




Association of renin and aldosterone with glucose metabolism in a Western European population: the KORA F4/FF4 study

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ABSTRACT

Introduction Primary aldosteronism is associated with impaired glucose tolerance. Whether plasma aldosterone and/or renin concentrations are associated with type 2 diabetes and continuous measures of glucose metabolism in the general population is still under debate.

Research design and methods The analyses included 2931 participants of the KORA F4 study at baseline and 2010 participants of the KORA FF4 study after a median follow-up of 6.5 years. The associations of active plasma renin and aldosterone concentrations with type 2 diabetes and continuous measures of glucose metabolism were assessed using logistic and linear regression models. Results were adjusted for sex, age, body mass index (BMI), estimated glomerular filtration rate, potassium, use of ACE inhibitors, angiotensin receptor blockers, beta blockers, diuretics and calcium channel blockers.

Results Cross-sectionally, renin was associated with type 2 diabetes (OR per SD: 1.25, 95% CI 1.10 to 1.43, $p < 0.001$), fasting glucose, 2-hour glucose, insulin, proinsulin, HOMA-B (homeostasis model assessment of beta cell function) and HOMA-IR (homeostasis model assessment of insulin resistance) (all p values < 0.001). Aldosterone was not associated with type 2 diabetes (OR: 1.04, 95% CI 0.91 to 1.19; $p = 0.547$) but with insulin, proinsulin and HOMA-IR (all p values < 0.001). The aldosterone–renin ratio was inversely associated with type 2 diabetes and several measures of glucose metabolism. Longitudinally, neither renin (OR: 1.12, 95% CI 0.92 to 1.36) nor aldosterone (OR: 0.91, 95% CI 0.74 to 1.11) were associated with incident type 2 diabetes. Renin was inversely associated with changes of insulin concentrations.

Conclusions In the KORA F4/FF4 study, renin and aldosterone were not associated with incident type 2 diabetes and largely unrelated to changes of measures of glucose metabolism. Cross-sectionally, aldosterone was associated with surrogate parameters of insulin resistance. However, these associations were not independent of renin.

INTRODUCTION

Increasing evidence indicates a bidirectional interplay of aldosterone with metabolic

Significance of this study

What is already known about this subject?

▶ Elevated aldosterone concentrations in primary aldosteronism are associated with impaired glucose tolerance and type 2 diabetes. The underlying mechanisms remain elusive, and the association of aldosterone and renin with glucose metabolism in the general population is still under debate.

What are the new findings?

▶ In a Western European general population, renin was associated with prevalent type 2 diabetes, continuous measures of glucose metabolism and the adipokines leptin and retinol-binding protein-4.
▶ Aldosterone was cross-sectionally associated with insulin resistance and leptin. These associations were not independent of renin.
▶ Neither renin nor aldosterone were longitudinally positively associated with incident type 2 diabetes or changes in continuous measures of glucose metabolism.

How might these results change the focus of research or clinical practice?

▶ Elevated renin and aldosterone are cross-sectionally associated with impaired glucose tolerance. However, no longitudinal associations with measures of glucose metabolism were detectable, indicating that moderately elevated aldosterone concentrations do not seem to play a major role for the development of impaired glucose metabolism in the general Western European population. Future research should focus on possible ethnic differences of the relation of aldosterone with type 2 diabetes.

alterations. Obesity may promote idiopathic hyperaldosteronism via secretory products of adipocytes stimulating mineralocorticoid secretion.^{1 2} Vice versa, overactivation of the mineralocorticoid receptor plays a role in

the pathophysiology of metabolic alterations, including dysglycemia.³

Preclinical data indicate an interference of aldosterone with both insulin secretion and insulin resistance. In mice, a high-fat diet leads to dysregulation of the renin–angiotensin–aldosterone system (RAAS),⁴ and aldosterone excess decreases glucose-stimulated insulin secretion.⁵ In rat skeletal muscle, elevated aldosterone inhibits the expression of the insulin receptor and the translocation of glucose transporter-4 to the plasma membrane, resulting in decreased glucose uptake.⁶ The effects of aldosterone on metabolism may partly be mediated by subclinical inflammatory responses and alterations in adipokine expression.⁷

In humans, the association of elevated aldosterone with alterations of glucose metabolism has mainly been studied in the setting of primary aldosteronism.⁸ Persons with primary aldosteronism are more likely to have type 2 diabetes (T2D) compared with the general population,⁹ and the aldosterone-to-renin ratio (ARR) within primary aldosteronism is higher in case of concomitant diabetes.¹⁰ Longitudinal data suggest a causal role of primary aldosteronism for impaired glucose tolerance (IGT), since adrenalectomy reduced glucose and insulin values,¹¹ improved insulin sensitivity,^{12 13} and restored a decreased first-phase insulin secretion in an intravenous glucose tolerance test¹⁴ as well as the insulin response to a hyperglycemic clamp.¹⁵ However, the findings for insulin sensitivity remain inconsistent, since Adler *et al*¹⁵ found a decreased insulin sensitivity after treatment with adrenalectomy or mineralocorticoid receptor antagonists.

Beyond primary aldosteronism, data from other populations support a relationship of aldosterone with glucometabolic alterations. Plasma aldosterone concentrations were associated with insulin resistance in patients with heart failure,¹⁶ in HIV-infected patients^{17 18} and in normotensive individuals.¹⁹ In general population-based settings, aldosterone was associated with the metabolic syndrome in two German populations²⁰ and with insulin resistance in men but not in women in an African-American population.²¹ Longitudinally, baseline plasma aldosterone was associated with the development of insulin resistance in a Japanese general population,²² renin and aldosterone were associated with incident T2D in an African-American population,²³ and the multiethnic study of atherosclerosis found an association of aldosterone, but not renin, with incident T2D. Of note, in the latter study, the association was stronger in Chinese and African-Americans as compared with Hispanic and non-Hispanic white Americans.²⁴

The aim of the present study was to determine the cross-sectional and longitudinal associations of renin and aldosterone with pre-diabetes, T2D and continuous measures of glucose metabolism in a large Western European population of mainly Caucasian ethnicity. In light of preliminary data indicating a relation of the RAAS with adipokines,^{1 7} we additionally examined the

cross-sectional associations of the RAAS parameters with selected adipokines.

METHODS

Study participants and definition of variables

The KORA (Cooperative Health Research in the Region of Augsburg) F4 (2006–2008) and FF4 (2013–2014) studies are follow-up examinations of the population-based KORA S4 study (1999–2001). All participants gave written informed consent. Recruitment and eligibility criteria for the KORA studies, study design, standardized sampling methods and data collection (medical history, medication, anthropometric and blood pressure measurements) have been described elsewhere.^{25 26}

Participants with a diabetes type other than type 2 or unknown glucose tolerance were excluded from the analyses (n=75). In the cross-sectional analysis, all variables necessary for the analysis of the association of renin and aldosterone with T2D were available in 2931 (out of 3080) participants. Measurements of glucose metabolism and adipokines were available in 1093–2743 participants depending on the outcome (online supplemental figure 1). Total proinsulin was measured in the first 1567 participants of the KORA F4 study. Adiponectin and omentin-1 were measured in participants aged ≥ 62 years.

Of the 2931 participants, 154 died before the follow-up examination and 697 declined participation in the FF4 survey or could not be contacted. The study sample in the longitudinal F4/FF4 examination comprised 1834 participants for the analysis of incident T2D. Participants with missing data for the continuous outcomes were excluded from the respective analyses. The numbers of participants included in each analysis are given in the results tables and illustrated in online supplemental figure 1. The median (first; third quartile) follow-up time was 6.5 (95% CI 6.3 to 6.6) years.

Criteria for clinically diagnosed diabetes mellitus were a validated medical diagnosis or current self-reported use of glucose-lowering agents. After an overnight fasting period, all participants without clinically diagnosed diabetes underwent a standard 75 g oral glucose tolerance test. Newly diagnosed diabetes, IGT, impaired fasting glucose (IFG), and normal glucose tolerance (NGT) were defined according to the 1999 WHO diagnostic criteria based on both fasting and postchallenge glucose values (T2D: ≥ 7.0 mmol/L fasting and/or ≥ 11.1 mmol/L 2-hour glucose; IFG: ≥ 6.1 mmol/L and < 7.0 mmol/L fasting glucose; IGT: ≥ 7.8 and < 11.1 mmol/L 2-hour glucose). Pre-diabetes was defined as IFG and/or IGT. Incident pre-diabetes/T2D was defined as progression from NGT to pre-diabetes (n=245) or T2D (n=38). Incident T2D (n=130) was defined as progression from NGT or pre-diabetes to T2D.

Arterial hypertension was defined as a systolic blood pressure ≥ 140 mm Hg and/or a diastolic blood pressure ≥ 90 mm Hg (mean values of the second and third

of three blood pressure measurements), and/or use of antihypertensive medication, given that the participants were aware of being hypertensive. The methods for 'study participants and definition of variables' are similar to those previously described.²⁷

Laboratory measurements

Blood samples were collected after an overnight fast of at least 8 hours in sitting position after a rest of 10 min (sitting) and were kept at room temperature until centrifugation. Plasma was separated immediately, serum after 30 min. Samples were assayed immediately or stored at -80°C . Plasma renin concentrations were measured using the Liaison active renin assay (Diasorin, Dietzenbach, Germany) using monoclonal antibodies to only detect active renin molecules without interference with prorenin. Intra-assay and interassay coefficients of variation were below 5.6% and 12.2%, respectively, and the functional sensitivity was $<2.0\ \mu\text{U}/\text{mL}$. Plasma aldosterone concentrations were measured with an inhouse immunofluorometric assay as described previously.²⁸ Interassay and intra-assay coefficients of variation were 15.2% and 7.3% in low, and 8.0% and 4.4% in high concentrations, respectively. Serum creatinine was determined with a modified Jaffe test (Krea Flex; Dade Behring, Deerfield, Illinois, USA). Glucose levels were measured in serum using a hexokinase method (GLUFlex, Dade Behring) at baseline and an enzymatic colorimetric method on a Dimension Vista 1500 instrument (Siemens) or the GLUC3 assay on a Cobas c702 instrument (Roche Diagnostics, Mannheim, Germany) at follow-up.²⁹ Hemoglobin A1c (HbA1c) was measured in hemolyzed whole blood using the cation-exchange high performance liquid chromatographic, photometric VARIANT II TURBO HbA1c Kit – 2.0 assay on a VARIANT II TURBO Hemoglobin Testing System (Bio-Rad Laboratories Inc, Hercules, USA). Insulin was measured by an electrochemiluminescence immunoassay on a Cobas e602 instrument (Roche) in KORA F4. KORA FF4 serum insulin concentrations were assessed by a solid-phase enzyme-labeled chemiluminescent immunometric assay on an Immulite 2000 systems analyzer (Siemens) or by an electrochemiluminescence immunoassay on a Cobas e602 instrument (Roche). Insulin values were calibrated to the Roche assay as described previously.²⁶ Intact proinsulin (frozen EDTA plasma) was measured by ELISA (intact human proinsulin ELISA, Cat.-No. EZHIPI-17K, Linco Research, St Charles, Missouri, USA). Chemerin serum concentrations were determined using a commercially available ELISA kit (Human Chemerin ELISA, BioVendor, Heidelberg, Germany) with a sensitivity of $0.1\ \text{ng}/\text{mL}$ and intra-assay and interassay coefficients of variance of 6.0% and 7.6%.³⁰ Plasma concentrations of retinol-binding protein-4 were measured by immunonephelometry using a BN II analyzer. The intra-assay and inter-assay coefficients of variation were $<10\%$.³¹ Leptin was measured by ELISA (Mercodia, Uppsala,

Sweden) with intra-assay and interassay coefficients of variation of $<10\%$. Serum concentrations of omentin-1 and adiponectin were measured using the Human Omentin-1 ELISA (BioVendor, Brno, Czech Republic) and the Human Total Adiponectin/Acrp30 Quantikine ELISA Kit (R&D Systems) with intra-assay coefficients of variation (CVs) of 2.0% and 4.0%, respectively, and interassay CVs of 3.8% and 8.0%, respectively.³² Progranulin serum concentrations were determined using the Progranulin human ELISA Kit AdipoGen from AdipoGen (Seoul, Korea).³⁰ Serum vaspin concentrations were quantified using a commercial ELISA kit (AdipoGen) with a sensitivity of $12\ \text{pg}/\text{mL}$. The intra-assay and interassay coefficients of variance were 1.3%–3.8% and 3.3%–9.1%, respectively.³⁰

Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (2009) based on serum creatinine.³³ Homeostasis model assessment of insulin resistance (HOMA-IR: fasting insulin (in pmol/L) \times fasting glucose (in mmol/L) \div 135), homeostasis model assessment of beta cell function (HOMA-B: fasting insulin ($\mu\text{U}/\text{mL}$) $\times 20 \div$ (glucose (mmol/L) – 3.5)%) were calculated in all participants except those with antihyperglycemic treatment.

Statistical analyses

Characteristics of the study participants were compared between participants without and with T2D using t-tests in case of approximately normally distributed variables. Mann-Whitney U-tests were performed for variables with skewed distributions. Binomial proportions were compared with χ^2 tests. The associations of renin, aldosterone and the ARR with pre-diabetes and T2D were assessed in logistic regression models. The associations with continuous dependent variables were examined in linear regression models. Continuous variables were transformed to a Gaussian distribution by probability integral transformation followed by inverse transform sampling, z-standardized and used in calculations per one SD increase. In multivariable logistic and linear regression analyses, the associations were adjusted for sex, age, BMI, arterial hypertension, eGFR, potassium, use of ACE inhibitors, angiotensin receptor blockers, beta blockers, diuretics and calcium channel blockers. For sensitivity analyses, the calculations were repeated after exclusion of participants taking ACE inhibitors, angiotensin receptor blockers, beta blockers, diuretics and calcium channel blockers (online supplemental tables 1–4 and 6). Participants taking glucose-lowering medication were excluded from the analyses involving continuous measures of glucose metabolism. For the longitudinal associations, the deltas of the continuous measures of glucose metabolism (follow-up value (KORA FF4) – baseline value (KORA F4)) were used as outcome variables. The level of statistical significance was set at 5% (two sided). Bonferroni correction for multiple testing was used (numbers of tests are given in the respective tables). The calculations

Table 1 Characteristics of the study participants at KOFA F4, overall and stratified by type 2 diabetes at baseline*

	N	Total study cohort	N	No diabetes †	N	Type 2 diabetes ‡	P value §
Male sex, n (%)	2931	1418 (48)	2598	1220 (47)	333	198 (59)	<0.001 ¶
Age (years)	2931	56.2±13.2	2598	54.8±12.9	333	67.0±9.3	<0.001**
BMI (kg/m ²)	2931	27.6±4.8	2598	27.2±4.6	333	31.2±5.1	<0.001**
eGFR (mL/min/1.73 m ²)	2931	89.3 (77.6; 100.0)	2598	90.6 (78.9; 101.2)	333	78.9 (64.7; 89.1)	<0.001††
Arterial hypertension, n (%)	2931	1122 (38)	2598	859 (33)	333	263 (79)	<0.001 ¶
Pre-diabetes, n (%)	2931	488 (16.6)	2598	488 (18.8)	–	–	–
HbA1c (%) ‡‡	2764	5.4 (5.2; 5.7)	2598	5.4 (5.2; 5.6)	333	6.1 (5.8; 6.6)	<0.001††
HbA1c (mmol/mol) ‡‡	2764	35.5 (33.3; 38.8)	2598	35.5 (33.3; 37.7)	333	43.2 (39.9; 48.6)	<0.001††
Fasting glucose (mg/dL) ‡‡	2764	93 (88; 101)	2598	93 (87; 100)	166 ††	122 (109; 135)	<0.001††
Fasting glucose (mmol/L) ‡‡	2764	5.16 (4.88; 5.61)	2598	5.16 (4.82; 5.55)	166††	6.77 (6.07; 7.49)	<0.001††
2-hour glucose (mg/dL)	2710	104 (87; 128)	2598	103 (86; 125)	112	214 (200; 241)	<0.001††
2-hour glucose (mmol/L)	2710	5.77 (4.77; 6.92)	2598	5.72 (4.77; 6.92)	112	11.88 (11.11; 13.36)	<0.001††
Insulin (pmol/L) ‡‡	2743	52.2 (37.2; 78.0)	2579	51.0 (36.6; 72.0)	164††	96 (66.0; 138.0)	<0.001††
Proinsulin (pmol/L) ‡‡	1438	2.9 (1.9; 4.5)	1356	2.8 (1.9; 4.2)	82††	6.9 (4.8; 10.1)	<0.001††
Proinsulin-to-insulin ratio ‡‡	1438	0.05 (0.04; 0.08)	1356	0.05 (0.04; 0.07)	82††	0.07 (0.05; 0.103)	<0.001††
HOMA-B ‡‡	2743	104.5 (76.9; 143.9)	2579	104.9 (77.9; 143.7)	164††	95.6 (69.9; 150.9)	0.179††
HOMA-IR ‡‡	2743	2.02 (1.37; 3.08)	2579	1.95 (1.34; 2.88)	164††	5.12 (3.29; 7.22)	<0.001††
Leptin (ng/mL)	2922	12.0 (5.3; 24.8)	2592	11.3 (5.0; 23.3)	330	20.3 (9.7; 41.5)	<0.001††
Retinol-binding protein-4 (g/L)	2922	0.042 (0.036; 0.049)	2592	0.042 (0.035; 0.049)	330	0.045 (0.039; 0.053)	<0.001††
Adiponectin (µg/mL)	1093	10.11 (6.57; 15.14)	862	10.78 (7.21; 16.01)	231	7.58 (5.32; 11.11)	<0.001††
Omentin-1 (ng/mL)	1093	489.0 (403.6; 580.8)	862	491.7 (406.6; 582.5)	231	480.8 (391.5; 576.6)	0.233 ††
Chemerin (ng/mL)	1702	167.2 (135.2; 199.6)	1461	165.9 (133.2; 197.8)	241	175.7 (145.6; 216.6)	<0.001††
Progranulin (ng/mL)	1702	137.3 (106.4; 176.5)	1461	136.0 (106.2; 175.6)	241	146.4 (109.7; 191.1)	0.084 ††
Vaspin (ng/mL)	1702	0.58 (0.32; 1.08)	1461	0.57 (0.31; 1.07)	241	0.69 (0.39; 1.14)	0.016 ††
Active plasma renin concentration (µU/mL)	2931	11.35 (6.2; 20.1)	2598	11.1 (6.1; 18.9)	333	15.35 (7.1; 36.6)	<0.001††
Aldosterone (ng/L)	2931	38 (26; 58)	2598	38 (26; 58)	333	38 (22; 60)	0.319††
Aldosterone-to-renin ratio	2931	5.68 (2.93; 10.75)	2598	5.89 (3.18; 11.11)	333	3.59 (1.54; 8.64)	<0.001††
Antihypertensive medication, n (%)	2931	909 (31)	2598	649 (25)	333	240 (72)	<0.001††
ACE inhibitors, n (%)	2931	384 (13)	2598	255 (10)	333	129 (39)	<0.001 ¶
Angiotensin receptor blockers, n (%)	2931	223 (8)	2598	172 (7)	333	51 (15)	<0.001 ¶
Beta blockers, n (%)	2931	554 (19)	2598	403 (15)	333	151 (45)	<0.001 ¶
Diuretics, n (%)	2931	521 (18)	2598	365 (14)	333	156 (47)	<0.001 ¶
Calcium channel blockers, n (%)	2931	230 (8)	2598	162 (6)	333	68 (20)	<0.001 ¶

*Mean ± SD, median (first quartile; third quartile), or number of participants (proportion in %).

†Normal glucose tolerance and pre-diabetes.

‡Known and newly diagnosed type 2 diabetes.

§The p value is related to the null hypothesis of no difference between participants without diabetes and with type 2 diabetes.

¶ χ^2 test.

**t-Test.

††Mann-Whitney U test.

‡‡Participants with glucose-lowering drugs were excluded; the median HbA1c of all participants with type 2 diabetes, including those using glucose-lowering medication, was 6.4% (5.9; 7.0) (46.4 mmol/mol (41.0; 53.0)).

BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HOMA-B, homeostasis model assessment of beta cell function; HOMA-IR, homeostasis model assessment of insulin resistance.

were performed using the statistical environment R V.3.6.0 (R Development Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2019).

RESULTS

Study population characteristics

Table 1 displays the baseline characteristics of the total study population and stratified by T2D. Active plasma renin concentrations were higher in participants with T2D, whereas aldosterone concentrations were similar in

participants with and without T2D. The ARR was lower in participants with T2D.

Cross-sectional associations of the RAAS parameters with pre-diabetes, T2D, measures of glucose metabolism and adipokines

Renin, but not aldosterone, was significantly positively associated with prevalent pre-diabetes and T2D. The ARR was inversely associated with T2D (table 2).

Table 3 displays the associations of the RAAS parameters with continuous measures of glucose metabolism.

Table 2 ORs (95% CI) for prevalent pre-diabetes (vs normal glucose tolerance) and prevalent type 2 diabetes (vs no type 2 diabetes) per SD increase of active plasma renin concentration, aldosterone and ARR

	Prevalent pre-diabetes (yes: n=488; no: n=2110)	P value	Prevalent type two diabetes (yes: n=333; no: n=2598)	P value
Renin	1.20 (1.07 to 1.35)	0.002	1.25 (1.10 to 1.43)	<0.001
Aldosterone	1.10 (0.98 to 1.24)	0.095	1.04 (0.91 to 1.19)	0.547
ARR	0.92 (0.82 to 1.03)	0.151	0.82 (0.72 to 0.93)	0.002

Bold print indicates significance after correction for multiple testing using the Bonferroni method ($p < 0.008$ ($0.05 \div 6$)).

The logistic regression models were adjusted for sex, age, BMI, arterial hypertension, eGFR, potassium, use of ACE inhibitors, angiotensin receptor blockers, beta blockers, diuretics and calcium channel blockers.

ARR, aldosterone-to-renin ratio; BMI, body mass index; eGFR, estimated glomerular filtration rate.

After Bonferroni correction for multiple testing, renin was positively associated with fasting glucose, 2-hour glucose, insulin, proinsulin, HOMA-B and HOMA-IR. In a sensitivity analysis, the associations of renin with insulin and HOMA-IR were additionally adjusted for fasting glucose and remained significant (β : 0.11 ± 0.02 and 0.09 ± 0.02 , respectively; $p < 0.001$ for both). Aldosterone was positively associated with insulin, proinsulin and HOMA-IR, whereas the ARR was inversely associated with fasting glucose, insulin and HOMA-IR. After correction for multiple testing, no significant associations of the RAAS parameters with HbA1c and the proinsulin-to-insulin ratio were found.

The associations of the RAAS parameters with adipokines are presented in table 4. After correction for multiple testing, renin was positively associated with leptin and retinol-binding protein-4, and aldosterone was positively associated with leptin. The ARR was not significantly associated with any adipokine.

Longitudinal analyses of the association of the RAAS parameters with pre-diabetes, T2D and continuous measures of glucose metabolism

None of the RAAS parameters was significantly associated with incident pre-diabetes and T2D (table 5 and online

supplemental table 4). Online supplemental tables 5 and 6 show the longitudinal associations of the RAAS parameters with deltas of continuous measures of glucose metabolism. After correction for multiple testing, renin was significantly inversely associated with changes in insulin, and the ARR was positively associated with changes in insulin. No other significant associations of the RAAS parameters with changes of continuous measures of glucose metabolism were observed after correction for multiple testing.

The results after exclusion of participants taking ACE inhibitors, angiotensin receptor blockers, beta blockers, diuretics and calcium channel blockers were comparable (online supplemental tables 1–4 and 6).

DISCUSSION

Renin was associated with prevalent but not with incident pre-diabetes and T2D in the population-based KORA F4/FF4 cohort. In line, renin and aldosterone were associated with continuous measures of glucose metabolism in the cross-sectional analysis but not with changes of these traits during follow-up. Of note, none of the associations of aldosterone with measures of glucose metabolism was independent of renin. In fact, the ARR was even inversely

Table 3 Cross-sectional beta estimates \pm SE of the associations of active plasma renin concentration, aldosterone and ARR (per SD) and continuous measures of glucose metabolism (per SD)

	N	Renin	Aldosterone	ARR
Fasting glucose	2764	0.08\pm0.02***	0.01 \pm 0.02	-0.07\pm0.02***
2-hour glucose	2710	0.08\pm0.02***	0.02 \pm 0.02	-0.06 \pm 0.02**
HbA1c	2764	0.05 \pm 0.02**	-0.01 \pm 0.02	-0.05 \pm 0.02**
Insulin	2743	0.13\pm0.02***	0.06\pm0.02***	-0.07\pm0.02***
Proinsulin	1438	0.11\pm0.03***	0.08\pm0.02***	-0.05 \pm 0.03*
Proinsulin-to-insulin ratio	1438	0.01 \pm 0.03	0.06 \pm 0.03*	0.02 \pm 0.03
HOMA-B	2743	0.09\pm0.02***	0.05 \pm 0.02**	-0.04 \pm 0.02*
HOMA-IR	2743	0.13\pm0.02***	0.06\pm0.02***	-0.08\pm0.02***

* $P < 0.05$; ** $p < 0.01$; *** $p < 0.001$; bold print indicates significance after correction for multiple testing using the Bonferroni method ($p < 0.0021$ ($0.05 \div 24$)).

The linear regression models were adjusted for sex, age, BMI, arterial hypertension, eGFR, potassium, use of ACE inhibitors, angiotensin receptor blockers, beta blockers, diuretics and calcium channel blockers.

ARR, aldosterone-to-renin ratio; BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HOMA-B, homeostasis model assessment of beta cell function; HOMA-IR, homeostasis model assessment of insulin resistance.

Table 4 Cross-sectional beta estimates±SE of the associations of active plasma renin concentration, aldosterone and ARR (per SD) and adipokines (per SD).

	N	Renin	Aldosterone	ARR
Leptin	2922	0.05±0.01***	0.05±0.01***	-0.01±0.01
Retinol-binding protein-4	2922	0.07±0.02***	0.04±0.02*	-0.03±0.02
Adiponectin	1093	-0.07±0.03*	-0.05±0.03	0.03±0.03
Omentin-1	1093	-0.01±0.04	0.00±0.03	-0.001±0.03
Chemerin	1702	0.04±0.03	0.02±0.02	-0.02±0.03
Progranulin	1702	-0.03±0.03	-0.01±0.03	0.02±0.03
Vaspin	1702	-0.01±0.03	0.07±0.02**	0.06±0.03*

*P<0.05; **p<0.01; ***p<0.001; bold print indicates significance after correction for multiple testing using the Bonferroni method ($p < 0.0024$ ($0.05 \div 21$)).

The linear regression models were adjusted for sex, age, BMI, arterial hypertension, eGFR, potassium, use of ACE inhibitors, angiotensin receptor blockers, beta blockers, diuretics and calcium channel blockers.

ARR, aldosterone-to-renin-ratio; BMI, body mass index; eGFR, estimated glomerular filtration rate.

associated with prevalent T2D and with fasting glucose, insulin and HOMA-IR. One possible explanation for the association of the RAAS parameters with prevalent diabetes might be hyperglycemia-induced RAAS activation. Indeed, renin was associated with fasting glucose and 2-hour glucose. However, although significant, these associations were moderate and do not fully explain the stronger associations of renin with insulin and insulin resistance, which remained significant after adjustment for fasting glucose.

Our findings indicate that the independent associations between aldosterone and alterations of glucose tolerance observed in primary aldosteronism^{8–15} are not readily transferable to a general population. In primary aldosteronism and in most preclinical studies, aldosterone values are considerably higher than in the general population. Furthermore, the association of primary aldosteronism with diabetes may partly be explained by concomitant subclinical hypercortisolism.³⁴

However, our data are also not fully consistent with some previous population-based studies. In a Japanese population, baseline plasma aldosterone was associated with the development of insulin resistance during follow-up.²² Renin was not measured in this study; thus, the dependence on RAAS activation could not be determined. Furthermore, since only 14 participants

developed diabetes during follow-up, an analysis of incident diabetes was not possible. In line with our data, HbA1c and fasting glucose were not associated with aldosterone at baseline.²² A positive association of both aldosterone and renin with incident diabetes was observed in African-Americans,²³ and an association of aldosterone, but not renin, with incident diabetes was shown in Chinese and African-Americans, in whom the association was significantly stronger than in Hispanic and non-Hispanic white Americans.²⁴ These data suggest ethnic variations in the associations of the RAAS with glucose metabolism. Importantly, ethnic differences have been observed for other RAAS effects. For instance, blacks have a higher sensitivity of blood pressure to aldosterone than whites.³⁵

Our study shows some discrepancies between cross-sectional and longitudinal results. There are several possible reasons for the observation of significant positive associations of renin with type 2 diabetes and continuous measures of glucose metabolism cross-sectionally but not longitudinally. Reverse causation, for example, activation of the RAAS by hyperglycemia and/or other associated factors, may be one explanation for the associations of renin with type 2 diabetes and measures of glucose metabolism in the cross-sectional analyses, which do not translate into longitudinal associations.

Table 5 ORs (95% CI) for incident pre-diabetes/type 2 diabetes (vs non-progressors to pre-diabetes/type 2 diabetes from normal glucose tolerance) and incident type 2 diabetes (vs non-progressors to type 2 diabetes from normal glucose tolerance or pre-diabetes) per SD increase of active plasma renin concentration, aldosterone and ARR

	Incident pre-diabetes/type 2 diabetes (yes: n=283; no: n=1260)	P value	Incident type 2 diabetes (yes: n=130; no: n=1704)	P value
Renin	1.05 (0.9–1.22)	0.538	1.12 (0.92–1.36)	0.257
Aldosterone	1.00 (0.86–1.16)	0.993	0.91 (0.74–1.11)	0.343
ARR	0.97 (0.83–1.13)	0.660	0.87 (0.71–1.05)	0.152

Significance level after correction for multiple testing using the Bonferroni method ($p < 0.008$ ($0.05 \div 6$)).

The logistic regression models were adjusted for sex, age, BMI, arterial hypertension, eGFR, potassium, use of ACE inhibitors, angiotensin receptor blockers, beta blockers, diuretics and calcium channel blockers.

ARR, aldosterone-to-renin ratio; BMI, body mass index; eGFR, estimated glomerular filtration rate.

Another possibility is residual confounding, which might occur despite careful adjustments of the analyses. Furthermore, a lack of power might have resulted in the non-significance of the association of renin with incident diabetes, since the number of incident type 2 diabetes cases was lower than the number of prevalent cases. Renin showed a trend towards a positive association with incident type 2 diabetes. The detection of a significant association in a larger study population cannot be excluded. However, aldosterone was neither cross-sectionally nor longitudinally associated with type 2 diabetes and the cross-sectional associations of aldosterone with insulin, proinsulin and HOMA-IR were not independent of renin. The OR for the association of aldosterone with incident type 2 diabetes was <1.0 , strongly arguing against a significant positive association, which might have been detectable in a larger study population.

Renin and aldosterone were associated with leptin, a finding in line with preclinical data showing that leptin might mediate aldosteronism in obesity. Previous data suggest a partially renin-independent relationship of aldosterone and leptin. Adrenocortical cells were demonstrated to coexpress CYP11B2 and leptin receptors.³⁶ Leptin directly induced aldosterone secretion in a preclinical model³⁶ and mediated hypertension via aldosterone-dependent mechanisms in female mice.³⁷ In addition to the direct relation to aldosterone, leptin also induces sympatho-excitatory effects and subsequent activation of the RAAS.³⁸ In our study, the association of aldosterone with leptin was not independent of renin (the ARR was not associated with leptin), suggesting a RAAS-dependency of leptin rather than a direct interaction with aldosterone in the general population.

Renin was further associated with retinol-binding protein-4 but not with the other assessed adipokines. Adiponectin was inversely associated with renin, but significance was not maintained after correction for multiple testing. Previously, influences on adiponectin expression and secretion were suggested to link aldosterone to the metabolic syndrome. In vitro, aldosterone perturbs adiponectin expression in 3T3-L1 adipocytes.³⁹ However, the influence of aldosterone on 3T3-L1 adipocytes appeared to be mediated mainly via the glucocorticoid receptor and thus required relatively high aldosterone concentrations.³⁹ In line, adiponectin levels were lower in patients with primary aldosteronism compared with patients with essential hypertension.⁴⁰ However, adiponectin and leptin expression was not increased in visceral adipose tissue of patients with aldosterone-producing adenoma.⁴¹ Our data indicate no major role for RAAS parameters for adiponectin concentrations in a general population. Also, the other investigated adipokines omentin-1, chemerin, progranulin and vaspin were not significantly related to renin or aldosterone. Thus, a wide interaction of the RAAS with adipose tissue secretory products in a general population is not suggested by these data.

Strengths and limitations

The findings of our study are based on a large and well-characterized prospective community-based study. Glucose tolerance status was assessed by oral glucose tolerance test at baseline and follow-up. Several further parameters for the characterization of glucose metabolism and measurements of both renin and aldosterone as well as of a number of adipokines were available. As the KORA study included nearly exclusively Caucasians, our results may not apply to other ethnic groups, and the study is not suitable to directly investigate the question of racial differences of RAAS effects. Many of the participants with diabetes used antihypertensive and/or diuretic medication. Although adjustment was performed, residual confounding cannot be excluded. However, the results after exclusion of participants on potentially confounding medication were similar. Proinsulin and some of the adipokines were available only in subgroups, limiting the generalizability and power of the concerned analyses. Renin and aldosterone were measured at baseline only, precluding the investigation of possible changes over time. No detailed data on salt intake or urinary sodium excretion were available. Dietary salt intake may affect glucose metabolism via RAAS and/or other parameters, although data are conflicting and the mechanisms remain unclear. In one study, dietary sodium restriction resulted in a decreased insulin sensitivity in participants with type 2 diabetes,⁴² whereas in another study including non-diabetic participants, sodium restriction did not affect insulin sensitivity but impaired insulin secretion.⁴³ However, higher sodium excretion was associated with a higher risk of type 2 diabetes in a meta-analysis of observational studies.⁴⁴ Therefore, RAAS-dependent and independent effects of dietary sodium on glucose metabolism cannot be excluded.

CONCLUSION

At baseline, renin was associated with prevalent pre-diabetes, T2D and continuous surrogate parameters of IGT and insulin sensitivity. Aldosterone was associated with insulin and HOMA-IR, whereas the ARR was inversely associated with prevalent T2D, fasting glucose, insulin and HOMA-IR, suggesting that aldosterone is associated with insulin resistance through the activation of the RAAS in a general Western European population. Renin, aldosterone and the ARR were not associated with incident T2D or changes in continuous measures of glucose metabolism.

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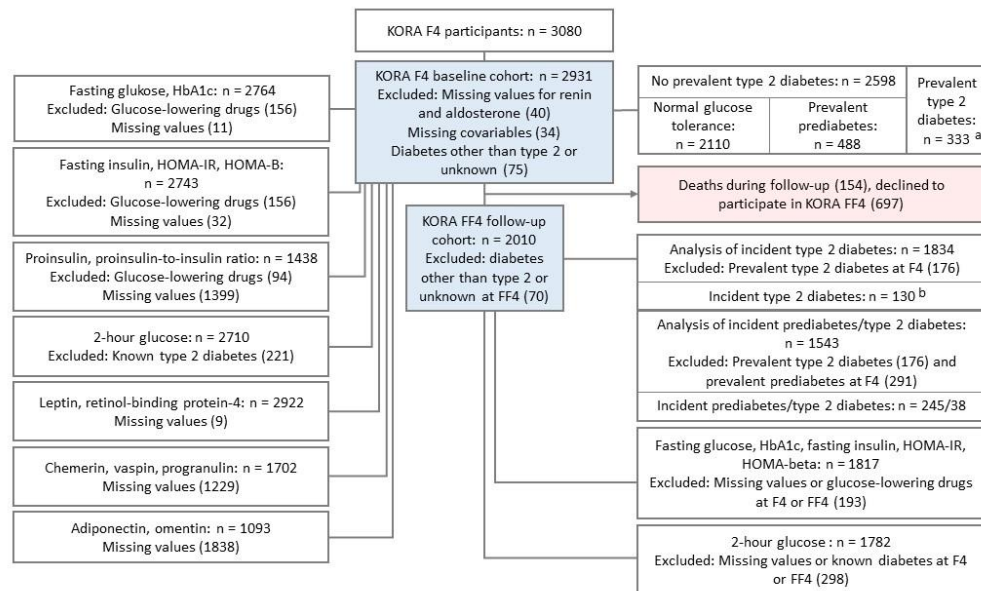
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- 1 **Supplementary Figure 1** Flow chart showing sample sizes and reasons for exclusions. The median
2 (1st; 3rd quartile) follow-up time was 6.5 (6.3; 6.6) years between KORA F and KORA FF4.



3

4 ^a In KORA F4, type 2 diabetes was newly diagnosed by oral glucose tolerance test in 112 participants
5 and was previously known in 221 cases.

6 ^b In KORA FF4, incident type 2 diabetes was newly diagnosed by oral glucose tolerance test in 70
7 participants and was diagnosed by the treating physician between F4 and FF4 in 60 participants. N =
8 92 participants with incident type 2 diabetes in KORA FF4 had progressed from prediabetes in KORA
9 F4, n = 38 participants had progressed from normal glucose tolerance in KORA F4.

10

11

12 **Supplementary Table 1** Odds ratios (95% confidence interval) for prevalent prediabetes (versus
13 normal glucose tolerance) and prevalent type 2 diabetes (versus no type 2 diabetes) per standard
14 deviation increase of active plasma renin concentration, aldosterone and ARR after exclusion of
15 participants taking angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta
16 blockers, diuretics or calcium channel blockers.

	Prevalent prediabetes (yes: n = 253; no: n = 1666)	P value	Prevalent type 2 diabetes (yes: n = 90; no: n = 1919)	P value
Renin	1.26 (1.08,1.46)	0.003	1.49 (1.18,1.89)	< 0.001
Aldosterone	1.17 (1,1.36)	0.048	1.05 (0.83,1.33)	0.685
ARR	0.93 (0.8,1.08)	0.329	0.72 (0.57,0.91)	0.005

17 Bold print indicates significance after correction for multiple testing using the Bonferroni method ($p <$
18 $0.008 (0.05 \div 6)$). Abbreviations: ARR: aldosterone-to-renin-ratio.

19 The logistic regression models were adjusted for sex, age, BMI, arterial hypertension, eGFR and
20 potassium.

21

22 **Supplementary Table 2** Cross-sectional beta estimates \pm standard error of the association of active
23 plasma renin concentration, aldosterone and ARR (per standard deviation increase) and continuous
24 measures of glucose metabolism (per standard deviation) after exclusion of participants taking
25 angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, diuretics or
26 calcium channel blockers.

	n	Renin	Aldosterone	ARR
Fasting glucose	1971	0.07 \pm 0.02 ***	0.01 \pm 0.02	-0.07 \pm 0.02 ***
2-hour glucose	1953	0.07 \pm 0.02 **	0.03 \pm 0.02	-0.04 \pm 0.02
HbA1c	1971	0.04 \pm 0.02	-0.01 \pm 0.02	-0.05 \pm 0.02 *
Insulin	1954	0.10 \pm 0.02 ***	0.07 \pm 0.02 ***	-0.04 \pm 0.02
Proinsulin	1001	0.08 \pm 0.03 *	0.08 \pm 0.03 **	-0.01 \pm 0.03
Proinsulin-to-insulin ratio	1001	-0.00 \pm 0.03	0.05 \pm 0.03	0.04 \pm 0.03
HOMA-B	1954	0.05 \pm 0.02 *	0.06 \pm 0.02 **	0.01 \pm 0.02
HOMA-IR	1954	0.11 \pm 0.02 ***	0.07 \pm 0.02 ***	-0.05 \pm 0.02 *

27 * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; bold print indicates significance after correction for multiple
28 testing using the Bonferroni method ($p < 0.0021$ ($0.05 \div 24$)). Abbreviations: ARR: aldosterone-to-
29 renin-ratio.

30 The linear regression models were adjusted for sex, age, BMI, arterial hypertension, eGFR and
31 potassium.

32

33 **Supplementary Table 3** Cross-sectional beta estimates \pm standard error of the association of active
34 plasma renin concentration, aldosterone and ARR (per standard deviation increase) and adipokines
35 (per standard deviation) after exclusion of participants taking angiotensin converting enzyme inhibitors,
36 angiotensin receptor blockers, beta blockers, diuretics or calcium channel blockers.

	n	Renin	Aldosterone	ARR
Leptin	2005	0.03 \pm 0.01 *	0.04 \pm 0.01 ***	0.01 \pm 0.01
Retinol-binding protein-4	2005	0.01 \pm 0.02	0.05 \pm 0.02 *	0.03 \pm 0.02
Adiponectin	455	-0.09 \pm 0.04 *	-0.04 \pm 0.04	0.03 \pm 0.04
Omentin-1	455	0.00 \pm 0.05	-0.06 \pm 0.05	-0.08 \pm 0.05
Chemerin	1047	0.05 \pm 0.03	0.01 \pm 0.03	-0.03 \pm 0.03
Progranulin	1047	-0.03 \pm 0.03	-0.04 \pm 0.03	0.00 \pm 0.03
Vaspin	1047	-0.03 \pm 0.03	0.05 \pm 0.03	0.07 \pm 0.03 *

37 * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; bold print indicates significance after correction for multiple
38 testing using the Bonferroni method ($p < 0.0024$ ($0.05 \div 21$)). Abbreviations: ARR: aldosterone-to-
39 renin-ratio.

40 The linear regression models were adjusted for sex, age, BMI, arterial hypertension, eGFR and
41 potassium.

42

43 **Supplementary Table 4** Odds ratios (95% confidence interval) for incident prediabetes/type 2
 44 diabetes (versus non-progressors to prediabetes/type 2 diabetes from normal glucose tolerance) and
 45 incident type 2 diabetes (versus non-progressors to type 2 diabetes from normal glucose tolerance or
 46 prediabetes) active plasma renin concentration, aldosterone and ARR (per standard deviation
 47 increase) after exclusion of participants taking angiotensin converting enzyme inhibitors, angiotensin
 48 receptor blockers, beta blockers, diuretics or calcium channel blockers.

	Incident prediabetes/type 2 diabetes (yes: n = 191 ^a ; no: n = 1068)	P value	Incident type 2 diabetes (yes: n = 67; no: n = 1362)	P value
Renin	1.23 (1.03-1.46)	0.023	1.15 (0.88-1.51)	0.316
Aldosterone	1.03 (0.86-1.24)	0.718	1.05 (0.80-1.39)	0.725
ARR	0.86 (0.72-1.03)	0.101	0.90 (0.68-1.17)	0.429

49 ^a Includes 167 cases of incident prediabetes in KORA FF4 and 24 cases of incident type 2 diabetes in
 50 KORA FF4 that had progressed from normal glucose tolerance in KORA F4.

51 Significance level after correction for multiple testing using the Bonferroni method ($p < 0.008$ ($0.05 \div$
 52 6)). Abbreviations: ARR: aldosterone-to-renin-ratio.

53 The linear regression models were adjusted for sex, age, BMI, arterial hypertension, eGFR and
 54 potassium.

55

56 **Supplementary Table 5** Longitudinal beta estimates \pm standard error of the association of active
 57 plasma renin concentration, aldosterone and ARR (per standard deviation increase) and deltas of
 58 continuous measures of glucose metabolism (per standard deviation).

Delta	n	Renin	Aldosterone	ARR
Fasting glucose	1817	-0.08 \pm 0.03 **	-0.00 \pm 0.02	0.07 \pm 0.03 **
2-hour glucose	1782	0.01 \pm 0.023	0.01 \pm 0.02	0.00 \pm 0.02
HbA1c	1817	-0.06 \pm 0.03 *	-0.02 \pm 0.02	0.03 \pm 0.03
Insulin	1817	-0.12 \pm 0.02 ***	-0.05 \pm 0.02 *	0.07 \pm 0.02 ***
HOMA-B	1817	0.03 \pm 0.03	0.01 \pm 0.02	-0.02 \pm 0.03
HOMA-IR	1817	-0.02 \pm 0.03	0.01 \pm 0.02	0.03 \pm 0.03

59 * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; bold print indicates significance after correction for multiple
 60 testing using the Bonferroni method ($p < 0.0028$ ($0.05 \div 18$)).

61 Abbreviations: ARR: aldosterone-to-renin-ratio.

62 The linear regression models were adjusted for sex, age, BMI, arterial hypertension, eGFR,
 63 potassium, use of angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta
 64 blockers, diuretics and calcium channel blockers.

65

66 **Supplementary Table 6** Longitudinal beta estimates \pm standard error of the association of active
 67 plasma renin concentration, aldosterone and ARR (per standard deviation increase) and deltas of
 68 continuous measures of glucose metabolism (per standard deviation) after exclusion of participants

69 taking angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta blockers,
70 diuretics or calcium channel blockers.

Delta	n	Renin	Aldosterone	ARR
Fasting glucose	1404	-0.03 ± 0.03	0.01 ± 0.03	0.02 ± 0.03
2-hour glucose	1387	-0.03 ± 0.03	-0.00 ± 0.03	0.02 ± 0.03
HbA1c	1404	0.00 ± 0.03	-0.02 ± 0.03	-0.03 ± 0.03
Insulin	1404	-0.10 ± 0.02 ***	-0.06 ± 0.02 *	0.04 ± 0.02
HOMA-B	1404	0.03 ± 0.03	0.00 ± 0.03	-0.03 ± 0.03
HOMA-IR	1404	0.01 ± 0.03	0.01 ± 0.03	-0.00 ± 0.03

71 * p < 0.05; ** p < 0.01; *** p < 0.001; bold print indicates significance after correction for multiple
72 testing using the Bonferroni method (p < 0.0028 (0.05 ÷ 18)). Abbreviations: ARR: aldosterone-to-
73 renin-ratio.

74 The linear regression models were adjusted for sex, age, BMI, arterial hypertension, eGFR and
75 potassium.

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