

## **SUPPLEMENTARY MATERIAL**

Table S1. Frequency and Odds Ratio (95% Confidence Interval) for Incident Chronic Kidney Disease by Quartile and Per Standard Deviation Higher Serum Endothelin-1 Level Stratified by Sex

Table S2. Frequency and Odds Ratio (95% Confidence Interval) for Incident Chronic Kidney Disease by Quartile and Per Standard Deviation Higher Serum Endothelin-1 Level Stratified by Diabetes Status

Table S3. Frequency and Odds Ratio (95% Confidence Interval) for Incident Chronic Kidney Disease by Quartile and Per Standard Deviation Higher Serum Endothelin-1 Level Stratified by Hypertension Status

Table S4. Baseline Characteristics of Included vs. Excluded Jackson Heart Study Participants

Figure S1. Kernel Density Plot of Log-Transformed Baseline Serum Endothelin-1 Levels by Sex

Table S1. Frequency and Odds Ratio (95% Confidence Interval) for Incident Chronic Kidney Disease<sup>a</sup> by Quartile and Per Standard Deviation Higher Serum Endothelin-1 Level

Stratified by Sex

	Quartile of Endothelin-1 (Range)					Continuous Endothelin-1	
	Quartile 1: 0.1-1.0 pg/mL	Quartile 2: 1.1-1.3 pg/mL	Quartile 3: 1.4-1.6 pg/mL	Quartile 4: 1.7-9.6 pg/mL	P-value for trend	Frequency or OR (95% CI) <sup>b</sup>	P-value
<b>Men</b>							
Incident CKD, % (n/N) <sup>a</sup>	3.1% (13/418)	8.4% (29/347)	5.9% (16/273)	8.9% (25/282)	0.005	6.3% (83/1,320)	--
Unadjusted	1 [Ref]	2.84 (1.45, 5.55)	1.94 (0.92, 4.10)	3.03 (1.52, 6.03)	0.008	1.28 (1.08, 1.53)	0.006
Adjusted for age	1 [Ref]	2.57 (1.30, 5.05)	1.64 (0.77, 3.49)	2.63 (1.31, 5.27)	0.03	1.25 (1.04, 1.52)	0.02
Adjusted for age and risk factors <sup>c</sup>	1 [Ref]	2.39 (1.02, 5.62)	1.86 (0.72, 4.79)	2.26 (0.90, 5.65)	0.16	1.23 (0.97, 1.57)	0.09
Adjusted for age, risk factors <sup>c</sup> , and eGFR	1 [Ref]	2.54 (1.07, 5.99)	1.89 (0.73, 4.86)	2.38 (0.95, 5.99)	0.14	1.24 (0.97, 1.59)	0.08
<b>Women</b>							
Incident CKD, % (n/N) <sup>a</sup>	4.6% (37/801)	5.9% (33/558)	8.8% (35/396)	8.6% (40/463)	0.008	6.5% (145/2,218)	--
Unadjusted	1 [Ref]	1.30 (0.80, 2.10)	2.00 (1.24, 3.23)	1.95 (1.23, 3.10)	0.001	1.26 (1.09, 1.46)	0.002
Adjusted for age	1 [Ref]	1.08 (0.66, 1.78)	1.50 (0.91, 2.47)	1.27 (0.78, 2.05)	0.20	1.12 (0.96, 1.32)	0.16
Adjusted for age and risk factors <sup>c</sup>	1 [Ref]	1.41 (0.78, 2.56)	1.48 (0.80, 2.76)	1.57 (0.88, 2.82)	0.15	1.15 (0.97, 1.38)	0.11

Adjusted for age, risk factors <sup>c</sup> , and eGFR	1 [Ref]	1.44 (0.79, 2.63)	1.50 (0.80, 2.79)	1.58 (0.87, 2.85)	0.15	1.16 (0.97, 1.40)	0.11
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<sup>a</sup> Incident chronic kidney disease = visit 3 eGFR <60 mL/min/1.73 m<sup>2</sup> and ≥30% eGFR decline from visit 1 to visit 3; N=all participants without CKD at baseline with non-missing endothelin-1 values within each endothelin-1 quartile

<sup>b</sup> Odds ratio (95% confidence interval) for incident chronic kidney disease<sup>a</sup> per one standard deviation higher endothelin-1 level (0.62 pg/mL)

<sup>c</sup> Risk factors: body mass index, smoking, hypertension, anti-hypertensive medication use, hemoglobin A1c, diabetes, total and high-density lipoprotein cholesterol, history of cardiovascular disease, C-reactive protein, hematocrit

CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; OR, odds ratio

Table S2. Frequency and Odds Ratio (95% Confidence Interval) for Incident Chronic Kidney Disease<sup>a</sup> by Quartile and Per Standard Deviation Higher Serum Endothelin-1 Level Stratified by Diabetes Status

	Quartile of Endothelin-1 (Range)					Continuous Endothelin-1	
	Quartile 1:	Quartile 2:	Quartile 3:	Quartile 4:	P-value	Frequency or	P-value
	0.1-1.0 pg/mL	1.1-1.3 pg/mL	1.4-1.6 pg/mL	1.7-9.6 pg/mL	for trend	OR (95% CI) <sup>b</sup>	
Diabetes							
Incident CKD, % (n/N) <sup>a</sup>	12.3% (26/212)	16.7% (24/144)	19.9% (26/131)	13.3% (20/151)	0.23	15.1% (96/643)	--
Unadjusted	1 [Ref]	1.43 (0.78, 2.61)	1.77 (0.98, 3.21)	1.09 (0.58, 2.04)	0.52	1.05 (0.85, 1.30)	0.65
Adjusted for age and sex	1 [Ref]	1.38 (0.75, 2.52)	1.65 (0.90, 3.01)	1.02 (0.54, 1.92)	0.70	1.04 (0.83, 1.29)	0.75
Adjusted for age, sex, and risk factors <sup>c</sup>	1 [Ref]	1.37 (0.61, 3.11)	2.03 (0.90, 4.60)	1.10 (0.48, 2.54)	0.65	1.11 (0.84, 1.46)	0.45
Adjusted for age, sex, risk factors <sup>c</sup> , and eGFR	1 [Ref]	1.45 (0.64, 3.33)	2.07 (0.91, 4.68)	1.14 (0.49, 2.64)	0.61	1.12 (0.85, 1.47)	0.43
No Diabetes							
Incident CKD, % (n/N) <sup>a</sup>	2.4% (24/1,007)	5.0% (38/760)	4.7% (25/537)	7.6% (45/593)	<0.001	4.6% (132/2,914)	--
Unadjusted	1 [Ref]	2.16 (1.28, 3.63)	2.00 (1.13, 3.54)	3.36 (2.03, 5.58)	<0.001	1.36 (1.19, 1.56)	<0.001
Adjusted for age and sex	1 [Ref]	1.78 (1.05, 3.04)	1.44 (0.80, 2.60)	2.30 (1.37, 3.88)	0.005	1.26 (1.09, 1.45)	0.001
Adjusted for age, sex, and risk factors <sup>c</sup>	1 [Ref]	2.00 (1.08, 3.69)	1.55 (0.79, 3.07)	2.35 (1.26, 4.35)	0.02	1.27 (1.09, 1.48)	0.003

Adjusted for age, sex, risk factors <sup>c</sup> , and eGFR	1 [Ref]	2.00 (1.08, 3.71)	1.53 (0.77, 3.04)	2.31 (1.24, 4.30)	0.03	1.28 (1.09, 1.50)	0.002
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<sup>a</sup> Incident chronic kidney disease = visit 3 eGFR <60 mL/min/1.73 m<sup>2</sup> and ≥30% eGFR decline from visit 1 to visit 3; N=all participants without CKD at baseline with non-missing endothelin-1 values within each endothelin-1 quartile

<sup>b</sup> Odds ratio (95% confidence interval) for incident chronic kidney disease<sup>a</sup> per one standard deviation higher endothelin-1 level (0.62 pg/mL)

<sup>c</sup> Risk factors: body mass index, smoking, hypertension, anti-hypertensive medication use, hemoglobin A1c, total and high-density lipoprotein cholesterol, history of cardiovascular disease, C-reactive protein, hematocrit

CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; OR, odds ratio

Table S3. Frequency and Odds Ratio (95% Confidence Interval) for Incident Chronic Kidney Disease<sup>a</sup> by Quartile and Per Standard Deviation Higher Serum Endothelin-1 Level Stratified by Hypertension Status

	Quartile of Endothelin-1 (Range)					Continuous Endothelin-1	
	Quartile 1: 0.1-1.0 pg/mL	Quartile 2: 1.1-1.3 pg/mL	Quartile 3: 1.4-1.6 pg/mL	Quartile 4: 1.7-9.6 pg/mL	P-value for trend	Frequency or OR (95% CI) <sup>b</sup>	P-value
Hypertension							
Incident CKD, % (n/N) <sup>a</sup>	6.7% (41/614)	10.4% (52/502)	10.0% (40/402)	11.8% (59/502)	0.03	9.5% (192/2,032)	--
Unadjusted	1 [Ref]	1.61 (1.05, 2.48)	1.54 (0.98, 2.43)	1.86 (1.23, 2.83)	0.007	1.21 (1.07, 1.36)	0.003
Adjusted for age and sex	1 [Ref]	1.46 (0.95, 2.27)	1.29 (0.81, 2.06)	1.55 (1.01, 2.38)	0.09	1.16 (1.02, 1.32)	0.02
Adjusted for age, sex, and risk factors <sup>c</sup>	1 [Ref]	1.84 (1.10, 3.10)	1.37 (0.78, 2.41)	1.95 (1.17, 3.28)	0.04	1.22 (1.06, 1.40)	0.005
Adjusted for age, sex, risk factors <sup>c</sup> , and eGFR	1 [Ref]	1.87 (1.11, 3.16)	1.37 (0.78, 2.41)	1.98 (1.18, 3.34)	0.04	1.23 (1.07, 1.41)	0.004
No Hypertension							
Incident CKD, % (n/N) <sup>a</sup>	1.5% (9/605)	2.5% (10/403)	4.1% (11/267)	2.5% (6/243)	0.13	2.4% (36/1,528)	--
Unadjusted	1 [Ref]	1.69 (0.68, 4.18)	2.85 (1.16, 6.95)	1.68 (0.59, 4.76)	0.11	1.17 (0.82, 1.66)	0.39
Adjusted for age and sex	1 [Ref]	1.46 (0.58, 3.67)	2.32 (0.94, 5.74)	1.32 (0.46, 3.78)	0.31	1.06 (0.73, 1.56)	0.75
Adjusted for age, sex, and risk factors <sup>c</sup>	1 [Ref]	2.58 (0.81, 8.21)	5.63 (1.75, 18.1)	2.33 (0.64, 8.53)	0.07	1.23 (0.82, 1.85)	0.31

Adjusted for age, sex, risk factors <sup>c</sup> , and eGFR	1 [Ref]	2.87 (0.89, 9.26)	6.45 (1.97, 21.1)	2.48 (0.65, 9.41)	0.05	1.32 (0.86, 2.01)	0.20
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<sup>a</sup> Incident chronic kidney disease = visit 3 eGFR <60 mL/min/1.73 m<sup>2</sup> and ≥30% eGFR decline from visit 1 to visit 3; N=all participants without CKD at baseline with non-missing endothelin-1 values within each endothelin-1 quartile

<sup>b</sup> Odds ratio (95% confidence interval) for incident chronic kidney disease<sup>a</sup> per one standard deviation higher endothelin-1 level (0.62 pg/mL)

<sup>c</sup> Risk factors: body mass index, smoking, hemoglobin A1c, diabetes, total and high-density lipoprotein cholesterol, history of cardiovascular disease, C-reactive protein, hematocrit

CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; OR, odds ratio

Table S4. Baseline Characteristics<sup>a</sup> of Included vs. Excluded Jackson Heart Study Participants

	Included in Cross-sectional Analysis (N=5,200)	Included in Prospective Analysis (N=3,538)	Excluded from Prospective Analysis (N=1,662)	P- value <sup>b</sup>
Age, years	55.4 (12.8)	53.9 (11.9)	58.6 (14.1)	<0.001
Male sex, %	36.7% (1,910)	37.3% (1,320)	35.5% (290)	0.21
Body mass index, kg/m <sup>2</sup>	31.7 (7.2)	31.8 (7.2)	31.7 (7.4)	0.58
Smoking, %	13.2% (682)	11.7% (412)	16.4% (270)	<0.001
Systolic blood pressure, mmHg	127.0 (18.4)	125.5 (17.1)	130.2 (20.6)	<0.001
Hypertension, %	61.4% (3,192)	57.1% (2,020)	70.7% (1,172)	<0.001
Antihypertensive medication use, %	61.6% (2,607)	57.3% (1,633)	70.3% (974)	<0.001
Hemoglobin A1c, %	6.0 (1.3)	5.9 (1.2)	6.2 (1.5)	<0.001
Diabetes, %	21.8% (1,131)	18.1% (638)	29.7% (493)	<0.001
Total cholesterol, mg/dL	199.3 (40.1)	198.9 (38.9)	200.3 (42.7)	0.25
HDL cholesterol, mg/dL	51.8 (14.6)	51.8 (14.3)	51.8 (15.4)	0.99
History of CVD, %	10.7% (557)	7.4% (260)	17.9% (297)	<0.001
C-reactive protein, mg/dL	0.51 (0.90)	0.48 (0.72)	0.58 (1.19)	<0.001
Hematocrit, %	39.3 (4.3)	39.6 (4.0)	38.8 (4.7)	<0.001
eGFR, mL/min/1.73 m <sup>2</sup>	94.1 (22.0)	97.9 (17.7)	86.0 (27.5)	<0.001
Urine albumin-to-creatinine ratio				
<30 mg/g	86.8% (2,164)	90.1% (1,586)	78.8% (578)	<0.001
30-300 mg/g	10.2% (255)	8.4% (8.4%)	14.6% (107)	



>300 mg/g	3.0% (75)	1.5% (26)	6.7% (49)	
Dietary protein intake, g/day	80.7 (37.4)	81.7 (37.4)	78.6 (37.2)	0.008
Dietary sodium intake, mg/day	3,446 (1,525)	3,457 (1,508)	3,423 (1,563)	0.48
Dietary acid load, mEq/day	11.0 (21.5)	11.6 (21.1)	9.5 (22.3)	0.002

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<sup>a</sup> Mean (standard deviation) for continuous variables; % (n) for categorical variables

<sup>b</sup> p-value for comparison of “excluded from prospective analysis” vs. “included in prospective analysis”

HDL, high-density lipoprotein; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate

