

ORIGINAL RESEARCH

# Diurnal Urinary Aldosterone Excretion and Potassium Intake During Pregnancy Are Associated With High Normal Blood Pressure in Early Childhood

Hajir Al-Jorani , MD; Richard Christian Jensen , MD, PhD; Tina K. Jensen , MD, PhD; Henrik Thybo Christesen , MD, PhD, DMSci; Jan Stener Jørgensen , MD, PhD, DMSci; Lucas Bacmeister , MD, PhD; Ralf Dechend , MD, PhD, DMSci; Dorte Glintborg , MD, PhD, DMSci; Boye L. Jensen , MD, PhD, DMSci; Marianne S. Andersen , MD, PhD, DMSci

**BACKGROUND:** Offspring blood pressure (OBP) may be programmed during pregnancy. Accordingly, maternal third-trimester 24-hour urine aldosterone levels are associated with fetoplacental trophic effects. Furthermore, high potassium and low sodium intakes are generally recommended in adults with normal renal function. We hypothesized that maternal 24-hour urine aldosterone levels were positively associated with OBP, and maternal intake of potassium and sodium may influence the association. The study aimed to investigate associations between maternal third-trimester 24-hour urine aldosterone, potassium and sodium intake, and OBP.

**METHODS:** In the prospective OCC (Odense Child Cohort), 475 mother–child dyads had 24-hour urine aldosterone from gestational week 29 and OBP (systolic and diastolic), at ages 3 and 18 months and 3 and 5 years. Maternal potassium and sodium intakes were calculated from 24-hour urine potassium and urine sodium excretions.

**RESULTS:** Increased maternal 24-hour urine aldosterone associated with higher systolic blood pressure in offspring at ages 3 months ( $\beta=0.54$  mmHg [95% CI, 0.29; 0.79]) and 18 months ( $\beta=0.24$  mmHg [95% CI, 0.03; 0.44]). One thousand mg/d increase in maternal potassium intake was associated with an average increase in offspring systolic blood pressure of 0.68 mmHg (95% CI, 0.02–1.34) up to age 5 years (pooled), with significant associations only in girls ( $\beta=1.14$  mmHg [95% CI, 0.21–2.08]). No significant association was seen between maternal sodium intake and OBP.

**CONCLUSIONS:** Elevated maternal 24-hour urine aldosterone and higher dietary potassium intake were associated with higher OBP but within normal range in young children, and girls were more susceptible to maternal potassium intake.

**REGISTRATION:** URL: <https://clinicaltrials.gov>. Unique identifier: ID NCT02183558.

**Key Words:** fetal programming ■ maternal aldosterone ■ maternal potassium ■ maternal sodium ■ offspring blood pressure ■ pregnancy

Fetal exposure to aldosterone is largely unrestricted across placenta,<sup>1</sup> and maternal aldosterone is trophic for placenta<sup>2</sup> and offspring birth weight (BW).<sup>3,4</sup> Normal placenta development requires aldosterone in animal models,<sup>5,6</sup> and placenta size was below average in adrenalectomized ewes, but size

Correspondence to: Hajir Al-Jorani, MD, PhD-student, Department of Endocrinology, Odense University Hospital, Klovevænget 5, 5000 Odense C – Denmark, Email: [hajir.al-jorani@rsyd.dk](mailto:hajir.al-jorani@rsyd.dk)

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## CLINICAL PERSPECTIVE

### What Is New?

- This large longitudinal cohort study is the first to comprehensively investigate the association between maternal third-trimester diurnal urinary aldosterone excretion and potassium intake and offspring blood pressure; our findings indicate that higher maternal urine aldosterone excretion and potassium intake were associated with higher offspring blood pressure but within normal range, up to age 5 years; moreover, girls were more susceptible to maternal potassium intake.

### What Are the Clinical Implications?

- There is no published evidence regarding normal blood pressure in young children. Higher potassium intake is endorsed in adults to lower elevated blood pressure outside pregnancy.
- Our findings of significant links between higher maternal dietary potassium intake and 24-hour urine aldosterone excretion and higher offspring blood pressure, within normal range, in young children may suggest that high normal blood pressure may be advantageous in early childhood; this is based on the assumption that high maternal potassium intake has beneficial transgenerational effects. Moreover, girls may be more susceptible to this effect.

## Nonstandard Abbreviations and Acronyms

<b>BW</b>	birth weight
<b>OBP</b>	offspring blood pressure
<b>OCC</b>	Odense Child Cohort
<b>GW</b>	gestational weeks
<b>PIH</b>	pregnancy-induced hypertension

normalized during aldosterone substitution.<sup>5</sup> Moreover, deletion of an aldosterone synthase gene in mice (*CYP11B2*) was associated with an increased number of necrotic placentas, reduced litter size, and lower BW.<sup>6</sup> Aldosterone is a trophic factor in pregnancy, where 10 to 20 times elevated maternal aldosterone<sup>7</sup> has beneficial fetoplacental effects,<sup>2</sup> also indirectly via interaction with placenta growth factors, angiogenic placenta growth factor, and antiangiogenic soluble receptor fms-like tyrosine kinase-1.<sup>8</sup> Furthermore, higher maternal aldosterone levels were associated with lower blood pressure (BP) in pregnancy.<sup>2</sup> Physiological

increase in aldosterone during pregnancy appears crucial for sodium retention but less so for potassium;<sup>9</sup> sodium retention is necessary for plasma volume expansion, which must occur to support growth and development of placenta and fetus.<sup>10–12</sup> However, we previously showed that a maternal diet rich in sodium and poor in potassium was linked to higher maternal BP, lower aldosterone levels, and preeclampsia, and fetal outcomes were affected by lower BW and placenta weight.<sup>2</sup> Apart from aldosterone, it is known that renin, angiotensinogen, and angiotensin II are elevated in a healthy pregnancy and may influence future fetal cardiovascular health.<sup>13</sup> Furthermore, high sodium intake inhibits the renin–angiotensin–aldosterone system in pregnancy, corresponding to outside pregnancy.<sup>14</sup>

Higher potassium and lower sodium intakes are associated with lower BP in adolescents<sup>15</sup> and adults,<sup>16</sup> but there is no available data on any programming effect of maternal intake of potassium and sodium on offspring cardiovascular health including offspring blood pressure (OBP).

The third-trimester is considered a window of sensitivity for fetal exposure to endogenous and exogenous hormones<sup>17</sup>; the maturing effects of cortisol are well known,<sup>18</sup> but there are fewer data on aldosterone.<sup>13</sup> Diurnal urine aldosterone gives the best integrated estimate for aldosterone status compared with plasma aldosterone, as plasma aldosterone is influenced by circadian rhythm, physical activity, and postural changes.<sup>19</sup>

To our knowledge, the concentration of maternal aldosterone and intake of potassium and sodium in association with OBP has not been investigated previously. However, a prospective study in adolescents demonstrated a sexual dimorphic positive association between levels of aldosterone and BP, where a single serum aldosterone measured at age 17 years was predictive of higher future systolic (SBP) and diastolic BP (DBP) in women at age 27 years,<sup>20</sup> in men, cross-sectional data at age 17 years showed that serum aldosterone was associated significantly with higher SBP.<sup>20</sup>

We aimed to investigate the associations between maternal third-trimester 24-hour urine aldosterone, potassium, and sodium intakes and offspring SBP and DBP from age 3 months to 5 years. We hypothesized that maternal 24-hour urine aldosterone levels were positively associated with OBP, and maternal intake of potassium and sodium may influence the association; we also tested the hypothesis that the relation may be affected by offspring sex.

## METHODS

The raw data that support the findings of this study are available from the corresponding author on reasonable

request. The OCC study was conducted in compliance with the Helsinki Declaration II and approved by the Regional Research Ethics Committee for Southern Denmark (No. S-20090130) as well as the Danish Data Protection Agency (J. No 2008-58-0035). Written informed consent was obtained from all participating women, and all procedures adhered to institutional guidelines.

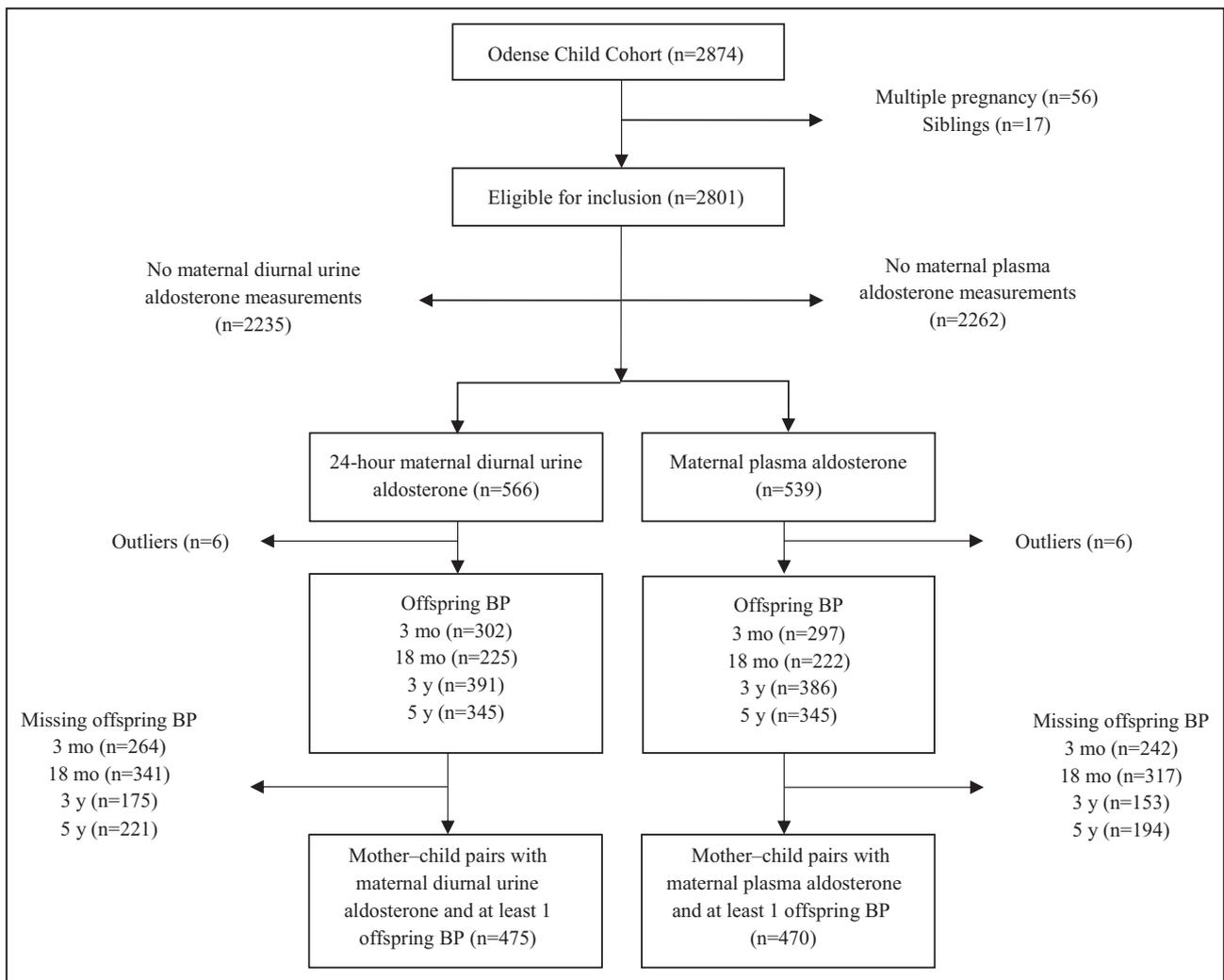
### Study Population

The present study is a substudy of the OCC (Odense Child Cohort), a longitudinal, unselected birth cohort study consisting of mothers and their children. Eligible pregnant women (<16 gestational weeks [GW]) who resided in the Municipality of Odense, Denmark, from January 2010 until December 2012, were invited to participate. Among the 2874 included women, 566 (20%) gave separate consent to donate fasting morning (7:30 AM to 10:10 AM) blood and 24-hour urine samples (GW 29) (Figure 1).

In this analysis, we excluded women with multiple pregnancies during the study period (n=56), and women with incomplete 24-hour urine samples (n=3; urine volume <500 mL/d or 24-hour urine creatinine excretion, <600 mg/d). Women with known hypertension, symptoms of preeclampsia, gestational hypertension defined as de novo BP >140/90 mmHg<sup>21</sup> (n=3), or confirmed gestational diabetes according to the Danish criteria (n=23) were also excluded.<sup>22</sup> The data from 6 outliers were excluded, as these observations were abnormally distant (>4 standardized residuals) from the majority of the data set.

### Laboratory Analysis

Twenty-four-hour urine and plasma aldosterone were measured with ELISA MS E-5200 (Labor Diagnostika Nord GmbH & CoKG, Nordhorn, Germany). Urine was diluted 1:50 with urine diluent (Labor Diagnostika) and incubated with 50 µL of aldosterone horseradish



**Figure 1. Flowchart of the study population in the Odense Child Cohort.** BP indicates blood pressure.

peroxidase conjugate for 1 hour.<sup>2</sup> A serial dilution was performed to secure accuracy. Between-assay coefficient of variation was 11.19% for urine aldosterone and 8.1% for plasma aldosterone analyses. According to the manufacturer, the ELISA has no cross-reactivity with progesterone and cortisol.

Concentrations of 24-hour urine potassium and urine sodium were analyzed with a flame photometer (EFUX 5057; Eppendorf, Hamburg, Germany). Potassium and sodium intakes estimated by surrogate measurements of 24-hour urine potassium and urine sodium excretions and 24-hour urine and plasmas aldosterone at GW 29.

## BP Measurements

Offspring SBP and DBP were measured by trained technicians at 3 and 18 months, and again at ages 3 and 5 years. At 3 months, OBP was recorded in a supine position, while at 18 months and 3 and 5 years, measurements were taken while the child was resting in a seated position. BP cuffs were placed to cover two-thirds of the upper left arm. OBP was measured twice on the left arm with an automatic Welch Allyn sphygmomanometer with a 60-second interval between measurements. Maternal BP was measured as part of routine clinical care by a general practitioner or midwife using an appropriately sized cuff. The measurements were recorded prospectively throughout pregnancy and later extracted through a retrospective review of medical charts.<sup>2,23,24</sup>

## Covariates

Information on maternal age, prepregnancy body mass index (BMI), parity (nulliparous versus parous), and smoking status (yes versus no) was collected through questionnaires and hospital records. Offspring sex was identified by clinical examination at birth. BW SD scores were calculated using the Scandinavian formula of Marsál et al.<sup>25</sup>

## Statistical Analyses

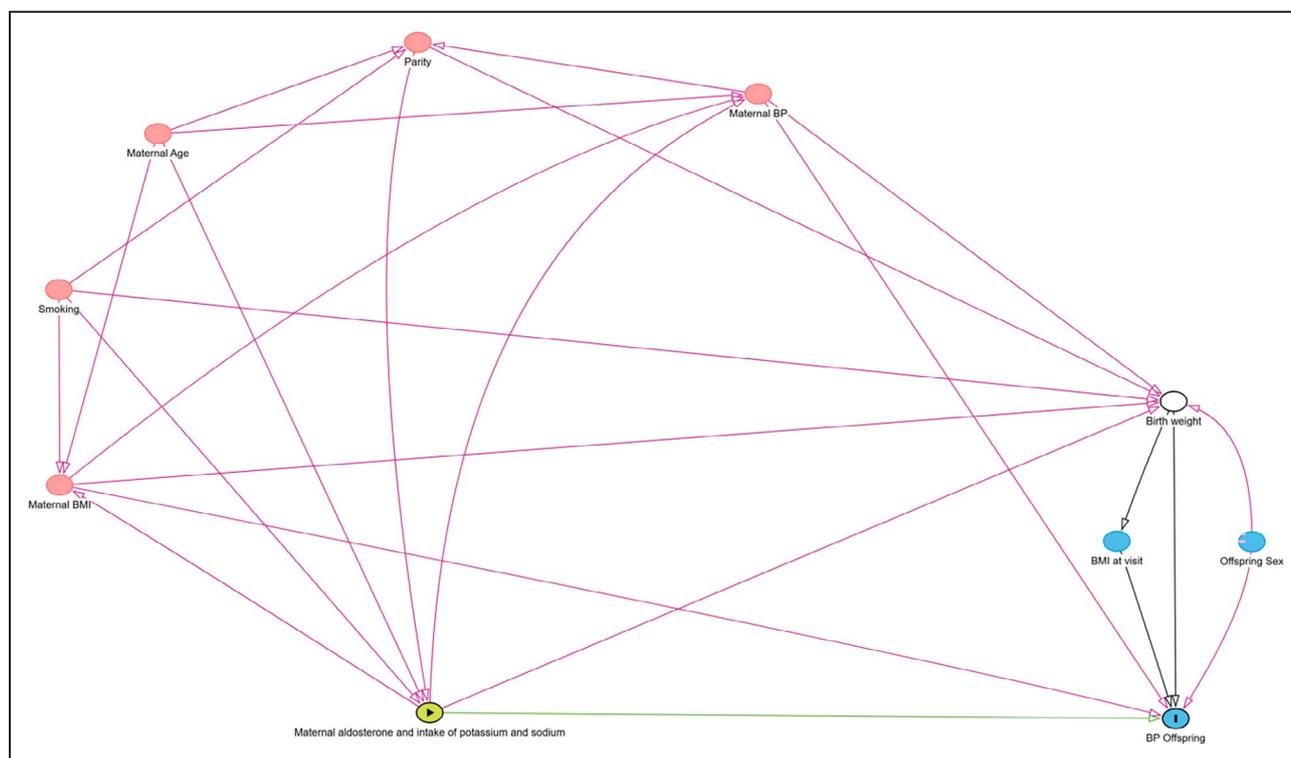
The distribution of data was assessed for normality through histograms and Q-Q plots. Normally distributed continuous variables were presented as mean±SD, nonnormally distributed continuous variables were presented as median and 90% range (5th to 95th percentiles), and categorical variables were shown as percentages. Comparisons of characteristics by offspring sex were performed by using the unpaired *t* test (normally distributed continuous variables) or Wilcoxon's rank-sum test (nonnormally distributed continuous variables) and the  $\chi^2$  test for categorical variables.

Random mixed-effects linear regression models were used for examining the associations between maternal 24-hour urine aldosterone, potassium, and

sodium intakes and OBP from age 3 months to 5 years. To account for the repeated OBP of the children, mother-child dyads were included as random effects. To investigate potential age-related differences in the associations, interaction terms between maternal exposure concentrations and study visit indicators (ages 3 and 18 months and 3 and 5 years) were incorporated into the random mixed-effects linear regression models. Pooled estimates, combining data from 3 and 18 months and from 3 and 5 years, were reported when the difference in slopes across visits was not significant ( $P>0.05$ ), in addition to estimates for visit-specific outcomes from the same models. The random mixed-effects linear regression models estimated the difference ( $\beta$  estimates) in OBP (pooled and visit-specific) per 1-unit increase in the maternal exposure concentration. The likelihood-ratio test was applied to test the interaction term between the exposure concentration and study visit on the association with OBP in all adjusted pooled random mixed-effects linear regression model.

The principles of directed acyclic graph were used to identify confounders when estimating assumptions of causal relations among variables, including exposure, outcome, and covariates.<sup>26</sup> In the directed acyclic graph (Figure 2), arrows represent the direction of causality from a potential cause to a possible effect. Maternal prepregnancy BMI was considered as a predictor for the OBP<sup>27</sup> and is positively associated with maternal aldosterone levels,<sup>27</sup> as well as potassium and sodium intakes.<sup>28</sup> Higher maternal BP has been associated with excessive sodium intake (>6 g/d).<sup>2</sup> Maternal age has been linked to higher aldosterone levels<sup>29</sup> and lower potassium concentrations.<sup>30</sup> Parity was positively associated with increased BP.<sup>31</sup> Smoking was associated with higher potassium levels,<sup>32</sup> and animal studies have demonstrated an association between smoking and lower aldosterone levels.<sup>33,34</sup> Additionally, offspring sex has been associated with sex differences in BP during childhood and adulthood.<sup>35</sup> An alternative directed acyclic graph, which includes potassium and sodium intakes as covariates, is illustrated in Figure S1.

In model 1, adjustments were made for maternal age, maternal prepregnancy BMI, parity, smoking status, offspring sex, and age at examination. In model 2, additional adjustments were included for maternal BP at GW 29 and offspring BMI at examination visit, as these variables were considered potential mediators in the association between maternal aldosterone levels and OBP (Figure 2). In the analyses regarding maternal potassium and sodium intake, 24-hour urine potassium, urine sodium, and urine sodium/potassium ratio, we also adjusted for BW in model 2, as BW could mediate the associations (Figure 2). Girls and boys differ in OBP<sup>35</sup>; effect modification by child sex in the associations between the respective exposure concentrations and OBP was evaluated by including an interaction



**Figure 2.** Directed acyclic graph illustrating causal pathway between maternal pregnancy aldosterone concentrations and intake of potassium and sodium (green node) and offspring BP (blue node with I). Red lines represent biasing paths. BMI indicates body mass index; and BP, blood pressure.

term (between exposure concentration and child sex) in all adjusted pooled regression models. These models were used to obtain sex-specific results. Interaction terms were tested with the likelihood-ratio test.

We performed a sensitivity analysis to examine the association between maternal 24-hour urine aldosterone, potassium intake, and OBP by excluding mothers who developed pregnancy-induced hypertension (PIH) between inclusion (<16 GW) and GW 28. Additionally, a separate sensitivity analysis including only mothers with PIH was performed. To assess the potential mediating effect of PIH, we conducted a separate analysis adjusting for PIH.

Model assumptions of all random mixed-effects linear regression models were validated through comprehensive residual analyses. Assumption of linearity between predictors and the outcome variables was visualized and validated graphically. Homoscedasticity and normality of residuals in models were graphically inspected. Multicollinearity was assessed formally using variance inflation factors. Two-sided  $P$  value <0.05 was considered as significant. The data were analyzed using STATA/IC version 16.0 (StataCorp, College Station, TX).

The study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.<sup>36</sup>

## RESULTS

Baseline maternal and offspring characteristics were presented in Table 1. A total of 475 mother–child pairs had complete maternal 24-hour urine sample and at least 1 OBP measurement. Among these, plasma aldosterone levels were available for 470 mothers. The women in the study cohort had a mean±SD age of 30±4.4 years, and a median BMI of 24.9 (5th–95th percentile 19.6–35.5) kg/m<sup>2</sup>. A majority of the included women were nulliparous (56%) and nonsmokers (96%). Mean±SD SBP and DBP were within normal range (119±11/74±8 mmHg). The average maternal concentrations of 24-hour urine aldosterone, plasma aldosterone, and potassium and sodium intakes are presented in Table 1.

Following study inclusion (<16 GW) and up to GW 28, 64 women developed PIH, which included pre-eclampsia (n=50) and gestational hypertension (n=14). Maternal characteristics were comparable when stratified by offspring sex (Table 1). There was no significant difference in 24-hour urine aldosterone, plasma aldosterone and 24-hour urine excretion of potassium and sodium between mothers carrying a girl and mothers carrying a boy, nor between mothers with normal BP or PIH (Table 1).

**Table 1. Maternal and Offspring Characteristics**

	All	Girls	Boys	P value
	N=475 (100%)	N=222 (47%)	N=253 (53%)	
Maternal characteristics				
Maternal age, y, mean±SD	30.0±(4.4)	29.9±(4.1)	29.9±(4.1)	0.50
Pregnancy BMI				
Median (5th–95th percentile)	24.9 (19.6–35.5)	24.3 (19.4–34.1)	25.1 (19.7–38.1)	0.14
Parity				
Nulliparous, %	56	55	57	
Parous, %	44	45	43	0.60
Smoking				
Yes, %	4	4	4	
No, %	96	96	96	0.68
Missing, %	0	0	0	
Systolic blood pressure at GW 29, mmHg				
Mean±SD	119±11	118±11	119±11	0.54
Missing, %	20	20	20	
Diastolic blood pressure at GW 29, mmHg				
Mean±SD	74±8	74±7	74±9	0.98
Missing, %	20	20	20	
Preeclampsia, %	11	10	12	0.50
Gestational hypertension, %	14	3	3	0.82
Sampling at GW 29				
24-h urine aldosterone, µg/d, mean±SD	12.4±3.3	12.2±3.2	12.5±3.3	0.33
Plasma aldosterone, pg/mL, mean±SD	157.0±39.8	154.8±40.4	159.0±39.2	0.25
Potassium intake, g/d, mean±SD	2.7±0.8	2.7±0.9	2.7±0.8	0.92
Sodium intake, g/d, mean±SD	8.4±2.9	8.3±2.8	8.4±2.9	0.81
24-h urine potassium, mmol/d, mean±SD	68.9±21.18	68.7±22.0	69.1±21.56	0.86
24-h urine sodium, mmol/d, mean±SD	143.5±50.2	141.9±48.1	144.9±52.1	0.47
24-h urine sodium/potassium ratio, mean±SD	2.2±1.0	2.2±0.8	2.2±1.1	0.81
Child characteristics				
Birth weight SD score				
Mean±SD	−0.04 (±1.00)	−0.06 (±0.96)	−0.03 (±1.05)	0.77
<−1%	18	18	17	
−1>1%	68	68	69	
>1%	14	14	14	
Age at 3-mo examination, mo				
Median (5th–95th percentile)	3.8 (2.7–5.5)	3.7 (2.7–5.6)	3.9 (2.7–5.3)	0.68
Missing, %	7	3	5	
Age at 18-mo examination, mo				
Median (5th–95th percentile)	18.9 (18.0–20.6)	18.8 (17.9–20.6)	18.9 (18.0–20.5)	0.83
Missing, %	11	10	11	
Age at 3-y examination, mo				
Median (5th–95th percentile)	36.1 (35.6–38.2)	36.1 (35.6–38.2)	36.1 (35.6–38.3)	0.68
Missing, %	12	11	13	
Age at 5-y examination, mo				
Median (5th–95th percentile)	60.1 (59.6–61.5)	60.1 (59.6–61.2)	60.1 (59.5–61.7)	0.15
Missing, %	24	20	28	
Offspring BMI at 3-mo examination				
Mean±SD	17.1±1.5	16.7±1.4	17.3±1.4	<0.001

(Continued)

**Table 1. Continued**

	All	Girls	Boys	P value
	N=475 (100%)	N=222 (47%)	N=253 (53%)	
Offspring BMI at 18-mo examination				
Mean±SD	16.6±1.2	16.5±1.2	16.7±1.1	0.03
Offspring BMI at 3-y examination				
Mean±SD	15.8±1.1	15.8±1.2	15.8±1.0	0.72
Offspring BMI at 5-y examination				
Mean±SD	15.4±1.2	15.5±1.2	15.3±1.2	0.18

P value, when comparing maternal and offspring characteristics between girls and boys using the *t* test (normally distributed variables) and Wilcoxon's rank-sum test (nonnormally distributed variables) for continuous variables, and the  $\chi^2$  test for categorical data. BMI indicates body mass index; and GW, gestational week.

Children were examined at ages 3 and 18 months and 3 and 5 years. At ages 3 and 18 months follow-up, there were 7% and 11% missing, respectively, and 12% and 24% missing at 3 and 5 years follow-up, respectively. The percentage of offspring exceeding +1 SD in estimated BW was 14%, while 18% of offspring had BW below -1SD.

As shown in [Table 2](#), 1  $\mu\text{g}/\text{day}$  increase in maternal 24-hour urine aldosterone was nonsignificantly associated with an average increase in offspring SBP by 0.14 mmHg (95% CI, -0.03 to 0.31; model 1) in the pooled study group (from age 3 months to 5 years). In this analysis, interaction terms between maternal 24-hour urine aldosterone and offspring visit indicated significant difference in the slopes from age 3 months to 5 years for OBP ( $P_{\text{int}}^{\dagger} < 0.01$ ) ([Table 2](#), models 1 and 2). At the respective visits for the whole study group, higher maternal 24-hour urine aldosterone was associated with significantly higher SBP at ages 3 months ( $\beta = 0.54$  mmHg [95% CI, 0.29–0.79]) and 18 months ( $\beta = 0.24$  mmHg [95% CI, 0.03–0.44]; [Table 2](#), model 1). In the crude associations between maternal third-trimester 24-hour urine aldosterone and offspring SBP, findings for girls were significantly different from estimates for boys ( $P_{\text{int}}^* = 0.01$ ; [Table 2](#)), but associations were attenuated after adjusting for confounders ( $P_{\text{int}}^* 0.60$ – $0.55$  for [Table 2](#), models 1 and 2). When stratifying according to offspring sex, higher maternal 24-hour urine aldosterone was nonsignificantly associated with increased SBP in girls and boys at ages 3 and 18 months and 3 years ([Table 2](#), model 1). No significant association was found between maternal 24-hour urine aldosterone and offspring DBP for pooled data or at any specific time points ([Table 2](#)). Additionally, 3 separate analyses were conducted: (1) adjusting for maternal potassium and sodium intakes, (2) adjusting for BW, and (3) adjusting for infants born small for gestational age. None of these adjustments substantially affected the positive significant associations between 24-hour urine aldosterone and offspring SBP up to age 5 years ([Tables S1 through S3](#)).

There were no significant associations between maternal plasma aldosterone during the third-trimester

and offspring SBP and DBP in the whole study group from age 3 months to 5 years (pooled) ([Table S4](#)).

In the pooled adjusted analyses, 1 g/d increase in maternal potassium intake was associated with a 0.68-mmHg increase in offspring SBP (95% CI: 0.02–1.34) from age 3 months to 5 years ([Table 3](#)). In this analysis, interaction terms between maternal potassium intake and offspring visit indicated a significant difference in the slopes from age 3 months to 5 years for offspring SBP ( $P_{\text{int}}^{\dagger} < 0.02$ ) ([Table 3](#), model 1). Higher maternal potassium intake was significantly associated with increased offspring SBP at age 3 months in the whole study group ( $\beta = 1.39$  mmHg [95% CI, 0.41–2.38]) but not at later time points ([Table 3](#)). In the interaction analyses between maternal potassium intake and offspring SBP, the estimates for girls were significantly different from those for boys ( $P_{\text{int}}^* = 0.01$ ; [Table 3](#), crude). However, this interaction was attenuated after adjusting for confounders ( $P_{\text{int}}^* 0.17$ – $0.33$  for [Table 3](#), models 1 and 2). For pooled data, 1 g/d increase in maternal potassium intake was significantly associated with an average increase in offspring SBP by 1.14 mmHg (95% CI, 0.21–2.08) in girls from age 3 months to 5 years ([Table 3](#), model 1). In visit-specific data stratified according to offspring sex, maternal potassium intake was associated with increased SBP in girls at ages 18 months ( $\beta = 2.68$  mmHg [95% CI, 0.84–4.52]) and 3 years ( $\beta = 1.69$  mmHg [95% CI, 0.24–3.14]; [Table 3](#), model 1).

Higher maternal 24-hour urine potassium was significantly associated with an average increase in offspring SBP in the whole study group, and in girls, from age 3 months to 5 years (pooled; [Table S2](#), model 1). In the pooled adjusted analyses including the whole study group, interaction terms between maternal 24-hour urine potassium and offspring visit indicated a significant difference in the slopes from age 3 months to 5 years for offspring SBP ( $P_{\text{int}}^{\dagger} = 0.02$ ), and findings for girls were significantly different from estimates for boys ( $P_{\text{int}}^* = 0.01$ ; [Table S5](#), crude) but were attenuated after adjusting for confounders ( $P_{\text{int}}^* 0.17$ – $0.33$  for [Table S5](#), models 1 and 2). At separate visits, increased

**Table 2. Average Difference of Offspring Blood Pressure at Ages 3 and 18 Months and 3 and 5 Years Pooled, and at Respective Visits for 1 mg/d Increase in Maternal 24-Hour Urinary Aldosterone Concentrations at GW 29**

	SBP $\beta$ (95% CI)			DBP $\beta$ (95% CI)			$P_{int}^*$	$P_{int}^\dagger$	$P_{int}^\ddagger$	$P_{int}^\S$			
	Total	Girls	Boys	Total	Girls	Boys							
Pooled													
Crude	475	222	253	0.14 (-0.02 to 0.31)	0.07 (-0.10 to 0.24)	0.19 (0.02 to 0.35)	0.01			0.01 (-0.14 to 0.13)	0.01 (-0.17 to 0.12)	0.01 (-0.14 to 0.15)	0.41
Model 1 <sup>†</sup>	473	221	252	0.14 (-0.03 to 0.31)	0.19 (-0.06 to 0.43)	0.11 (-0.13 to 0.32)	0.60	<0.01		-0.004 (-0.15 to 0.14)	0.02 (-0.19 to 0.23)	-0.02 (-0.22 to 0.17)	0.76
Model 2 <sup>‡</sup>	378	177	201	0.13 (-0.06 to 0.31)	0.19 (-0.08 to 0.46)	0.08 (-0.17 to 0.32)	0.55	<0.001		-0.04 (-0.19 to 0.11)	-0.01 (-0.23 to 0.22)	-0.07 (-0.27 to 0.14)	0.69
Respective visits													
3 mo													
Model 1 <sup>†</sup>	302	138	164	0.54 (0.29 to 0.79)	0.42 (-0.04 to 0.88)	0.33 (-0.6 to 0.71)				0.11 (-0.11 to 0.33)	0.12 (-0.31 to 0.53)	-0.09 (-0.43 to 0.26)	
Model 2 <sup>‡</sup>	243	114	129	0.47 (0.20 to 0.74)	0.48 (-0.01 to 0.96)	0.05 (-0.37 to 0.47)				0.01 (-0.22 to 0.25)	0.25 (-0.18 to 0.68)	-0.31 (-0.69 to 0.06)	
18 mo													
Model 1 <sup>†</sup>	225	102	123	0.24 (0.03; 0.44)	0.52 (-0.01; 1.06)	0.38 (-0.09; 0.85)				0.13 (-0.04; 0.31)	0.21 (-0.26; 0.69)	0.31 (-0.12; 0.72)	
Model 2 <sup>‡</sup>	185	83	102	0.19 (-0.03; 0.41)	0.47 (-0.11; 1.06)	0.43 (-0.07; 0.93)				0.07 (-0.11; 0.26)	-0.12 (-0.64; 0.41)	0.25 (-0.21; 0.71)	
3 y													
Model 1 <sup>†</sup>	391	194	201	0.02 (-0.16 to 0.21)	0.11 (-0.26 to 0.49)	-0.03 (-0.39 to 0.34)				-0.03 (-0.18 to 0.13)	-0.01 (-0.34 to 0.33)	-0.11 (-0.43 to 0.21)	
Model 2 <sup>‡</sup>	305	149	156	0.01 (-0.19 to 0.20)	0.10 (-0.31 to 0.52)	0.11 (-0.28 to 0.50)				-0.04 (-0.21 to 0.12)	-0.05 (-0.41 to 0.32)	-0.07 (-0.41 to 0.28)	
5 y													
Model 1 <sup>†</sup>	345	174	171	-0.15 (-0.41 to 0.09)	-0.06 (-0.46 to 0.33)	-0.26 (-0.64 to 0.12)				-0.16 (-0.37 to 0.06)	-0.12 (-0.47 to 0.23)	-0.11 (-0.44 to 0.24)	
Model 2 <sup>‡</sup>	271	137	134	-0.11 (-0.38 to 0.16)	-0.11 (-0.56 to 0.33)	-0.24 (-0.65 to 0.17)				-0.16 (-0.41 to 0.08)	-0.16 (-0.56 to 0.23)	-0.09 (-0.45 to 0.28)	

BMI indicates body mass index; DBP, diastolic blood pressure; GW, gestational week; and SBP, systolic blood pressure.

<sup>†</sup>Interaction between exposure and offspring sex (girls and boys), tested with the likelihood-ratio test.

<sup>‡</sup>Interaction between exposure and visit (ages 3 and 18 mo and 3 and 5 y), tested with the likelihood-ratio test.

<sup>§</sup>Mixed modeling 1: Adjusted for maternal age, maternal prepregnancy BMI, parity, smoking status, offspring sex, and age at examination visit.

<sup>¶</sup>Mixed modeling 2: Adjusted for maternal age, maternal prepregnancy BMI, parity, smoking status, offspring sex, age at examination visit, maternal blood pressure at GW 29 and offspring BMI at examination visit.

**Table 3. Average Difference of Offspring Blood Pressure at Ages 3 and 18 Months and 3 and 5 Years Pooled, and at Respective Visits for 1 Unit g/d Increase in Maternal Potassium Intake During GW 29**

	N Total	N Girls	N Boys	SBP $\beta$ (95% CI)			DBP $\beta$ (95% CI)			$P_{int}^*$	$P_{int}^\dagger$
				Total	Girls	Boys	Total	Girls	Boys		
Pooled											
Crude	475	222	253	0.68 (0.03 to 1.33)	0.44 (-0.23 to 1.11)	0.92 (0.25 to 1.61)	0.01	0.06 (-0.48 to 0.61)	0.01 (-0.56 to 0.57)	0.12 (-0.44 to 0.69)	0.47
Model 1 <sup>†</sup>	473	221	252	0.68 (0.02 to 1.34)	1.14 (0.21 to 2.08)	0.22 (-0.71 to 1.14)	0.17	0.08 (-0.48 to 0.64)	0.26 (-0.54 to 1.05)	-0.09 (-0.88 to 0.71)	0.54
Model 2 <sup>‡</sup>	378	177	201	0.64 (-0.11 to 1.41)	0.99 (-0.03 to 2.00)	0.25 (-0.83 to 1.34)	0.33	-0.13 (-0.76 to 0.50)	-0.06 (-0.91 to 0.78)	-0.20 (-1.11 to 0.70)	0.82
Respective visits											
3 mo											
Model 1 <sup>†</sup>	302	138	164	1.39 (0.41 to 2.38)	0.76 (-0.98 to 2.50)	-0.03 (-1.58 to 1.53)		0.002 (-0.87 to 0.88)	-0.42 (-1.98 to 1.13)	-0.30 (-1.69 to 1.08)	
Model 2 <sup>‡</sup>	243	114	129	1.03 (-0.09 to 2.14)	0.75 (-1.05 to 2.56)	-1.19 (-3.02 to 0.64)		-0.79 (-1.77 to 0.19)	-0.97 (-2.58 to 0.63)	-1.32 (-2.95 to 0.31)	
18 mo											
Model 1 <sup>†</sup>	225	102	123	0.65 (-0.15 to 1.45)	2.68 (0.84 to 4.52)	0.61 (-1.16 to 2.37)		0.39 (-0.30 to 1.09)	0.69 (-0.95 to 2.33)	0.33 (-1.24 to 1.91)	
Model 2 <sup>‡</sup>	185	83	102	0.48 (-0.41 to 1.38)	2.36 (0.36 to 4.37)	1.24 (-0.79 to 3.26)		-0.02 (-0.78 to 0.75)	-0.35 (-2.14 to 1.44)	0.07 (-1.74 to 1.88)	
3 y											
Model 1 <sup>†</sup>	391	194	201	0.33 (-0.39 to 1.05)	1.69 (0.24 to 3.14)	0.25 (-1.31 to 1.81)		0.09 (-0.53 to 0.71)	0.79 (-0.51 to 2.08)	-0.17 (-1.56 to 1.21)	
Model 2 <sup>‡</sup>	305	149	156	0.33 (-0.49 to 1.15)	1.31 (-0.27 to 2.88)	0.62 (-1.22 to 2.45)		0.05 (-0.64 to 0.74)	0.82 (-0.57 to 2.22)	0.17 (-1.46 to 1.80)	
5 y											
Model 1 <sup>†</sup>	345	174	171	0.38 (-0.62 to 1.38)	-0.12 (-1.61 to 1.37)	-0.14 (-1.76 to 1.47)		-0.08 (-0.96 to 0.81)	-0.17 (-1.49 to 1.15)	-0.21 (-1.64 to 1.24)	
Model 2 <sup>‡</sup>	271	137	134	0.75 (-0.38 to 1.87)	-0.05 (-1.67 to 1.57)	0.43 (-1.41 to 2.28)		0.17 (-0.82 to 1.15)	-0.25 (-1.71 to 1.19)	0.14 (-1.50; 1.79)	

BMI indicates body mass index; DBP, diastolic blood pressure; GW, gestational week; and SBP, systolic blood pressure.

<sup>†</sup>Interaction between exposure and offspring sex (girls and boys), tested with the likelihood-ratio test.

<sup>‡</sup>Interaction between exposure and visit (ages 3 and 18 mo and 3 and 5 y), tested with the likelihood-ratio test.

<sup>§</sup>Mixed modeling 1: Adjusted for maternal age, maternal prepregnancy BMI, parity, smoking status, offspring sex and age at examination visit.

<sup>¶</sup>Mixed modeling 2: Adjusted for maternal age, maternal prepregnancy BMI, parity, smoking status, offspring sex, age at examination visit, maternal blood pressure at gestational week 29, offspring BMI at examination visit and birth weight SD score.

concentrations of maternal 24-hour urine potassium were significantly associated with higher SBP at age 3 months in the whole study group and at ages 18 months and 3 years for girls (Table S5, model 1).

No significant association was found between maternal sodium intake, maternal 24-hour urine sodium and average change in OBP in the whole study group from age 3 months to 5 years (pooled; Tables S6 and S7). In the pooled adjusted analyses including the whole study group, interaction terms between maternal sodium intake/24-hour urine sodium and offspring visit indicated significant difference in the slopes from age 3 months to 5 years for offspring SBP ( $P_{\text{int}}^{\dagger}=0.02$ ). There were no significant associations between maternal sodium intake/24-hour urine sodium and offspring SBP (Tables S6 and S7, model 1). Higher maternal sodium intake/24-hour urine sodium was associated with lower DBP only at age 3 months in the whole study group (Tables S6 and S7, model 1), but interaction terms between maternal sodium intake/24-hour urine sodium and offspring visit were nonsignificantly different in the slopes from age 3 months to 5 years for offspring ( $P_{\text{int}}^{\dagger}=0.17$ ; Tables S6 and S7, model 1).

Maternal 24-hour urine sodium/potassium ratio during the third-trimester was not significantly associated with offspring SBP and DBP (Table S8).

Excluding mothers with PIH from association analyses had no substantial influence on the positive associations between maternal 24-hour urine aldosterone, potassium intake, and OBP (Tables S9 and S12). Furthermore, a sensitivity analysis including only mothers with PIH showed no substantial changes in the associations between maternal 24-hour urine aldosterone, potassium intake, and OBP (Tables S10 and S13). Finally, adjustment for PIH had no effect on the associations between maternal 24-hour urine aldosterone, potassium intake, and OBP (Tables S11 and S14).

## DISCUSSION

In this longitudinal study, higher maternal third-trimester 24-hour urine aldosterone was associated with higher offspring SBP but within normal range at ages 3 and 18 months in 475 healthy mother–child dyads. Furthermore, higher maternal potassium intake was associated with an average increase in offspring SBP but within normal range up to 5 years, with significant findings in girls. We observed no association between maternal sodium intake and OBP.

To our knowledge, this is the first clinical study on maternal aldosterone and OBP. However, preclinical studies suggested that the renin–angiotensin–aldosterone system is required for fetal programming of renal function, as a suppressed renin–angiotensin–aldosterone

system resulted in impaired kidney development and lower nephron number.<sup>37,38</sup> A recent review by Falkner et al<sup>13</sup> emphasized the importance of prenatal environment and OBP. However, there are no robust data on the ideal OBP considering future risk of cardiovascular disease. Girls and boys have similar BP until puberty, but after puberty boys tend to develop higher BP compared with girls.<sup>13,39</sup> Our finding of a significant positive association between maternal potassium intake and OBP in girls up to age 5 years, along with the absence of an association with the 24-hour urine sodium/potassium ratio is surprising, as it is well-known that higher potassium intake is associated with lower BP in adolescents<sup>15</sup> and adults.<sup>16</sup> Our findings suggest that higher potassium intake during pregnancy may be beneficial, aligning with the recent European Society of Hypertension guideline recommending higher potassium intake for managing arterial hypertension.<sup>40</sup> However, the risk or benefit of higher OBP but within normal range in young children is unknown.<sup>13</sup> We observed sexual dimorphism concerning higher OBP susceptibility to maternal potassium intake in girls, whereas the aspect of offspring sex was less obvious regarding maternal aldosterone. We previously observed sexual dimorphism in OBP susceptibility to cortisol exposure, as boys had slightly lower OBP when exposed to higher maternal cortisol in utero<sup>41</sup>; cortisol is well recognized as a major factor in fetal maturation including the cardiovascular system.<sup>42</sup> In line with our data, Hu et al<sup>43</sup> examined the potential programming effect of fetal maturation on OBP. They used DNA methylation as a biomarker for maturation, and the authors<sup>43</sup> reported that increased prenatal maturation was associated with lower OBP in boys up to age 15 years.

The demonstrated temporal nature of early visit-specific significant associations between maternal aldosterone and OBP at ages 3 and 18 months may reflect that the impact of maternal aldosterone during pregnancy attenuates over time, suggesting that other elements may also affect OBP, such as intrinsic factors of the child but also extrinsic factors like pre- and postnatal environmental determinants, including maternal progesterone levels. The placenta produces large amounts of progesterone, which is a substrate for maternal aldosterone production in zona glomerulosa of the adrenal gland.<sup>44</sup> Of note, in contrast to aldosterone, progesterone is a partial mineralocorticoid receptor antagonist.<sup>45</sup> During pregnancy, aldosterone and progesterone correlate significantly, and the effects of progesterone on the renin–angiotensin system are more pronounced than aldosterone.<sup>44,46</sup> The known high levels of progesterone during the third-trimester may theoretically influence the observed positive association between aldosterone and OBP, as well as the lack of association between sodium and OBP.

The main strengths of this study lie in the high number of mother–child dyads enrolled, and we have used the recommended gold-standard 24-hour maternal urine collections during the third-trimester to assess maternal aldosterone, potassium, and sodium intakes. The prospective OBP measurements were standardized by measuring BP twice on the left arm, positioned at heart level in a seated position, following a brief rest, using the same sphygmomanometer. Despite OBP was not measured 3 times as recommended, we had a consistent approach with the same device mastered by the same technician. There are few missing data at the respective visits up to age 3 years and reasonably low up to age 5 years. Regular quality control checks were conducted for both data collection and the sphygmomanometer. Furthermore, there was no loss to follow-up within the study population, since none of the participants withdrew their informed consent, and the participants were allowed to skip an examination visit without being considered as lost to follow-up. Potential confounding effects of maternal age, prepregnancy BMI, parity, smoking status, BP and offspring age, BMI, and BW were addressed by adjustment of analyses. We conducted several sensitivity analyses considering PIH. We adjusted for 24-hour urine aldosterone, potassium, and sodium intake, and infants born small for gestational age.

There are some limitations to be noted. Despite 24-hour urinary excretion is considered the gold standard for estimation of potassium and sodium intakes,<sup>16,47</sup> improper or noncompliant collection can under- or overestimate excretion. To minimize this potential risk, we excluded urine volume <500 mL/d or 24-hour urine creatinine excretion <600 mg/d. We acknowledge the superiority of liquid chromatography–tandem mass spectrometry to assess aldosterone levels; however, according to the manufacturer, the present ELISA should not significantly cross-react with progesterone or cortisol and demonstrates valid performance in house regarding intra- and interassay variation. The participants were healthy pregnant women, and included women were almost all of White descent residing in the Municipality of Odense; hence, racial differences can influence the OBP differently,<sup>48</sup> and a defined location can introduce selection bias.

## CONCLUSIONS

Maternal third-trimester 24-hour urine aldosterone and potassium intake were positively associated with higher offspring SBP up to age 5 years, with higher susceptibility to maternal potassium intake in girls.

Our finding of higher normal-range OBP in young children exposed to higher maternal aldosterone or more maternal potassium intake in toddlers may

suggest, that higher OBP, but within normal range, is not an adversity. The increased susceptibility to maternal potassium in girls also adds to this suggestion, as girls tend to have lower BP compared with boys after puberty. However, more studies are needed to confirm these findings, such as the planned follow-up in OCC including BP.

## ARTICLE INFORMATION

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### Affiliations

Department of Endocrinology, Odense University Hospital, Odense, Denmark (H.A., R.C.J., D.G., M.S.A.); Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark (H.A., H.T.C.); Department of Clinical Pharmacology, Pharmacy and Environmental Medicine, University of Southern Denmark, Odense, Denmark (R.C.J., T.K.J.); Odense Child Cohort, Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense, Denmark (T.K.J., H.T.C., J.S.J.); Clinic for Cardiology and Angiology, University Heart Center Freiburg–Bad Krozingen, Medical Center–University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany (L.B.); Experimental and Clinical Research Center, a Cooperation Between the Max-Delbrück-Center for Molecular Medicine in the Helmholtz Association and the Charité–Universitätsmedizin Berlin, Berlin, Germany (R.D.); HELIOS Clinic Berlin-Buch, Department of Cardiology and Nephrology, Berlin, Germany (R.D.); and Institute for Molecular Medicine, University of Southern Denmark, Odense, Denmark (B.L.J.).

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### Disclosures

None.

### Supplemental Material

Tables S1–S16  
Figure S1

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