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Positive relationship of sleep apnea to hyperaldosteronism in an ethnically diverse population

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Objective **Approximately, 50–60% of patients with sleep apnea have hypertension. To explore a mechanism of this relationship, we compared its prevalence in a hypertensive population with and without hyperaldosteronism.**

Methods **Using the Kaiser Permanente Southern California database, hypertensive individuals who had plasma aldosterone and plasma renin activity measured between 1 January 2006 and 31 December 2007 were evaluated. Hyperaldosteronism was defined as an aldosterone : renin ratio more than 30 and plasma aldosterone more than 20 ng/dl or an aldosterone : renin ratio more than 50 (ng/dl : ng/ml per h). Hypertension was identified by International Classification of Disease, Ninth Revision (ICD-9) coding and sleep apnea was defined by ICD-9 coding or procedural coding for dispensation of positive airway devices.**

Results **Of 3428 hypertensive patients, 575 (17%) had hyperaldosteronism. Sleep apnea was present in 18% (105) with hyperaldosteronism vs. 9% (251) without hyperaldosteronism ($P<0.001$). Odds ratio for sleep apnea in patients with hyperaldosteronism was 1.8 (95% confidence interval 1.3–2.6) after controlling for other sleep apnea risk factors. No ethnic group was at greater risk for sleep apnea.**

Conclusion **The prevalence of sleep apnea in a diverse hypertensive population is increased in patients with hyperaldosteronism, even when controlling for other sleep apnea risk factors.** *J Hypertens* **29:1553–1559 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Keywords: hyperaldosterone, sleep apnea, secondary hypertension

Abbreviations: AASK, African–American study of kidney disease and hypertension; BiPAP, bi-level positive airway pressure; CHF, congestive heart failure; ICD-9, International Classification of Disease Ninth Revision; KPSC, Kaiser Permanente Southern California; MDRD, Modification of Diet in Renal Disease; OR, odds ratio; PRA, plasma renin activity; RAAS, renin–angiotensin–aldosterone system

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Introduction

Sleep apnea and hypertension frequently coexist. Thus, approximately 50–60% of sleep apnea patients also have hypertension [1–4]. Several hypotheses have been proposed to explain these relationships, including sympathetic nervous system hyperactivity, oxidative stress, endothelial dysfunction from repeated arousals, and fat distribution [5–7]. Activation of the renin–angiotensin–aldosterone system (RAAS), in particular aldosterone excess, has also been hypothesized to contribute to both disease processes [8].

Aldosterone increases fluid retention by increasing sodium reabsorption in the distal tubule; the higher body sodium content increases renal water retention, thereby leading to volume-mediated hypertension in susceptible individuals [9]. These patients usually have suppressed plasma renin activity (PRA) levels. Hypothetically, fluid accumulation can lead to secondary peripharyngeal edema and impact upper airway resistance, which worsens the severity of sleep apnea [10,11]. Previous studies have demonstrated a relationship between sleep apnea and hyperaldosteronism in patients with resistant hypertension [12,13]. These studies have involved small numbers of patients and have been limited in their ethnic diversity.

Adrenal aldosterone secretion is stimulated by plasma renin–angiotensin activity, increased serum potassium levels, and increased serum adrenocorticotropic hormone [14,15]. Originally, a high plasma aldosterone level together with suppressed PRA and hypokalemia was used to distinguish primary from secondary aldosteronism that might be caused instead by hyper-reninemia and/or hyperkalemia. Since in recent years it has been proposed that hypokalemia does not always occur in patients with an adrenal secreting tumor, the aldosterone : renin ratio has been used instead to screen for hyperaldosteronism. A high ratio suggests a high aldosterone state that is independent of the renin–angiotensin system.

Hyperaldosteronism can result from diverse underlying mechanisms such as aldosterone-producing adenomas, unilateral or bilateral adrenal hyperplasia, malignancy, or familial disorders [16]. Patients with

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hyperaldosteronism have greater cardiovascular and mortality rates [17,18], thus prompting endocrine society guidelines to specify treatments [19].

The aim of this study was to compare in a large and ethnically diverse population the prevalence of sleep apnea in hypertensive patients with hyperaldosteronism and without hyperaldosteronism. We hypothesized that hyperaldosteronism is associated with higher prevalence of sleep apnea. Because of the heterogeneous demographic nature of the Kaiser Permanente healthcare system in Southern California, our results would not only constitute one of the largest studies to explore the association between aldosterone and sleep apnea, but would also serve to extend findings to a large, ethnically diverse population.

Methods

Patient population and data collection

This was a retrospective cohort study using historical data in the Kaiser Permanente Southern California (KPSC) database which was collected over a 2-year period – from 1 January 2006 through 31 December 2007. KPSC is an integrated health system consisted of a prepaid health plan with 12 medical centers and over 100 satellite clinics throughout Southern California. Members have similar access to medications, healthcare personnel, and facilities. The ethnic diversity and socioeconomic distribution parallels the state of California. In December 2007, the health plan had an enrollment of over 3.27 million members. Data were extracted from records compiled from routine clinical practice. This study was approved by the regional institutional review board and was exempt from written consent forms.

Participants were included in the analysis if they carried a diagnosis of hypertension and had concurrent measurements of plasma aldosterone (ng/dl) and PRA levels (ng/ml per h). Hypertension was identified based on International Classification of Disease, Ninth Revision (ICD-9) coding. The accuracy of ICD-9 coding for the diagnosis of hypertension was internally validated by The Permanente Medical Group (Rhonda Woodling Hypertension Task Force). In 1999, the internal hypertension registry totaling 386 710 patients was used to determine the positive predictive value of ICD-9 coding for hypertension based on number of times hypertension was coded. An individual who had hypertension coded once had a positive predictive value of 89%, whereas someone coded at least twice had a positive predictive value of 98% [20]. Of the participants who were eventually identified as hypertensive in our study population, 96% had two or more hypertension ICD-9 diagnoses.

A plasma aldosterone : PRA ratio at least 30 (ng/dl : ng/ml per h) and a plasma aldosterone more than 20 ng/dl is reported to have a sensitivity and specificity for the identification of primary hyperaldosteronism of approximately 90% [21]. Alternatively, a plasma aldosterone : PRA ratio at least 50 is reportedly sufficient for the diagnosis of hyperaldosteronism [22]. We combined these two approaches by using both a plasma aldosterone : PRA ratio at least 30 with a plasma aldosterone level at least 20 ng/dl and a plasma aldosterone : PRA at least 50 to identify patients with hyperaldosteronism.

The diagnosis of sleep apnea was based on inpatient and outpatient ICD-9 diagnosis codes for sleep apnea (327.20, 327.21, 327.23, 780.51, 780.53, and 780.57) or by dispensation of continuous positive airway pressure or bi-level positive airway pressure (BiPAP) devices as indicated on the health plan database that records device dispensations. Internal validation of sleep apnea diagnosis by either ICD-9 coding or device coding revealed a positive predictive value of 88% as previously described [23].

Demographic variables of age, sex, ethnicity, and BMI were obtained. BMI more than 30 kg/m^2 was stratified into class I–III obesity, that is, 30 to less than 35, 35 to less than 40, and at least 40 kg/m^2, respectively. Selected laboratory variables included serum potassium, bicarbonate, and creatinine. Serum creatinine was used to estimate glomerular filtration rate (eGFR) according to the 4-point Modification of Diet in Renal Disease (MDRD) Eq. [24]. The values used for the abovementioned variables were those obtained closest in time to the measured aldosterone and PRA levels. Age was also separated into the following categories: 18 to less than 30, 30 to less than 45, 45 to less than 60, and at least 60 years. The presence of diabetes mellitus and congestive heart failure (CHF) were also identified using ICD-9 coding.

Medication usage was evaluated and separated into three categories based its effects on the renin–angiotensin system and were categorized as follows: natriuretic medications that included diuretics (loop, distal) and other (calcium channel blockers, α-blockers), renin–angiotensin system blockers (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers), or renin–angiotensin system suppressors (β-blockers and clonidine) [9].

Statistical analysis

All statistical calculations were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina, USA). Descriptive statistics are presented as mean ± SD. SD. Continuous and categorical variables were compared using Student's t-test and χ^2 test, respectively. Multivariate logistic regression, adjusted for age, sex, BMI categories, diabetes mellitus, and CHF, was used to estimate the odds ratio (OR) of variables associated with sleep apnea. All candidate predictors were examined via unadjusted and multivariate adjusted logistic regression models. Independent multivariate logistic regressions

were performed with each ethnic subset (whites, African–Americans, Hispanics). Generalized additive model, an extension of generalized linear models, was used to explore and visualize the relationship between estimated sleep apnea OR and aldosterone/PRA ratio after adjusting for CHF, diabetes mellitus, sex, race, and age.

Results

Of the 3428 hypertensive patients in the KPSC health system who had aldosterone and PRA levels during the 2-year study period, 575 (17%) had hyperaldosteronism [HA(+)] and 2853 (83%) did not [(HA(−)]; only 356 (10%) had sleep apnea. Descriptive characteristics of the hypertensive population and according to hyperaldosteronism diagnosis are presented in Table 1.

Characteristics of patients with hyperaldosteronism

Patients with hyperaldosteronism were slightly older, more likely to be men and African–American, and had higher SBP and DBP (Table 1). They had lower serum potassium, higher serum bicarbonate, higher plasma aldosterone (29 vs. 12 ng/dl), and much lower PRA (0.3 vs. 5.3 ng/ml per h). They were taking 4.5 vs. 3.4 antihypertensive medications. Only serum creatinine level and eGFR were not different. Because of the large sample size in both hyperaldosterone and nonhyperaldosterone groups, the estimated sample standard errors were small and *P* values were low for a majority of the comparisons.

Sleep apnea was present in 18% ($n = 105$) of the 575 participants defined as having hyperaldosteronism and in only 9% (251) of the participants without hyperaldosteronism ($P < 0.001$).

Ethnicity prevalence and medication usage

African–Americans (34%) and whites (33%) carried the highest prevalence of hyperaldosteronism in this cohort followed by Hispanics (16%), others (14%), and Asians (2%). In terms of antihypertensive medication usage, those diagnosed with hyperaldosteronism were taking more of all three classes of medication (Table 2). On average, patients with hyperaldosteronism were on one more (4.5 vs. 3.4) antihypertensive medication (Table 1). Despite this, their blood pressure was not as well controlled (145/81 vs. 137/77, $P < 0.001$, Table 1).

Multivariate regression analysis for sleep apnea

Results for the multivariate logistic regression model adjusted for age, sex, BMI categories, diabetes mellitus, and CHF are presented in Table 3. The OR for sleep apnea was 1.8 [95% confidence interval (CI) 1.3–2.6] in hypertensive patients with hyperaldosteronism as opposed to those hypertensive patients without hyperaldosteronism.

The spline graph from the adjusted generalized additive model supports the multiple logistic regression analyses

Table 1 Baseline characteristics and laboratory findings in patients with and without hyperaldosteronism by aldosterone–renin ratio testing ($n = 3428$)

		ARR testing		
Characteristics	All ($n = 3428$)	HA(−) ($n = 2853$)	HA(+) ($n = 575$)	*P*
Age (years)[a]	57.2 ± 0.3	56.5 ± 0.3	60.9 ± 0.5	<0.001
18–30 years (%)	7.4	9.0	1.0	
31–45 years (%)	15	17	9.7	
46–60 years (%)	32	30	40	
60+ years (%)	45	44	50	
Men (%)	42	41	48	
	<0.001			
Ethnicity (%)[a]				<0.001
White	35	36	29	
African–American	20	18	32	
Hispanic	19	19	17	
Asian	8.0	9.0	7.0	
Other	18	19	15	
Obstructive sleep apnea (%)	10	8.8	18	<0.001
Weight (lbs)	186.4 ± 0.9	184.3 ± 1.0	196.4 ± 2.4	<0.001
Height (inches)	65.9 ± 0.1	65.7 ± 4	66.4 ± 4	0.004
BMI (kg/m^2)	30.1 ± 0.1	29.9 ± 0.1	31.0 ± 0.3	0.002
SBP (mmHg)	138.3 ± 0.3	137.0 ± 0.5	144.8 ± 1.0	<0.001
DBP (mmHg)	77.9 ± 0.2	77.3 ± 0.3	80.9 ± 0.5	<0.001
Potassium (meq/l)	4.0 ± 0.01	4.1 ± 0.01	3.8 ± 0.02	<0.001
CO_2 (meq/l)	27.4 ± 0.1	27.3 ± 0.7	28.4 ± 0.1	<0.001
Aldosterone (ng/dl)	14.8 ± 0.4	11.9 ± 0.2	29.3 ± 1.4	<0.001
Plasma renin activity (ng/ml per h)	4.4 ± 0.18	5.3 ± 0.21	0.3 ± 0.02	<0.001
Aldosterone/renin ratio	30.1 ± 0.7	7.4 ± 0.2	1142 ± 6.8	<0.001
Antihypertensive drugs (no.)	3.6 ± 0.05	3.4 ± 0.05	4.1 ± 0.1	<0.001
Creatinine (mg/dl)	1.3 ± 0.02	1.3 ± 0.02	1.2 ± 0.05	0.4
Glomerular filtration rate	69.5 ± 0.5	69.4 ± 0.6	70.0 ± 1.1	0.7

Data are presented as mean ± standard errors (SE). ARR, aldosterone : renin ratio; HA, hyperaldosteronism. [a] χ^2.

Table 2 Medication usage by presence or absence of hyperaldosteronism

Medication type	HA(−) #, meds/pt	HA(+) #, meds/pt	P^*
Natriuretics	1490 (0.52)	444 (0.77)	<0.001
Diuretics[a]	1127 (0.40)	288 (0.50)	<0.001
Others[b]	941 (0.33)	337 (0.59)	<0.001
RAS blockers[c] (ACE-I, ARB)	1349 (0.47)	367 (0.64)	<0.001
RAS suppressors[d] (BB, clonidine)	1183 (0.42)	403 (0.70)	<0.001

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; HA, hyperaldosteronism; meds, medications; RAS, renin–angiotensin system. * χ^2. [a] Diuretics – aldosterone receptor blockers, thiazide diuretics, loop diuretics. [b] Other – calcium channel blockers, α-blockers. [c] RAS blockers – angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, direct renin inhibitors. [d] RAS suppressors – β-receptor blockers, centrally acting α-antagonists (guanfacine, clonidine) reserpine, methyldopa.

(Fig. 1). At an aldosterone-to-PRA ratio greater than 30, the lower bounds of the CI for OR of sleep apnea stays above 1.0 indicating the beginning of a trend toward sleep apnea in patients with hyperaldosteronism. Increasing age was associated with an increased risk of sleep apnea; however, the greatest risk occurred in the middle-aged (46–60 years) patients (OR = 6.8, 95% CI 1.6–29.0). Incremental increases in BMI categories beginning from overweight to class III obesity increased the risk for sleep apnea with a 23-fold increase in odds of having sleep apnea in patients with class III obesity (OR = 23, 95% CI 12–43) compared to those with BMI less than 25 kg/m^2.

No specific racial or ethnic group was at greater risk for having sleep apnea on the multivariate analysis. Subset analyses examining whites (OR = 1.3, 95% CI 0.98–1.8), African–Americans (OR = 0.88, 95% CI 0.63–1.2), and Hispanics (OR = 0.94, 95% CI 0.65–1.3) independently in the multivariate regression analysis also did not reveal that any one of these three groups was at greater risk for sleep apnea.

Table 3 Variables associated with sleep apnea on multiple logistic regression analysis with adjustment for other covariates in the column ($n = 3428$)

Variable	OR	95% CI
HA (+)	1.8	1.3–2.6
Male sex	3.1	2.3–4.2
Age 31–45	3.4	0.8–15
Age 46–60	6.8	1.6–29
Age 60+	4.7	1.0–20
BMI 25–29 vs. <25	2.0	1.0–3.7
BMI >29 vs. <25		
Class I obesity	7.0	3.8–13
Class II obesity	10	5.5–20
Class III obesity	23	12–43
Race		
White	1.0 (reference)	
African–American	0.8	0.5–1.1
Hispanic	0.8	0.5–1.1
Asian	1.0	0.6–1.9
Other	0.6	0.4–1.0
CHF	2.2	1.6–3.1
Diabetes mellitus	1.7	1.2–2.2

Multivariate logistic regression, adjusted for age, sex, BMI categories, diabetes mellitus, and congestive heart failure (CHF), was used to estimate the odds ratio (OR) of variables associated with sleep apnea. CI, confidence interval; HA, hyperaldosteronism.

Discussion

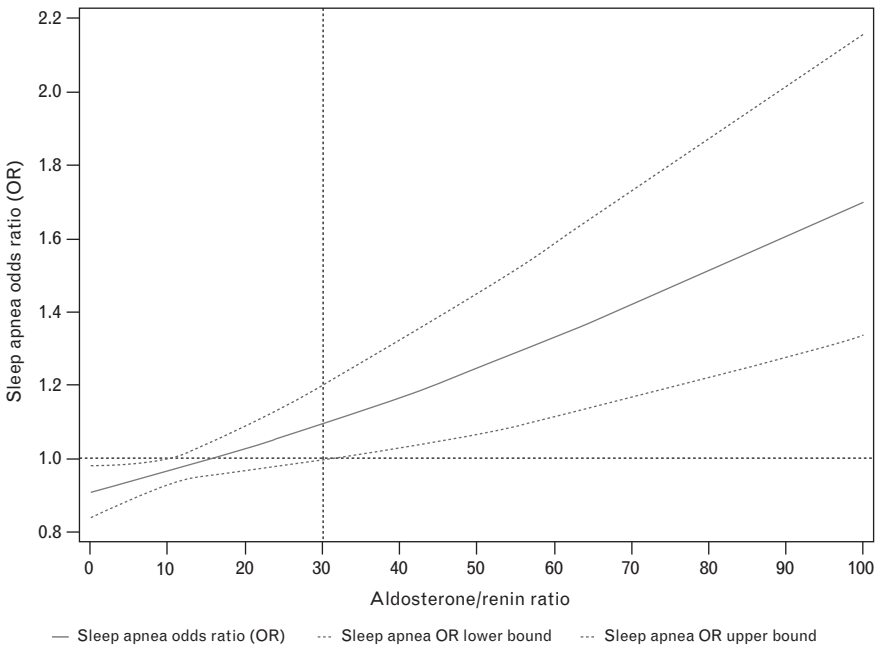
Examining an ethnically diverse historical cohort of hypertensive patients in whom plasma aldosterone and PRA were measured concurrently, we found a two-fold greater prevalence of sleep apnea in hypertensive patients diagnosed with hyperaldosteronism compared to hypertensive patients without hyperaldosteronism. To our knowledge, the current analysis includes one of the largest cohorts in which this relationship was evaluated.

Epidemiological, cross-sectional, and prospective studies have indicated that hypertension often co-exists with sleep apnea [1–4,25,26]. This relationship is even stronger among resistant hypertensive patients [13,27]. Hyperaldosteronism has been found to be present in up to 20% of patients with resistant hypertension [28,29]. It has been hypothesized that aldosterone may contribute to both sleep apnea and resistant hypertension [29].

Previous studies have demonstrated that aldosterone is positively correlated with sleep apnea among resistant hypertensive patients but not among nonhypertensive sleep apnea patients [27]. Moreover, Calhoun *et al.* [12] reported that in patients with resistant hypertension, aldosterone is positively correlated with sleep apnea in participants with high but not normal aldosterone levels.

Due to the many shared risk factors for hypertension and sleep apnea, previous investigators have commented on the difficulty in confirming a direct relationship between aldosterone and sleep apnea [30]. Risk factors such as sex, advancing age, and BMI may all be associated with sleep apnea and hypertension. Our findings demonstrate an increased odds of sleep apnea with hyperaldosteronism after controlling for these potential confounders (sex, age, BMI, ethnicity, diabetes mellitus, CHF). Further supporting a causal link between hyperaldosteronism and sleep apnea, a recent interventional study demonstrated a reduction in severity of sleep apnea with the use of an aldosterone antagonist [31]. The use of continuous positive airway pressure as a treatment for sleep apnea has also revealed a reduction in aldosterone levels after 3 months [32]. These results, in combination with our current findings, support the relationship between

Fig. 1



At an aldosterone-to-plasma renin activity ratio greater than 30, the lower bounds of the confidence interval for odds ratio of sleep apnea stays above 1.0 indicating the beginning of a statistical significance for sleep apnea for patients with hyperaldosteronism.

aldosterone as either a mediator or intermediary of sleep apnea in hypertensive patients.

Our study revealed a peak age for prevalence of sleep apnea in the middle-aged group and not the oldest group, which is similar to the population prevalence distribution for sleep apnea [23,33–35]. We hypothesize that because sleep apnea is an independent risk factor for death from any cause, patients with sleep apnea do not advance to an older age and, thus, prevalence is lower in the 60+ age group [36].

One of the strengths of our study was that African–Americans, Latinos, and Asians were well represented (20, 19, and 8%, respectively). Data are currently scarce in describing the relation between hyperaldosteronism and sleep apnea beyond the African–American and white population [37]. African–Americans have been described to have high prevalence of sleep apnea [38,39]. However, data comparing the prevalence of hyperaldosteronism in African–Americans to whites are inconsistent [29,40]. In our study, we found that African–Americans were the only ethnic group to have a higher prevalence of both sleep apnea and hyperaldosteronism compared to whites, Hispanics, and Asians. Previous studies have already demonstrated aldosterone is an important mediator of hypertension in African–Americans as an ethnic subset [41]. These studies and others such as the African–American study of kidney disease and hypertension (AASK) suggest that African–Americans have beneficial outcomes from medications directed at the renin–angiotensin–aldosterone system [42]. Whether this benefit might extend to those with hyperaldosteronism and sleep apnea presents an interesting possibility.

Whether hyperaldosteronism plays a role in predisposing other ethnicities to sleep apnea has yet to be fully investigated. Our basic findings indicate that it may not be a major risk factor, as prevalence of hyperaldosteronism among other ethnicities with sleep apnea did not differ much. Furthermore, when whites, African–Americans, and Hispanics were examined independently as predictors for sleep apnea controlling for other risk factors of sleep apnea, no increased odds for sleep apnea were observed regardless of ethnicity.

Because our data are retrospective, a conscious effort to have our participants stop antihypertensive medications that affect aldosterone or renin activity levels was impossible. In addition, participants likely had different levels of physical activity and had blood samples drawn at various times throughout the day. These may all contribute to variability in the aldosterone and PRA [43,44]. The effects of medication usage on aldosterone : PRA ratio are a potential confounder in our analyses. As a majority of antihypertensive medications affect PRA and aldosterone levels [45–47], it would affect the diagnostic criteria used to identify hyperaldosteronism. Gallay *et al.* [48] prospectively examined the effect of antihypertensive medications on plasma aldosterone. Similar to our study,

while on antihypertensive medications of various classes (angiotensin receptor blockers, β-blockers, calcium channel blockers, diuretics, and α-blockers), 17% of their participants had hyperaldosteronism confirmed by further diagnostic testing.

The current study is strengthened by the large number of ethnically diverse participants. Given the epidemiologic nature of our study, important study limitations include the inability to infer causality. Furthermore, because our diagnosis of sleep apnea in a fixed population was based solely on ICD-9 codes, there is the likelihood of selection bias by excluding those with sleep apnea who have not been coded properly or including individuals with resolved sleep apnea. However, the use of ICD-9 codes to identify diagnosis is rather conservative and commonplace when examining data from large healthcare databases [49,50].

The major limitation of our study is that we examined data from patients who for various clinical indications had plasma aldosterone and PRA levels drawn as part of routine clinical care. Though our study population was large with over 3000 patients, it is a mere fraction of the entire KPSC membership population at the time. Thus, the study population likely represents a special subpopulation of hypertensive patients wherein healthcare providers deemed these patients as to be needing workup with these laboratory studies. The generalizability to others including hypertensive patients and nonhypertensive individuals is questionable. However, our comparisons were directed within this subset population comparing hyperaldosterone and nonhyperaldosterone patients. Because of this inherent selection bias, our conclusions are limited to those who were tested with plasma aldosterone and PRA levels and nothing beyond. Our findings serve as an impetus to conduct a large prospective study randomly testing all hypertensive individuals for both hyperaldosteronsim and sleep apnea. Such a study would more definitively determine whether sleep apnea is indeed more prevalent in those with hyperaldosteronism.

In conclusion, our findings support existing data that sleep apnea is more prevalent in hypertensive patients with hyperaldosteronism. This holds true even when controlling for other common risk factors for sleep apnea.

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