria. Each SD higher baseline concentration of ICAM-1, VCAM-1, FVIII, and E-Selectin were associated with a 10% to 15% higher odds of CKD independent of other risk factors. Only higher FVIII was associated with incident albuminuria. Taken together, these results suggest a role for endothelial dysfunction in the development of CKD, which deserves future mechanistic study.

To our knowledge, this is the first epidemiological study of ICAM-1, VCAM-1, or E-selectin and future kidney outcomes. Previous cohort studies implicated FVIII as a risk factor for incident eGFR decline,[16,17] and our data provide further support for this association. Other prospective studies reported associations of higher interleukin-6 with kidney outcomes,[16,18] and interleukin-6 is highly correlated with each of the biomarkers studied here.[33,34] Recent data from the Atherosclerosis Risk in Communities (ARIC) study examined the associations of thousands of protein aptamers with ≥50% decline in eGFR over 14 years. Although this study reported independent associations with other cell adhesion molecules, none of the markers examined in our study were independently associated with their outcome of eGFR decline and point estimates were not reported.[19] There are several possible explanations for these differences. First, the ARIC study did not delineate between incident CKD and CKD progression, whereas we focused on the former by



	Model 1*	Model 2†	Model 3‡	Model 4‖
ICAM-1	1.13 (1.06, 1.20)	1.11 (1.04, 1.19)	1.03 (0.96, 1.10)	0.96 (0.90, 1.03)
VCAM-1	1.09 (1.02, 1.15)	1.05 (0.98, 1.12)	1.04 (0.97, 1.12)	1.00 (0.93, 1.08)
Factor VIII	1.19 (1.12, 1.27)	1.14 (1.07, 1.21)	1.12 (1.05, 1.19)	1.08 (1.00, 1.15)
E-selectin	1.07 (1.00, 1.14)	1.08 (1.01, 1.15)	1.01 (0.94, 1.08)	0.94 (0.88, 1.01)

Figure 3. Odds ratios and 95% CIs for incident albuminuria per 1 SD increment of biomarkers of endothelial dysfunction. Model 1 was unadjusted.
[a]Model adjusted for age, sex, race, and geographic region of residence.
[b]Model 3 was further adjusted for body mass index, hypertension, diabetes, coronary artery disease, smoking status, and dyslipidemia.
[c]Model 4 was further adjusted for baseline eGFR and ACR.
Regression models were weighted to reflect the entire cohort from which this subcohort was sampled. Albuminuria was defined as ACR ≥30 mg/g. 1 log-transformed SD was, as follows: ICAM-1, 0.25 ln(ng/ml); VCAM-1, 0.36 ln(ng/ml); factor VIII, 0.32 ln (%); E-selectin, 0.46 ln(ng/ml).
ACR, urinary albumin-to-creatinine ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate by 2021 CKD-EPI equation by serum creatinine and cystatin C; ICAM-1, intercellular cellular adhesion molecule 1.

excluding participants with prevalent CKD and using rigorously defined outcomes for incident CKD. CKD is known to cause a proatherogenic, proinflammatory state which, in conjunction with increased oxidative stress and uremic damage from decreased kidney clearance, can directly cause and/or accelerate endothelial dysfunction.[35,36] The different endothelial molecules highlighted by REGARDS and ARIC could implicate separate pathways for CKD initiation and progression; however, this requires further study to understand. Second, differences in laboratory approaches may be relevant, because ARIC relied upon aptamer multiplex assays, and we measured biomarkers using immunoassay. Limited data suggest that proteomic multiplex has less favorable reliability for several inflammatory markers, including interleukin-6.[37] However, there are no data for the comparative reliability of these methods for the markers studied here; thus, it is uncertain how this may have affected the ARIC results. More research is needed to characterize how these proteins, or the pathways they represent, mark and/or directly impact CKD risk and progression.

The positive associations of these biomarkers of endothelial dysfunction with incident CKD shed light on mechanisms that may be important to CKD initiation. Inflammation and vascular oxidative stress are well-established risk factors for CKD incidence and progression.[18,38] ICAM-1 and VCAM-1 are expressed by both leukocytes and endothelial cells, but direct endothelial activation is required for E-selectin expression and FVIII release from the subendothelium.[39] Although each biomarker had independent association when modeled separately, the complete attenuation of the associations of ICAM-1 and VCAM-1 in our model with all 4 markers suggests that inflammatory markers may not link endothelial activation and CKD risk. ICAM-1 and VCAM-1 also mark early atherosclerotic changes,[40,41] which may underpin previous epidemiologic data linking dyslipidemia to CKD risk.[42-44] Further, the complex bidirectional association between inflammation and coagulation suggests a role for chronic coagulation activation in the renal vasculature. Higher FVIII levels are common in CKD, are associated with venous thromboembolism in CKD, and mediate the association of CKD with venous

thromboembolism.[10,45] Repeated formation of microthrombi in the kidney with resultant oxidative damage could cause CKD, but data supporting this is scarce. Renal vaso-occlusive lesions have been described in antiphospholipid syndrome nephropathy.[46] Nevertheless, histologic microthrombus burden is not associated with kidney outcomes in lupus nephritis[47] and the importance of microthrombi in acute kidney injury in the setting of COVID-19 is uncertain.[48] Our findings are hypothesis generating in nature and additional work is warranted to understand the mechanism(s) underlying these associations.

Beyond the renal vasculature, the similar strength of association of higher FVIII with incident CKD and albuminuria also highlights a potential role for coagulation in glomerular integrity. Endothelial dysfunction is a known driver of diabetic nephropathy[49-51]; however, the role of procoagulant pathways in the initiation of albuminuria is not well-established outside of fibrin-mediated[52] and preeclamptic glomerular injuries.[53] Nevertheless, glomerular endothelial cells are 1 of the few tissues that produce FVIII mRNA.[54] Other data implicates the proinflammatory cytokine nuclear factor kappa B as a key regulator of glomerular aging,[55] and nuclear factor kappa B also mediates FVIII expression.[56] Separately, our results indicating null (ICAM-1 and VCAM-1) and possibly inverse (E-selectin) associations between the proinflammatory biomarkers and incident albuminuria was unexpected and future research is needed to understand the complex interaction between inflammation and coagulation in the initiation of albuminuria.

We identified a nonlinear threshold effect for the association of E-selectin with CKD. This may be important to understanding E-selectin's role in CKD pathogenesis. Few studies have addressed such nonlinear associations; however, previous data suggest a nonlinear association of E-selectin with incident diabetes[57] and individuals with diabetes have increased glomerular and interstitial expression of E-selectin.[58] Future studies should determine if, and how, E-selectin marks processes important to CKD initiation.

Previous studies established endothelial dysfunction as a deleterious mechanism by which CKD leads to accelerating cardiovascular disease and mortality[59-62]; those studies showed mechanisms related to chronic inflammation, oxidative stress, atherosclerosis, and uremic damage with decreased renal clearance in CKD.[63-65] Our observational results expand this to implicate endothelial dysfunction as a possible mechanism similarly important to CKD initiation, which suggests an cyclical injury pattern between endothelial damage and decreasing kidney function. Taken together, available evidence suggests that the endothelium is a target for preventing and/or attenuating CKD and its cardiovascular sequelae. This should be determined by future mechanistic studies.

There are several limitations to consider in interpreting this study. First, we acknowledge the potential for survival bias. It is possible that participants with substantial endothelial dysfunction were more likely to die before the second study visit and were not included in this analysis. In other REGARDS analyses on hypertension and stroke risk, this selection bias was minimal.[66,67] Any bias likely led to underestimation of risk; thus, true associations may be greater than reported here. Second, we did not measure all markers of endothelial dysfunction; thus, others may be of interest to future work. Third, we were unable to perform time-to-event analyses because we only had 2 measurements of kidney function at the initial and follow-up visits. Fourth, we did not measure endothelial dysfunction directly because there is no single common measurement of this. Brachial artery reactivity measurement had poor reliability in another large cohort study and is cumbersome to implement in a large cohort.[68] Fifth, though we attempted to comprehensively account for confounders, we acknowledge the possibility of residual unmeasured confounding. Finally, we did not obtain 24-hour urine samples for urinary albumin excretion, or repeat urine samples to account for temporal variability, but this is difficult in large population studies.[69]

This study had several strengths. The study is a large cohort study of community dwelling Black and White individuals with substantial follow-up, high retention over time, and high power for the study questions. We measured several candidate markers of endothelial dysfunction. Covariates and outcome measures were carefully measured in standardized fashion.

In this study, higher blood concentrations of ICAM-1, VCAM-1, E-selectin, and FVIII were independently associated with incident CKD, and higher FVIII was associated with incident albuminuria. Future studies should determine the mechanisms by which these molecules mark and/or cause kidney disease.

DISCLOSURE

All the authors declared no competing interests.

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DATA AVAILABILITY STATEMENT

REGARDS data are not publicly available due to ethical and legal restrictions. To abide by its obligations with National Institutes of Health/National Institute of Neurological Disorders and Stroke and the Institutional Review Board of the University of Alabama at Birmingham, REGARDS facilitates data sharing through formal data use agreements. Any investigator is welcome to access the REGARDS data, including statistical code, through this process. Requests for data access may be sent to regardsadmin@uab.edu. According to REGARDS policy, the aims and analysis plan for this manuscript were prespecified and reviewed and approved by the REGARDS publications committee, which also reviewed the final manuscript and assured the *a priori* plans were followed.

SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Figure S1. Cohort exclusion criteria and outcomes for incident CKD.

Figure S2. Cohort exclusion criteria and outcomes for incident albuminuria.

Figure S3. Pairwise correlations of baseline concentrations of biomarkers of endothelial dysfunction.

Figure S4. Correlations of baseline eGFR and concentrations of biomarkers of endothelial dysfunction.

Figure S5. Odds ratios and 95% confidence intervals for incident CKD in a fully adjusted model including 4 biomarkers of endothelial dysfunction.

Figure S6. Spline plots for nonlinear associations of E-selectin with incident CKD.

Figure S7. Spline plots for nonlinear associations of E-selectin with incident 30% eGFR decline.

Figure S8. Fully adjusted spline plots for the association of E-selectin with incident albuminuria.

Table S1. Baseline cohort characteristics by circulating ICAM-1.

Table S2: Baseline cohort characteristics by circulating VCAM-1.

Table S3. Baseline cohort characteristics by circulating factor VIII.

Table S4. Baseline cohort characteristics by circulating VCAM-1.

Table S5. Odds ratios and 95% confidence intervals for incident albuminuria by quartiles of biomarkers of endothelial dysfunction.

Table S6. Odds ratios and 95% confidence intervals for incident ≥30% decline in eGFR by quartiles of biomarkers of endothelial dysfunction.

Table S7. Odds ratios and 95% confidence intervals for incident albuminuria by quartiles of biomarkers of endothelial dysfunction.

STROBE Checklist.

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