Original Article

Association of Serum Glucocorticoids with Various Blood Pressure Indices in Patients with Dysglycemia and Hypertension: the Henan Rural Cohort Study*

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Abstract

Objective To our knowledge, no definitive conclusion has been reached regarding the relationship between glucocorticoids and hypertension. Here, we aimed to explore the characteristics of glucocorticoids in participants with dysglycemia and hypertension, and to analyze their association with blood pressure indicators.

Methods The participants of this study were from the Henan Rural Cohort study. A total of 1,688 patients 18–79 years of age were included in the matched case control study after application of the inclusion and exclusion criteria. Statistical methods were used to analyze the association between glucocorticoids and various indices of blood pressure, through approaches such as logistic regression analysis, trend tests, linear regression, and restricted cubic regression.

Results The study population consisted of 552 patients with dysglycemia and hypertension (32.7%). The patients with co-morbidities had higher levels of serum cortisol (P = 0.009) and deoxycortisol (P < 0.001). The adjusted odds ratios (and 95% confidence intervals) for dysglycemia with hypertension were 1.55 (1.18, 2.04) for the highest tertile of Ln-cortisol compared with the lowest tertile. Additionally, the highest Ln-deoxycortisol levels were associated with increased prevalence of dysglycemia with hypertension by 159% (95% confidence interval: 122%, 207%).

Conclusions Serum deoxycortisol was positively correlated with systolic blood pressure, pulse pressure, mean arterial pressure, mean blood pressure, and mean proportional arterial pressure. Glucocorticoids (deoxycortisol and cortisol) increase the risk of hypertension in people with dysglycemia, particularly in those with T2DM.

Key words: Glucocorticoids; Dysglycemia with hypertension; Blood pressure; Chinese rural

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INTRODUCTION

Hypertension is a common complication or comorbidity of diabetes mellitus whose prevalence is associated with diabetes type, age, obesity, race, and other factors[1-3]. The incidence of both hypertension and diabetes is increasing, and 20%–60% of people with type 2 diabetes mellitus (T2DM) have been reported to have concomitant hypertension[4]. Furthermore, approximately 30% of the patients with T2DM in Chinese outpatient clinics also have a clinical diagnosis of hypertension[5]. The coexistence of T2DM with hypertension is associated with multiple cardiometabolic risk factors and significantly increases the risk of cardiovascular disease, stroke, nephropathy, and retinopathy, as well as the mortality rate, in patients with diabetes[6]. In contrast, controlling hypertension can significantly decrease the risk of diabetes complications and slow the rate of development[7-10].

Glucocorticoids (including cortisol and corticosterone) have been implicated in a broad range of physiological functions, such as regulating metabolism and blood pressure, as well as stress and inflammatory responses; therefore, they are indispensable in maintaining survival[11,12]. Glucocorticoids also induce insulin resistance, hyperglycemia, and hyperlipidemia through a variety of mechanisms[13]. Research[14] has shown that morning cortisol levels are positively correlated with the body mass index (BMI), waist-to-hip ratio, and levels of blood glucose, insulin, and triglycerides. Another study has suggested that people with T2DM have higher levels of morning cortisol, and these levels are negatively correlated with the insulin sensitivity index[15]. According to the literature, endogenous glucocorticoids increase blood pressure[16,17]. However, in patients prescribed synthetic corticoids, the prevalence of the hypertension greatly varies, between 0% and 90%[18,19].

To our knowledge, no definitive conclusion has been reached regarding the relationship between glucocorticoids and hypertension. Glucocorticoids regulate blood pressure by acting on multiple organs, as reported in many clinical observations and experimental studies[20-24]. Therefore, to investigate whether glucocorticoids might be involved in the pathogenesis of diabetes and hypertension, we aimed to explore the characteristics of glucocorticoids in people with dysglycemia and hypertension by analyzing their association with blood pressure indicators.

METHODS

Study Population

The participants in this study were from the Henan Rural Cohort study, which included 39,259 people 18–79 years of age in five rural regions of Henan province in China at baseline (2015–2017). The cohort details have been described elsewhere[25]. A matched case study[26] was performed after the exclusion of participants taking sex steroid related drugs. Consequently, 925 patients with T2DM were selected, and all cases were matched with participants with impaired fasting glycemia (IFG), on the basis of normal fasting glucose, sex, and age (± 3 years) in the same general population. Finally, 2,775 participants were recruited. In this analysis, we excluded individuals who had normal blood glucose (n = 925) and lacked clinical parameters for blood pressure (n = 4). We also excluded individuals with gestational hypertension (n = 15) and kidney disease (n = 143). After this exclusion process, a total of 1,688 participants 18–79 years of age were included in the final analysis. This study was approved by the Zhengzhou University Life Science Ethics Committee [code: (2015) MEC (S128)]. All participants in the study provided signed written informed consent.

Patient and Public Involvement Statement

Patients or the public were not involved in designing, conducting, reporting, or disseminating our research.

Data Collection

Previously validated questionnaires[25,27] were used by trained investigators to collect demographic (age, sex, education, income, etc.), and lifestyle (smoking, drinking, and exercise) information, as well illness history through face-to-face interviews. The level of education was classified into illiteracy, primary school, middle school, and high school or higher education. Marital status was categorized into married or cohabiting, widowed/divorced/separated, and single. Per capita monthly income was classified into three levels [< 500, between 500 and 999, and ≥ 1,000 renminbi (RMB)]. Smoking status was defined as smoking at least one cigarette per day for 6 consecutive months, and was categorized into never, once, and current. Drinking status was defined as drinking alcohol at least 12 times per

year. Physical activity was evaluated with the international physical activity short questionnaire and categorized into low, moderate, and high levels[28].

The investigators measured anthropometric variables, and all participants were asked to wear light clothing and no shoes. Height and weight were measured twice with a standard right-angle device and a weight measurement device (V. BODY HBF-371, OMRON, Japan) to the nearest 0.1 cm and 0.1 kg, respectively[29]. BMI was calculated as body weight (kg) divided by height squared (m^2). Blood pressure was measured three times at 30 s intervals in seated participants with an electronic sphygmomanometer (HEM-770AFuzzy, Omron, Japan) after the participants had rested for 5 min, and the mean value was used for analysis[30]. Pulse pressure (PP), mean arterial pressure (MAP), mean blood pressure (MBP), and mean proportional arterial pressure (MPAP) were calculated with the following Formulas[31,32]:

$$PP = SBP - DBP \quad (1)$$

$$MAP = \frac{1}{3} \times SBP + \frac{2}{3} \times DBP = \frac{SBP + 2 \times DBP}{3} \quad (2)$$

$$MBP = \frac{1}{2} \times SBP + \frac{1}{2} \times DBP = \frac{SBP + DBP}{2} \quad (3)$$

$$MPAP = SBP \times \left(\frac{SBP}{SBP + DBP}\right) + DBP\left(\frac{DBP}{SBP + DBP}\right) = \frac{SBP^2 + DBP^2}{SBP + DBP} \quad (4)$$

Laboratory Measurements

Fasting venous blood was collected from each participant after a fast of at least 8 h, with no anticoagulant treatment. The samples were then centrifuged immediately after coagulation, and the serum was stored at –80 °C. Fasting plasma glucose (FPG) was measured with a Roche Cobas C501 automatic biochemical analyzer. The serum levels of glucocorticoids (cortisol, deoxycortisol, and cortisone) were measured with liquid chromatography-tandem mass spectrometry on a Waters XEVO TQ-S system (Waters, Milford, MA, USA). We used blind determination when the case or control status of each sample analyzed in the same run was unknown. Values below the limit of detection and undetectable results were replaced with the value of half the detection limit.

Ascertainment of Dysglycemia

IFG and T2DM were collectively referred to as dysglycemia, and the diagnostic criteria for IFG and T2DM were those recommended by the American Diabetes Association (2002) and World Health Organization (1999) guidelines. Excluding type 1 diabetes, gestational diabetes, and other special types of diabetes, we defined IFG as 6.1 mmol/L ≤ FPG < 7.0 mmol/L, or 5.7% < HbA1C < 6.5%. T2DM was defined as FPG ≥ 7.0 mmol/L, or HbA1C > 6.5%, or a self-reported previous diagnosis of diabetes by a physician and administration of antiglycemic agents in the prior 2 weeks.

Ascertainment of Hypertension

A diagnosis of hypertension, as recommended by the Chinese guidelines for the prevention and treatment hypertension (revised 2010)[33], was defined according to the following standards: 1) SBP ≥ 140 mmHg and or DBP ≥ 90 mmHg; 2) self-reported hypertension diagnosed by a physician and current use of antihypertensive treatment in the prior 2 weeks. Participants who reported non-hypertension but were found to be hypertensive when measured were considered to have undiagnosed hypertension.

Statistical Analysis

Continuous non-normal variables are expressed in median (quartiles) and compared with the Mann-Whitney U test, whereas categorical variables are expressed as a percentage and compared with a chi-squared test. To explore the potential nonlinear relationships and evaluate dose-response relationships, we categorized serum glucocorticoid (cortisol, deoxycortisol, and cortisone) levels in tertiles, and used the lowest tertiles as the reference. Serum glucocorticoid levels and blood pressure indicators were log-transformed (Ln-) to better approximate a normal distribution. Logistic regression analysis was used to estimate the association between serum glucocorticoids and the risk of dysglycemia with hypertension. The odds ratio (*OR*) and 95% confidence interval (*CI*) of dysglycemia with hypertension are reported in tertiles in separate models. We performed trend tests by entering the categorical variables as continuous variables in the logistic regression models. Stratified logistic regression was also performed. Linear regression was also used to examine the relationships between the serum levels of glucocorticoids (Ln-cortisol, Ln-deoxycortisol, and Ln-cortisone) and characteristics of hypertension

(Ln-SBP, Ln-SDP, Ln-PP, Ln-MAP, Ln-MBP, and Ln-MPAP). Multivariable adjustment modelling was performed as follows: model 1 was adjusted for age, sex, education, marital status, and per capita monthly income; model 2 was adjusted for the same parameters as model 1, plus drinking and smoking status; and model 3 was adjusted for the same parameters as model 2, plus BMI and physical activity. To further observe the association between continuous serum glucocorticoid (cortisol, deoxycortisol and cortisone) levels and hypertension, we used restricted cubic regression splines. Statistical analyses were performed in SPSS software, version 21.0 (SPSS Inc., Chicago) and SAS V.9.1 (SAS Institute). Two-sided test *P* values < 0.05 were considered statistically significant.

RESULTS

Basic Characteristics

The study population contained of 552 cases of dysglycemia with hypertension (32.7%) and 1,136 cases of dysglycemia with non-hypertension (67.3%). Participants with hypertension were more likely to have a lower education, per capita monthly income, and physical activity level (Table 1). Participants with hypertension appeared to have higher BMI, SBP, DBP, PP, MAP, MBP, MPAP, FPG, serum cortisol, and serum deoxycortisol.

Trend between Serum Ln-glucocorticoids and Blood Pressure

To observe the trend between Ln-glucocorticoids and BP, we generated restricted spline curves for serum Ln-glucocorticoids (Supplementary Figure S1, available in www.besjournal.com). As demonstrated, elevated SBP was associated with increased serum deoxycortisol levels. However, no significant differences in the trends were observed for the relationship between SBP and serum Ln-cortisol or Ln-cortisone. A similar trend between Ln-glucocorticoids and DBP was also observed.

Association between Serum Ln-glucocorticoids and Dysglycemia with Hypertension

Table 2 shows the association between serum Ln-glucocorticoids and dysglycemia with hypertension. The *OR*s (95% *CI*s) of participants with the highest tertile of the Ln-cortisol were 1.42 (1.11, 1.83) and 1.55 (1.18, 2.04), as compared with the lowest tertile in the crude and full-adjusted model. In the crude model, the highest tertile of the Ln-deoxycortisol was significantly associated with an increased risk of dysglycemia with hypertension (*OR*: 1.57, 95% *CI*: 1.23, 2.00), as compared with the lowest tertile. After adjustment for covariates (model 1–3), the *OR*s (95% *CI*s) were 1.56 (1.21, 2.01), 1.56 (1.21, 2.01), and 1.59 (1.22, 2.07), respectively. No significant correlation was observed between serum Ln-cortisone and dysglycemia with hypertension in both the crude and adjusted models.

The results of stratified logistic regression showed that participants who were male, were unmarried/divorced/widowed, or had a low BMI or low physical activity had higher risk in the association between serum Ln-deoxycortisol and dysglycemia with hypertension (Figure 1). No significant correlation was observed between Ln-cortisol or Ln-cortisone and dysglycemia with

Table 1. Characteristics of the study population with dysglycemia with and without hypertension

Variables	Dysglycemia with hypertension		x^2/z	*P*
	No	Yes		
	n = 1,136 (67.3%)	*n* = 552 (32.7%)		
Age (years)	60.00 (53.00, 65.00)	63.00 (56.00, 68.00)	−6.84	< 0.001
Sex, *n* (%)			34.96	< 0.001
Male	486 (42.8)	154 (27.9)		
Female	650 (57.2)	398 (72.1)		
Education, *n* (%)			18.01	0.001
Illiteracy	258 (22.7)	169 (20.6)		
Primary school	343 (20.2)	176 (31.9)		
Middle school	412 (36.3)	164 (29.7)		
High school or higher	123 (10.8)	43 (7.8)		

Continued

Variables	Dysglycemia with hypertension		x^2/z	*P*
	No	Yes		
	n = 1,136 (67.3%)	*n* = 552 (32.7%)		
Marital status, *n* (%)			4.36	0.225
Married/cohabiting	1,105 (89.3)	483 (87.5)		
Widowed/divorced/separated	100 (8.8)	63 (11.4)		
Single	21 (1.8)	6 (1.1)		
Per capita monthly income (RMB), *n* (%)			3.84	0.429
< 500	462 (40.7)	238 (43.1)		
500–999	347 (30.5)	172 (31.2)		
≥ 1,000	327 (28.7)	142 (25.7)		
Smoking habit, *n* (%)			26.33	< 0.001
Never	815 (71.8)	452 (81.9)		
Once	89 (7.8)	41 (7.4)		
Current	232 (20.4)	59 (10.7)		
Drinking status, *n* (%)			8.36	0.015
Never	920 (81.0)	468 (84.8)		
Once	63 (5.5)	36 (6.5)		
Current	153 (13.5)	48 (8.7)		
Physical activity, *n* (%)			17.99	< 0.001
Low	281 (24.7)	177 (32.1)		
Moderate	539 (47.4)	268 (48.6)		
High	316 (27.8)	107 (19.4)		
BMI (kg/m^2)	24.25 (22.15, 26.48)	25.86 (23.73, 28.04)	−9.20	< 0.001
SBP (mmHg)	117.00 (109.00, 126.00)	143.00 (132.00, 152.00)	−26.21	< 0.001
DBP (mmHg)	72.00 (66.00, 78.00)	84.00 (77.00, 91.00)	−21.04	< 0.001
PP (mmHg)	45.00 (39.00, 51.00)	58.00 (49.00, 67.00)	−19.36	< 0.001
MAP (mmHg)	87.67 (80.67, 93.33)	104.33 (96.33, 110.67)	−25.16	< 0.001
MBP (mmHg)	95.00 (88.00, 101.50)	113.50 (105.13, 121.38)	−25.95	< 0.001
MPAP (mmHg)	100.32 (93.49, 107.28)	121.14 (112.93, 129.08)	−26.38	< 0.001
FPG (mmol/L)	5.93 (5.10, 7.63)	6.56 (5.37, 8.46)	−5.09	< 0.001
HbA1c (%)	6.10 (5.80, 7.20)	6.40 (5.90, 760)	−4.02	< 0.001
Serum cortisol (ng/mL)	141.95 (96.10, 189.25)	153.50 (105.33, 200.30)	−2.63	0.009
Serum deoxycortisol (ng/mL)	0.30 (0.20, 0.40)	0.30 (0.20, 0.50)	−3.87	< 0.001
Serum cortisone (ng/mL)	12.90 (9.50, 16.10)	12.90 (10.00, 16.60)	−0.89	0.373
Ratio of serum cortisol to cortisone	10.64 (7.66, 15.35)	10.96 (7.66, 15.35)	−1.04	0.300

Note. Continuous variables are expressed in median (quartiles) and compared with Mann-Whitney U test; categorical variables are expressed in percentage and compared by chi-squared test. BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; MAP: mean arterial pressure; MBP: mean blood pressure; MPAM: mean proportional arterial pressure; FPG: fasting plasma glucose; HbA1c: hemoglobin A1c.

hypertension after stratification by baseline characteristics (Supplementary Table S1, available in www.besjournal.com). In addition, when the association between serum Ln-glucocorticoids and dysglycemia with hypertension was stratified by T2DM and IFG (Table 3), the strongest association was observed between Ln-glucocorticoids and T2DM with hypertension. The results of further sensitivity analysis (Supplementary Table S2, available in www.besjournal.com) showed that the *OR* (95% *CI*) of the highest tertile of serum deoxycortisol was 1.682 (1.242, 2.277) after removal of the hypertension controlled population (n = 167).

Association between Ln-glucocorticoids and Ln-blood Pressure

Figure 2 shows the positive correlation between deoxycortisol and various indices of blood pressure. After adjustment for multiple variables and comparison with tertile 1, only the third tertile of Ln-deoxycortisol was associated with a 0.033 mmHg (95% *CI*: 0.016, 0.050) higher Ln-SBP, 0.036 mmHg (0.019, 0.052) higher Ln-DBP, 0.043 mmHg (0.015, 0.071) higher Ln-PP, 0.037 mmHg (0.021, 0.052) higher Ln-MAP, 0.037 mmHg (0.021, 0.053) higher Ln-MBP, and 0.037 mmHg (0.021, 0.054) higher Ln-MPAP. The results for other models are shown in Supplementary Table S3, available in www.besjournal.com.

DISCUSSION

This study established the prevalence of co-morbidities among rural residents of Henan, China. The prevalence of hypertension (32.7%) among people with dysglycemia was not unexpected and has been described in many studies worldwide[4,34-36]. Patients with co-morbidities had higher levels of serum cortisol and deoxycortisol. Glucocorticoids are important insulin anti-regulatory hormones that strongly inhibit insulin action[37]. Increased

Table 2. Association between serum Ln-glucocorticoids and dysglycemia with hypertension

Item	Crude		Model 1		Model 2		Model 3	
	OR (95% *CI*)	*P* value	*OR* (95% *CI*)	*P* value	*OR* (95% *CI*)	*P* value	*OR* (95% *CI*)	*P* value
Serum Ln-cortisol								
Tertile 1	1		1		1		1	
Tertile 2	1.203 (0.934, 1.551)	0.152	1.198 (0.922, 1.556)	0.177	1.194 (0.919, 1.551)	0.184	1.253 (0.953, 1.646)	0.106
Tertile 3	1.422 (1.107, 1.828)	0.006	1.419 (1.096, 1.837)	0.008	1.411 (1.089, 1.828)	0.009	1.552 (1.183, 2.036)	0.001
P_{trand}	0.006		0.008		0.009		0.001	
Serum Ln-deoxycortisol								
Tertile 1	1		1		1		1	
Tertile 2	1.030 (0.803, 1.321)	0.817	1.034 (0.799, 1.337)	0.799	1.035 (0.800, 1.340)	0.792	0.988 (0.755, 1.292)	0.927
Tertile 3	1.565 (1.225, 1.999)	< 0.001	1.558 (1.210, 2.006)	0.001	1.557 (1.209, 2.005)	0.001	1.591 (1.222, 2.072)	0.001
P_{trand}	0.001		0.001		0.001		0.001	
Serum Ln-cortisone								
Tertile 1	1		1		1		1	
Tertile 2	0.975 (0.760, 1.252)	0.845	1.040 (0.804, 1.345)	0.764	1.036 (0.801, 1.340)	0.789	0.988 (0.755, 1.292)	0.928
Tertile 3	1.078 (0.841, 1.381)	0.555	1.111 (0.861, 1.434)	0.419	1.101 (0.852, 1.422)	0.462	1.060 (0.812, 1.385)	0.668
P_{trand}	0.557		0.420		0.463		0.667	

Note. Model 1 was adjusted by age, sex, education, marital status, and per capita monthly income. Model 2 was further adjusted by drinking and smoking status, based on model 1. Model 3 was further adjusted by BMI and physical activity, based on model 2. Ln-, natural log-transformed.

glucocorticoids therefore may promote insulin resistance, visceral obesity, and hypertension[38]. Animal studies have shown that glucocorticoid action in the bone impairs osteoblast function, thus contributing to insulin resistance[39,40]. Similarly, patients are prone to developing diabetes in response to high glucocorticoid levels[41]. Excess glucocorticoids can lead to abnormal metabolism and cardiovascular function, thereby inducing hypertension, hyperglycemia, and insulin resistance, which is also commonly found in patients with Cushing syndrome and metabolic syndrome[42,43].

Our research highlighted that SBP increased with increasing serum deoxycortisol levels. Furthermore, DBP increased with increasing cortisol levels. Abundant evidence has indicated that glucocorticoids, through effects entirely independent of the mineralocorticoid receptor, induce sustained blood pressure elevation in both animals and humans[44-47]. Glucocorticoids improve vascular tension and maintain blood pressure by enhancing the sensitivity of vascular smooth muscle to catecholamine[48,49]. Glucocorticoids therefore regulate blood pressure through the function of the heart, vascular endothelial cells, and vascular smooth muscle[23,50,51]. Consequently, increasing evidence indicates that spontaneous hypertension is associated with the abnormal secretion of glucocorticoids.

Glucocorticoids (deoxycortisol and cortisol) increase the risk of hypertension in people with

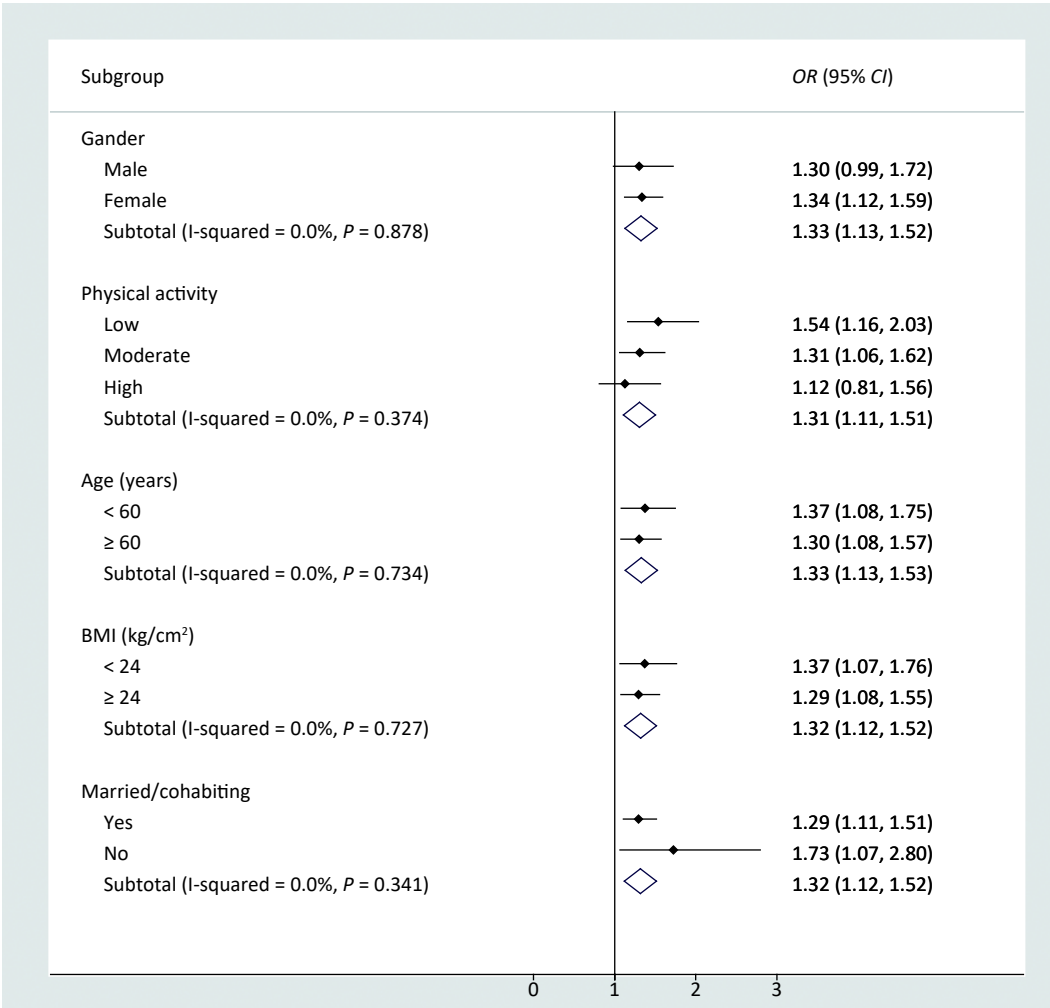

Figure 1. Association between serum Ln-deoxycortisol and dysglycemia with hypertension, stratified by baseline characteristics. The odds ratio (*OR*) and 95% confidence interval (*CI*) were calculated by stratified logistic regression adjusted for age, sex, education, marital status, per capita monthly income, drinking and smoking status, BMI, and physical activity. BMI: body mass index.

dysglycemia, particularly those with T2DM. However, the levels of serum glucocorticoids have rarely been reported in pre-diabetic populations. The highest tertile of the Ln-cortisol was significantly associated with an increased risk of pre-diabetes, as compared with the lowest tertile. In a study on a

Table 3. Association between serum Ln-glucocorticoids and dysglycemia with hypertension, stratified by T2DM and IFG

Item	T2DM, *n* = 838		IFG, *n* = 850	
	OR (95% *CI*)	*P* value	*OR* (95% *CI*)	*P* value
Serum Ln-cortisol				
Tertile 1	1		1	
Tertile 2	1.156 (0.786, 1.700)	0.462	1.359 (0.913, 2.022)	0.130
Tertile 3	1.530 (1.051, 2.228)	0.027	1.555 (1.041, 2.325)	0.031
P_{trand}	0.026		0.031	
Serum Ln-deoxycortisol				
Tertile 1	1		1	
Tertile 2	1.051 (0.722, 1.530)	0.796	0.861 (0.580, 1.277)	0.456
Tertile 3	1.717 (1.180, 2.498)	0.005	1.429 (0.974, 2.095)	0.068
P_{trand}	0.006		0.105	
Serum Ln-cortisone				
Tertile 1	1		1	
Tertile 2	0.956 (0.651, 1.404)	0.819	0.965 (0.658, 1.417)	0.857
Tertile 3	0.987 (0.673, 1.447)	0.946	1.047 (0.712, 1.541)	0.814
P_{trand}	0.957		0.829	

Note. T2DM: type 2 diabetes mellitus; IFG: impaired fasting glucose; *OR:* odds ratio; *CI*: confidence interval. Ln-, natural log-transformed. The model was adjusted by age, sex, education, marital status, per capita monthly income, drinking and smoking status, BMI, and physical activity.

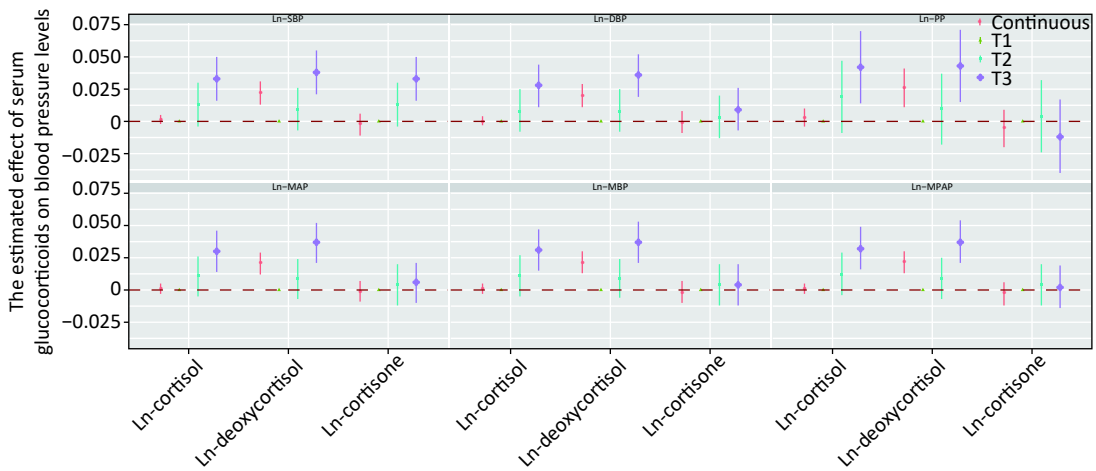

Figure 2. Estimated effect of serum glucocorticoids on blood pressure levels. The β coefficients were assessed by a linear regression model adjusted by age, sex, education, marital status, per capita monthly income, drinking and smoking status, BMI, and physical activity. SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; MAP: mean arterial pressure; MBP: mean blood pressure; MPAM: mean proportional arterial pressure. Ln-, natural log-transformed.

Chinese population[15], the level of plasma cortisol in the T2DM group (5.85 nmol/L) was higher than that in controls (2.7 nmol/L), $P < 0.05$. A meta-analysis of 93 randomized controlled trials has shown that patients exposed to glucocorticoids have twice the risk of hypertension as those exposed to placebo [odds ratio, 2.2 (1.4–3.8)][52]. Glucocorticoid-mediated hypertension has been commonly thought to be moderated by excess sodium and water reabsorption by the renal mineralocorticoid receptor[53,54]. In addition, glucocorticoids have been implicated in the regulation of blood pressure via a wide variety of extrarenal tissues, including the vascular smooth muscle, vascular endothelium, central nervous system, and adipose tissue[22,23,43,55,56].

This study was performed in a large sample cohort, including serum specimens from 1,688 participants with a wide age span. The major strength of this study is that it is the first of its kind, to our knowledge, to assess the relationship between glucocorticoids and an increased risk of hypertension in populations with dysglycemia (including pre-diabetes and T2DM). Moreover, the relationship between glucocorticoids and indices of blood pressure was explored through restrictive cubic spline analysis. Notwithstanding, several study limitations should also be considered. Although glucocorticoid levels fluctuate over time, we used the same morning fasting blood as that performed in other studies to detect glucocorticoids. We did not exclude the participants who used glucocorticoid drugs, because no relevant information was collected. Moreover, this was a case-control study and therefore could not determine whether the association was a causal or coincidental phenomenon. Finally, this was a single study limited to the Chinese Han population, thus potentially limiting the extrapolation of these findings to other racial groups.

CONCLUSIONS

Glucocorticoids (deoxycortisol and cortisol) increase the risk of hypertension in people with dysglycemia, particularly those with T2DM. High levels of serum glucocorticoids may promote higher SBP, PP, and MAP in people with dysglycemia and hypertension. Given that people with T2DM are already at increased risk of hypertension, patients with higher levels of glucocorticoids should have their blood pressure verified regularly and treated appropriately.

DECLARATIONS

Ethics Approval and Consent to Participate

This study was conducted according to the guidelines of the Declaration of Helsinki, and the Ethics Committee of Zhengzhou University approved all procedures involving human participants/patients. Written informed consent was obtained from all participants/patients.

Consent for Publication

All authors have read and approve this version of the article, and due care has been taken to ensure the integrity of the work.

Availability of Data and Materials

The data that support the findings of this study are available from The Henan Rural Cohort, but restrictions apply to the availability of these data, which were used under license for the current study and thus are not publicly available. However, data are available from the authors upon reasonable request and with permission of The Henan Rural Cohort.

Competing Interests

The authors declare no conflicts of interest. Research data are not shared.

Author's Contributions

XL, WJL, and ZXM conceived and designed the study. SBP, CL, DDZ, SCY, JJG, JSL, and CJW performed the investigation. YX, XL, and DDW analyzed the data. YX wrote the manuscript. All authors read and approved the final manuscript.

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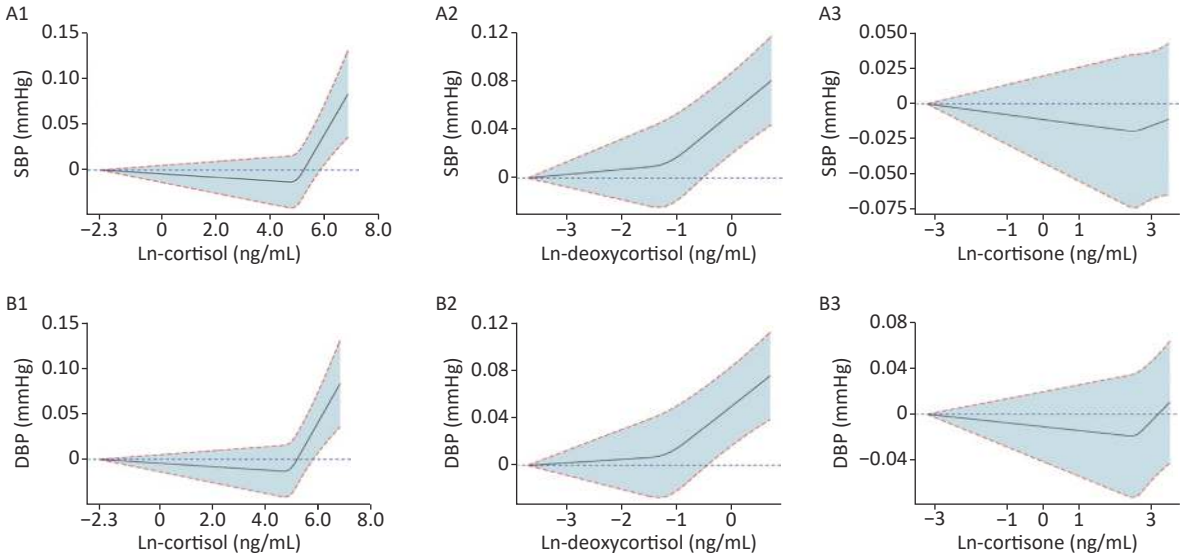

Supplementary Figure S1. Mean and 95% confidence intervals of SBP (A1–A3) and DBP (B1–B3) along with changes in serum Ln-cortisol, Ln-deoxycortisol, and Ln-cortisone from restricted cubic splines analysis, adjusted for age, sex, education, marital status, per capita monthly income, drinking and smoking status, BMI, and physical activity. SBP: systolic blood pressure; DBP: diastolic blood pressure. Ln-, natural log-transformed.

Supplementary Table S1. Association between serum Ln-glucocorticoids and dysglycemia with hypertension, stratified by baseline characteristics

Item	Serum Ln-cortisol				Serum Ln-deoxycortisol				Serum Ln-cortisone			
	OR	lower *CI*	upper *CI*	*P*	*OR*	lower *CI*	upper *CI*	*P*	*OR*	lower *CI*	upper *CI*	*P*
Sex												
Male	0.980	0.877	1.095	0.717	1.301	0.985	1.719	0.064	0.885	0.691	1.134	0.335
Female	1.007	0.933	1.086	0.857	1.335	1.121	1.591	0.001	1.061	0.901	1.249	0.481
Physical activity												
Low	1.070	0.942	1.214	0.299	1.537	1.162	2.034	0.003	0.859	0.668	1.106	0.239
Moderate	1.015	0.922	1.117	0.761	1.311	1.062	1.619	0.012	1.126	0.913	1.390	0.268
High	0.923	0.825	1.033	0.162	1.125	0.810	1.563	0.483	1.013	0.763	1.345	0.930
Age (years)												
< 60	1.051	0.943	1.173	0.368	1.374	1.080	1.748	0.010	1.073	0.864	1.332	0.523
≥ 60	0.996	0.893	1.045	0.387	1.302	1.078	1.573	0.006	0.960	0.799	1.154	0.960
BMI (kg/cm^2)												
< 24	1.040	0.925	1.169	0.512	1.370	1.066	1.761	0.014	1.047	0.822	1.334	0.708
≥ 24	0.980	0.909	1.057	0.603	1.295	1.078	1.554	0.006	0.995	0.842	1.177	0.956
Married/cohabiting												
Yes	0.991	0.927	1.059	0.783	1.295	1.108	1.514	0.001	0.989	0.857	1.141	0.877
No	1.029	0.843	1.255	0.781	1.726	1.066	2.795	0.026	1.204	0.733	1.977	0.464

Note. *OR*: odds ratio; *CI*: confidence interval; BMI: body mass index. Ln-, natural log-transformed.

Supplementary Table S2. Association between serum Ln-glucocorticoids and dysglycemia with hypertension, excluding the population with controlled hypertension

Item	*OR* (95% *CI*)	*P* value
Serum Ln-cortisol		
Tertile 1	1	
Tertile 2	1.239 (0.909, 1.689)	0.175
Tertile 3	1.682 (1.242, 2.277)	0.001
P_{trand}	0.001	
Serum Ln-deoxycortisol		
Tertile 1	1	
Tertile 2	1.239 (0.909, 1.689)	0.173
Tertile 3	1.682 (1.242, 2.277)	0.001
P_{trand}	0.001	
Serum Ln-cortisone		
Tertile 1	1	
Tertile 2	1.007 (0.745, 1.362)	0.964
Tertile 3	1.082 (0.802, 1.460)	0.604
P_{trand}	0.602	

Note. The model was adjusted by age, sex, education, marital status, per capita monthly income, drinking and smoking status, BMI, and physical activity. *OR*: odds ratio; *CI*: confidence interval; Ln-: natural log-transformed.

Supplementary Table S3. Association of Ln-glucocorticoids with Ln-blood pressure

Item	Linear regression β coefficients			
	Unadjusted	Model 1	Model 2	Model 3
Ln-SBP				
Ln-cortisol				
Continuous	0.002 (−0.003, 0.006)	0.002 (−0.002, 0.006)	0.002 (−0.002, 0.006)	0.001 (−0.002, 0.005)
Tertile 1	Referent	Referent	Referent	Referent
Tertile 2	0.013 (−0.006, 0.031)	0.009 (−0.009, 0.027)	0.009 (−0.008, 0.027)	0.013 (−0.004, 0.030)
Tertile 3	0.032 (0.014, 0.050)	0.030 (0.012, 0.047)	0.028 (0.011, 0.046)	0.033 (0.016, 0.050)
Ln-deoxycortisol				
Continuous	0.026 (0.016, 0.036)	0.025 (0.015, 0.034)	0.024 (0.015, 0.034)	0.022 (0.013, 0.031)
Tertile 1	Referent	Referent	Referent	Referent
Tertile 2	0.017 (−0.001, 0.034)	0.015 (−0.002, 0.032)	0.015 (−0.002, 0.032)	0.009 (−0.007, 0.026)
Tertile 3	0.046 (0.028, 0.064)	0.043 (0.025, 0.061)	0.042 (0.025, 0.060)	0.038 (0.021, 0.055)
Ln-cortisone				
Continuous	−0.001 (−0.011, 0.008)	−0.001 (−0.010, 0.008)	−0.001 (−0.010, 0.008)	−0.002 (−0.011, 0.006)
Tertile 1	Referent	Referent	Referent	Referent
Tertile 2	0.003 (−0.015, 0.022)	0.008 (−0.010, 0.026)	0.007 (−0.010, 0.025)	0.013 (−0.004, 0.030)
Tertile 3	0.004 (−0.015, 0.022)	0.006 (−0.012, 0.024)	0.006 (−0.012, 0.024)	0.033 (0.016, 0.050)

Continued

Item	Linear regression β coefficients			
	Unadjusted	Model 1	Model 2	Model 3
Ln-SDP				
Ln-cortisol				
Continuous	0.001 (−0.003, 0.005)	0.001 (−0.00, 0.005)	0.001 (−0.003, 0.005)	< 0.001 (−0.003, 0.004)
Tertile 1	Referent	Referent	Referent	Referent
Tertile 2	0.001 (−0.017, 0.019)	0.004 (−0.014, 0.022)	0.004 (−0.015, 0.022)	0.008 (−0.008, 0.025)
Tertile 3	0.022 (0.004, 0.041)	0.024 (0.005, 0.042)	0.022 (0.003, 0.040)	0.028 (0.011, 0.044)
Ln-deoxycortisol				
Continuous	0.022 (0.012, 0.032)	0.024 (0.014, 0.033)	0.023 (0.013, 0.033)	0.020 (0.011, 0.029)
Tertile 1	Referent	Referent	Referent	Referent
Tertile 2	0.012 (−0.006, 0.030)	0.015 (−0.003, 0.033)	0.015 (−0.003, 0.033)	0.008 (−0.008, 0.025)
Tertile 3	0.040 (0.022, 0.059)	0.042 (0.024, 0.060)	0.041 (0.023, 0.059)	0.036 (0.019, 0.052)
Ln-cortisone				
Continuous	0.002 (−0.007, 0.012)	0.002 (−0.007, 0.012)	0.002 (−0.008, 0.011)	−0.001 (−0.009, 0.008)
Tertile 1	Referent	Referent	Referent	Referent
Tertile 2	0.010 (−0.008, 0.029)	0.010 (−0.009, 0.028)	0.008 (−0.010, 0.026)	0.003 (−0.013, 0.020)
Tertile 3	0.017 (−0.001, 0.035)	0.017 (−0.002, 0.035)	0.016 (−0.002, 0.034)	0.009 (−0.007, 0.026)
Ln-PP				
Ln-cortisol				
Continuous	0.002 (−0.005, 0.010)	0.033 (−0.004, 0.010)	0.003 (−0.004, 0.010)	0.003 (−0.004, 0.010)
Tertile 1	Referent	Referent	Referent	Referent
Tertile 2	0.030 (−0.002, 0.061)	0.017 (−0.012, 0.045)	0.017 (−0.011, 0.046)	0.019 (−0.009, 0.047)
Tertile 3	0.046 (0.015, 0.078)	0.038 (0.010, 0.066)	0.039 (0.010, 0.067)	0.042 (0.014, 0.070)
Ln-deoxycortisol				
Continuous	0.033 (0.016, 0.050)	0.027 (0.012, 0.042)	0.027 (0.012, 0.042)	0.026 (0.011, 0.041)
Tertile 1	Referent	Referent	Referent	Referent
Tertile 2	0.024 (−0.007, 0.054)	0.014 (−0.014, 0.041)	0.014 (−0.014, 0.041)	0.010 (−0.018, 0.037)
Tertile 3	0.056 (0.025, 0.088)	0.045 (0.017, 0.074)	0.045 (0.017, 0.073)	0.043 (0.015, 0.071)
Ln-cortisone				
Continuous	−0.006 (−0.023, 0.010)	−0.006 (−0.021, 0.008)	−0.005 (−0.020, 0.009)	−0.005 (−0.020, 0.009)
Tertile 1	Referent	Referent	Referent	Referent
Tertile 2	−0.007 (−0.039, 0.024)	0.005 (−0.023, 0.034)	0.006 (−0.022, 0.034)	0.004 (−0.024, 0.032)
Tertile 3	−0.018 (−0.049, 0.014)	−0.011 (−0.039, 0.017)	−0.009 (−0.038, 0.019)	−0.012 (−0.040, 0.017)

Continued

Item	Linear regression β coefficients			
	Unadjusted	Model 1	Model 2	Model 3
Ln-MAP				
Ln-cortisol				
Continuous	0.001 (−0.003, 0.005)	0.001 (−0.003, 0.005)	0.001 (−0.003, 0.005)	0.001 (−0.003, 0.005)
Tertile 1	Referent	Referent	Referent	Referent
Tertile 2	0.007 (−0.011, 0.024)	0.006 (−0.011, 0.024)	0.006 (−0.011, 0.023)	0.011 (−0.005, 0.026)
Tertile 3	0.027 (0.010, 0.044)	0.026 (0.009, 0.043)	0.025 (0.008, 0.042)	0.030 (0.014, 0.046)
Ln-deoxycortisol				
Continuous	0.024 (0.015, 0.033)	0.024 (0.015, 0.033)	0.024 (0.014, 0.033)	0.021 (0.012, 0.029)
Tertile 1	Referent	Referent	Referent	Referent
Tertile 2	0.014 (−0.002, 0.031)	0.015 (−0.002, 0.032)	0.015 (−0.002, 0.032)	0.009 (−0.007, 0.024)
Tertile 3	0.043 (0.026, 0.060)	0.043 (0.026, 0.060)	0.042 (0.025, 0.059)	0.037 (0.021, 0.052)
Ln-cortisone				
Continuous	0.001 (−0.008, 0.010)	0.001 (−0.008, 0.010)	< 0.001 (−0.008, 0.009)	−0.001 (−0.009, 0.007)
Tertile 1	Referent	Referent	Referent	Referent
Tertile 2	0.007 (−0.010, 0.024)	0.009 (−0.008, 0.026)	0.008 (−0.009, 0.025)	0.004 (−0.012, 0.020)
Tertile 3	0.011 (−0.006, 0.028)	0.012 (−0.005, 0.029)	0.011 (−0.006, 0.028)	0.006 (−0.010, 0.021)
Ln-MBP				
Ln-cortisol				
Continuous	0.001 (−0.003,0.005)	0.002 (−0.002, 0.006)	0.001 (−0.003, 0.006)	0.001 (−0.003, 0.005)
Tertile 1	Referent	Referent	Referent	Referent
Tertile 2	0.008 (−0.009, 0.026)	0.007 (−0.010, 0.024)	0.007 (−0.010, 0.024)	0.011 (−0.005, 0.027)
Tertile 3	0.028 (0.011, 0.046)	0.027 (0.010, 0.044)	0.026 (0.009, 0.043)	0.031 (0.015, 0.047)
Ln-deoxycortisol				
Continuous	0.025 (0.015, 0.034)	0.024 (0.015, 0.033)	0.024 (0.015, 0.033)	0.021 (0.013, 0.030)
Tertile 1	Referent	Referent	Referent	Referent
Tertile 2	0.015 (−0.002, 0.032)	0.015 (−0.002, 0.032)	0.015 (−0.002, 0.031)	0.009 (−0.006, 0.024)
Tertile 3	0.044 (0.027, 0061)	0.043 (0.026, 0.060)	0.042 (0.025, 0.059)	0.037 (0.021, 0.053)
Ln-cortisone				
Continuous	< 0.001 (−0.009, 0.009)	< 0.001 (−0.008, 0.009)	< 0.001 (−0.009, 0.009)	−0.002 (−0.010, 0.007)
Tertile 1	Referent	Referent	Referent	Referent
Tertile 2	0.006 (−0.011, 0.023)	0.009 (−0.008, 0.026)	0.008 (−0.009, 0.025)	0.004 (−0.012, 0.020)
Tertile 3	0.009 (−0.009, 0.026)	0.010 (−0.007, 0.027)	0.010 (−0.007, 0.027)	0.004 (−0.012, 0.020)

Continued

Item	Linear regression β coefficients			
	Unadjusted	Model 1	Model 2	Model 3
Ln-MPAP				
Ln-cortisol				
Continuous	0.002 (−0.003, 0.006)	0.002 (−0.002, 0.006)	0.002 (−0.002, 0.006)	0.001 (−0.003, 0.005)
Tertile 1	Referent	Referent	Referent	Referent
Tertile 2	0.011 (−0.007, 0.029)	0.009 (−0.009, 0.026)	0.009 (−0.009, 0.026)	0.012 (−0.004, 0.029)
Tertile 3	0.030 (0.013, 0.048)	0.029 (0.011, 0.046)	0.027 (0.010, 0.045)	0.032 (0.016, 0.049)
Ln-deoxycortisol				
Continuous	0.025 (0.016, 0.035)	0.024 (0.015, 0.034)	0.024 (0.015, 0.033)	0.022 (0.013, 0.030)
Tertile 1	Referent	Referent	Referent	Referent
Tertile 2	0.016 (−0.001, 0.033)	0.015 (−0.002, 0.032)	0.015 (−0.002, 0.032)	0.009 (−0.007, 0.025)
Tertile 3	0.045 (0.027, 0.063)	0.043 (0.025, 0.060)	0.042 (0.025, 0.059)	0.037 (0.021, 0.054)
Ln-cortisone				
Continuous	−0.001 (−0.010, 0.009)	< 0.001 (−0.009, 0.009)	< 0.001 (−0.009, 0.008)	−0.002 (−0.010, 0.006)
Tertile 1	Referent	Referent	Referent	Referent
Tertile 2	0.005 (−0.013, 0.022)	0.009 (−0.009, 0.026)	0.008 (−0.010, 0.025)	0.004 (−0.012, 0.020)
Tertile 3	0.006 (−0.012, 0.023)	0.008 (−0.010, 0.025)	0.008 (−0.010, 0.025)	0.002 (−0.014, 0.019)

Note. Model 1 was adjusted by age, sex, education, marital status, and per capita monthly income. Model 2 was further adjusted by drinking and smoking status, based on model 1. Model 3 was further adjusted by BMI and physical activity, based on model 2. SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; MAP: mean arterial pressure; MBP: mean blood pressure; MPAM: mean proportional arterial pressure. Ln-: natural log-transformed.