Subclinical Primary Aldosteronism and eGFR Decline Over Time

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Key Points

- This prospective study of 976 adults measured the association between subclinical primary aldosteronism and kidney outcomes.
- Among a general healthy adult population, subclinical primary aldosteronism was associated with steeper decline in eGFR over time.
- Primary aldosteronism pathophysiology spans a wide unrecognized continuum that parallels the risk for kidney disease.

Abstract

Background Primary aldosteronism, an overt form of renin-independent aldosterone production, leads to steeper eGFR decline compared with primary hypertension. Mounting evidence suggests that milder forms of renin-independent aldosterone production (subclinical primary aldosteronism) are highly prevalent; however, the link between subclinical primary aldosteronism and eGFR decline remains unknown.

Methods This prospective cohort study included 976 Canadian adults aged 40–69 years, with predominantly normal BP or mild untreated hypertension, from the randomly sampled, population-based CARTaGENE cohort. Aldosterone and renin concentrations were measured at enrollment (2009–2010). Creatinine and cystatin C were measured at enrollment and 5–7 years postenrollment. Multivariable linear mixed regression models were used to measure the associations of aldosterone, renin, and the aldosterone-to-renin ratio (ARR) with eGFR decline over time.

Results The mean (SD) age of participants was 53 (7) years; 51% were female. Mean BP was 121 (15)/72 (10) mm Hg, and 11% had BP ≥140/90 mm Hg. Mean $eGFR_{CrCysC}$ was 109 (16) ml/min per 1.73 m^2. At higher ARR levels, there was steeper mean eGFR decline over time (Tertile 1 [ARR, ≤0.49 ng/dl per mU/L]: −1.40 [1.77] ml/min per 1.73 m^2/yr, Tertile 2 [ARR, 0.50–0.87 ng/dl per mU/L]: −1.48 [1.75] ml/min per 1.73 m^2/yr, Tertile 3 [ARR, >0.87 ng/dl per mU/L]: −1.57 [1.79] ml/min per 1.73 m^2/yr; $P = 0.01$), representing 11% steeper decline in the highest versus lowest ARR tertile. At lower renin levels, there was steeper mean eGFR decline over time (Tertile 1 [renin, ≤9.2 mU/L]: −1.59 [1.80] ml/min per 1.73 m^2/yr, Tertile 2 [renin, 9.3–15.9 mU/L]: −1.53 [1.77] ml/min per 1.73 m^2/yr, Tertile 3 [renin, >15.9 mU/L]: −1.33 [1.72] ml/min per 1.73 m^2/yr; $P = 0.04$), representing 16% steeper eGFR decline in the lowest versus highest renin tertile. There was no significant association between aldosterone and eGFR change over time ($P = 0.50$). All aforementioned associations were independent of BP and were consistent among participants with normal BP in isolation.

Conclusions Independent of BP, elevated ARR and suppressed renin were associated with steeper eGFR decline over time.

JASN 00: 1–10, 2026. doi: https://doi.org/10.1681/ASN.0000001039

Introduction

Primary aldosteronism is the most common and modifiable form of secondary hypertension.[1] Primary aldosteronism pathophysiology is defined by renin-independent aldosterone production from one or both adrenal glands leading to inappropriate mineralocorticoid receptor activation. While the bulk of the literature surrounding the negative consequences of primary aldosteronism focuses on cardiovascular disease,[2–4] primary aldosteronism also leads to disproportionately high rates of kidney disease compared with primary hypertension, independent of BP. The kidney manifestations of primary aldosteronism include

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Received: October 13, 2025 **Accepted:** February 9, 2026
Published Online Ahead of Print: February 13, 2026

steeper decline in eGFR over time and, subsequently, a heightened risk of CKD.[5–8] Importantly, early diagnosis and implementation of aldosterone-targeted therapies effectively mitigate the adverse kidney effects of primary aldosteronism.[5,6,8–11] Specifically, aldosterone-targeted therapy that induces a rise in renin has been associated with lower risk for cardiovascular[3,12] and kidney disease[9] and has thus been codified by international consensus statements[13] and clinical practice guidelines.[14]

Historically, guideline-recommended testing for primary aldosteronism has been restricted to high-risk populations, such as resistant hypertension and hypertension with hypokalemia. However, growing recognition of the high prevalence of primary aldosteronism across the spectrum of hypertension has prompted several recent guidelines to recommend broader primary aldosteronism screening, including all adults with hypertension.[14,15] Diagnostic testing relies on measuring aldosterone and renin to determine whether historically defined biochemical thresholds are met to apply the diagnostic label of primary aldosteronism. Yet a growing body of evidence challenges this categorical framework, showing that renin-independent aldosteronism spans a continuum of severity well beyond its historical confines.[1,16–25] These studies demonstrate that when renin is low or suppressed, even modest aldosterone production may be indicative of primary aldosteronism pathophysiology. Because these milder forms of renin-independent aldosteronism go unrecognized in clinical practice, they are often referred to as subclinical primary aldosteronism.[16,21,23,24] Subclinical primary aldosteronism leads to inappropriate mineralocorticoid receptor activation, increased kaliuresis, accelerated arterial stiffening, BP elevation, adverse cardiac remodeling, and incident cardiovascular events.[1,16–23,25] However, it remains unknown whether subclinical primary aldosteronism contributes to a heightened risk of adverse kidney outcomes.

In this study, we conducted a prospective cohort study to measure the associations of aldosterone, renin, and the aldosterone-to-renin ratio (ARR) with changes in eGFR over time in a large, randomly sampled, and population-based cohort of Canadian adults. Participants enrolled in CARTaGENE were investigated to test the hypothesis that the presence and magnitude of subclinical primary aldosteronism are associated with steeper decline in kidney function over time.

Methods

Study Design

Prospective analyses were performed to measure the associations of ARR, renin, and aldosterone with changes in eGFR over time in a population-based cohort of Canadian adults. The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational studies (Supplemental Table 1).[26] All participants provided written informed consent at the time of enrollment. Study protocols were approved by the *Comité d'éthique de la recherche du CIUSSS-NIM* (ID# 2017-1358) and the Ottawa Health Science Network Research Ethics Board (ID# 20200475-01H).

Data Source and Study Cohort

CARTaGENE (https://cartagene.qc.ca) is an ongoing population-based cohort designed to evaluate determinants of chronic disease among Canadian adults. Details of CARTaGENE design and enrollment have been published previously.[27] In brief, 19,996 adults aged 40–69 years were enrolled between August 2009 and October 2010 across four metropolitan regions in the province of Québec. Participants were randomly invited using the provincial *Régie de l'assurance-maladie du Québec* universal health care database using complex random stratified sampling of 1% of the population base. Participants were selected such that the cohort was representative of the general adult population of Québec, on the basis of sociodemographic characteristics. At the baseline visit, participants underwent standardized assessments including demographic surveys, medical history, dietary intake (through the validated Canadian Diet History Questionnaire II),[28] anthropometric measurements, and medication use along with blood and urine sample collection by a research nurse. Individuals were excluded if they had missing laboratory data or were prescribed antihypertensive medication at enrollment. BP was measured with standardized technique three times at 2-minute intervals using the Omron HEM-907XL device (Omron, Lake Forest, IL), and the mean was reported. Hypertension was defined using both BP ≥140/90 mm Hg and ≥130/80 mm Hg thresholds to reflect varying international guidelines.[15,29,30] Albuminuria was measured with a spot urine albumin-creatinine ratio (UACR) and categorized as per Kidney Disease: Improving Global Outcomes definitions: normal to mildly increased (<30 mg/g), moderately increased (30–300 mg/g), and severely increased (>300 mg/g).[31] Diabetes mellitus was defined as use of any glucose-lowering medication or by laboratory criteria: hemoglobin A1c ≥6.5%, fasting glucose ≥126 mg/dl, or a random glucose ≥200 mg/dl. Prior cardiovascular disease was defined as a history of acute coronary syndrome, stroke, or heart failure ascertained from self-reported questionnaires or *Régie de l'assurance-maladie du Québec*–linked administrative records (from 1998 to enrollment). At 5–7 years postenrollment, a randomly selected subset of 1309 CARTaGENE participants was recalled to participate in the Canadian Alliance for Healthy Hearts and Minds (CAHHM) study, which included repeat blood sampling and medication data collection.[32] Participants recalled for CAHHM formed the present study population.

Exposures: Aldosterone and Renin

At CARTaGENE enrollment, nonfasting blood samples were collected with participants in the seated position and then placed on ice immediately after collection. Samples were then processed into serum and plasma aliquots for immediate storage at −176°C. Sampling was performed without any adjustment to participants' home medications. Frozen EDTA plasma samples were thawed immediately before measurement of aldosterone and renin. Aldosterone and renin concentrations were measured using chemiluminescent immunoassays on the Liaison analyzer (DiaSorin Inc., Stillwater, MN). These assays are used for clinical practice and regular quality control testing, as

part of laboratory quality assurance practices, confirmed imprecision (coefficient of variation) as ≤10% at clinically relevant concentrations. The lower limit of reporting for renin concentration was 1.0 ng/L (1.67 mU/L); to avoid overinflation of the ARR, measures below this were assigned a value of 0.9 ng/L (1.50 mU/L).

Outcomes: eGFR Change Over Time

Kidney function was assessed using eGFR, derived from plasma creatinine and cystatin C measured at baseline and at the follow-up visit 5–7 years later. Creatinine was measured enzymatically on a Roche cobas 501 instrument (Roche Diagnostics, Laval, Québec, Canada). The calibrators and reagents used in the creatinine assay were adjusted to the isotope dilution mass spectrometry standard. Cystatin C was measured by an immunoturbidimetric assay on the Roche cobas 501 instrument. eGFR was calculated using the 2021 CKD Epidemiology Collaboration creatinine/cystatin C–based formula as the combination of these filtration markers provides enhanced accuracy beyond either marker in isolation, particularly at higher eGFR values.[33]

Statistical Analysis

Baseline characteristics are summarized as means (SD) or medians (interquartile range), as appropriate. Categorical variables are presented as number (%). Linear mixed regression models were used to measure the associations of ARR, renin, and aldosterone with eGFR change over time. Distinct models were built for each exposure of interest. Random effects at the individual level were added to the models to account for dependency between eGFR observations. Models were adjusted for the following covariates selected *a priori* and ascertained at enrollment: age, sex, self-reported race/ethnicity, systolic BP, body mass index, diabetes mellitus, prior cardiovascular disease, baseline eGFR, albuminuria, serum sodium, serum potassium, and use of hormone replacement therapy. Given established differences in renin-angiotensin-aldosterone system (RAAS) physiology between female patients and male patients,[34] analyses were conducted for the overall cohort and stratified by sex. eGFR changes over time are reported as beta coefficients (95% confidence intervals) and were derived from the interaction term between the exposure of interest and time. Linear associations of each exposure of interest with eGFR changes were conducted after log-transformation because of highly skewed distributions and reported per one SD higher value of the measure. Nonlinear analyses of each exposure of interest with eGFR changes over time were assessed with restricted cubic splines, using three knots at standard locations, and displayed graphically. The following sensitivity analyses were performed: (*1*) exclusion of participants with BP ≥140/90 mm Hg at enrollment, (*2*) exclusion of participants with BP ≥130/80 mm Hg at enrollment, (*3*) further adjustment for 24-hour dietary potassium and sodium intake among participants who completed the Canadian Diet History Questionnaire II,[28] (*4*) exclusion of participants who initiated antihypertensive medications between enrollment and follow-up, (*5*) exclusion of participants who met criteria for potentially being diagnosed with primary aldosteronism according to the 2025 Endocrine Society guideline criteria (aldosterone ≥10 ng/dl, renin ≤8.2 mU/L, and ARR >2.5 ng/dl per mU/L),[14] (*6*) exclusion of participants with albuminuria ≥30 mg/g at baseline, and (*7*) using linear regression models for eGFR change over time rather than mixed models. Statistical significance was defined as a two-sided P value < 0.05. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary NC) and *R* Software 4.1.0 (*R* Project for Statistical Computing, Auckland, New Zealand).

Results

Baseline Characteristics

Of the original 19,996 CARTaGENE participants, 1309 were recalled for follow-up blood sampling as part of the CAHHM study (Figure 1). After excluding individuals with missing laboratory data (n=127) or baseline antihypertensive medication use (n=206), owing to potential influence on aldosterone, renin, and kidney function, 976 participants were included in the final analytic sample. Baseline characteristics are shown in Table 1. The mean (SD) age was 53 (7) years with equal representation by sex (51% female, 49% male). The mean systolic and diastolic BP were 121 (15) and 72 (10) mm Hg, respectively; 300 participants (31%) had BP ≥130/80 mm Hg, and 104 participants (11%) had BP ≥140/90 mm Hg. Diabetes and prior cardiovascular disease were present in 24 (2%) and 11 (1%) participants, respectively. Median (interquartile range) ARR, aldosterone, and renin values were 0.65 (0.42–1.03) ng/dl per mU/L, 7.59 (5.84–10.33) ng/dl, and 12.5 (7.5–17.8) mU/L, respectively—full distributions displayed in Supplemental Figure 1. Mean creatinine, cystatin C, and $eGFR_{CrCysC}$ were 0.87 (0.17) mg/dl, 0.73 (0.15) mg/L, and 109 (16) ml/min per 1.73 m^2, respectively. Median UACR was 0 (0–4) mg/g, with 25 participants (2.6%) having moderately increased albuminuria (30–300 mg/g) and no participants having severely increased albuminuria (>300 mg/g). Median estimated 24-hour dietary sodium and potassium intake were 2377 (1562–3151) mg and 3180 (2307–4225) mg, respectively. Mean interval from study entry to follow-up was 6.2 (0.5) years.

Associations of ARR, Renin, and Aldosterone with eGFR Change Over Time

Figure 2 displays the associations of ARR, renin, and aldosterone with eGFR change over time on the basis of the multivariable models. Higher ARR was associated with steeper mean eGFR decline over time (P = 0.01; Figure 2A). This corresponds to 11% steeper mean eGFR decline in the highest versus lowest ARR tertile—Tertile 1 (ARR, ≤0.49 ng/dl per mU/L): −1.40 (1.77) ml/min per 1.73 m^2/yr, Tertile 2 (ARR, 0.50–0.87 ng/dl per mU/L): −1.48 (1.75) ml/min per 1.73 m^2/yr, Tertile 3 (>0.87 ng/dl per mU/L): −1.57 (1.79) ml/min per 1.73 m^2/yr. Similarly, lower renin was associated with steeper mean eGFR decline over time (P = 0.04; Figure 2B). This corresponds to 16% steeper mean eGFR decline in the lowest versus highest renin tertile—Tertile 1 (renin, ≤9.2 mU/L): −1.59 (1.80) ml/min per 1.73 m^2/yr, Tertile 2 (renin, 9.3–15.9 mU/L): −1.53 (1.77) ml/min per 1.73 m^2/yr, Tertile 3 (renin, >15.9 mU/L): −1.33 (1.72)

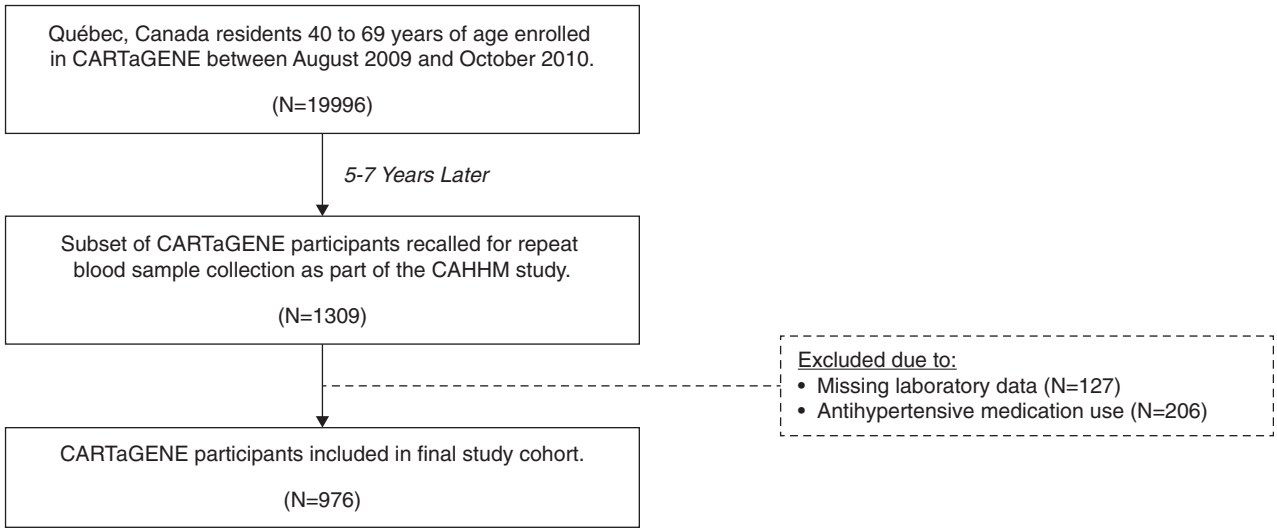

Figure 1. Study flow chart. CAHHM, Canadian Alliance for Healthy Hearts and Minds.

ml/min per 1.73 m^2/yr. There was no significant association between aldosterone and eGFR change over time (P = 0.50; Figure 2C). No evidence for nonlinearity was identified in the associations of ARR (P for nonlinearity = 0.44), renin (P for nonlinearity = 0.17), and aldosterone (P for nonlinearity = 0.70) with eGFR change over time.

Sex-Stratified Associations

Figure 3 presents the multivariable-adjusted associations of ARR, renin, and aldosterone with eGFR change over time stratified by sex. Consistent patterns of association between the exposures of interest and eGFR changes over time were present for female patients and male patients.

Sensitivity Analyses

All aforementioned sensitivity analyses yielded results of similar directionality to the primary analysis (Supplemental Table 2).

Discussion

In this large population-based prospective cohort study of Canadian adults with predominantly normal BP or mild untreated hypertension and relatively few comorbidities, subclinical primary aldosteronism was associated with steeper eGFR decline over time. These findings highlight a clinically significant link between subclinical primary aldosteronism and kidney disease risk that occurs before the onset, or early in the course, of hypertension. Furthermore, by adjusting for BP, this study demonstrated a BP-independent association between subclinical primary aldosteronism and kidney disease risk, consistent with what occurs in overt and classically defined primary aldosteronism.[3,4] While the absolute differences seen in this study were modest, the presence of a significant association between subclinical primary aldosteronism and kidney function decline over time in a general healthy cohort provides powerful mechanistic insights into a potential important role it may play in CKD incidence and progression. Specifically, future research should examine the magnitude of this association in patient populations such as hypertension and CKD, which are more strongly enriched with subclinical primary aldosteronism.

Placed in the context of prior work, this study extends the evidence base for the clinical relevance of subclinical primary aldosteronism by demonstrating its negative association with kidney health. Previous studies on subclinical primary aldosteronism have primarily focused on its association with cardiovascular health, including incident hypertension, adverse cardiac remodeling, and incident cardiovascular events.[1,16–22,25] While the cardiovascular manifestations of overt and classically defined primary aldosteronism garner most of the attention, it is important to remember that primary aldosteronism also leads to a disproportionately higher risk for adverse kidney outcomes including steeper eGFR decline and a higher incidence of CKD, independent of BP.[5–8] This study now demonstrates that such adverse kidney outcomes also occur with milder forms of renin-independent aldosteronism falling below the traditional biochemical thresholds used to define overt primary aldosteronism and among individuals without a classical phenotype to warrant guideline-recommended screening for primary aldosteronism.

These findings further strengthen the argument against the historical approach to primary aldosteronism whereby semiarbitrary biochemical thresholds are used to define this condition solely among individuals with hypertension plus other high-risk clinical features. Rather, primary aldosteronism pathophysiology spans a vast continuum of severity well beyond these historical confines. The PATHWAY-2 study showed that renin-independent aldosteronism, below the biochemical thresholds conventionally used to diagnose overt primary aldosteronism, are highly prevalent among individuals with resistant hypertension thereby providing physiologic rationale for why mineralocorticoid receptor antagonists are the most effective add-on therapy for this population.[35,36] Subsequent studies have extended subclinical primary aldosteronism to be highly prevalent in milder cases of hypertension and in individuals with normal BP, populations not traditionally

Table 1. Baseline characteristics of the study cohort of Québec (Canada) residents aged 40–69 years at CARTaGENE enrollment (2009–2010)

Characteristic	Value
Total (*N*)	976
Age, yr, mean (SD)	53 (7)
Sex, *N* (%)	
Female	494 (51)
Male	482 (49)
Self-reported race/ethnicity, *N* (%)	
Other	57 (6)
White	919 (94)
Vital signs and anthropometrics, mean (SD)	
Systolic BP, mm Hg	121 (15)
Diastolic BP, mm Hg	72 (10)
Height, cm	168 (9)
Weight, kg	74 (15)
BMI, kg/m^2	26.2 (4.5)
Comorbidities, *N* (%)	
Hypertension defined by BP ≥130/80 mm Hg	300 (31)
Hypertension defined by BP ≥140/90 mm Hg	104 (11)
Cardiovascular disease	11 (1)
Diabetes mellitus	24 (2)
Active smoking	122 (13)
Lab measurements	
ARR, ng/dl per mU/L, median (IQR)	0.65 (0.42–1.03)
Aldosterone, ng/dl, median (IQR)	7.59 (5.84–10.33)
Renin, mU/L, median (IQR)	12.5 (7.5–17.8)
Creatinine, mg/dl, mean (SD)	0.87 (0.17)
Cystatin C, mg/L, mean (SD)	0.73 (0.15)
$eGFR_{CrCysC}$, ml/min per 1.73 m^2, mean (SD)[a]	109 (16)
UACR, mg/g, median (IQR)	0 (0–4)
Normal to mildly increased albuminuria (<30 mg/g), *N* (%)	951 (97)
Moderately increased albuminuria (30–300 mg/g)	25 (3)
Severely increased albuminuria (>300 mg/g)	0 (0)
Sodium, mEq/L, mean (SD)	139 (2)
Potassium, mEq/L, mean (SD)	4.3 (0.5)
Hemoglobin A1c, %, mean (SD)	5.6 (0.5)
Daily dietary intake, mg, median (IQR)[b]	
Sodium	2377 (1562–3151)
Potassium	3180 (2307–4225)
Medication use, *N* (%)	
Antihypertensive medication	0 (0)
Aspirin	60 (6)
Statin	109 (11)
Hormone replacement therapy	78 (8)
Time from study entry to follow-up, yr, mean (SD)	6.2 (0.5)

ARR, aldosterone-to-renin ratio; BMI, body mass index; IQR, 25th–75th percent interquartile range; UACR, urine albumin-creatinine ratio.
[a]Calculated using the race-free 2021 CKD-Epidemiology Collaboration combined creatinine/cystatin C equation.[33]
[b]Assessed through the Canadian Diet History Questionnaire II.[28] Data available for 737 participants (76% of cohort).

considered for aldosterone and renin testing.[1,16–22,25] Therefore, such individuals with subclinical primary aldosteronism go undetected in modern-day clinical practice. This existing evidence base enhanced by the present study highlights the clinical importance of primary aldosteronism pathophysiology as a contributor to long-term cardiovascular and kidney disease risk.

Another important finding from this study is that aldosterone, in isolation, was not associated with steeper eGFR decline. Instead, the results show that only renin-independent aldosterone production, as evidenced by an elevated ARR, was associated with steeper eGFR decline. This is consistent with prior work showing that aldosterone alone is not necessarily harmful when physiologically regulated (*i.e.*, renin-dependent aldosteronism).[16,21] Indeed, this finding supports the pragmatic approach of using low or suppressed renin alone (without aldosterone or ARR) to reliably identify individuals likely to benefit from aldosterone-targeted therapy.[35–37] In fact, a recent argument has been made that suppressed renin alone may serve as a superior screening test to ARR for identifying primary aldosteronism.[38]

This study may explain some of the variability that is known to occur with age-related eGFR decline. As part of the normal aging process, eGFR begins to decline starting in early adulthood because of a progressive loss of functioning nephrons.[39] While the traditional teaching is that adults lose approximately 1 ml/min per 1.73 m^2 per year starting in their third decade of life,[40] this differs on the basis of the eGFR equation used particularly among older adults where creatinine-based equations suggest slower decline (mean [SD] decline of −0.4 [3.6] ml/min per 1.73 m^2/yr) and cystatin C–based equations suggest faster decline (mean [SD] decline of −1.8 [2.6] ml/min per 1.73 m^2/yr).[41] Importantly, there is a large degree of variability in the rate of eGFR decline in the general population that remains unexplained.[42] Given its expansive continuum of dysregulated aldosterone production and inappropriate mineralocorticoid receptor activation, subclinical primary aldosteronism may play a role in explaining some of the variability of eGFR trajectories and normal kidney aging that exists within the general population.

The association between subclinical primary aldosteronism and kidney health may have important future implications supporting a paradigm shift in the early management of hypertension and kidney disease prevention. Aldosterone-targeted therapies already play a foundational role in kidney disease management. Among individuals with CKD, mineralocorticoid receptor antagonists are effective in reducing proteinuria, slowing disease progression, and lowering cardiovascular risk.[43] For example, the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD), Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIDELIO-DKD), and Combination Effect of Finerenone and Empagliflozin in Participants with CKD and Type 2 Diabetes Using a Urinary Albumin-to-Creatinine Ratio Endpoint (CONFIDENCE) randomized trials demonstrated that the non-steroidal mineralocorticoid receptor antagonist finerenone effectively lowers the risk of both adverse kidney and cardiovascular outcomes among individuals with CKD and type 2 diabetes.[44–46] Similarly, the emerging new-generation aldosterone synthase inhibitors are showing early promise in improving kidney outcomes for patients with CKD. In a phase 2 randomized controlled trial of CKD patients with eGFR 30–89 ml/min per 1.73 m^2 and a UACR ratio of 200–5000 mg/g, the aldosterone synthase inhibitor vicadrostat significantly reduced albuminuria beyond that

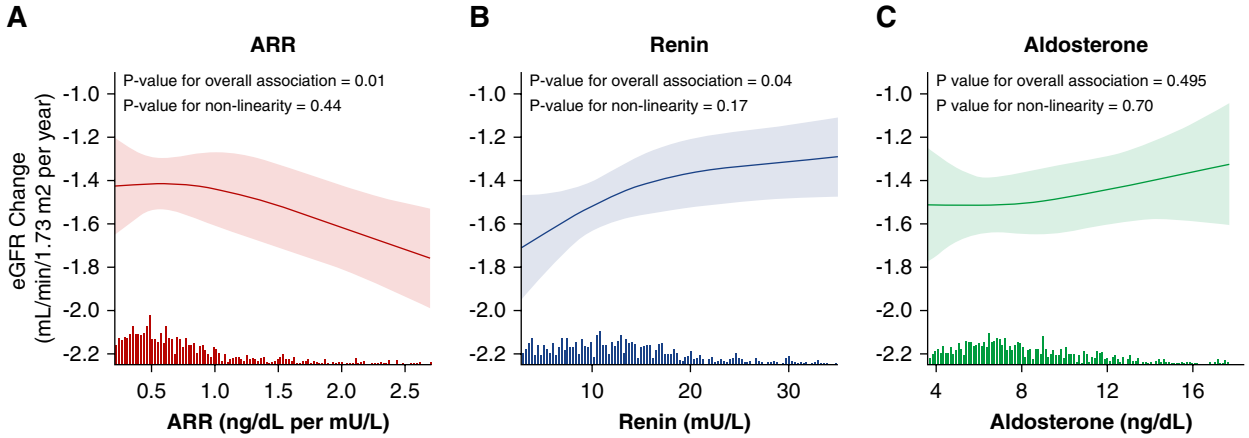

Figure 2. Associations of ARR, renin, and aldosterone with eGFR change over time. The solid line and the shaded area display the eGFR change over time and 95% CI, respectively, associated with each level of ARR (A), renin (B), and aldosterone (C). The bottom part of each panel displays the distribution of the exposure of interest. ARR, aldosterone-to-renin ratio; CI, confidence interval.

of placebo in a dose-dependent fashion.[47] A large phase 3 trial (EASi-KIDNEY) is now underway to determine whether vicadrostat plus empagliflozin reduces the rates of CKD progression and major adverse cardiovascular events in patients with CKD compared with empagliflozin alone.[48] In overt primary aldosteronism, aldosterone-targeted therapies including adrenalectomy and mineralocorticoid receptor antagonists effectively reduce proteinuria and slow CKD progression.[5,6,8–11] As prior work has demonstrated that subclinical primary aldosteronism is associated with a substantially higher risk for incident hypertension,[16,21] this indicates that a large proportion of individuals who have traditionally been labeled as having primary hypertension actually have aldosterone-driven/mineralocorticoid receptor–mediated hypertension because of subclinical primary aldosteronism. This study now shows that such individuals with subclinical primary aldosteronism experienced steeper eGFR decline over time, similar to what is seen in overt and classically defined primary aldosteronism.[5–8] Therefore, early detection of, and intervention for, subclinical primary aldosteronism may serve to slow eGFR decline over time and prevent CKD. Future research should study whether early diagnosis of subclinical primary aldosteronism (*e.g.*, at the initial diagnosis of hypertension or prehypertension) and initiation of aldosterone-targeted therapies, including

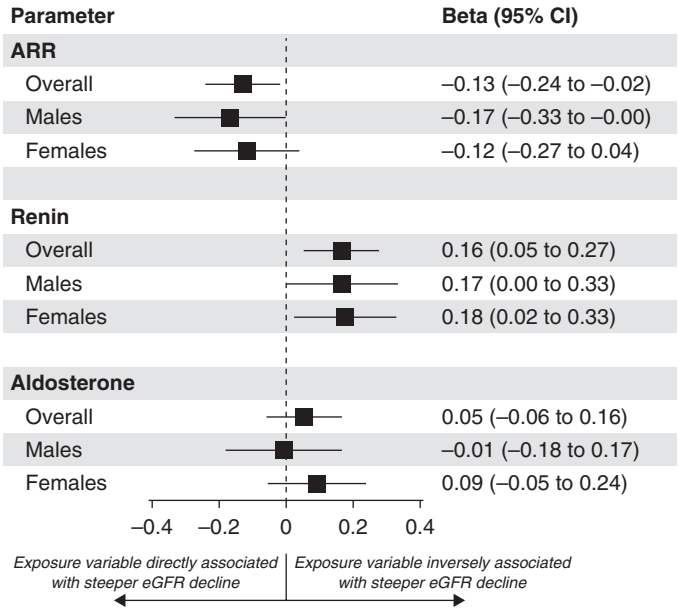

Figure 3. Sex-specific associations of ARR, renin, and aldosterone with eGFR change over time. Associations are reported as beta coefficients (95% CI) for one SD higher log-transformed exposure of interest. Models are adjusted for age, sex (except the male-stratified/female-stratified analyses), self-reported race/ethnicity, systolic BP, body mass index, diabetes mellitus, prior cardiovascular disease, baseline eGFR, albuminuria category, serum sodium, serum potassium, and use of hormone replacement therapy.

mineralocorticoid receptor antagonists and aldosterone synthase inhibitors,[49] may provide a novel strategy to mitigate kidney and cardiovascular risk for a large proportion of the hypertensive population.

Strengths of this study include a large population-based cohort representative of the general Canadian adult population, use of complex random stratified sampling and standardized data collection, assessment of potentially nonlinear associations using splines, and combined measurements of creatinine and cystatin C to determine eGFR. However, this study must be interpreted within the context of several limitations. First, the study design was observational, thus allowing for assessment of association but not causation. While individuals taking medications that may affect aldosterone, renin, and eGFR were excluded and other variables known to influence aldosterone, renin, and eGFR were adjusted for in the multivariable models, unmeasured confounding may still have been present. Second, eGFR was only determined at index and at 5–7 years follow-up on the basis of the CARTaGENE and CAHHM protocols for blood collection. Therefore, there were only two time points for eGFR measurement, which predisposes to sensitivity from random variation in creatinine and cystatin C, which would bias the results toward the null. However, the large population size still allowed for sufficient power to detect significant trends in eGFR decline. Third, urine samples were collected only at enrollment and not at follow-up. Thus, although we could adjust for baseline albuminuria, we were unable to assess changes in albuminuria over time. Fourth, the study findings may not generalize to all populations. For instance, most of the participants in CARTaGENE self-identified as being of White race. As differences in aldosterone and renin profiles are known to be present among Black individuals,[19] generalizability to predominantly Black populations may be limited. Fifth, aldosterone was measured through immunoassay, which may overestimate its concentration relative to mass spectrometry.[50] However, the analyses focused on differences in aldosterone rather than comparison of absolute values or thresholds. Therefore, the absolute aldosterone levels were less important than the interplay between aldosterone with renin and interindividual comparisons. Sixth, renin concentration may have lower accuracy than renin activity in low or very low renin states, which is hypothesized to relate to some degree of interference from prorenin.[51] This may have attenuated the magnitude of associations between renin, along with ARR, and eGFR change over time. Seventh, this study was conducted with participants consuming an *ad lib* diet without standardizing dietary sodium intake, which can influence aldosterone and renin levels, though generally in the same direction thereby minimizing the effect on assessment of renin-independent aldosteronism. Nevertheless, the magnitude of this influence may differ between aldosterone and renin, which could affect the ARR. Notably, estimated dietary sodium intake was available for a subset of participants, and a sensitivity analysis controlling for this yielded similar results to the primary analysis. Finally, aldosterone and renin profiles were determined on the basis of single measurements. The inherent intraindividual variability in these measurements may have resulted in some degree of misclassification, which may have biased associations toward the null.[52]

In conclusion, this prospective population-based cohort study of predominantly individuals with normal BP or mild hypertension demonstrated that the presence and magnitude of subclinical primary aldosteronism are associated with steeper eGFR decline over time in a BP-independent manner. These findings further challenge the traditional approach of treating primary aldosteronism as a categorical disease and reaffirm the concept of a continuum of primary aldosteronism pathophysiology that parallels the risk for both kidney and cardiovascular disease, even before the onset of hypertension. Future studies should examine whether early detection of subclinical primary aldosteronism may provide guidance surrounding prognosis and personalized treatment strategies to slow kidney function decline and reduce cardiovascular risk for this large but under-recognized population.

Disclosures

Disclosure forms, as provided by each author, are available with the online version of the article at http://links.lww.com/JSN/F708.

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Funding

G. Hundemer: Institute of Nutrition, Metabolism and Diabetes (PJT-175027, PJT-198110), Kidney Foundation of Canada (851937-21KHRG, 24KHRG-1251453), and Lorna Jocelyn Wood Chair for Kidney Research. L.C. Desbiens: Fonds de Recherche du Québec—

Santé. M. Agharazii: Fonds de Recherche du Québec—Santé. A. Vaidya: National Institutes of Health (R01 DK115392, R01 HL153004, and R01 HL155834). R. Goupil: Canadian Institutes of Health Research (PJT-173313), Fonds de Recherche du Québec—Santé, and Société québécoise d'hypertension artérielle—Bourse Jacques-de-Champlain Award.

Acknowledgments

We thank the CARTaGENE participants and staff for their contribution and support to research.

Declarative Statements

This study includes clinical experimentation and received Institutional Review Board or Ethics Committee approval. All patients provided written informed consent. This study includes clinical experimentation and complies with the Declaration of Helsinki.

Data Availability Statements

Original data generated for the study will be made available upon reasonable request to the corresponding author. Data Type: Observational Data. Reason for Restricted Access: Based on CARTaGENE's policy, some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/JSN/F709.

Supplemental Figure 1. Distribution of ARR, renin, and aldosterone in study participants.

Supplemental Table 1. Strengthening the Reporting of Observational Studies in Epidemiology REporting of studies Conducted using Observational Routinely collected health Data statement checklists.

Supplemental Table 2. Sensitivity analyses for the multivariable associations of aldosterone, renin, and ARR with eGFR change over time.

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