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The association of aldosterone and endothelin-1 with incident diabetes among African Americans: The Jackson Heart Study

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Abstract

Introduction: African Americans (AAs) have the highest prevalence of hypertension among United States racial/ethnic groups. Regulators of blood pressure, such as aldosterone and endothelin-1, impact glucose regulation. The relationship between these factors and incident diabetes is not well elucidated among AAs.

Methods: Among 3914 AA participants without prevalent diabetes in the Jackson Heart Study, linear regression models were used to examine cross-sectional associations of exposures (aldosterone, endothelin-1, and a combined aldosterone-endothelin-1 score [2–8]) with glycemic measures (fasting plasma glucose [FPG], HbA1c, homeostatic model assessments of beta cell function [HOMA-β] and insulin resistance [HOMA-IR]). Longitudinal associations of exposures with incident diabetes were examined using Cox proportional hazard models. Models were adjusted for age, sex, education, occupation, systolic blood pressure, smoking, physical activity, dietary intake, alcohol use and adiponectin.

Results: Aldosterone and the combined aldosterone-endothelin score were positively associated with FPG, HOMA-IR, and HOMA-β (all $p < 0.05$). Endothelin-1 was negatively associated with FPG but positively associated with HOMA-β (both $p < 0.05$). Only the aldosterone-endothelin score was positively associated with HbA1c ($p < 0.01$). A 1-SD higher serum aldosterone and endothelin-1 was associated with a 22 % and 14 % higher risk of incident diabetes, respectively,

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

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while a 1-point higher aldosterone-endothelin score was associated with a 13 % higher risk of incident diabetes after adjustment for diabetes risk factors (all $p < 0.01$).

Conclusions: Aldosterone and endothelin-1, factors integral in blood pressure regulation, may play a significant role in the development of diabetes among AAs.

Keywords

Aldosterone; Endothelin-1; Diabetes; African Americans

1. Introduction

African Americans (AAs) have a greater incidence and prevalence of type 2 diabetes mellitus (T2DM) compared to Non-Hispanic Whites (NHW) (Benoit et al., 2019). Hypertension may be a risk factor for the development of diabetes. In the Multi-Ethnic Study of Atherosclerosis (MESA), blood pressure <120/80 mm Hg compared to ≥140/90 mm Hg was associated with a 46 % lower diabetes risk among AAs (Joseph et al., 2016a). These findings align with previous studies showing a positive association between higher blood pressure and hypertension with risk of diabetes (Gress et al., 2000; Brancati et al., 2000; Golden et al., 2003).

Aldosterone, the end effector of the renin-angiotensin-aldosterone system, and endothelin-1, a peptide secreted by vascular endothelial cells in response to sheer stress, pulsatile stretch, neurohormones, thrombin, cytokines and growth factors, may modulate both hypertension and diabetes risk in AAs. We previously showed that aldosterone is dose-dependently associated with insulin resistance and risk of incident diabetes over 8 years among AAs in the Jackson Heart Study (JHS) (Joseph et al., 2016b). Aldosterone activates the serine/threonine-protein kinase-1 in skeletal muscle in a mineralocorticoid receptor (MR) dependent manner which ultimately prevents the translocation of GLUT4 to the cell membrane. Furthermore, the expression of gluconeogenic enzymes are upregulated by aldosterone leading to higher hepatic glucose output (Luther, 2014). Endothelin-1 reduces glucose uptake in skeletal muscle and elevated levels are observed among patients with T2DM (Shemyakin et al., 2011; Takahashi et al., 1990). In addition, endothelin-1 is positively associated in a non-linear fashion with a combined endpoint of incident impaired glucose tolerance or diabetes over 10 years among Scandinavian women but not men (Olausson et al., 2016). However, the association of endothelin-1 with incident diabetes has not been studied in AAs.

Given that AAs have a higher prevalence of hypertension, diabetes and their complications compared to NHWs (Murtaugh, 2003; Drazner et al., 2005; Williams, 2014), it is critical to explore whether factors that regulate blood pressure are also involved in diabetes pathophysiology among AAs. Thus, we examined the individual and combined longitudinal associations of aldosterone and endothelin-1 with incident diabetes among AAs in the JHS.

2. Methods

2.1. Study population

The JHS is a prospective cohort study of 5306 AA adults, aged 21–94 years from the tri-county area of metropolitan Jackson, Mississippi. The baseline examination was performed between 2000 and 2004, with two subsequent follow-up examinations between 2005–2008 and 2009–2013. The design of the study has been described elsewhere (Taylor et al., 2005).The JHS was approved by the institutional review boards of the participating institutions and informed consent was obtained from all participants. For this analysis, participants with prevalent diabetes at baseline (n = 1218) or missing data on exposures (n = 31), outcomes or important covariates including education (n = 15), waist circumference (n = 5), alcohol intake (n = 23), systolic blood pressure (n = 12), smoking status (n = 36), and adiponectin (n = 52) were excluded from the analysis. After these exclusions, 3914 participants were included in the main analysis.

2.2. Exposures

The primary exposures assessed were serum aldosterone and endothelin-1 from the baseline examination (2000–2004). Fasting blood samples were collected in the supine position and processed using a standardized protocol. Plasma and serum samples were centrifuged within 2 h of blood collection, stored at −70 °C, and sent to central laboratories (University of Minnesota). Serum aldosterone was measured by radioimmunoassay (Coat-a-count aldosterone, Siemens, Munich, Germany) and the intra-assay coefficients of variation were 8.7 % for low and 6.2 % for high aldosterone concentrations (Musani et al., 2013). Plasma endothelin-1 levels were measured in picograms per milliliter by QuantiGlo Human ET-1 Immunoassay (R&D Systems Inc.).

2.3. Outcomes

The primary cross-sectional outcomes in this analysis were fasting glucose, homeostatic model assessments of beta cell function (HOMA-β) and insulin resistance (HOMA-IR), and hemoglobin A1c (A1c). Fasting glucose and insulin concentrations were measured on a Vitros 950 or 250 Ortho-Clinical Diagnostics analyzer using standard procedures that met the College of American Pathologists accreditation requirement (Carpenter et al., 2004). A HPLC system (Tosoh Corp) was used to measure A1c. Insulin resistance and β-cell function were estimated using the following formula: HOMA-IR = (fasting plasma glucose [millimoles per liter] × fasting plasma insulin [milliunits per milliliter]) / 22.5 and HOMA-β = (20 × fasting plasma insulin) / (fasting plasma glucose − 3.5)% (Matthews et al., 1985). The primary longitudinal outcome was incident diabetes developed by Exam 3 among those free of diabetes at Exam 1. Diabetes was defined as HbA1c ≥ 6.5 % (48 mmol/mol), fasting blood glucose ≥ 126 mg/dL, taking T2DM medications and/or with a self-reported physician diagnosis (American Diabetes Association, 2013). The time of incident diabetes was defined as the midpoint between the last examination without diabetes and the examination at which diabetes developed among persons without diabetes at baseline.

2.4. Covariates

Baseline information was obtained during clinic visits or at home using standardized questionnaires including: demographics, occupation (management/professional versus not), level of education (less than versus greater than or equal to a Bachelor's degree), tobacco use (current smoking versus not), alcohol use (any alcohol intake in the past 12 months versus not), medical conditions and current prescription medication usage. Cali-brated devices were used by certified technicians and nurses to measure participants' weight and height. Body mass index (BMI) was calculated as weight (kilograms)/ height^2 (meters). Waist circumference in centimeters was calculated as the average of two measurements around the umbilicus. Resting seated blood pressure was measured twice at 5-minute intervals using an appropriately sized cuff with standard Hawksley random-zero instruments and measurements were averaged for analysis. Physical activity and dietary intake were categorized according to the American Heart Association 2020 Cardiovascular health guidelines as poor, intermediate or ideal health, as described previously (Lloyd-Jones et al., 2010). Serum concentrations of total adiponectin were measured by an ELISA system (R&D systems; Minneapolis, MN) with inter-assay coefficient of variation of 8.8 % (Joseph et al., 2016b).

2.5. Statistical analyses

Baseline characteristics were presented stratified by a combined aldosterone/endothelin-1 (aldosterone-endothelin) score. This score was created by coding aldosterone and endothelin-1 values individually in quartiles (1–4 points from lowest to highest quartile). The sum of these two values created a score ranging from two to eight. Significance of differences in baseline measures across categories of BMI were calculated using chi-square (χ^2) for categorical variables, one-way ANOVA for normally-distributed continuous variables, and Kruskal-Wallis test for non-normally-distributed continuous variables. In the continuous analyses, aldosterone and endothelin-1 were standardized as follows: z-Aldosterone or z-Endothelin-1 = $(x_i - \mu) / s$, where x_i was the value of the individual observation, μ was the sample mean, and s was the standard deviation of the measure. In the cross-sectional analyses, HOMA-IR and HOMA-β were log-transformed prior to analysis due to skewed distributions. Multivariate linear regression modeling was performed to examine the cross-sectional associations between continuous measures of aldosterone, endothelin-1, and the aldosterone-endothelin score with log-HOMA-IR, log-HOMA-β, fasting plasma glucose, and HbA1c. In the longitudinal analyses, Cox proportional hazards modeling was performed to examine the associations of: 1) the continuous and categorical (quartiles) of aldosterone and endothelin-1 with incident diabetes; and 2) the categorical association of the aldosterone-endothelin score with incident diabetes. Models were adjusted as follows: Model 1: Unadjusted; Model 2: age, gender, education, occupation, systolic blood pressure, smoking, physical activity, dietary intake, alcohol use; Model 3: Model 2+ BMI; and Model 4: Model 2 + adiponectin. We also explored whether there was significant interaction by age, gender, diabetes status (normal vs. prediabetes) and/or obesity status (BMI <30 vs. BMI ≥ 30 kg/m^2). Finally, a composite marker from the combination of the independent biomarkers (aldosterone, endothelin-1, HOMA-IR, and HOMA-β) or their combinations based on the linear predictor (i.e., the $\mathbf{X\beta}$ piece) from the Cox model was

created. The basic demographic variables (age, sex, education, and occupation) and the composite marker's ability to predict diabetes risk was determined through hazard ratios and ROC curves/C-indices on the test data.

We conducted a sensitivity analysis which involved excluding individuals with a history of stroke, coronary heart disease (CHD), or heart failure and taking medications that impact the RAAS system including mineralocorticoid receptor antagonists, angiotensin converting enzyme inhibitors and angiotensin receptor blockers. Statistical significance was defined as two-sided alpha < 0.05 and <0.10 for interactions. Given the exploratory nature of the analyses, the results were reported at a nominal level. The main cross-sectional and longitudinal analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). The R programming language was used to conduct the C-index analysis and to create Figs. 1–3 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Baseline characteristics

The baseline characteristics of participants in the final analytical sample (n = 3914) are presented in Table 1. The average participant was 53.7 (SD 13.0) years old, had a BMI of 31.1 kg/m^2 (SD 7.1), was more likely to be female (62.5 %), had less than a Bachelor's degree (65.7 %), and non-smoking (86.2 %). Those in higher quantiles of the aldosterone-endothelin score were older with higher BMIs, waist circumferences, systolic blood pressure, fasting glucose, and HOMA-IR. Men and those with a history of stroke, heart failure, or coronary artery disease made up a greater proportion of participants in higher quantiles of the aldosterone-endothelin score. There was a graded relationship between the aldosterone-endothelin score and the incidence rate of diabetes where those with a score of 8 had more than a 3-fold higher incidence rate of diabetes than those with a score of 2.

3.2. Association of aldosterone, endothelin-1 and aldosterone-endothelin-1 score with HOMA-IR, HOMA-β, and fasting plasma glucose

The cross-sectional associations of aldosterone, endothelin-1, and the combined aldosterone-endothelin-1 score with selected measures of glycemia are presented in Table 2. A 1-SD higher serum aldosterone level and 1-point higher aldosterone-endothelin-1 score was associated with a 9.13 % and 4.84 % higher log-HOMA-IR (both p < 0.0001) at the baseline exam after adjustment for standard diabetes risk factors and BMI. Contrarily, a 1-SD higher endothelin-1 level was associated with a 1.79 % lower log-HOMA-IR (p = 0.032) in the same model. Adjustment for adiponectin instead of BMI (model 4) caused the association between endothelin-1 and log-HOMA-IR to become non-significant but slightly augmented associations with aldosterone and the combined score. All predictors were positively associated with log-HOMA-β. A 1-SD higher aldosterone and endothelin-1, and a 1-point higher aldosterone-endothelin-1 score were associated with a 4.85 %, 1.77 %, and 3.64 % higher HOMA-β (all p < 0.05) after adjustment for standard risk factors and BMI with similar findings with adjustment for adiponectin. A 1-SD higher serum aldosterone level and 1-point higher aldosterone-endothelin-1 score was associated with

an 86 % ($p < 0.0001$) and 25.2 % ($p = 0.004$) higher fasting plasma glucose, while a 1-SD higher endothelin-1 was associated with a 60.9 % ($p < 0.0001$) lower fasting plasma glucose at baseline (Model 3). Adjustment for adiponectin rather than BMI augmented the associations for aldosterone and the combined score but attenuated the association with endothelin-1 (Model 4). Aldosterone and endothelin-1 were not significantly associated with HbA1c. However, 1-point higher combined score was associated with a 1.31 % higher HbA1c ($p = 0.004$) with similar finding with adjustment for adiponectin.

3.3. Association of aldosterone, endothelin-1, and aldosterone-endothelin-1 score with incident diabetes

The associations between standardized aldosterone and endothelin-1 as well as the aldosterone-endothelin score with incident diabetes are presented in Table 3. A 1-point higher aldosterone-endothelin score was associated with a 13 % higher risk while a 1-SD higher aldosterone was associated with a 22 % higher risk of incident diabetes, respectively (both $p < 0.01$, Model 3). Adjusting for adiponectin instead of BMI did not change the significance of association for both measures (model 4). Endothelin-1 trended towards a positive association with incident diabetes in the continuous model adjusting for standard risk factors and BMI ($p = 0.053$). Following adjustment for adiponectin instead of BMI, a 1-SD higher endothelin-1 was associated with a 14 % higher risk of incident diabetes ($p < 0.001$). There was evidence of a graded association for both the aldosterone-endothelin score and aldosterone in the model adjusting for adiponectin (Figs. 1 & 2 [left panel], Supplemental Table 1 & 2, respectively). The positive association between endothelin-1 and incident diabetes in Model 4 was driven by individuals with endothelin-1 levels in Quartile 4 (Fig. 2 [right panel], Supplemental Table 2). There was no evidence of effect modification by age, sex, glycemic status (normoglycemic vs. prediabetes), BMI category, or hypertension status (Supplemental Table 3). Excluding individuals with pre-existing stroke, CHD, or Heart Failure did not alter the significance of associations between aldosterone, endothelin-1, and the combined score with respect to incident diabetes across all models (Supplemental Table 4).

3.4. Discriminatory power of HbA1c, HOMA-IR, aldosterone, endothelin-1, and the aldosterone-endothelin-1 score for incident diabetes

Results of the C-index analysis are presented in Fig. 3 and Supplemental Table 5. Aldosterone, endothelin-1 and the two in combination were modest predictors of incident diabetes ranging from C-indices of 0.574 to 0.596. Individually, HbA1c (C-index 0.779, 95 % CI: 0.758, 0.799) was the strongest discriminator of incident diabetes followed by HOMA-IR (C-index 0.720, 95 % CI: 0.699, 0.741). The addition of aldosterone, endothelin, or both to HbA1c or HOMA-IR did not significantly improve prediction of incident diabetes.

4. Discussion

4.1. Overall findings

In the current study, a 1-SD higher aldosterone was associated with a 22 % higher risk of incident diabetes over a median of 7.4 years among all participants. A 1-point higher

combined aldosterone-endothelin-1 score was associated with a 13 % higher risk of incident diabetes and a score of 5–6 and 7–8 compared to 2 was associated with a higher risk of diabetes in a graded manner with the highest risk in the 7–8 category (144 % and 175 %, respectively). Assessment of the association between categorical aldosterone measures and risk of incident diabetes revealed a positive, monotonic relationship, while endothelin-1 was associated with higher risk of incident diabetes in quartile 4 vs. 1.

4.2. Comparison with previous studies

In contrast to the current study, endothelin-1 was positively associated with fasting plasma glucose in rural Bangladeshi women. Additionally, fasting insulin levels were not associated with endothelin-1 which is partially discordant with our finding that endothelin-1 is associated with HOMA-β which rises with increasing insulin and declines with decreasing glucose (Akter et al., 2015). There have been limited investigations assessing the association of endothelin-1 with incident dysglycemia. Among 1099 participants in the Scandinavian Vara-Skövde Cohort, there was no statistically significant association between endothelin-1 and impaired glucose tolerance/T2DM among men. However, among women, there was evidence of a U-shaped association between endothelin-1 and dysglycemia. Compared to quartile 1, women in quartile 2 of endothelin-1 had 4.5 times odds of IGT/T2DM while those in quartile 3 had no increased odds of incident diabetes or impaired glucose tolerance. However, women with endothelin-1 levels in quartile 4 had 4.2 times higher odds of IGT/T2DM compared to quartile 1 after adjustment for age, municipality, waist:hip ratio, apoB/A1, hsCRP, systolic blood pressure, and baseline HOMA-IR (Olausson et al., 2016). Our findings are partially discordant with those from the Scandinavian Vara-Skövde Cohort. Though we found a positive association between endothelin-1 and incident diabetes when controlling for standard diabetes risk factors and adiponectin, we did not find evidence of effect modification by sex (Supplemental Table 5). These discrepancies may be explained by several factors. First, our outcome did not include incident impaired glucose tolerance. Second, there are potential epigenetic differences due to environment and geography. African Americans in the deep US South exposed to generational systemic racism leading to epigenetic changes that increase risk for metabolic disease in both men and women. Third, there were differences in covariate selection. Finally, participants in the JHS were older, had higher BMIs, and systolic blood pressures and were thus at higher cardiometabolic risk at the baseline exam. It has been previously shown that the marginal influence of an additional risk factor for individuals at high baseline risk for cardiometabolic disease is lower compared to individuals at lower baseline risk (Joseph et al., 2017, 2019). Population-based Biomarkers for Cardiovascular Risk Assessment in Europe (BiomarCaRE) Consortium data was used to examine the association of C-terminal-proET-1 (CT-proET-1, a biologically stable surrogate for endothelin-1) with incident type 2 diabetes in Europe. CT-proET-1 was positively associated with incident type 2 diabetes with a hazard ratio of 1.10 (95 % CI: 1.03; 1.18) per 1-SD increase of CT-proET-1 (Sujana et al., 2022). Additionally, Mendelian randomization was performed using one SNP that is specific for CT-proET-1 in the endothelin-1 gene (rs5370) and showed a significant association between genetically predicted CT-proET-1 with incident type 2 diabetes (Sujana et al., 2022). The findings from the JHS are concordant with the BiomarCaRE findings in a European population.

The findings with respect to aldosterone are consistent with the extant literature. The associations of aldosterone with dysglycemia has been previously investigated in the Multi-Ethnic Study of Atherosclerosis (MESA) and in the JHS with significant dose-dependent associations between aldosterone, insulin resistance and incident diabetes in both cohorts (Joseph et al., 2016b; Joseph et al., 2018). Additionally, aldosterone is a partial mediator of the association of lifestyle and clinical factors (smoking, diet, physical activity, BMI, and cholesterol) with incident diabetes (Kesireddy et al., 2023). These prior findings in MESA and JHS for aldosterone in combination with the aforementioned endothelin-1 findings suggest that individuals with concomitantly high aldosterone and endothelin-1 may have a greater risk of incident diabetes. The graded increase in diabetes risk with the combined aldosterone-endothelin-1 score supports these findings. However, the addition of aldosterone and endothelin-1 to the standard diabetes prediction models provided minimal additional predictive power (Fig. 3). Thus, the analyses suggest that these factors may mediate their effect through increasing insulin resistance rather than through an independent pathway.

4.3. Mechanism

Endothelin-1 is a potent vasoconstrictor and antagonizes nitric oxide through decreasing its bioavailability (Cersosimo and DeFronzo, 2006). Thus, its role in the development of hypertension is widely recognized. However, in vitro and in vivo rodent studies also suggest that endothelin-1 plays a role in the development of insulin resistance. Pretreatment of skeletal muscle with endothelin-1 reduces insulin-stimulated glucose transport by >20 %, and five days of in vivo endothelin-1 infusion leads to impairments in insulin signaling and promotes whole-body insulin resistance in rodents (Wilkes et al., 2003). These findings have been extended in human in vitro and in vivo studies. Endothelin-1 pretreatment impaired insulin signaling in adipocytes (Ishibashi et al., 2001) and endothelin-1 infusion caused a 31 % decrease in total body glucose uptake in a small study of healthy men without family histories of diabetes who underwent a hyperinsulinemic-euglycemic clamp (Ottosson-Seeberger et al., 1997). Further supporting a role for endothelin-1 in the development of the insulin-resistant phenotype, the antagonism of Endothelin receptor type A increased insulin-stimulated glucose uptake in the legs of obese individuals (Lteif et al., 2007). However, no change was observed among lean individuals. The elevated levels of insulin in serum more commonly observed in obesity may contribute to these differential findings. Indeed, in vitro studies have identified insulin as a stimulator of endothelin-1 production and high insulin levels in vivo are associated with increased endothelin-1 levels in the circulation (Sarafidis and Bakris, 2007). As a result, endothelin receptor type-A may be chronically activated to a greater extent in obese individuals resulting in tissue insulin resistance. This would result in a self-reinforcing cycle of increasing insulin and endothelin-1. Paradoxically, we identified a negative cross-sectional association between endothelin-1 and fasting plasma glucose. This phenomenon may be explained by endothelin-1 stimulating insulin levels which may acutely decrease fasting glucose. This hypothesis is supported by the positive cross-sectional association observed between endothelin-1 and HOMA-β. Interestingly, when controlling for adiponectin instead of BMI, the magnitude of the negative association between endothelin-1 and glucose was nearly halved. Endothelin-1 stimulates adiponectin secretion in adipocytes. However, chronic exposure to endothelin-1 inhibits the stimulating effect on adiponectin of both endothelin-1

and insulin in the acute setting. The desensitization of adipocytes by chronically elevated endothelin-1 seems to mimic the effect of exposure to the endothelin receptor type A antagonist BQ-610, which inhibits the ability of endothelin-1 to acutely increase adiponectin levels (Clarke et al., 2003). Thus, the effect on the association between endothelin-1 and glucose seen after controlling for adiponectin may be explained, in part, by individuals with chronically high endothelin-1 failing to acutely increase adiponectin expression. Given the insulin sensitizing effect of adiponectin on tissues, a reduction in adiponectin would lead to higher circulating glucose. In the longitudinal analysis, there is a trend towards an association of endothelin-1 with incident diabetes after controlling for diabetes risk factors and BMI (HR 1.08, 95 % CI: 1.00, 1.17). However, there was a significant association after controlling for adiponectin instead of BMI (HR 1.14, 95 % CI: 1.06, 1.24). Chronically elevated endothelin-1 may increase risk for dysglycemia via: 1) increased vasoconstriction leading to decreased nitric oxide bioavailability leading to reduced insulin and nutrient blood flow to target tissues (Cersosimo and DeFronzo, 2006); 2) a positive feedback loop between insulin and endothelin-1; and 3) a reduced ability of adipocytes to produce adiponectin in response to acute increases in endothelin-1 and insulin (Cersosimo and DeFronzo, 2006).

The role of aldosterone in the impairment of glucose metabolism has been well described (Luther, 2014). Briefly, aldosterone is known to induce abnormalities glucose metabolism via mineralocorticoid receptor dependent and independent mechanisms. In vitro, aldosterone impairs insulin secretion in pancreatic beta-cells via reactive oxygen species and impairs insulin sensitivity in adipose and skeletal muscle tissues through its effects on potassium levels and inflammation (Luther, 2014). Our findings reinforce the importance of aldosterone and shed light on the role of endothelin-1, another factor critical in blood pressure regulation, in the development of dysglycemia at the population level. Additionally, our work further supports the previous findings of the interactions between the endothelin system and the renin-angiotensin aldosterone system (Rossi, 1999). Evidences indicate that angiotensin II can stimulate the transcription of endothelin-1, which can in turn upregulate aldosterone production (Belloni et al., 1996).

4.4. Strengths and limitations

Our study has several strengths. First, the JHS is a large, socioeconomically diverse cohort of AAs. Second, 556 participants developed type 2 diabetes between the baseline exam and follow-up thus giving us sufficient statistical power to investigate the study question. Finally, we had standardized assessments of biomarkers, used validated surveys, and adjusted for several factors that affect both the exposure and the outcome. Our study should be interpreted in light of several limitations. First, participants in the JHS cohort reside in a single geographic area in the southern United States which may limit the generalizability of the findings to other AAs. Second, aldosterone and endothelin-1 were collected on a single day at the baseline exam and we were unable to assess changes during the follow-up assessment. Finally, the results were reported at the nominal level due to the exploratory nature of the analysis.

5. Conclusion

To conclude, we report novel associations of higher endothelin-1 and a combined aldosterone-endothelin-1 score with incident diabetes and confirm the previous of finding of association of aldosterone with incident diabetes in a large cohort of AAs. Aldosterone and endothelin-1 did not improve diabetes risk prediction compared to the HOMA-IR or HbA1c, suggesting that both of these markers may be functioning through similar pathway (i.e. skeletal muscle insulin resistance). Thus, this study sheds further light on the role of peptides and hormones that may serve dual roles in blood pressure regulation and diabetes pathophysiology and may represent novel targets for prevention and treatment of both hypertension, T2DM, and its complications in AAs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

The data is available through the Jackson Heart Study.

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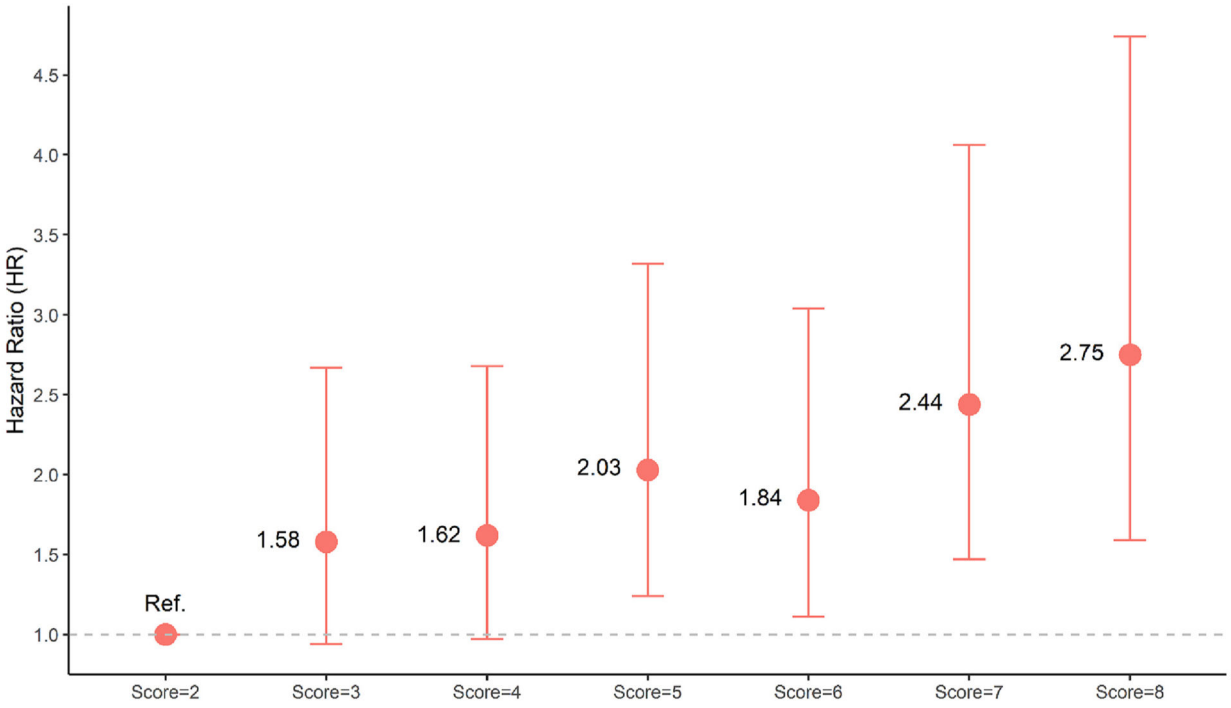

Fig. 1. The association between the aldosterone endothelin-1 score and incident diabetes (n = 3914).

The model depicted was adjusted for age, gender, education, occupation, systolic blood pressure, smoking, physical activity (AHA-LS7 variable), dietary intake (AHA-LS7 variable), alcohol use, and adiponectin. The aldosterone-endothelin score for each participant was created by adding together an individual's aldosterone and endothelin-1 quartiles. For example, an individual with an aldosterone level in quartile 2 and endothelin-1 level in quartile 3 would have an aldosterone-endothelin score of 5. Corresponding data with this figure is presented in Supplemental Table 1, Model 4. Interpretation: Those with an aldosterone-endothelin score of 8 had a 175 % higher risk of incident diabetes compared to those with an aldosterone-endothelin score of 2.

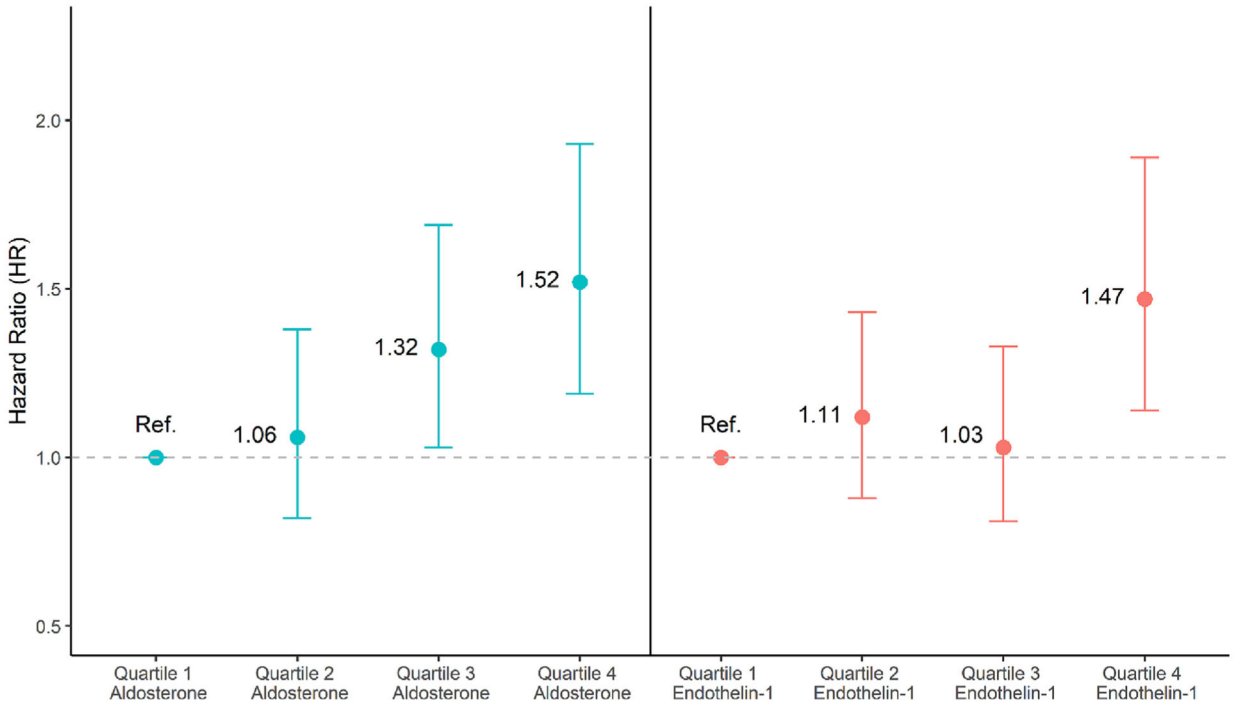

Fig. 2.

The association between quartiles of aldosterone and endothelin-1 with incident diabetes (n = 3914). Legend: The model depicted was adjusted for age, gender, education, occupation, systolic blood pressure, smoking, physical activity (AHA-LS7 variable), dietary intake (AHA-LS7 variable), alcohol use, and adiponectin. Corresponding data with this figure is presented in Supplemental Table 2, Model 4. Interpretation: Those with an aldosterone level in quartile 4 had 52 % higher risk of incident diabetes compared to those with aldosterone levels in quartile 1.

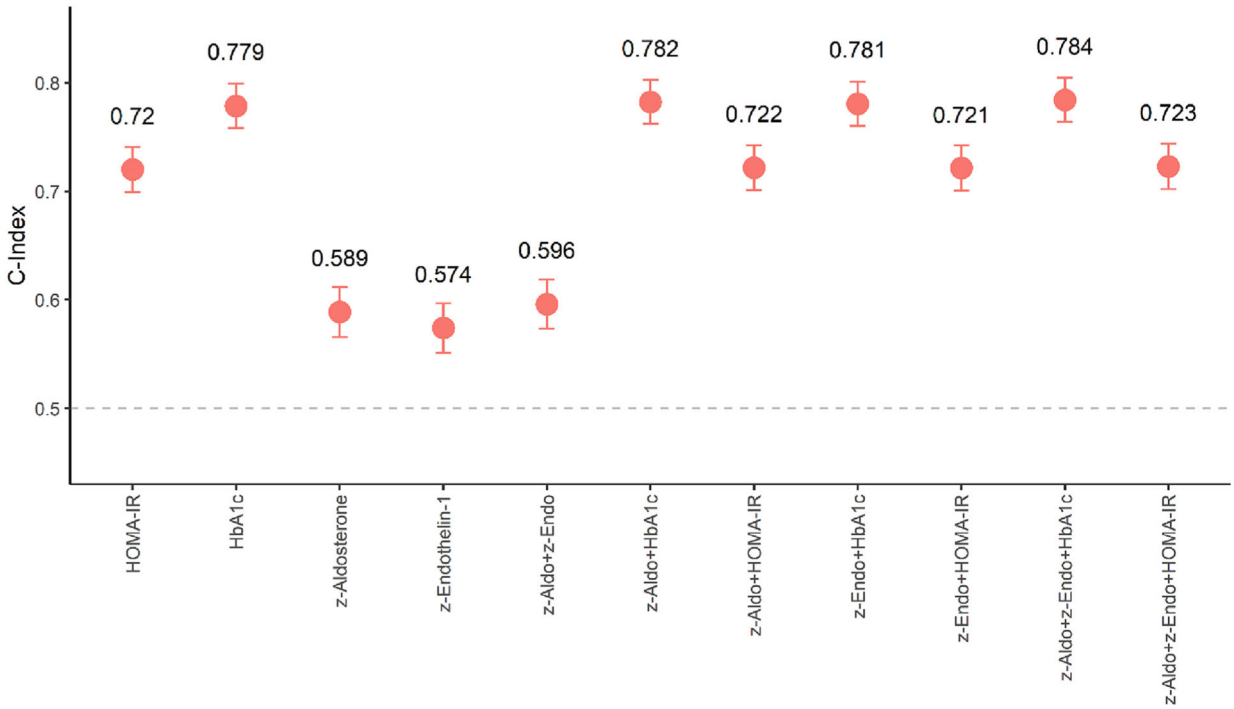

Fig. 3.

C-index prediction modeling for incident type 2 diabetes (n = 3914). Legend: The model depicted was adjusted for age, gender, education, and occupation. Corresponding data with this figure is presented in Supplemental Table 4, Model 1. All values depicted correspond to the respective model's C-index. Abbreviations: z-Aldo = z-Aldosterone; z-Endo = z-Endothelin-1; HOMA-IR = Homeostatic Model Assessment of Insulin Resistance; HbA1c = hemoglobin A1c.

Table 1

Baseline characteristics.

	Overall (n = 3914)[a]	**Score = 2 (n = 254)[b]**	**Score = 3 (n = 533)**	**Score = 4 (n = 731)**	**Score = 5 (n = 941)**	**Score = 6 (n = 718)**	**Score = 7 (n = 491)**	**Score = 8 (n = 246)**	**p-Value**
Gender (n, %)									<0.0001
Female	2445 (62.5)	195 (76.8)	390 (73.2)	455 (62.2)	577 (61.3)	416 (57.9)	272 (55.4)	140 (56.9)	
Male	1469 (37.5)	59 (23.2)	143 (26.8)	276 (37.8)	364 (38.7)	302 (42.1)	219 (44.6)	106 (43.1)	
Education (n, %)									0.0251
Bachelor's degree	1341 (34.3)	92 (36.2)	198 (37.2)	254 (34.8)	339 (36.0)	221 (30.8)	154 (31.4)	83 (33.7)	
Other	2573 (65.7)	162 (63.8)	335 (62.8)	477 (65.2)	602 (64.0)	497 (69.2)	337 (68.6)	163 (66.3)	
Occupation (n, %)									0.0037
Management/professional	1445 (36.9)	100 (39.4)	222 (41.7)	274 (37.5)	351 (37.3)	248 (34.5)	165 (33.6)	85 (34.6)	
Other	2469 (63.1)	154 (60.6)	311 (58.3)	457 (62.5)	590 (62.7)	470 (65.5)	326 (66.4)	161 (65.4)	
Current smoking (n, %)									<0.0001
No	3375 (86.2)	233 (91.7)	489 (91.7)	643 (88.0)	808 (85.9)	602 (83.8)	403 (82.1)	197 (80.1)	
Yes	539 (13.8)	21 (8.3)	44 (8.3)	88 (12.0)	133 (14.1)	116 (16.2)	88 (17.9)	49 (19.9)	
Current alcohol intake (n, %)									0.6327
No	1975 (50.5)	145 (57.1)	282 (52.9)	344 (47.1)	460 (48.9)	358 (49.9)	258 (52.6)	128 (52.0)	
Yes	1939 (49.5)	109 (42.9)	251 (47.1)	387 (52.9)	481 (51.1)	360 (50.1)	233 (47.4)	118 (48.0)	
History of stroke (n, %)									0.0436
No	3786 (96.7)	247 (97.2)	514 (96.4)	713 (97.5)	914 (97.1)	696 (96.9)	473 (96.3)	229 (93.1)	
Yes	128 (3.3)	7 (2.8)	19 (3.6)	18 (2.5)	27 (2.9)	22 (3.1)	18 (3.7)	17 (6.9)	
History of heart failure (n, %)									<0.0001
No	3689 (94.3)	246 (96.8)	522 (97.9)	708 (96.8)	903 (96.0)	659 (91.8)	439 (89.4)	212 (86.2)	
Yes	225 (5.7)	8 (3.2)	11 (2.1)	23 (3.2)	38 (4.0)	59 (8.2)	52 (10.6)	34 (13.8)	
History of coronary heart disease (n, %)									0.0001
No	3714 (94.9)	246 (96.8)	510 (95.7)	702 (96.0)	898 (95.4)	676 (94.2)	461 (93.9)	221 (89.8)	
Yes	200 (5.1)	8 (3.2)	23 (4.3)	29 (4.0)	43 (4.6)	42 (5.8)	30 (6.1)	25 (10.2)	
AHA Physical Activity (n, %)									0.0003
Ideal health	823 (21.0)	56 (22.1)	95 (17.8)	137 (18.7)	230 (24.4)	161 (22.4)	95 (19.3)	49 (19.9)	
Intermediate health	1270 (32.5)	92 (36.2)	198 (37.2)	251 (34.3)	295 (31.4)	235 (32.7)	134 (27.3)	65 (26.4)	

	Overall (n = 3914)[a]	Score = 2 (n = 254)[b]	Score = 3 (n = 533)	Score = 4 (n = 731)	Score = 5 (n = 941)	Score = 6 (n = 718)	Score = 7 (n = 491)	Score = 8 (n = 246)	p-Value
Poor health	1821 (46.5)	106 (41.7)	240 (45.0)	343 (46.9)	416 (44.2)	322 (44.9)	262 (53.4)	132 (53.7)	
AHA Dietary Intake (n, %)									0.1920
Ideal health	29 (0.7)	2 (0.8)	3 (0.6)	4 (0.5)	10 (1.1)	3 (0.4)	5 (1.0)	2 (0.8)	
Intermediate health	1381 (35.3)	80 (31.5)	176 (33.0)	236 (32.3)	358 (38.0)	275 (38.3)	175 (35.6)	81 (32.9)	
Poor health	2504 (64.0)	172 (67.7)	354 (66.4)	491 (67.2)	573 (60.9)	440 (61.3)	311 (63.3)	163 (66.3)	
Age	53.7 (13.0)	50.9 (13.5)	52.7 (12.3)	53.4 (13.0)	52.5 (12.7)	54.1 (13.1)	55.9 (12.8)	58.1 (13.0)	<0.0001
Body-mass Index (kg/m^2)	31.1 (7.1)	30.1 (6.1)	30.5 (6.6)	30.9 (6.9)	31.0 (7.3)	31.5 (7.3)	31.5 (7.4)	32.3 (7.8)	<0.0001
Waist circumference (cm)	98.6 (15.7)	94.0 (14.1)	95.6 (14.6)	98.5 (15.9)	98.0 (15.5)	99.9 (15.8)	101.3 (15.8)	103.5 (17.0)	<0.0001
Systolic blood pressure (mm Hg)	125.8 (18.2)	121.3 (17.4)	122.9 (16.5)	124.3 (16.8)	124.9 (17.7)	127.6 (18.9)	129.8 (19.7)	131.2 (19.8)	<0.0001
Fasting glucose (mg/dL)	90.4 (8.9)	88.5 (8.3)	88.7 (9.0)	90.2 (8.4)	90.3 (9.3)	91.2 (8.6)	91.4 (9.1)	92.7 (9.1)	<0.0001
ln HOMA-IR	1.1 (0.6)	0.9 (0.5)	1.0 (0.5)	1.1 (0.5)	1.1 (0.6)	1.2 (0.5)	1.2 (0.6)	1.3 (0.6)	<0.0001
ln HOMA-β	5.3 (0.5)	5.2 (0.5)	5.2 (0.5)	5.3 (0.5)	5.3 (0.5)	5.3 (0.5)	5.3 (0.5)	5.4 (0.5)	<0.0001
Incident rate of diabetes per 1000 person-years	24.29	11.33	19.59	20.29	24.62	26.02	34.74	37.59	<0.0001
Serum aldosterone (ng/dL)	4.3 (2.5, 6.9)	1.9 (1.9, 2.1)	2.5 (1.9, 3.3)	3.2 (1.9, 4.6)	4.4 (2.7, 6.7)	5. 7(4.1, 8.3)	7.2 (5.6, 9.3)	9.8 (8.1, 13.5)	<0.0001
Endothelin-1 (pg/mL)	1.2 (1.0, 1.6)	0.8 (0.7, 0.9)	1.0 (0.8, 1.1)	1.1 (0.9, 1.4)	1.2 (1.0, 1.6)	1.4 (1.2, 1.7)	1.6 (1.4, 2.0)	2.0 (1.8, 2.3)	<0.0001
Adiponectin	4413.2 (2767.1, 6832.5)	5017.4 (3369.9, 7929.4)	4807.3 (3008.7, 7064.8)	4456.5 (2899.7, 6870.7)	4425.5 (2757.4, 7051.8)	3918.7 (2637.0, 6069.9)	3917.9 (2402.6, 6304.4)	4551.1 (2650.9, 6828.2)	<0.0001

p-Value: Cochran-Armitage Trend test was used to test the trend between score with categorical variables (gender, education, occupation, smoking, drinking, history of stroke, history of heart failure and history of coronary heart disease).

Cochran-Mantel-Haenszel test was used to test the association between ordered variable score with the other categorical variables (AHA Physical Activity, AHA Dietary Intake). Linear regression was used to test the trend between score and all continuous variables.

Poisson regression analysis was used to test the association between score and incident rate of diabetes.

Aldosterone, endothelin-1 and adiponectin were log transformed.

[a] Aldosterone/endothelin-1 score was created by coding aldosterone and endothelin-1 in quartiles (e.g. 1–4 points from lowest to highest quartile) and creating a score of 2–8.

[b] Mean (SD).

Table 2

Association of HOMA-IR, HOMA-B, fasting glucose and hemoglobin A1c with serum aldosterone, endothelin-1 or aldosterone-endothelin-1 score (n = 3914[*]).

Predictor	Model 1	Model 2	Model 3	Model 4
	Beta (95 % CI), p-value	**Beta (95 % CI), p-value**	**Beta (95 % CI), p-value**	**Beta (95 % CI), p-value**
Dependent variable: log HOMA-IR				
z-Serum aldosterone	0.0979 (0.0807, 0.1152), <0.001	0.1005 (0.0834, 0.1176), <0.001	0.0874 (0.0717, 0.1030), <0.001	0.0924 (0.0765, 0.1084), <0.001
z-Endothelin-1	−0.0039 (−0.0216, 0.0138), 0.666	0.0002 (−0.0179, 0.0183), 0.984	− 0.0181 (−0.0347, −0.0016), 0.032	0.0112 (−0.0057, 0.0281), 0.196
Score[a]	0.0551 (0.0441, 0.0660), <0.001	0.0625 (0.0515, 0.0735), <0.001	0.0473 (0.0371, 0.0575), <0.001	0.0535 (0.0431, 0.0638), <0.001
Dependent variable: log HOMA-B				
z-Serum aldosterone	0.0492 (0.0330, 0.0655), <0.001	0.0552 (0.0399, 0.0706), <0.001	0.0474 (0.0326, 0.0622), <0.001	0.0504 (0.0355, 0.0653), <0.001
z-Endothelin-1	−0.0077 (−0.0241, 0.0087), 0.357	0.0282 (0.0122, 0.0443), <0.001	0.0175 (0.0020, 0.0330), 0.027	0.0348 (0.0193, 0.0504), <0.001
Score[a]	0.0229 (0.0126, 0.0331), <0.001	0.0447 (0.0349, 0.0546), <0.001	0.0358 (0.0262, 0.0454), <0.001	0.0394 (0.0298, 0.0490), <0.001
Dependent variable: Fasting glucose				
z-Serum aldosterone	1.0316 (0.7512, 1.3121), <0.001	0.9617 (0.6954, 1.2280), <0.001	0.8587 (0.5975, 1.1199), <0.001	0.8981 (0.6360, 1.1601), <0.001
z-Endothelin-1	0.1667 (−0.1178, 0.4513), 0.251	−0.4622 (−0.7411, −0.1833), 0.001	−0.6093 (−0.8826, −0.3360), <0.001	−0.3767 (−0.6513, −0.1021), 0.007
Score[a]	0.6586 (0.4818, 0.8355), <0.001	0.3736 (0.2009, 0.5463), <0.001	0.2523 (0.0822, 0.4225), 0.004	0.3014 (0.1311, 0.4718), <0.001
Dependent variable: Hemoglobin A1c				
z-Serum aldosterone	0.0190 (0.0044, 0.0337), 0.011	0.0162 (0.0020, 0.0303), 0.026	0.0107 (−0.0033, 0.0246), 0.134	0.0126 (−0.0013, 0.0265), 0.076
z-Endothelin-1	0.0306 (0.0159, 0.0453), <0.001	0.0086 (−0.0062, 0.0233), 0.253	0.0013 (−0.0132, 0.0158), 0.857	0.0139 (−0.0005, 0.0284), 0.058
Score[a]	0.0277 (0.0186, 0.0368), <0.001	0.0192 (0.0101, 0.0283), <0.001	0.0131 (0.0041, 0.0220), 0.004	0.0151 (0.0061, 0.0240), <0.001

Score[a]: By coding aldosterone and endothelin-1 in quantiles (e.g. 1–4 in quartiles), Thus, a score of 2–8 (aldosterone quartiles + endothelin-1 quartiles) will be created. Aldosterone and Endothelin-1 were transformed to z-scores, $z = (x - \mu) / \sigma$, where x is the observed value, μ is the mean of the sample, and σ is the standard deviation of the sample.

Model 1: unadjusted.

Model 2: Age, gender, education, occupation, systolic blood pressure, smoking, physical activity (AHA-LS7 variable), dietary intake (AHA-LS7 variable), and alcohol use.

Model 3: Model 2 + BMI.

Model 4: Model 2 + adiponectin.

Log-transformed dependent and level independent variable:

1 standard deviation above the mean of aldosterone would result in a $(e^{\beta} - 1) * 100$ percentage change in log-HOMA-IR or log-HOMA-β.

* Exclude participants with prevalent T2DM at baseline and participants missing data on independent variables (aldosterone, endothelin-1) and baseline covariates.

Table 3

Association of aldosterone and endothelin-1 with incident diabetes (n = 3914).

Predictor	Model 1	Model 2	Model 3	Model 4
	HR (95 % CI), p-value	HR (95 % CI), p-value	HR (95 % CI), p-value	HR (95 % CI), p-value
z-Serum aldosterone	1.24 (1.16, 1.31), <0.001	1.24 (1.16, 1.32), <0.001	1.22 (1.14, 1.31), <0.001	1.22 (1.14, 1.31), <0.001
z-Endothelin-1	1.16 (1.08, 1.24), <0.001	1.12 (1.04, 1.21), 0.003	1.08 (1.00, 1.17), 0.053	1.14 (1.06, 1.24), <0.001
Score [a]	1.17 (1.11, 1.24), <0.001	1.15 (1.09, 1.22), <0.001	1.13 (1.07, 1.19), <0.001	1.13 (1.07, 1.19), <0.001

Model 1: unadjusted.

Model 2: Age, gender, education, occupation, systolic blood pressure, smoking, physical activity (AHA-LS7 variable), dietary intake (AHA-LS7 variable), and alcohol use.

Model 3: Model 2 + BMI.

Model 4: Model 2 + adiponectin.

Score[a]: By coding aldosterone and endothelin-1 in quantiles (e.g. 1–4 in quartiles), Thus, a score of 2–8 (aldosterone quartiles + endothelin-1 quartiles) will be created. Interpretation: 1-SD above the mean of aldosterone was associated with a 24 % higher risk of incident diabetes over a 16-year period in the fully adjusted model (model 2). A 1-point higher Aldosterone-Endothelin-1 Score was associated with a 15 % higher risk of incident diabetes over a 16-year period in the fully adjusted model (model 2).