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The Spectrum of Subclinical Primary Aldosteronism and Incident Hypertension

A Cohort Study

Jenifer M. Brown, MD; Cassianne Robinson-Cohen, PhD; Miguel Angel Luque-Fernandez, MSc, MPH, PhD; Matthew A. Allison, MD, MPH; Rene Baudrand, MD; Joachim H. Ix, MD, MS; Bryan Kestenbaum, MD, MS; Ian H. de Boer, MD, MS; and Anand Vaidya, MD, MMSc

Background: Primary aldosteronism is recognized as a severe form of renin-independent aldosteronism that results in excessive mineralocorticoid receptor (MR) activation.

Objective: To investigate whether a spectrum of subclinical renin-independent aldosteronism that increases risk for hypertension exists among normotensive persons.

Design: Cohort study.

Setting: National community-based study.

Participants: 850 untreated normotensive participants in MESA (Multi-Ethnic Study of Atherosclerosis) with measurements of serum aldosterone and plasma renin activity (PRA).

Measurements: Longitudinal analyses investigated whether aldosterone concentrations, in the context of physiologic PRA phenotypes (suppressed, ≤0.50 μg/L per hour; indeterminate, 0.51 to 0.99 μg/L per hour; unsuppressed, ≥1.0 μg/L per hour), were associated with incident hypertension (defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or initiation of antihypertensive medications). Cross-sectional analyses investigated associations between aldosterone and MR activity, assessed via serum potassium and urinary fractional excretion of potassium.

Results: A suppressed renin phenotype was associated with a higher rate of incident hypertension than other PRA phenotypes (incidence rates per 1000 person-years of follow-up: suppressed renin phenotype, 85.4 events [95% CI, 73.4 to 99.3 events]; indeterminate renin phenotype, 53.3 events [CI, 42.8 to 66.4 events]; unsuppressed renin phenotype, 54.5 events [CI, 41.8 to 71.0 events]). With renin suppression, higher aldosterone concentrations were independently associated with an increased risk for incident hypertension, whereas no association between aldosterone and hypertension was seen when renin was not suppressed. Higher aldosterone concentrations were associated with lower serum potassium and higher urinary excretion of potassium, but only when renin was suppressed.

Limitation: Sodium and potassium were measured several years before renin and aldosterone.

Conclusion: Suppression of renin and higher aldosterone concentrations in the context of this renin suppression are associated with an increased risk for hypertension and possibly also with increased MR activity. These findings suggest a clinically relevant spectrum of subclinical primary aldosteronism (renin-independent aldosteronism) in normotension.

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For author affiliations, see end of text.
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With an estimated prevalence of 5% to 20% among patients with hypertension, primary aldosteronism (PA) is the most common and modifiable form of secondary hypertension (1–7). The disorder is characterized by autonomous secretion of aldosterone, independent of renin, which results in excessive activation of the mineralocorticoid receptor (MR). Excessive stimulation of the renal and extrarenal MR in PA has been associated with hypertension and cardiovascular disease, independent of blood pressure (8–14), highlighting the important role of MR antagonists in mitigating the systemic sequelae of renin-independent aldosteronism.

Although PA is usually described as a clinical phenotype of severe hypertension and hypokalemia caused by adrenal neoplasia, recent evidence points to another potentially prevalent cause of autonomous aldosterone secretion by abnormal cell clusters within *morphologically normal* adrenal glands: aldosterone-producing cell clusters (15–18).

Furthermore, recent physiology studies have challenged the notion that PA is a categorical disease by showing a continuous spectrum of renin-independent aldosteronism in normotension, ranging from subtle to overtly autonomous (19). In this regard, the overt PA that we currently recognize in severe hypertension (20) may be only the "tip of the iceberg" in the spectrum of renin-independent aldosteronism and excessive MR activation. Recognizing a potentially milder and expanded continuum of renin-independent aldosteronism, one that originates in normotension and is associated with inappropriate MR activation, may allow mitigation of MR-mediated cardiovascular disease at an earlier stage.

We conducted a longitudinal cohort study that used physiologic phenotypes of autonomous aldosterone secretion and MR activity. We investigated untreated normotensive participants enrolled in MESA (Multi-Ethnic Study of Atherosclerosis) to test the hy-

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pothesis that those with higher serum aldosterone levels in the context of renin suppression (renin-independent aldosterone secretion) would have a higher risk for hypertension than normotensive participants without renin suppression. Furthermore, we investigated whether MR activity corresponded with these renin and aldosterone phenotypes.

METHODS

Study Population

MESA is a multicenter cohort study of 6814 community-dwelling adults aged 45 to 84 years, established to study subclinical cardiovascular disease risk and progression (21). Participants without evidence of clinical cardiovascular disease were recruited between August 2000 and July 2002 from 6 U.S. study sites and examined every 2 to 3 years over approximately 10 years through December 2011, when examination 5 was completed (22). All participants provided informed consent, and the study was approved by institutional review boards at all participating sites.

For a random subset of 1960 participants, serum aldosterone and plasma renin activity (PRA) were measured at either examination 2 (between September 2002 and February 2004) or 3 (between March 2004 and September 2005), as previously described (23). We included only those who had aldosterone and PRA assessments, were normotensive (systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg), and did not use any antihypertensive medications (24) at the time of serum aldosterone and PRA measurement (n = 850) (**Appendix Figure**, available at Annals.org).

Assessment of Aldosterone Levels in the Context of Renin Activity

Aldosterone was measured by competition-based radioimmunoassay (DiaSorin) (intra-assay coefficients of variation between 6.30% and 8.87%) and PRA by radioimmunoassay (DiaSorin) (interassay coefficients of variation between 6.89% and 18.38%) (23). Both aldosterone and PRA were measured in duplicate and averaged.

We created a priori phenotypic categories based on commonly seen and accepted thresholds to reflect hypothesized renin–angiotensin–aldosterone system and mineralocorticoid receptor (MR) activation physiology. Participants with PRA of 0.50 μg/L per hour or less (n = 392) were classified as having a "suppressed renin phenotype" that could reflect a state of suppressed renin–angiotensin–aldosterone activity or inappropriate renin-independent aldosterone secretion and MR activation, depending on the corresponding aldosterone levels. Participants with PRA of at least 1.0 μg/L per hour (n = 187) were classified as having an "unsuppressed renin phenotype," or a state of potentially appropriate MR activation in the setting of physiologic renin-dependent secretion of aldosterone. Participants with PRA between 0.51 and 0.99 μg/L per hour (n = 271) were classified as having an "indeterminate renin phenotype."

Assessment of Incident Hypertension

Blood pressure was measured in triplicate using a Dinamap PRO 100 automated oscillometric sphygmomanometer (GE Medical Systems) after 5 minutes of rest in a seated position, as described previously (23). The last 2 of 3 measurements of systolic and diastolic blood pressure were averaged for the analysis. Antihypertensive medication use was determined by medication inventory: At each study examination, participants brought in all medications used in the preceding 2 weeks and study staff transcribed the name, dose, and frequency of each from its container. Staff then asked participants about their adherence to each medication over the past 2 weeks.

Demographic and Laboratory Characterization of the Study Participants

At each study visit, participants completed self-administered questionnaires; had standardized interviews to evaluate demographics, medical history, medication use, and substance use; and had body mass index measured by trained study staff (25). Fasting venous blood samples were obtained after 12 hours of overnight fasting and at least 5 minutes of seated posture, and a random urine sample was collected. Specimens were immediately flash frozen, processed, and stored at −80 °C and were then thawed for analysis (23). Estimated glomerular filtration rate was calculated from serum creatinine measurements using the Chronic Kidney Disease Epidemiology Collaboration equation (26). Serum and urinary sodium, potassium, creatinine, and albumin were measured as previously described (22), and these values were used to calculate the urinary fractional excretion of potassium and predicted 24-hour urinary sodium excretion using the INTERSALT (International Cooperative Study on Salt, Other Factors, and Blood Pressure) equation (27, 28). Serum and urinary concentrations of sodium and potassium were measured only at examination 1.

Statistical Analysis

Our analytic approach was 2-fold (**Appendix Figure**). We did a longitudinal analysis to investigate the hypothesis that persons with the suppressed renin phenotype were more likely to have subclinical renin-independent aldosteronism and an increased risk for incident hypertension. We then did a cross-sectional analysis to investigate the hypothesis that those with the suppressed renin phenotype would have increased MR activity.

We used multivariable discrete Cox proportional hazard models (PROC PHREG procedure with discrete ties in SAS) to evaluate the association between serum aldosterone and incident hypertension by renin phenotypes and report the results as hazard ratios (29). We computed standardized marginal risk differences for renin and aldosterone phenotypes using weighted, adjusted, discrete hazard models (30). Incident hypertension events were assessed only at each follow-up exam-

Table 1. Characteristics of Study Participants in the Longitudinal Analysis*

Characteristic	Suppressed Renin Phenotype (PRA ≤0.50 μg/L per h) (*n* = 392)		Indeterminate Renin Phenotype (PRA, 0.51–0.99 μg/L per h) (*n* = 271)		Unsuppressed Renin Phenotype (PRA ≥1.0 μg/L per h) (*n* = 187)	
	<Median	≥Median	<Median	≥Median	<Median	≥Median
Participants, *n*	247	145	135	136	44	143
Mean age (SD), *y*	63.5 (9.3)	63.0 (9.2)	61.0 (9.0)	59.8 (7.7)	59.3 (9.1)	59.8 (9.3)
Female, *n (%)*	128 (51.8)	79 (54.5)	64 (47.4)	60 (44.1)	17 (38.6)	45 (31.5)
Race/ethnicity, *n (%)*						
White	104 (42.1)	61 (42.1)	63 (46.7)	62 (45.6)	15 (34.1)	67 (46.9)
Hispanic	51 (20.6)	33 (22.8)	45 (33.3)	37 (27.2)	18 (40.9)	50 (35.0)
African American	54 (21.9)	24 (16.6)	11 (8.1)	10 (7.4)	3 (6.8)	5 (3.5)
Chinese American	38 (15.4)	27 (18.6)	16 (11.9)	27 (19.9)	8 (18.2)	21 (14.7)
Mean BMI (SD), *kg/m²*	26.9 (4.9)	27.1 (4.9)	27.8 (4.9)	27.1 (5.2)	27.2 (5.4)	26.7 (4.7)
Mean fasting blood glucose level (SD)						
mmol/L	5.14 (1.48)	5.19 (0.95)	5.26 (1.19)	5.50 (1.88)	5.33 (1.5)	5.41 (1.9)
mg/dL	93 (27)	94 (17)	95 (21)	99 (34)	96 (27)	98 (34)
Mean blood pressure (SD), *mm Hg*						
Systolic	116.1 (13.3)	116.8 (13.6)	111.0 (12.9)	111.1 (12.5)	108.0 (11.2)	111.7 (14.5)
Diastolic	68.3 (8.5)	68.3 (8.7)	65.9 (9.1)	68.3 (8.1)	67.9 (8.2)	68.5 (8.2)
Mean eGFR (SD), *mL/min/1.73 m²*	83.8 (15.0)	81.0 (15.1)	84.6 (14.4)	83.2 (13.4)	85.2 (14.8)	84.5 (15.7)
Urinary albumin–creatinine ratio, *n (%)*						
Normal (<3.5 mg/mmol)	237 (96.0)	137 (94.5)	131 (97.0)	129 (94.9)	39 (88.6)	135 (94.4)
Microalbuminuria (3.5–35.0 mg/mmol)	10 (4.1)	8 (5.5)	4 (3.0)	6 (4.4)	4 (9.1)	6 (4.2)
Macroalbuminuria (≥35.0 mg/mmol)	0 (0)	0 (0)	0 (0)	1 (0.7)	1 (2.3)	2 (1.4)
Mean LDL cholesterol level (SD)						
mmol/L	3.0 (0.8)	3.0 (0.9)	3.1 (0.9)	3.0 (0.7)	3.0 (0.6)	3.1 (0.8)
mg/dL	115 (29)	116 (33)	119 (33)	115 (28)	117 (23)	118 (29)
Mean physical activity (SD), *MET min/wk*	1406.1 (1957.3)	1454.5 (1773.8)	1296.5 (1668.1)	1487.6 (1932.15)	1308.5 (2437.9)	1572.8 (1849.9)
Smoking status, *n (%)*						
Never	113 (45.8)	85 (58.6)	53 (39.3)	69 (50.7)	26 (59.1)	56 (39.2)
Former	95 (38.5)	44 (30.3)	63 (46.7)	45 (33.1)	10 (22.7)	64 (44.8)
Current	35 (14.2)	15 (10.3)	19 (14.1)	22 (16.2)	8 (18.2)	22 (15.4)
Unknown	4 (1.6)	1 (0.7)	0 (0)	0 (0)	0 (0)	1 (0.7)
Current alcohol use, *n (%)*	132 (53.4)	77 (53.1)	72 (53.3)	80 (58.8)	18 (40.9)	95 (66.4)
Oral estrogen use, *n (%)*	16 (6.5)	10 (6.9)	7 (5.2)	8 (5.9)	1 (2.3)	11 (7.7)
NSAID use, *n (%)*	36 (14.6)	15 (10.3)	19 (14.1)	19 (14.0)	6 (13.6)	11 (7.7)

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Table 1–Continued

Characteristic	Suppressed Renin Phenotype (PRA ≤0.50 μg/L per h) (*n* = 392)		Indeterminate Renin Phenotype (PRA, 0.51–0.99 μg/L per h) (*n* = 271)		Unsuppressed Renin Phenotype (PRA ≥1.0 μg/L per h) (*n* = 187)	
	<Median	≥Median	<Median	≥Median	<Median	≥Median
Highest education level, *n (%)*						
None to grade 11	37 (15.0)	25 (17.2)	14 (10.4)	22 (16.2)	9 (20.5)	30 (21.0)
High school to some college	75 (30.4)	45 (31.0)	40 (29.6)	42 (30.9)	14 (31.8)	39 (27.3)
Associate's, bachelor's, or professional degree	135 (54.7)	75 (51.7)	81 (60.0)	72 (52.9)	21 (47.7)	74 (51.2)
Annual income, *n (%)*						
<$30 000	79 (32.0)	53 (36.6)	32 (23.7)	44 (32.4)	17 (38.6)	46 (32.2)
$30 000–$75 000	111 (44.9)	44 (30.3)	72 (53.3)	55 (40.4)	15 (34.1)	54 (37.8)
>$75 000	57 (23.1)	48 (33.1)	31 (23.0)	37 (27.2)	12 (27.3)	43 (30.1)
No health insurance, *n (%)*	17 (6.9)	11 (7.6)	9 (6.7)	10 (7.4)	4 (9.1)	10 (7.0)
Aldosterone level, *pmol/L*						
Mean (SD)	241.3 (66.9)	475.6 (102.8)	252.1 (71.0)	503.2 (129.6)	271.0 (64.6)	584.1 (225.3)
Median (IQR)	246.7 (192.4–295.1)	449.9 (401.9–527.5)	266.3 (195.6–313.9)	468.1 (406.9–559.5)	288.2 (225.2–326.4)	521.5 (448.8–642.4)
PRA, *μg/L per h*						
Mean (SD)	0.28 (0.12)	0.28 (0.13)	0.69 (0.13)	0.75 (0.13)	1.81 (1.02)	1.76 (0.90)
Median (IQR)	0.29 (0.19–0.37)	0.29 (0.17–0.40)	0.66 (0.57–0.78)	0.86 (0.65–0.92)	1.39 (1.17–1.87)	1.55 (1.17–1.93)
ARR, *pmol/L per μg/L per h*						
Mean (SD)	1672 (4784)	3589 (8616)	384 (142)	697 (223)	181 (73)	371 (145)
Median (IQR)	849 (636–1300)	1603 (1154–3053)	373 (272–491)	644 (542–804)	197 (136–235)	355 (273–448)
Serum aldosterone and PRA, *n (%)*						
Measured at examination 2	93 (37.7)	48 (33.1)	47 (34.8)	54 (39.7)	17 (38.6)	55 (38.5)
Measured at examination 3	154 (62.3)	97 (66.9)	88 (65.2)	82 (60.3)	27 (61.4)	88 (61.5)

ARR = aldosterone-to-renin ratio; BMI = body mass index; eGFR = estimated glomerular filtration rate; IQR = interquartile range; LDL = low-density lipoprotein; MET = metabolic equivalent of task; NSAID = nonsteroidal anti-inflammatory drug; PRA = plasma renin activity.
* Baseline characteristics are presented corresponding to when serum aldosterone and PRA were measured, at examination 2 or 3. Characteristics are stratified by phenotypes of renin and serum aldosterone levels <median values (quartiles 1 and 2; aldosterone <349.7 pmol/L) or ≥median values (quartiles 3 and 4; aldosterone ≥349.7 pmol/L). Percentages may not sum to 100 due to rounding.

ination and were defined as development of systolic blood pressure of at least 140 mm Hg, development of diastolic blood pressure of at least 90 mm Hg, or initiation of any antihypertensive medication at a follow-up visit. Participants who did not develop hypertension were censored at their final follow-up examination. Covariates included baseline age, sex, race, body mass index, low-density lipoprotein cholesterol level, fasting blood glucose level, smoking status, alcohol consumption, medication use, physical activity, educational attainment, income, and insurance status. Exploratory models further included systolic blood pressure, estimated glomerular filtration rate, and proteinuria. We tested the interactions between serum aldosterone and phenotypes of renin and incident hypertension in adjusted interaction models using multiplicative terms in the regression models with Wald tests to evaluate significance.

Multivariable linear regression models were used to assess associations between serum aldosterone and biomarkers of MR activity in each renin phenotype, adjusting for sodium balance using serum sodium and predicted 24-hour urinary sodium excretion in addition to other potential confounding factors. We used adjusted interaction models to assess whether serum aldosterone and renin phenotypes were associated with serum and urinary potassium.

Analyses were done using SAS, version 9.4 (SAS Institute), and Stata, version 15 (StataCorp). A *P* value less than 0.05 was considered to be statistically significant for all analyses.

Role of the Funding Source

The funding sources had no role in the collection, analysis, or interpretation of the data; writing of the manuscript; or the decision to submit for publication.

Table 2. Renin Phenotype and the Multivariable-Adjusted Risk for Incident Hypertension*

Variable	Suppressed Renin Phenotype (PRA ≤0.50 μg/L per h)	Indeterminate Renin Phenotype (PRA, 0.51 to 0.99 μg/L per h)	Unsuppressed Renin Phenotype (PRA ≥1.0 μg/L per h)
Eligible participants, *n*	392	271	187
Total incident hypertension events, *n*	168	80	55
Person-years at risk	1969	1501	1013
Unadjusted			
Incidence rate of hypertension, *events per 1000 person-years*	85.4 (73.4 to 99.3)	53.3 (42.8 to 66.4)	54.5 (41.8 to 71.0)
Risk difference, *events per 1000 person-years*	30.1 (11.5 to 50.1)	−1.2 (−19.7 to 17.3)	0 (reference)
Relative risk	1.74 (1.24 to 2.44)	0.98 (0.67 to 1.43)	1.00 (reference)
Model 1†			
Risk difference, *events per 1000 person-years*	38.8 (8.6 to 69.0)	−4.4 (−38.6 to 29.8)	0 (reference)
Relative risk	1.59 (1.12 to 2.26)	0.98 (0.67 to 1.44)	1.00 (reference)
Model 2‡			
Risk difference, *events per 1000 person-years*	48.1 (15.8 to 80.4)	−7.1 (−44.3 to 30.1)	0 (reference)
Relative risk	1.68 (1.16 to 2.44)	0.94 (0.63 to 1.40)	1.00 (reference)
Exploratory model§			
Risk difference, *events per 1000 person-years*	28.4 (−4.4 to 61.2)	−1.0 (−46.9 to 26.1)	0 (reference)
Relative risk	1.27 (0.85 to 1.88)	0.93 (0.61 to 1.41)	1.00 (reference)

PRA = plasma renin activity.
* Relative risks are hazard ratios from Cox models representing risk for incident hypertension compared with the unsuppressed renin phenotype. Values in parentheses are 95% CIs.
† Adjusted for baseline age, sex, and race/ethnicity (white or Chinese, African, or Hispanic American).
‡ Adjusted for model 1 variables plus baseline body mass index, cigarette smoking status (never, former, current, or unknown), weekly physical activity measured in metabolic-equivalent-of-task minutes per week, alcohol use (yes/no), education level (no school to grade 11; high school to some college; or associate's, bachelor's, or other professional degree), annual income (<$30 000, $30 000 to $75 000, or >$75 000), health insurance status (yes/no), oral estrogen use (yes/no), nonsteroidal anti-inflammatory drug use (yes/no), and fasting blood glucose and low-density lipoprotein cholesterol levels.
§ Adjusted for model 2 variables plus baseline systolic blood pressure, estimated glomerular filtration rate, and urinary albumin–creatinine ratio.

RESULTS

Participant Characteristics

Baseline characteristics of the study population at the time of serum aldosterone and PRA measurements are shown in Table 1. Among 850 participants, 46% (*n* = 392) displayed a suppressed renin phenotype. When compared with participants with higher renin activity, those with a suppressed renin phenotype were older, were more likely to be female and African American, and had higher systolic blood pressure. Of note, although these participants had the lowest serum aldosterone concentrations, they had markedly elevated aldosterone-to-renin ratios (>750 pmol/L per μg/L per hour or >30 ng/dL per ng/mL per hour in conventional units) because they also had the lowest PRA (18) (Table 1).

Renin Phenotype and Incident Hypertension

Participants with a suppressed renin phenotype had a higher incidence rate of hypertension than those with indeterminate and unsuppressed renin phenotypes (incidence rates per 1000 person-years of follow-up: suppressed renin phenotype, 85.4 events [95% CI, 73.4 to 99.3 events]; indeterminate renin phenotype, 53.3 events [CI, 42.8 to 66.4 events]; unsuppressed renin phenotype, 54.5 events [CI, 41.8 to 71.0 events]). They also had a significantly higher risk for incident hypertension than those with the unsuppressed renin phenotype (adjusted hazard ratio, 1.68 [CI, 1.16 to 2.44]; adjusted risk difference, 48.1 excess events [CI, 15.8 to 80.4 events] per 1000 person-years) (Table 2). Additional exploratory analyses, including adjustments for baseline blood pressure and kidney function—factors that may be considered confounders but are also considered to be in the causal pathway because they are negatively affected by renin-independent aldosteronism (14, 31, 32)—attenuated the effect estimates and significance but did not meaningfully alter the direction of the findings (Table 2).

Aldosterone, Renin, and Incident Hypertension

Higher aldosterone levels were significantly associated with a higher risk for hypertension, but only in the context of a suppressed renin phenotype (Table 3). Effect estimates suggest an 18% (CI, 3% to 36%) higher risk for incident hypertension per 100-pmol/L increase in aldosterone levels when PRA was less than 0.50 μg/L per hour (Table 3). The same trends were also seen when aldosterone was analyzed as a categorical variable (quartiles); the relationship between higher aldosterone quartiles and incident hypertension was evident when renin was suppressed but not when renin was unsuppressed (Figure 1 and Appendix Table 1, available at Annals.org).

In an exploratory analysis restricted to participants who had their final longitudinal blood pressure assess-

ment without concurrent use of antihypertensive medications (that is, including only untreated normotensive and hypertensive participants and excluding those who initiated antihypertensive therapy), higher aldosterone levels were associated with a greater increase in systolic blood pressure, independent of baseline blood pressure and other confounders, but only when renin was suppressed (Appendix Table 2, available at Annals.org).

MR Activity

We examined biomarkers of MR activity (serum potassium and urinary fractional excretion of potassium) to investigate whether the risk for hypertension might be mediated by MR. Characteristics of the study population at examination 1, when biomarkers of MR activity were available, were similar to those at examinations 2 and 3, when aldosterone and PRA were measured (Appendix Table 3, available at Annals.org). The mean serum sodium and potassium, predicted 24-hour urinary sodium balance (approximately 4 g of sodium per day), and urinary fractional excretion of potassium did not differ notably across renin phenotypes (Appendix Table 3). Despite this similarity in group means, in participants with a suppressed renin phenotype we saw a statistically significant association between higher serum aldosterone and lower serum potassium concentrations within the normal range (4.0 to 5.5 mmol/L) and higher urinary fractional excretion of potassium (Table 4). In contrast, we saw no statistically significant relationship between serum aldosterone levels and serum or urinary potassium in higher renin phenotypes, where MR activation was hypothesized to be more physiologic and appropriate (Table 4).

DISCUSSION

We report evidence from a large and ethnically diverse cohort of untreated normotensive persons, showing that higher serum aldosterone concentrations in the setting of suppressed renin activity (that is, renin-independent aldosteronism) are associated with increased risk for incident hypertension despite overall lower absolute aldosterone concentrations. These findings underscore the concept that the risk for aldosterone-mediated hypertension is not dictated by the absolute level of serum aldosterone, but rather by aldosterone autonomy from its dominant regulators, renin and angiotensin II. Of note, higher aldosterone levels were associated with lower serum potassium and higher urinary fractional excretion of potassium, but only when renin was suppressed. Collectively, these findings indicate an expanded spectrum of clinically relevant renin-independent aldosteronism, and possibly MR activation, that increases the risk for hypertension in a normotensive population never suspected to have autonomous aldosterone secretion or PA.

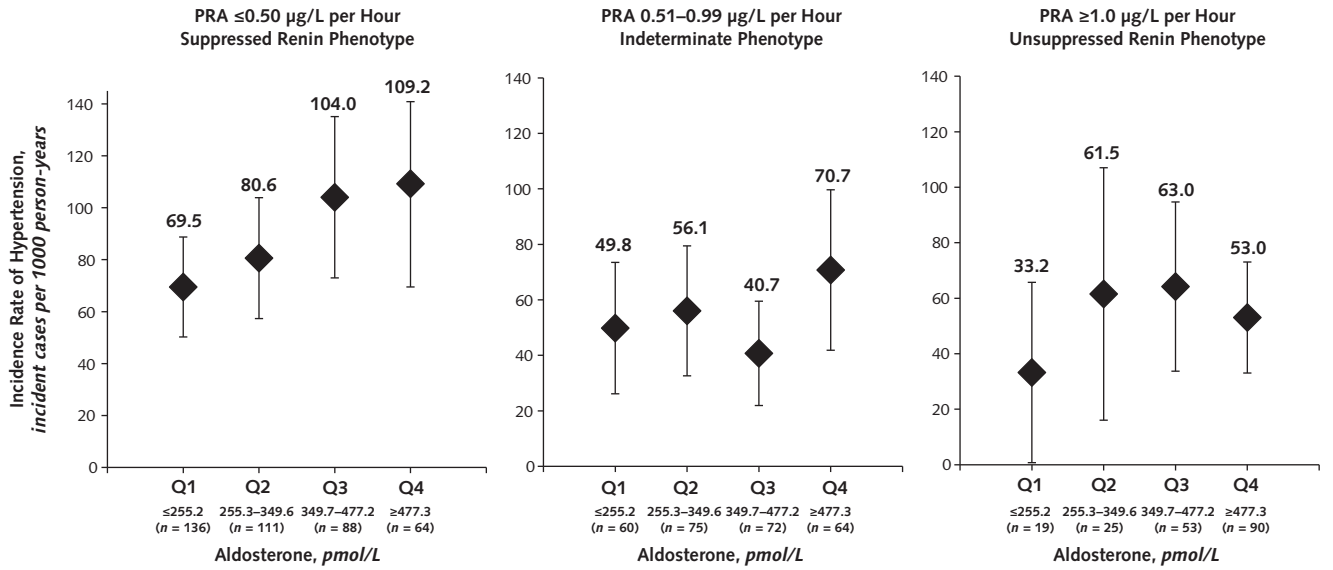
The results of this physiology-based longitudinal study challenge the long-standing dogma on the arbitrary definitions of PA and on the pathogenesis and treatment of hypertension. First, these results support the notion that renin-independent aldosterone secretion need not be a pathologic phenotype reserved only for severe cases of PA; rather, it may be a common phenotype associated with subtle and inappropriate MR activity that can even exist among normotensive persons (19, 33). Second, a substantial proportion of cases of hypertension may not be "essential" (or idiopathic); rather, the current findings suggest that MR-mediated hypertension may be a common pathogenic mechanism. Because MR antagonists are widely available, this potentially large subset of MR-mediated hypertension may respond to targeted therapy. Third, if the latter is implicated, treatment guidelines for new-onset hypertension may be improved by using a renin phenotype–guided approach that more liberally incorporates MR antagonists in an individualized manner, as has been successful in resistant hypertension (34–37). Ultimately, however, these findings and challenges to existing dogma stem from an observational design;

Table 3. Multivariable-Adjusted Relative Risk for Incident Hypertension With Aldosterone as a Continuous Variable, by Renin Phenotype

Variable	Suppressed Renin Phenotype (PRA ≤0.50 μg/L per h)	Indeterminate Renin Phenotype (PRA, 0.51–0.99 μg/L per h)	Unsuppressed Renin Phenotype (PRA ≥1.0 μg/L per h)	*P* for Interaction
Eligible participants, *n*	392	271	187	
Total incident hypertension events, *n*	168	80	55	
Person-years at risk	1969	1501	1013	
Hazard ratio (95% CI)*				
Unadjusted	1.16 (1.03–1.32)	1.09 (0.94–1.26)	1.06 (0.94–1.19)	0.57
Multivariable model 1†	1.18 (1.04–1.34)	1.12 (0.96–1.30)	1.07 (0.94–1.21)	0.59
Multivariable model 2‡	1.18 (1.03–1.36)	1.12 (0.96–1.32)	1.07 (0.93–1.23)	0.69
Exploratory model§	1.15 (0.99–1.35)	1.13 (0.94–1.35)	1.04 (0.89–1.21)	0.36

PRA = plasma renin activity.
* Units are risk for incident hypertension per 100 pmol/L of serum aldosterone.
† Adjusted for baseline age, sex, and race/ethnicity (white or Chinese, African, or Hispanic American).
‡ Adjusted for model 1 variables plus baseline body mass index, cigarette smoking status (never, former, current, or unknown), weekly physical activity measured in metabolic-equivalent-of-task minutes per week, alcohol use (yes/no), education level (no school to grade 11; high school to some college; or associate's, bachelor's, or other professional degree), annual income (<$30 000, $30 000 to $75 000, or >$75 000), health insurance status (yes/no), oral estrogen use (yes/no), nonsteroidal anti-inflammatory drug use (yes/no), and fasting blood glucose and low-density lipoprotein cholesterol levels.
§ Adjusted for model 2 variables plus baseline systolic blood pressure, estimated glomerular filtration rate, and urinary albumin–creatinine ratio.

Figure 1. Renin-independent aldosteronism and the incidence rate of hypertension.



Unadjusted incidence rate of hypertension (number of incident cases per 1000 person-years at risk) by phenotypes of renin and quartiles of aldosterone. To convert PRA from SI to conventional units: 1 µg/L/h = 1 ng/mL/h. To convert aldosterone from SI to conventional units: 1 pmol/L = 0.036 ng/dL. Quartiles of aldosterone in conventional units are <9.23 ng/dL (Q1), 9.23–12.73 ng/dL (Q2), 12.74–17.32 ng/dL (Q3), and ≥17.32 ng/dL (Q4). PRA = plasma renin activity; Q = quartile.

therefore, they may serve as a foundation for future intervention studies that use MR antagonists.

The current findings extend and build on prior studies. Our cross-sectional physiology studies have shown that a suppressed renin phenotype can predict the degree of autonomous aldosterone secretion and MR activation (38). We previously showed that healthy normotensive persons with a suppressed renin phenotype exhibit a continuum of nonsuppressible aldosterone secretion associated with greater urinary potassium excretion, indicating a spectrum of renin-independent aldosterone secretion and corresponding MR activation in normotension (19). A prior longitudinal study of mostly white normotensive persons in the Framingham Heart Study reported higher serum aldosterone levels associated with an increased risk for hypertension over 4 years (39); however, renin phenotype and biomarkers of MR activity (such as potassium regulation) were not available to implicate the mechanism for the outcome. These prior cross-sectional and longitudinal findings suggested that excessive aldosterone in normotension may be an independent risk factor for hypertension but also raised questions about how "clinically relevant" autonomous aldosterone secretion should be assessed.

The most specific characterization of PA, and less severe autonomous and renin-independent aldosteronism, involves renin suppression, inappropriate secretion of aldosterone relative to renin and sodium status, and excessive MR activation. In this regard, our current study provides a unique and fairly comprehensive characterization of clinically relevant renin-independent aldosteronism. It included measures of both renin activity and serum aldosterone, measures of potassium and sodium homeostasis to assess MR activity, a long follow-up, and an ethnically diverse population that permitted assessments suggesting that normotensive African Americans and women may have higher rates of subclinical renin-independent aldosteronism. Taken together, the results frame the spectrum of renin-independent aldosteronism in normotension, and the pathogenesis of MR-mediated hypertension, with greater clarity and scope.

Our study design was observational and community-based and therefore did not include interventions to control dietary factors that influence renin and aldosterone. Day-to-day variability in dietary sodium and potassium intake could have influenced our renin and aldosterone results, an issue further compounded by the fact that sodium and potassium phenotyping occurred years before renin and aldosterone phenotyping. However, the sodium and potassium balances were similar across renin phenotypes (**Appendix Table 3**), and large cohort studies have shown intra-individual correlation and reasonable reproducibility in these metrics over 1 to 3 years of follow-up (40, 41).

More important, this limitation does not degrade the validity of our observational findings, which are supported by physiologic principles. The decoupling of elevated aldosterone levels and suppression of renin associated with the highest risk for incident hypertension (**Figure 1**, *left*) cannot be explained by dietary sodium balance, but only as an autonomous or renin-independent aldosteronism. Conversely, renin-dependent aldosterone secretion (**Figure 1**, *right*) cannot be ascribed to autonomous aldosterone secretion because renin was not suppressed and was therefore presumptively physiologic. Furthermore, the group

with a suppressed renin phenotype (PRA ≤0.50 μg/L per hour) probably comprised participants with "normal" physiology who had appropriately suppressed renin and aldosterone levels and relatively high sodium intake, those who had autonomous aldosteronism despite renin suppression and high sodium intake (renin-independent aldosterone secretion), and possibly also those with suppressed renin and aldosterone due to nonaldosterone MR ligands that were not directly assessed in the current study (42, 43). Thus, this heterogeneous mixture of normal (physiologic) and abnormal (pathophysiologic) phenotypes when PRA was 0.50 μg/L per hour or less should have favored the null hypothesis by decreasing the likelihood and detectability of autonomous aldosteronism. That our main findings occurred despite this heterogeneity should increase confidence that the renin-independent aldosteronism associated with incident hypertension can be detected in a real-world setting despite ad libitum dietary sodium intake.

We propose the expanded spectrum of renin-independent aldosteronism in Figure 2 on the basis of these results. At its most severe, PA is characterized by an overt clinical phenotype of severe or resistant hypertension or hypokalemia (Figure 2, *A*). This overt PA is readily recognized by the highly sensitive aldosterone-to-renin ratio screen and confirmed using a recommended confirmatory test (20). The presumptive histopathology underlying overt PA is typically an aldosterone-producing adenoma or bilateral adrenocortical hyperplasia (20). Although the aldosterone-to-renin ratio is a highly sensitive tool for detecting PA in severe hypertensive or hypokalemic populations (20), some studies have shown that when confirmatory testing for PA is applied to populations with no obvious clinical phenotype for PA or MR overactivation, a surprisingly high prevalence of PA is still detected (Figure 2, *B*). Studies in mildly hypertensive populations have shown that 3% to 20% of persons with stage 1 hypertension show overt biochemical confirmation for PA on salt suppression, fludrocortisone, or captopril suppression tests (44–46) and that the degree of renin suppression predicts the severity of PA (44). Even in cohorts that are entirely normotensive, 3% to 14% have been confirmed to have overt biochemical PA with a concomitant increased risk for hypertension (19, 33). Therefore, this extension of the renin-independent aldosteronism continuum is pertinent because PA screening is *not* recommended for normotensive or mildly hypertensive patients, yet the prevalence of unrecognized yet biochemically overt PA may be substantial (47) (Figure 2, *B*).

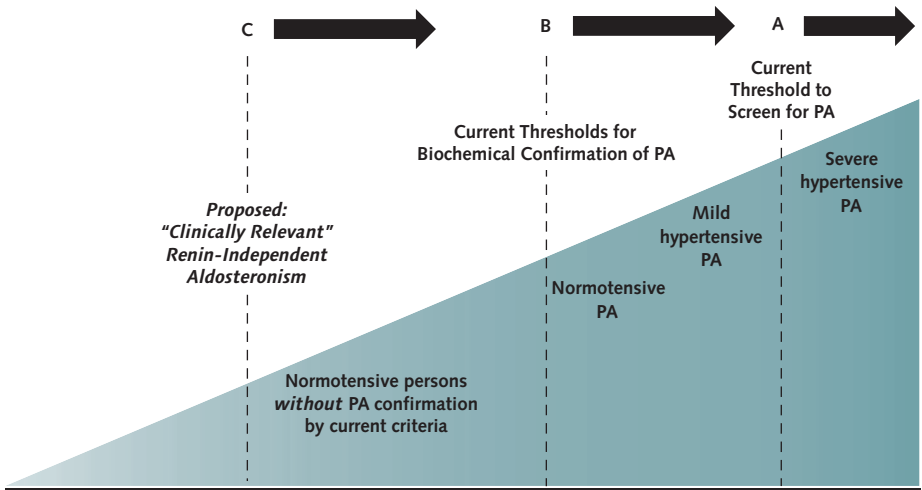
We now propose that the spectrum of clinically relevant renin-independent aldosteronism may extend even to persons with no apparent clinical syndrome of excessive MR activation and who fall below the current thresholds used to confirm PA (Figure 2, *C*). Participants in this study were untreated, normotensive, and normokalemic and without known PA, and yet nearly half showed a phenotype of renin suppression wherein higher aldosterone levels within the normal range (mean, about 300 to 335 pmol/L or about 11 to 12 ng/dL in conventional units) were associated with an increased risk for hypertension and potential evidence for high MR activity. Although MESA participants did not have confirmatory tests to check for occult normo-

Table 4. Cross-sectional Relationship Between Serum Aldosterone Levels and Indicators of Mineralocorticoid Receptor Activity, by Renin Activity Level*

Variable	Mean Serum Potassium Level (SD), *mmol/L*	Mean Serum Aldosterone Level (SD), *pmol/L*	Unadjusted		Adjusted†		*P* for Interaction‡
			Change in Serum Potassium Level per 100 pmol/L of Serum Aldosterone, *mmol/L*	*P* Value	Change in Serum Potassium Level per 100 pmol/L of Serum Aldosterone, *mmol/L*	*P* Value	
Serum potassium							0.012
PRA ≤0.50 μg/L per h	4.36 (0.32)	328.0 (139.8)	−0.033	0.007	−0.034	0.002	
PRA, 0.51 to 0.99 μg/L per h	4.35 (0.32)	378.1 (163.4)	0.010	0.42	0.002	0.86	
PRA ≥1.0 μg/L per h	4.33 (0.29)	510.4 (239.7)	−0.004	0.66	0.006	0.56	
	Mean Urinary FeK (SD), %		**Change in Urinary FeK per 100 pmol/L of Serum Aldosterone, %**		**Change in Urinary FeK per 100 pmol/L of Serum Aldosterone, %**		
Urinary FeK							0.041
PRA ≤0.50 μg/L per h	11.9 (5.3)	328.0 (139.8)	0.421	0.033	0.501	0.008	
PRA, 0.51 to 0.99 μg/L per h	11.0 (4.9)	378.1 (163.4)	0.191	0.49	0.068	0.73	
PRA ≥1.0 μg/L per h	11.5 (4.8)	510.4 (239.7)	−0.097	0.55	0.010	0.95	

FeK = fractional excretion of potassium; PRA = plasma renin activity.
* The relationship between serum aldosterone and serum potassium levels and serum aldosterone and urinary FeK by renin phenotype is shown.
† Adjusted for factors at examination 1: age, sex, race/ethnicity (white or Chinese, African, or Hispanic American), body mass index, education level (no school to grade 11; high school to some college; or associate's, bachelor's, or other professional degree), fasting blood glucose level, systolic blood pressure, serum sodium level, predicted 24-h urinary sodium excretion based on the INTERSALT (International Cooperative Study on Salt, Other Factors, and Blood Pressure) equation, and estimated glomerular filtration rate.
‡ Interaction between PRA phenotypes and aldosterone as a continuous variable and adjusted for all factors at examination 1.

Figure 2. The proposed severity spectrum of renin-independent aldosteronism.



Disease	*Subclinical Primary Aldosteronism: "Syndrome of Renin-Independent Aldosteronism"*	Unrecognized Yet Biochemically Overt PA	Overt PA
Obvious clinical syndrome of excessive MR activation?	No	No	Yes
Biochemical confirmation of PA using *current* thresholds?	No	Yes	Yes
Histopathology	*Aldosterone-producing cell clusters*		*APA/BAH*

APA = aldosterone-producing adenoma; BAH = bilateral adrenal hyperplasia; MR = mineralocorticoid receptor; PA = primary aldosteronism. **A.** The Endocrine Society clinical practice guidelines recommend screening for PA using the aldosterone-to-renin ratio in severe or resistant hypertension. This practice of screening for a very high aldosterone-to-renin ratio (>750–830 pmol/L per μg/L per hour or >20–30 ng/dL per ng/dL per hour in conventional units) is highly sensitive for detecting patients with severe hypertensive PA: those with an obvious clinical syndrome of excessive MR activation (hypertension or hypokalemia) who are confirmed to have biochemically overt PA and likely have an APA or BAH as the cause of their disease. **B.** Using confirmatory testing thresholds recommended by The Endocrine Society (such as oral or intravenous sodium loading, flurdrocortisone suppression, or captopril challenge), researchers have seen that a substantial portion of normotensive and mildly hypertensive persons, populations for whom PA screening is not routinely recommended, have biochemically overt PA. These patients have unrecognized yet biochemically overt PA. **C.** Even below the Endocrine Society–recommended thresholds of what is currently considered biochemical confirmation of PA, a continuum of renin-independent aldosteronism exists among healthy normotensive and mildly hypertensive persons, in whom no obvious clinical syndrome of MR overactivation is apparent. These persons have subtle evidence of renin-independent aldosteronism (renin suppression with inappropriately "normal" or high aldosterone levels) and higher risk for developing incident hypertension (as seen in the current study). This phenotype may best be described as "subclinical primary aldosteronism" or a "syndrome of clinically relevant renin-independent aldosteronism." The newly described and prevalent histopathology of aldosterone-producing cell clusters provides one potential explanation for this expanded continuum of subtle autonomous aldosteronism.

tensive PA, we have seen similar results before. Prior studies of untreated normotensive and hypertensive persons without PA have described a broad spectrum of aldosterone suppressibility with sodium loading (48, 49).

Why might a syndrome of renin-independent aldosteronism that imparts inappropriate MR activation and cardiovascular risk be so prevalent? The recent discovery of aldosterone-producing cell clusters provides the most compelling evidence to account for this frequency of dysregulated aldosterone physiology (**Figure 2**, *C*). Aldosterone-producing cell clusters are histopathologic findings of large clusters of CYP11B2 (also known as aldosterone synthase) expression that invade the zona fasciculata, harbor pathogenic mutations known to increase aldosterone secretion, and are not suppressed in the presence of volume expansion or aldosterone excess (15, 16). Of note, aldosterone-producing cell clusters have been found in more than 50% of morphologically normal adrenal glands (with no apparent tumor or hyperplasia) and increase in prevalence with older age (18), consistent with our current findings that autonomous aldosterone secretion may be a common pathogenic contributor to incident hypertension.

Our observations that a large proportion of normotensive persons have clinically relevant renin-independent aldosteronism (or subclinical primary aldosteronism) raises the question of whether MR antagonists may be a "targeted therapy" in patients with new-onset hypertension, or even prehypertension, with a suppressed renin phenotype. Most hypertension treatment guidelines do not emphasize the early use of MR antagonists or include a phenotype-driven approach based on renin or aldosterone (50). However, prior studies suggest that such an approach may indeed be more important than currently believed. Intervention studies in patients with severe and resistant hypertension and a low-renin phenotype have shown that use of MR antagonists provides superior blood pressure control (34–36) and cardiovascular benefit (37).

Furthermore, the addition of MR antagonists in resistant hypertension seems to be most beneficial to participants with the lowest renin (36).

This study has several important limitations. First, the baseline measures for the longitudinal analysis were obtained at examination 2 or 3, depending on when PRA and aldosterone were measured; however, cross-sectional analyses to assess MR activity relied on serum and urinary measures of potassium that were obtained only at examination 1. Although this resulted in comparisons of aldosteronism phenotypes with measures of MR activity across examinations, we used these comparisons as a cross-sectional and mechanistic validation of our longitudinal findings, and in this regard, our 2 analyses were complementary and consistent. It should be noted that all participants were normotensive and *untreated* at examination 2 or 3 (when aldosterone and PRA were measured), and therefore these phenotypic characteristics were likely stable and representative of each participant's renin and aldosterone phenotype (40, 41). Second, renin and aldosterone were measured on ad libitum dietary sodium intake. Third, the physiology between renin and aldosterone is complex, heterogeneous, and dynamic across a large continuum and therefore likely contributed to the fact that our simple interaction models were not statistically significant and CIs for phenotypes and incident hypertension overlapped. This suggests that other factors contribute to hypertension and that larger studies with greater power may provide more precise estimates of the risk for hypertension associated with renin and aldosterone phenotypes. Fourth, confirmatory testing for PA to identify participants who may have had unrecognized yet overt biochemical PA despite being normotensive was not done (33); however, our overarching message of using renin to identify normotensive persons who may have clinically relevant renin-independent aldosteronism and may benefit from MR antagonists would not have changed. Finally, our data are observational in nature and could be limited by residual confounding rather than representing etiologic relationships.

In addition to demonstrating the public health relevance of overt PA as a modifiable risk factor for cardiovascular disease, our results indicate a much broader and more subtle spectrum of renin-independent aldosteronism and MR activation that extends into healthy normotensive persons, a population in which PA is never suspected (20). In the context of a suppressed renin phenotype in normotension, even serum aldosterone levels that seem normal may be autonomous and result in inappropriate MR activation and a higher risk for hypertension. Our findings suggest that autonomous (or primary) aldosterone secretion may be more common than currently recognized and that it may play an important role in the pathogenesis of hypertension. Future studies using a renin phenotype–driven approach may efficiently identify new-onset or mild hypertension, or even high-risk prehypertension, with renin-independent aldosteronism that could preferentially benefit from MR antagonists.

From Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, Boston, Massachusetts; Vanderbilt University, Nashville, Tennessee; University of Washington, Seattle, Washington; London School of Hygiene & Tropical Medicine, London, United Kingdom; Pontificia Universidad Católica de Chile, Santiago, Chile; and University of California San Diego and Veterans Affairs San Diego Healthcare System, San Diego, California.

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Reproducible Research Statement: *Study protocol:* Available at www.mesa-nhlbi.org. *Statistical code:* Requests will be considered on a case-by-case basis by Dr. Vaidya (e-mail, anandvaidya@bwh.harvard.edu). *Data set:* Available with approvals from the MESA steering committee and local institutional ethics board(s).

Requests for Single Reprints: Anand Vaidya, MD, MMSc, Center for Adrenal Disorders, Division of Endocrinology, Diabetes, and Hypertension, Brigham and Women's Hospital, Harvard Medical School, 221 Longwood Avenue, RFB, Boston, MA 02115; e-mail, anandvaidya@bwh.harvard.edu.

Current author addresses and author contributions are available at Annals.org.

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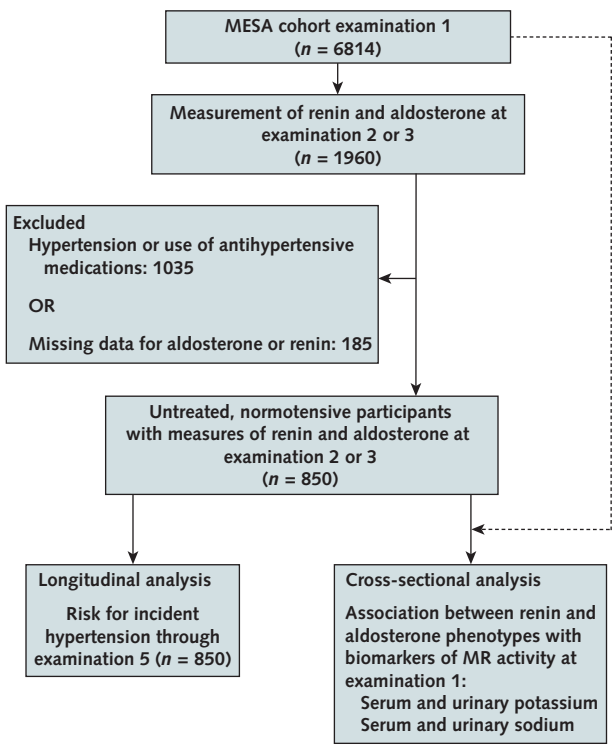
Current Author Addresses: Dr. Brown: Division of Cardiovascular Medicine, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115.
Dr. Robinson-Cohen: Division of Nephrology, Vanderbilt University, 1161 21st Avenue South, D-3100 Medical Center North, Nashville, TN 37232.
Dr. Luque-Fernandez: Department of Epidemiology, London School of Hygiene and Tropical Medicine, London WC1E 7HT, United Kingdom.
Dr. Allison: Department of Family Medicine and Public Health, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92093.
Dr. Baudrand: Department of Endocrinology, School of Medicine, Pontificia Universidad Católica de Chile, Santiago 8330074, Chile.
Dr. Ix: Division of Nephrology, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92093.
Drs. Kestenbaum and de Boer: Division of Nephrology, Department of Medicine, University of Washington, 410 9th Avenue, Seattle, WA 98104.
Dr. Vaidya: Center for Adrenal Disorders, Division of Endocrinology, Diabetes, and Hypertension, Brigham and Women's Hospital, Harvard Medical School, 221 Longwood Avenue, RFB, Boston, MA 02115.

Author Contributions: Conception and design: J.M. Brown, C. Robinson-Cohen, M.A. Allison, R. Baudrand, A. Vaidya.
Analysis and interpretation of the data: J.M. Brown, C. Robinson-Cohen, M.A. Luque-Fernandez, M.A. Allison, R. Baudrand, J.H. Ix, B. Kestenbaum, I.H. de Boer, A. Vaidya.
Drafting of the article: J.M. Brown, C. Robinson-Cohen, R. Baudrand, A. Vaidya.
Critical revision of the article for important intellectual content: J.M. Brown, C. Robinson-Cohen, M.A. Allison, R. Baudrand, J.H. Ix, B. Kestenbaum, I.H. de Boer, A. Vaidya.
Final approval of the article: J.M. Brown, C. Robinson-Cohen, M.A. Luque-Fernandez, M.A. Allison, R. Baudrand, J.H. Ix, B. Kestenbaum, I.H. de Boer, A. Vaidya.
Provision of study materials or patients: J.H. Ix, I.H. de Boer.
Statistical expertise: C. Robinson-Cohen, M.A. Luque-Fernandez, R. Baudrand, J.H. Ix, A. Vaidya.
Obtaining of funding: M.A. Allison, I.H. de Boer, A. Vaidya.
Administrative, technical, or logistic support: A. Vaidya.
Collection and assembly of data: M.A. Allison.

Appendix Figure. Study flow diagram.



Determination of the final study population, and which study examination variables were assessed for the longitudinal and cross-sectional analyses. MESA = Multi-Ethnic Study of Atherosclerosis; MR = mineralocorticoid receptor.

Appendix Table 1. Aldosterone and the Multivariable-Adjusted Risks for Incident Hypertension, by Renin Phenotype*

Variable	Suppressed Renin Phenotype (PRA ≤0.50 μg/L per h)				Indeterminate Renin Phenotype (PRA, 0.51 to 0.99 μg/L per h)			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Eligible participants, *n*	136	111	88	57	60	75	72	64
Incident hypertension events, *n*	50	46	43	29	17	22	18	23
Person-years at risk	719	571	414	266	341	392	442	325
Unadjusted incident rate of hypertension, *events per 1000 person-years*	69.5 (52.2 to 90.9)	80.6 (59.7 to 106.5)	104.0 (76.1 to 138.6)	109.2 (74.4 to 154.5)	49.8 (30.0 to 78.2)	56.1 (36.1 to 83.6)	40.7 (24.9 to 63.1)	70.7 (46.0 to 104.5)
Unadjusted risk difference, *events per 1000 person-years*	0 (reference)	11.1 (−19.1 to 41.4)	35.5 (−2.0 to 71.1)	40.0 (−4.4 to 84.1)	0 (reference)	6.2 (−27.0 to 39.5)	−9.1 (−39.3 to 21.1)	20.9 (−16.4 to 58.3)
Unadjusted HR	1.00 (reference)	1.19 (0.76 to 1.88)	1.69 (1.05 to 3.10)	1.80 (1.05 to 3.10)	1.00 (reference)	1.12 (0.57 to 2.23)	0.80 (0.39 to 1.62)	1.45 (0.73 to 2.89)
Model 1 risk difference, *events per 1000 person-years*†	0 (reference)	10.6 (−28.2 to 49.4)	53.1 (10.5 to 95.5)	49.9 (7.4 to 92.4)	0 (reference)	4.7 (−59.5 to 69.1)	−32.4 (−100 to 351)	35.5 (−29.7 to 100.8)
Model 1 HR†	1.00 (reference)	1.15 (0.73 to 1.83)	1.76 (1.08 to 2.85)	1.83 (1.06 to 3.18)	1.00 (reference)	1.02 (0.50 to 2.04)	0.77 (0.37 to 1.58)	1.46 (0.72 to 2.93)
Model 2 risk difference, *events per 1000 person-years*‡	0 (reference)	−8.0 (−78.6 to 62.6)	56.6 (22.5 to 110.8)	62.7 (12.0 to 113.4)	0 (reference)	11.4 (−75.6 to 98.4)	−18.7 (−139.0 to 101.5)	58.5 (−38.1 to 155.2)
Model 2 HR‡	1.00 (reference)	1.15 (0.69 to 1.91)	1.87 (1.11 to 3.15)	1.71 (0.93 to 3.15)	1.00 (reference)	1.01 (0.49 to 2.09)	0.55 (0.24 to 1.22)	1.47 (0.70 to 3.11)
Exploratory model HR‖	1.00 (reference)	1.22 (0.71 to 2.11)	1.87 (1.05 to 3.34)	1.60 (0.82 to 3.08)	1.00 (reference)	1.13 (0.51 to 2.52)	0.61 (0.26 to 1.46)	1.33 (0.58 to 3.02)

HR = hazard ratio; PRA = plasma renin activity; Q = quartile.

* Results are incident rates, risk differences, and relative risks for hypertension for each aldosterone Q in the context of renin phenotype. Aldosterone Qs compared with Q1 as the reference. Effect estimates are HRs. Units of HRs are risk for incident hypertension in relation to Q1 of aldosterone. Q1 = aldosterone level ≤255.2 pmol/L; Q2 = aldosterone level between 255.3 and 349.6 pmol/L; Q3 = aldosterone level between 349.7 and 477.2 pmol/L; and Q4 = aldosterone level ≥ 477.3 pmol/L. Values in parentheses are 95% CIs.

† Adjusted for baseline age, sex, and race/ethnicity (white or Chinese, African, or Hispanic American).

‡ Adjusted for model 1 variables plus baseline body mass index, cigarette smoking status (never, former, current, or unknown), weekly physical activity measured in metabolic-equivalent-of-task minutes per week, alcohol use (yes/no), education level (no school to grade 11; high school to some college; associate's, bachelor's, or other professional degree), annual income (<$30 000, $30 000-75 000, >$75 000), health insurance status (yes/no), oral estrogen use (yes/no), nonsteroidal anti-inflammatory medication use (yes/no), fasting blood glucose, low-density lipoprotein cholesterol.

§ Risk differences could not be calculated because of lack of model convergence.

‖ Adjusted for model 2 variables plus baseline systolic blood pressure, estimated glomerular filtration rate, and urinary albumin–creatinine ratio.

Appendix Table 1–Continued

Unsuppressed Renin Phenotype (PRA ≥1.0 μg/L per h)				*P* for Interaction
Q1	**Q2**	**Q3**	**Q4**	
19	25	53	90	
4	7	17	27	
120	114	270	509	
33.2 (10.6 to 80.4)	61.5 (26.9 to 12.2)	63.0 (37.9 to 98.8)	53.0 (35.7 to 76.1)	
0 (reference)	28.3 (−27.7 to 84.3)	30.7 (−13.8 to 75.3)	19.8 (−18.4 to 58.1)	
1.00 (reference)	1.97 (0.53 to 7.35)	2.13 (0.67 to 6.76)	1.68 (0.56 to 5.10)	0.66
0 (reference)	106.6 (−74.2 to 287)	68.1 (−48.0 to 184)	37.5 (−60.0 to 135)	
1.00 (reference)	1.75 (0.46 to 6.68)	1.67 (0.51 to 5.44)	1.43 (0.46 to 4.39)	0.55
0 (reference)	46.3 (−61.7 to 154.3)	§	§	
1.00 (reference)	2.69 (0.62 to 11.7)	1.80 (0.49 to 6.62)	1.43 (0.42 to 4.88)	0.47
1.00 (reference)	2.13 (0.48 to 9.44)	0.98 (0.26 to 3.74)	1.00 (0.29 to 3.50)	0.135

Appendix Table 2. Serum Aldosterone in the Context of Renin Phenotypes and the Change in Systolic Blood Pressure

Variable	Suppressed Renin Phenotype (PRA ≤0.50 μg/L per h)	Indeterminate Renin Phenotype (PRA, 0.51 to 0.99 μg/L per h)	Unsuppressed Renin Phenotype (PRA ≥1.0 μg/L per h)	*P* for Interaction
Participants, *n**	261	214	151	
Mean change in systolic blood pressure (SD), *mm Hg*†	4.9 (10.9)	4.2 (10.9)	4.2 (11.2)	
Unadjusted change in systolic blood pressure per 100 pmol/L of aldosterone (95% CI)	1.31 (0.32 to 2.30)	0.09 (−0.83 to 1.02)	0.49 (−0.36 to 1.34)	0.31
Multivariable-adjusted change in systolic blood pressure per 100 pmol/L of aldosterone (95% CI)‡	1.17 (0.11 to 2.24)	0.21 (−0.70 to 1.11)	0.57 (−0.38 to 1.52)	0.44

PRA = plasma renin activity.
* Analyses restricted to participants whose final systolic blood pressure assessment in follow-up was obtained without the use of antihypertensive medications (i.e., untreated hypertensive and normotensive persons, *n* = 626).
† The change in systolic blood pressure is defined as the systolic blood pressure measured on the final examination in follow-up minus the systolic blood pressure assessed at the baseline examination.
‡ Multivariable model adjusted for baseline age, sex, race/ethnicity (white or Chinese, African, or Hispanic American), body mass index, cigarette smoking status (never, former, current, or unknown), weekly physical activity measured in metabolic-equivalent-of-task minutes per week, alcohol use (yes/no), education level (no school to grade 11; high school to some college; associate's, bachelor's, or other professional degree), annual income (<$30 000, $30 000-75 000, >$75 000), health insurance status (yes/no), oral estrogen use (yes/no), nonsteroidal anti-inflammatory medication use (yes/no), fasting blood glucose, low-density lipoprotein cholesterol, and systolic blood pressure.

Appendix Table 3. Demographic and Biochemical Characteristics of Participants for Cross-sectional Analyses*

Characteristic	Suppressed Renin Phenotype (PRA ≤0.50 μg/L per h)	Indeterminate Renin Phenotype (PRA, 0.51-0.99 μg/L per h)	Unsuppressed Renin Phenotype (PRA ≥1.0 μg/L per h)
Participants, *n*	392	271	187
Mean age (SD), *y*	60.6 (9.3)	57.6 (8.5)	57.0 (9.3)
Female sex, *n (%)*	207/52.8	124/45.8	62/33.2
Race/ethnicity, *n (%)*			
White	165 (42.1)	125 (46.1)	82 (43.9)
Hispanic	84 (21.4)	82 (30.3)	68 (36.4)
African American	78 (19.9)	21 (7.8)	8 (4.3)
Chinese American	65 (16.6)	43 (15.9)	29 (15.5)
Mean BMI (SD), kg/m^2	27.1 (4.8)	27.3 (4.9)	26.6 (4.7)
Mean fasting blood glucose (SD), *mmol/L*	5.07 (1.18)	5.28 (1.75)	5.18 (1.45)
Mean systolic blood pressure (SD), *mm Hg*	118.0 (14.9)	114.6 (15.8)	113.9 (14.3)
Mean diastolic blood pressure (SD), *mm Hg*	69.6 (8.7)	69.2 (9.3)	70.3 (8.5)
Mean eGFR (SD), $mL/min/1.73\ m^2$	79.7 (14.1)	81.8 (13.4)	83.0 (14.0)
Smoking status, %			
Never smoker	56.4	48.7	46.8
Former	29.6	37.3	33.9
Current	14.0	14.0	19.4
Serum aldosterone, *pmol/L*			
Mean (SD)	328.0 (139.8)	378.1 (163.4)	510.4 (239.7)
Median (IQR)	305.8 (227.2–410.1)	353.2 (266.3–468.3)	473.1 (356.8–600.6)
PRA, *μg/L per h*			
Mean (SD)	0.28 (0.13)	0.72 (0.14)	1.77 (0.93)
Median (IQR)	0.29 (0.19–0.38)	0.70 (0.60–0.83)	1.52 (1.17–1.92)
ARR, *pmol/L per μg/L per h*			
Mean (SD)	2381 (6526)	541 (244)	326 (154)
Median (IQR)	1094 (728–1703)	518 (373–663)	312 (213–412)
Mean serum sodium (SD), *mmol/L*	147.0 (3.4)	147.3 (3.3)	147.2 (3.4)
Mean urinary sodium–creatinine ratio (SD), *mmol/g*	1.14 (0.60)	1.06 (0.56)	0.99 (0.52)
Mean predicted urinary sodium excretion (SD), *mg/d*†	4243 (854)	4116 (835)	3888 (791)
Mean serum potassium (SD), *mmol/L*	4.36 (0.32)	4.35 (0.32)	4.33 (0.29)
Mean urinary potassium–creatinine ratio (SD), *mmol/g*	0.58 (0.27)	0.54 (0.25)	0.55 (0.24)
Mean urinary FeK (SD), *% of potassium excreted*	11.9 (5.3)	11.0 (4.9)	11.5 (4.8)

ARR = aldosterone–renin ratio; BMI = body mass index; eGFR = estimated glomerular filtration rate; FeK = fractional excretion of potassium; IQR = interquartile range; PRA = plasma renin activity.
* All presented characteristics are from examination 1 except for aldosterone, PRA, and the ARR, which represent the renin–angiotensin–aldosterone phenotype from either examination 2 or 3.
† Based on the INTERSALT (International Cooperative Study on Salt, Other Factors, and Blood Pressure) equation.