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Correlation of Urinary Excretion of Sodium  
With Severity of Sleep-Disordered Breathing in Children:  
A Preliminary Study

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**Key words:** blood pressure, brain natriuretic peptide, natriuresis, obstructive sleep apnea, snoring

## Abstract

**Background:** Nocturnal urinary sodium excretion is related to blood pressure (BP) levels. Elevated BP and increased nocturnal natriuresis have been demonstrated in adults with sleep apnea. Although evidence indicates increased BP in children with obstructive sleep-disordered breathing (SDB), it is unknown whether these children have also enhanced urinary sodium excretion.

**Objective:** To evaluate the effects of SDB and morning BP on urinary sodium excretion.

**Methods:** Consecutive children with snoring (n=95) underwent polysomnography and morning BP measurement. Fractional excretion of sodium ( $FE_{Na}$ ) was the primary outcome measure and was calculated using sodium and creatinine concentrations in early morning serum and urine specimens.

**Results:** Subjects with moderate-to-severe SDB had similar log-transformed  $FE_{Na}$  to that of children with mild SDB and higher than children with primary snoring:  $-0.13 \pm 0.53$  vs.  $-0.28 \pm 0.41$  vs.  $-0.61 \pm 0.65$  ( $p=0.657$  and  $p=0.003$ ). Obstructive apnea-hypopnea index was significantly related to  $FE_{Na}$  after adjustment for age, gender and body mass index z-score ( $p=0.002$ ). Children with moderate-to-severe SDB had similar systolic BP z-scores to those of subjects with mild SDB and higher than participants with primary snoring:  $0.7 \pm 1.2$  vs.  $0.1 \pm 1.0$  vs.  $-0.02 \pm 1.0$  ( $p=0.074$  and  $p=0.046$ ). In addition, participants with diastolic BP z-scores in the upper quartile of measured values had higher  $FE_{Na}$  than subjects with z-scores in the lower quartiles:  $-0.08 \pm 0.39$  vs.  $-0.41 \pm 0.57$  ( $p=0.007$ ).

**Conclusions:** Morning natriuresis is related to severity of SDB in children and this association may be mediated in part by elevated BP. (249 words)

## Introduction

Obstructive sleep apnea-hypopnea is an established risk factor for cardiovascular disease in adults.<sup>1</sup> Elevated blood pressure (BP) and increased BP variability are some of the mechanisms that may contribute to cardiovascular morbidity.<sup>1-4</sup> Obstructive events during sleep are accompanied by episodically increased sympathetic output, intermittent peripheral vasoconstriction and repeated BP surges.<sup>5</sup> The baroreflex system, which should regularly smooth these BP fluctuations, has reduced sensitivity in sleep apneic adults.<sup>4</sup>

Renal excretion of sodium and water is an additional protective mechanism against elevated BP.<sup>6</sup> The rate of nocturnal natriuresis in healthy adults and children is positively associated with BP levels, a phenomenon described by the term “pressure natriuresis”.<sup>7,8</sup> Indeed, increased nocturnal diuresis and natriuresis have been reported in adults with obstructive sleep apnea-hypopnea compared to healthy controls.<sup>9-11</sup> Renal sodium excretion correlates with diastolic BP levels and diminishes after treatment of sleep apnea with nasal continuous positive airway pressure (nCPAP).<sup>9-11</sup> Hence, it has been proposed that increased BP in adults with sleep apnea may be responsible for the enhanced nocturnal natriuresis in these patients.<sup>10</sup>

Although recent evidence suggests that similar to adults, children with obstructive sleep-disordered breathing (SDB) have high levels of sympathetic activity, increased BP levels and BP variability and reduced sensitivity of the baroreflex system,<sup>12-16</sup> no pediatric studies have explored the potential relationship between severity of intermittent upper airway obstruction during sleep and natriuresis. Thus, in the current investigation

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3 it was hypothesized that there is a positive association of urine excretion of sodium with  
4 severity of SDB.  
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## 7 8 Patients and Methods 9

### 10 11 **Participants and clinical evaluation** 12

13 The study protocol was approved by the Larissa University Hospital Ethics  
14 Committee and parents of participants provided informed consent. Consecutive children  
15 with snoring (> 3 nights/week) for the last six months who were referred to the Sleep  
16 Disorders Laboratory for polysomnography were recruited in the study. *Exclusion*  
17 *criteria* for participation were: i) symptoms of respiratory tract infection or acute  
18 gastroenteritis; ii) history of renal disease or use of diuretics or antihypertensive  
19 medications; and iii) history of cardiovascular, neuromuscular or genetic disorders.  
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22 All subjects underwent physical examination. Body mass index (BMI) and BMI  
23 z-score were calculated.<sup>17</sup> Obesity was defined as BMI z-score > 1.645.<sup>17</sup> Participants  
24 voided in the evening prior to polysomnography and none of them had urine loss or  
25 voided overnight. Upon morning arousal from sleep and after the child had been sitting  
26 quietly for about 5 minutes, BP was measured three times using the right arm and a cuff  
27 of appropriate size (Dinamap Pro 100; Criticon; Tampa, FL, USA). To adjust for the  
28 effects of age, gender and height, BP z-scores were determined.<sup>18</sup>  
29

30 Shortly after BP measurement and without having drunk any water, children were  
31 instructed to empty their bladder in a container and venipuncture was also performed.  
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33 Urine and venous blood samples were collected and processed immediately in the Central  
34 Biochemistry Laboratory. Serum and urine sodium and creatinine concentrations were  
35 measured using standard laboratory methods.  
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## Polysomnography

Overnight polysomnography in a single night was performed under the supervision of trained personnel.<sup>19</sup> The following parameters were recorded: electroencephalogram (C3/A2, C4/A1, O1/A2); right and left oculogram; submental and tibial electromyogram; body position; electrocardiogram; thoracic and abdominal wall motion; oronasal airflow; and oxygen saturation of hemoglobin.

Obstructive apnea was defined as the presence of chest/abdominal wall motion in the absence of airflow for at least two breaths in duration.<sup>20</sup> Hypopnea was: i) a reduction in the airflow signal amplitude of at least 50% compared to baseline; ii) in the presence of chest/abdominal wall motion; and iii) associated with oxygen desaturation of hemoglobin equal to or greater than 4% or with an arousal. Obstructive apnea-hypopnea index (OAHI) was equal to the number of obstructive and mixed apneas (apneas with both central and obstructive components) and hypopneas per hour of sleep.

## Primary outcome measure

Fractional urinary excretion of sodium ( $FE_{Na}$ ) was the primary outcome measure.  $FE_{Na}$  was calculated as:

$$FE_{Na} = \frac{\text{(urine sodium concentration X serum creatinine concentration)}}{\text{(urine creatinine concentration X serum sodium concentration)}}.$$

All concentrations were measured in early morning urine and serum specimens, and were expressed in mg/dL.  $FE_{Na}$  values were log-transformed (natural logarithm) to approach a normal distribution.

## Data analysis

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3 Severity of SDB was classified as: i) primary snoring (OAHl < 1 episode/hour);  
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5 ii) mild SDB (OAHl 1-5 episodes/h); and iii) moderate-to-severe SDB (OAHl > 5  
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7 episodes/hour). The three groups of children were compared in terms of age, gender,  
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9 obesity status, BP and polysomnography indices using  $\chi^2$  for categorical characteristics  
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11 and one-way analysis of variance (ANOVA), followed by post-hoc tests (Bonferroni), for  
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13 continuous variables.  
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18 BP measurements were categorized as those: i) in the upper quartile of values for  
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20 all participants; or ii) in the lower three quartiles of BP values for all participants.  
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22 Univariate logistic regression analysis was applied to assess the risk for having systolic or  
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24 diastolic BP in the upper quartile of measurements, in children with moderate-to-severe  
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26 or mild SDB compared to those with primary snoring (reference group).  
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30 Two general linear models (GLM) were tested to describe the potential effects on  
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32  $FE_{Na}$  of: i) severity of SDB; ii) systolic or diastolic BP; and iii) the interaction of SDB  
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34 severity with systolic or diastolic BP, after adjustment for age, gender and obesity (SPSS  
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36 version 16.0; SPSS, Chicago, IL). In order to assess whether natriuresis was increasing  
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38 linearly to severity of SDB, linear regression analysis was carried out using  $FE_{Na}$  as the  
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40 dependent variable and OAHl, age, gender and BMI z-score as independent variables.  
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## 47 Results

### 48 49 50 51 **Subjects' characteristics**

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53 A total of 95 children were recruited. Subjects' characteristics and  
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55 polysomnography findings are summarized in Table 1. There were no significant  
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3 differences in terms of age, female-to-male ratio, body mass index z-score or proportion  
4 of obese subjects between the three study groups. Children with moderate-to-severe SDB  
5 had similar morning systolic BP z-score to those of subjects with mild SDB and higher  
6 than subjects with primary snoring ( $p=0.074$  and  $p=0.046$ , respectively). A non-  
7 significant trend for higher diastolic BP with higher OAHl was noted (Table 1).  
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### 15 **Effects of SDB severity and BP on $FE_{Na}$**

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18 The cut-off value separating the upper quartile from the lower quartiles for  
19 systolic BP z-score was 0.78. The respective cut-off value for diastolic BP z-score was  
20 1.14. Children with moderate-to-severe SDB-but not with mild SDB-were at increased  
21 risk for having systolic BP in the upper quartile of measured values compared to subjects  
22 with primary snoring [odds ratios (95% confidence intervals): 4.12 (1.12-15.16);  $p =$   
23 0.033 and 1.33 (0.36-4.97);  $p=0.669$ ]. The association between severity of SDB and  
24 diastolic BP was not significant ( $p>0.05$ ).  
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35 SDB and diastolic BP had significant effects on  $FE_{Na}$  ( $p<0.05$  and  $p=0.007$ ,  
36 respectively), whereas systolic BP had no effect on  $FE_{Na}$  ( $p=0.715$ ) (Table 2 and Figure  
37 1). More specifically, subjects with moderate-to-severe SDB had similar log-transformed  
38  $FE_{Na}$  to that of children with mild SDB ( $p=0.657$ ) and higher than participants with  
39 primary snoring ( $p=0.003$ ). The interactions between SDB and systolic or diastolic BP  
40 were not significant ( $p=0.246$  and  $p=0.225$ , respectively). In linear regression analysis,  
41 OAHl was significantly associated with  $FE_{Na}$  after adjustment for age, gender and BMI z-  
42 score ( $p=0.002$ ) (Table 3).  
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## Discussion

In the present study, it was demonstrated that severity of SDB and morning BP in children have significant effect on renal excretion of sodium. Since sleep apnea in childhood has been related to elevated BP,<sup>15,21</sup> the association between SDB and natriuresis may be mediated in part by BP elevation.

According to traditional physiology teaching, systemic BP and blood volume are tightly regulated.<sup>6</sup> Any increase in systemic BP is buffered by activation of the baroreflex system (arterial, venous and cardiac baroreceptors, brainstem, sympathetic and parasympathetic neurons) that decreases heart rate, cardiac output and systemic vascular resistance. BP elevation promotes renal excretion of sodium and water both directly, by decreased renal tubular reabsorption of sodium (pressure natriuresis), and indirectly via reduced activity of the renin-angiotensin-aldosterone system.<sup>6-8</sup> Moreover, any blood volume expansion leads to atrial and ventricular distention, and release of ANP and BNP.<sup>22,23</sup> Natriuretic peptides inhibit renal tubular reabsorption of sodium and accentuate renal sodium filtration.<sup>24</sup>

Studies in adults and children with sleep apnea indicate that at the termination of obstructive events repetitive increases in systemic BP take place.<sup>25-27</sup> Although the baroreflex system should normally attenuate excessive BP variability, both adults and children with obstructive sleep apnea have reduced nighttime baroreflex gain and increased BP variability.<sup>4,16</sup> Therefore, reduction of the intravascular volume by renal excretion of sodium and water could be another defense mechanism to or biomarker of SDB-related BP fluctuations. Studies in sleep apneic adults have consistently shown increased nocturnal renal excretion of sodium that diminishes after treatment with

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3 nCPAP. <sup>9-11,28</sup> Results of the present investigation extend the observations from adults to  
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5 children with obstructive SDB. Of note, children with obstructive sleep apnea or primary  
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7 snoring have increased prevalence of nocturnal enuresis that frequently resolves after  
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9 adenotonsillectomy or treatment of adenoidal hypertrophy and SDB with nasal  
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11 corticosteroids. <sup>29-32</sup> Increased nocturnal natriuresis and diuresis could conceivably  
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13 contribute to nocturnal urine loss.  
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18 The exact pathophysiologic mechanisms underlying increased renal excretion of  
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20 sodium in sleep apnea have not been elucidated. Similarly to the current report, Gjorup et  
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22 al have found that diastolic BP and  $FE_{Na}$  in sleep apneic adults were positively correlated.  
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24 <sup>10</sup> Hence, the investigators proposed that this association may be due to pressure  
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26 natriuresis. Other studies have revealed increased levels of ANP and BNP that could  
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28 represent the pathophysiologic link between sleep apnea and nocturnal diuresis and  
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30 natriuresis. <sup>33,34</sup>  
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35 A few methodologic issues should be discussed. First, sodium and creatinine  
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37 concentrations in an early morning urine specimen were used to calculate  $FE_{Na}$ . Since the  
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39 recruited children have not voided overnight, we speculate that the calculated  $FE_{Na}$   
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41 reflects nocturnal urinary excretion of sodium. Second, hydration status and sodium  
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43 losses via the sweat glands and the gastrointestinal system and daily sodium intake may  
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45 influence  $FE_{Na}$ . Nevertheless, none of the study participants was dehydrated, was  
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47 exposed to high temperatures or had symptoms or signs of gastroenteritis. Third, recent  
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49 studies have documented significant associations between systolic or diastolic BP and  
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51 severity of SDB using ambulatory BP monitoring. <sup>15,21</sup> A trend for higher morning  
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53 diastolic BP with increasing OAH1 was identified in the present report and the absence of  
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3 statistical significance may be attributed to the fact that overnight BP monitoring was not  
4 performed in the current report. Finally, a healthy control group including children  
5 without SDB, who were of normal weight or overweight, was not included. The absence  
6 of such a group possibly limited the statistical comparisons and the delineation of an  
7 interaction effect between SDB, obesity and BP in natriuresis. Furthermore, the use of a  
8 control group with OAH1 < 1 episode/hour may be suboptimal, since even primary  
9 snoring could be associated with BP elevation.<sup>35</sup>

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20 In conclusion, severity of obstructive SDB and diastolic BP are positively  
21 associated with urinary excretion of sodium in childhood. Natriuresis may be a defense  
22 mechanism to systemic blood pressure fluctuations related to intermittent upper airway  
23 obstruction during sleep.  
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## REFERENCES

1. Somers VIKKI, White DP, Amin R, Abraham WT, Costa F, Culebras A, Daniels S, Floras JS, Hunt CE, Olson LJ, Pickering TG, Russell R, Woo M, Young T. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. *J Am Coll Cardiol* 2008;52:686-717.
2. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000;342:1378-1384.
3. Narkiewicz K, Montano N, Cogliati C, van de Borne PJ, Dyken ME, Somers VK. Altered cardiovascular variability in obstructive sleep apnea. *Circulation* 1998;98:1071-1077.
4. Bonsignore MR, Parati G, Insalaco G, Marrone O, Castiglioni P, Romano S, Di Rienzo M, Mancina G, Bonsignore G. Continuous positive airway pressure treatment improves baroreflex control of heart rate during sleep in severe obstructive sleep apnea syndrome. *Am J Respir Crit Care Med* 2002;166:279-286.
5. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest* 1995;96:1897-1904.

- 1  
2  
3 6. Vander A, Sherman J, Luciano D. Human Physiology: The mechanisms of body  
4 function. New York: Mc Graw Hill; 2001.  
5
- 6  
7 7. Lurbe E, Alvarez V, Liao Y, Torro I, Cremades B, Redon J, Cooper R. Obesity  
8 modifies the relationship between ambulatory blood pressure and natriuresis in  
9 children. *Blood Press Monit* 2000;5:275-280.  
10
- 11 8. Staessen JA, Birkenhager W, Bulpitt CJ, Fagard R, Fletcher AE, Lijnen P, Thijs  
12 L, Amery A. The relationship between blood pressure and sodium and potassium  
13 excretion during the day and at night. *J Hypertens* 1993;11:443-447.  
14
- 15 9. Zhang L, Huang X, Li X, Wu Q. Alterations in renal function in patients with  
16 obstructive sleep apnea syndrome and effects of continuous positive airway  
17 pressure. *Chin Med J (Engl)* 1997;110:915-918.  
18
- 19 10. Gjorup PH, Sadauskiene L, Wessels J, Nyvad O, Strunge B, Pedersen EB.  
20 Increased nocturnal sodium excretion in obstructive sleep apnoea. Relation to  
21 nocturnal change in diastolic blood pressure. *Scand J Clin Lab Invest* 2008;68:11-  
22 21.  
23
- 24 11. Rodenstein DO, D'Odemont JP, Pieters T, Aubert-Tulkens G. Diurnal and  
25 nocturnal diuresis and natriuresis in obstructive sleep apnea. Effects of nasal  
26 continuous positive airway pressure therapy. *Am Rev Respir Dis* 1992;145:1367-  
27 1371.  
28
- 29 12. Amin RS, Carroll JL, Jeffries JL, Grone C, Bean JA, Chini B, Bokulic R, Daniels  
30 SR. Twenty-four-hour ambulatory blood pressure in children with sleep-  
31 disordered breathing. *Am J Respir Crit Care Med* 2004;169:950-956.  
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13. Kaditis AG, Alexopoulos EI, Damani E, Hatzi F, Chaidas K, Kostopoulou T, Tzigeroglou A, Gourgoulialis K. Urine levels of catecholamines in Greek children with obstructive sleep-disordered breathing. *Pediatr Pulmonol* 2009;44:38-45.
  14. Snow AB, Khalyfa A, Serpero LD, Capdevila OS, Kim J, Buazza MO, Gozal D. Catecholamine alterations in pediatric obstructive sleep apnea: effect of obesity. *Pediatr Pulmonol* 2009;44:559-567.
  15. Li AM, Au CT, Sung RY, Ho C, Ng PC, Fok TF, Wing YK. Ambulatory blood pressure in children with obstructive sleep apnoea: a community based study. *Thorax* 2008;63:803-809.
  16. McConnell K, Somers VK, Kimball T, Daniels S, VanDyke R, Fenchel M, Cohen A, Willging P, Shamsuzzaman A, Amin R. Baroreflex gain in children with obstructive sleep apnea. *Am J Respir Crit Care Med* 2009;180:42-48.
  17. Ogden CL, Kuczmarski RJ, Flegal KM, Mei Z, Guo S, Wei R, Grummer-Strawn LM, Curtin LR, Roche AF, Johnson CL. Centers for Disease Control and Prevention 2000 growth charts for the United States: improvements to the 1977 National Center for Health Statistics version. *Pediatrics* 2002;109:45-60.
  18. National High Blood Pressure Education Program Working Group. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics* 2004;114:555-576.
  19. Li AM, Wing YK, Cheung A, Chan D, Ho C, Hui S, Fok TF. Is a 2-night polysomnographic study necessary in childhood sleep-related disordered breathing? *Chest* 2004;126:1467-1472.

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58  
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20. American Thoracic Society. Standards and indications for cardiopulmonary sleep studies in children. *Am J Respir Crit Care Med* 1996;153:866-878.
  21. Amin R, Somers VK, McConnell K, Willging P, Myer C, Sherman M, McPhail G, Morgenthal A, Fenchel M, Bean J, Kimball T, Daniels S. Activity-adjusted 24-hour ambulatory blood pressure and cardiac remodeling in children with sleep disordered breathing. *Hypertension* 2008;51:84-91.
  22. Dietz JR. Release of natriuretic factor from rat heart-lung preparation by atrial distension. *Am J Physiol* 1984;247:R1093-1096.
  23. Nakagawa O, Ogawa Y, Itoh H, Suga S, Komatsu Y, Kishimoto I, Nishino K, Yoshimasa T, Nakao K. Rapid transcriptional activation and early mRNA turnover of brain natriuretic peptide in cardiocyte hypertrophy. Evidence for brain natriuretic peptide as an "emergency" cardiac hormone against ventricular overload. *J Clin Invest* 1995;96:1280-1287.
  24. Yoshimura M, Yasue H, Morita E, Sakaino N, Jougasaki M, Kurose M, Mukoyama M, Saito Y, Nakao K, Imura H. Hemodynamic, renal, and hormonal responses to brain natriuretic peptide infusion in patients with congestive heart failure. *Circulation* 1991;84:1581-1588.
  25. Leuenberger U, Jacob E, Sweer L, Waravdekar N, Zwillich C, Sinoway L. Surges of muscle sympathetic nerve activity during obstructive apnea are linked to hypoxemia. *J Appl Physiol* 1995;79:581-588.
  26. Ringler J, Basner RC, Shannon R, Schwartzstein R, Manning H, Weinberger SE, Weiss JW. Hypoxemia alone does not explain blood pressure elevations after obstructive apneas. *J Appl Physiol* 1990;69:2143-2148.

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27. O'Driscoll DM, Foster AM, Ng ML, Yang JS, Bashir F, Nixon GM, Davey MJ, Anderson V, Walker AM, Trinder J, Horne RS. Acute cardiovascular changes with obstructive events in children with sleep disordered breathing. *Sleep* 2009;32:1265-1271.
28. Baruzzi A, Riva R, Cirignotta F, Zucconi M, Cappelli M, Lugaresi E. Atrial natriuretic peptide and catecholamines in obstructive sleep apnea syndrome. *Sleep* 1991;14:83-86.
29. Alexopoulos EI, Kostadima E, Pagonari I, Zintzaras E, Gourgoulianis K, Kaditis AG. Association between primary nocturnal enuresis and habitual snoring in children. *Urology* 2006;68:406-409.
30. Sans Capdevila O, Crabtree VM, Kheirandish-Gozal L, Gozal D. Increased morning brain natriuretic peptide levels in children with nocturnal enuresis and sleep-disordered breathing: a community-based study. *Pediatrics* 2008;121:e1208-1214.
31. Weider DJ, Sateia MJ, West RP. Nocturnal enuresis in children with upper airway obstruction. *Otolaryngol Head Neck Surg* 1991;105:427-432.
32. Alexopoulos EI, Kaditis AG, Kostadima E, Gourgoulianis K. Resolution of nocturnal enuresis in snoring children after treatment with nasal budesonide. *Urology* 2005;66:194.
33. Krieger J, Follenius M, Sforza E, Brandenberger G, Peter JD. Effects of treatment with nasal continuous positive airway pressure on atrial natriuretic peptide and arginine vasopressin release during sleep in patients with obstructive sleep apnoea. *Clin Sci (Lond)* 1991;80:443-449.

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35. Li AM, Au CT, Ho C, Fok TF, Wing YK. Blood pressure is elevated in children with primary snoring. *J Pediatr* 2009;155:362-368 e361.

For Peer Review

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### Figure legends

**Figure 1.** Mean log-transformed fractional urinary excretion of sodium ( $\ln FE_{Na}$ ) in the three groups of children with SDB according to morning diastolic blood pressure (BP) level (diastolic BP in the upper quartile vs. in the lower quartiles). Less negative  $\ln FE_{Na}$  values indicate higher excretion of sodium.

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## Tables

**Table 1.** Subjects' characteristics, polysomnography findings and fractional urinary excretion of sodium ( $FE_{Na}$ ) values.

Variables	Primary snoring	Mild SDB	Moderate-to-severe SDB
	n = 26	n = 41	n = 28
Age (years)	6.6 ± 2.8	6.6 ± 2.7	5.7 ± 2.0
Female gender (%)	9 (34.6)	24 (58.5)	11 (39.3)
Body mass index z-score	0.8 ± 1.1	0.7 ± 1.4	1.1 ± 1.6
Obese (%)	7 (26.9)	9 (22)	10 (35.7)
Systolic BP (mmHg)	97.1 ± 11.0	97.9 ± 12.2	103.1 ± 13.5
Systolic BP z-score *	-0.02 ± 1.0	0.1 ± 1.0	0.7 ± 1.2
Diastolic BP (mmHg)	61.4 ± 8.8	62.3 ± 7.3	64.1 ± 7.6
Diastolic BP z-score	0.5 ± 0.8	0.6 ± 0.7	0.8 ± 0.8
OAH index † (episodes/hour)	0.6 ± 0.2	2.5 ± 1.2	15.4 ± 10.0
Respiratory arousal index † (episodes/hour)	0.3 ± 0.1	1.4 ± 0.8	5.5 ± 3.6
Oxygen desaturation of hemoglobin (≥ 4%) index † (episodes/hour)	0.8 ± 0.5	3.0 ± 1.7	17.3 ± 11.9
SpO <sub>2</sub> nadir † (%)	92.6 ± 1.5	88.9 ± 3.1	81.2 ± 6.6
$FE_{Na}$ ‡	0.65 ± 0.35	0.81 ± 0.28	1.02 ± 0.61

\* p = 0.046 for comparison of moderate-to-severe SDB group vs. primary snoring group

† p < 0.001 for comparisons of moderate-to-severe SDB group vs. mild SDB or vs. primary snoring groups

‡ p=0.005 for comparison of moderate-to-severe SDB group vs. primary snoring group

**Abbreviations**

**BP** Blood pressure

**Table 2.** Effects of severity of sleep-disordered breathing (SDB) and diastolic blood pressure (BP) on log-transformed fractional urinary excretion of sodium ( $\ln\text{FE}_{\text{Na}}$ ) adjusted for age, gender and obesity. Less negative  $\ln\text{FE}_{\text{Na}}$  values indicate higher excretion of sodium.

	<b>Primary snoring</b>	<b>Mild SDB</b>	<b>Moderate-to-severe SDB</b>	<b>Overall effect of diastolic BP<sup>†</sup></b>
<b>Diastolic BP in the upper quartile</b>	-0.15 ± 0.37 n = 7	-0.02 ± 0.30 n = 7	-0.06 ± 0.48 n = 10	-0.08 ± 0.39 n = 24
<b>Diastolic BP in the lower quartiles</b>	-0.78 ± 0.66 n = 19	-0.34 ± 0.41 n = 34	-0.17 ± 0.56 n = 18	-0.41 ± 0.57 n = 71
<b>Overall effect of SDB<sup>*</sup></b>	-0.61 ± 0.65 n = 26	-0.28 ± 0.41 n = 41	-0.13 ± 0.53 n = 28	

\* p = 0.043 for the effect of severity of SDB on  $\ln\text{FE}_{\text{Na}}$

† p = 0.007 for the effect of diastolic BP on  $\ln\text{FE}_{\text{Na}}$ ; the interaction between SDB and diastolic BP was not significant (p=0.225).

**Table 3.** Multiple linear regression analysis model assessing the association of log-transformed fractional urinary excretion of sodium ( $\ln\text{FE}_{\text{Na}}$ ) with OAHl adjusted for age, gender and BMI z-score.

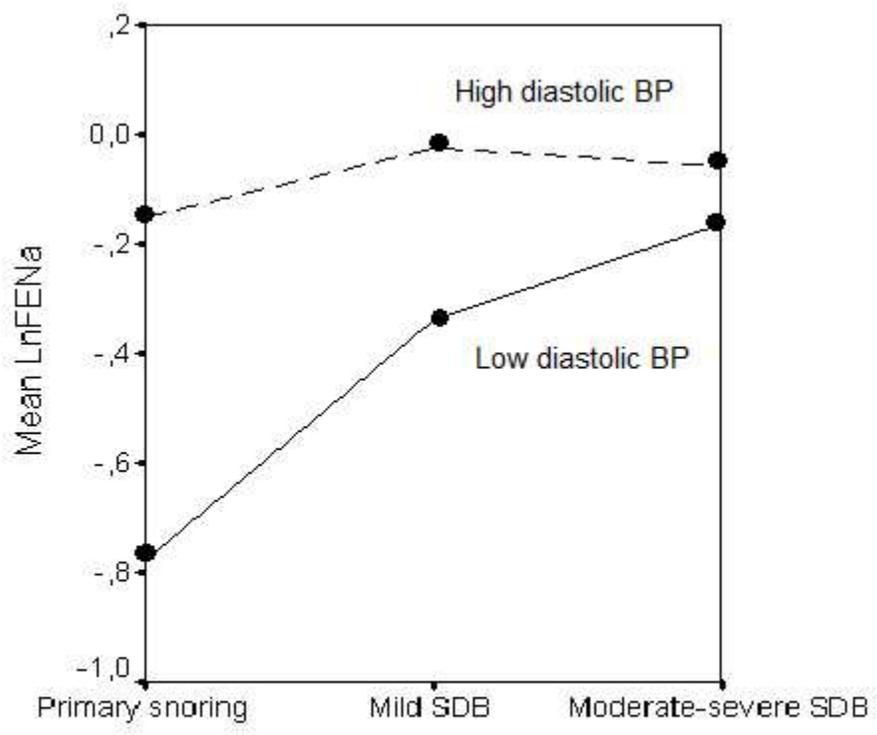
Parameters	$\beta$ standardized coefficient	p values
Age	0.004	0.964
Gender	0.002	0.982
BMI z-score	0.103	0.305
OAHl	0.329	0.002

#### Abbreviations

**BMI** Body mass index

**OAHl** Obstructive apnea-hypopnea index

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6 We are submitting the second revision of our manuscript PPUL-10-0080 entitled  
7 “Correlation of urinary excretion of sodium with severity of sleep-disordered  
8 breathing in children: A preliminary study”. In preparing our revised manuscript, we  
9 have taken under consideration the Reviewer’s comments.  
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12 Along with the marked-up and the clean version of the revised manuscript, we are  
13 submitting a point-by-point response to the Reviewer’s comments. We will be glad to  
14 make any other changes if necessary.  
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17 Sincerely,  
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21 A. Kaditis, MD  
22 Sleep Disorders Laboratory  
23 Larissa University Hospital  
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## RESPONSE TO REVIEWER'S COMMENTS

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1. **“In pg 6 para 2, some non-significant results were presented in details with ORs and CI. As these data were non-significant, their ORs are meaningless in a strict sense and their detail reportings are misleading (mild SDB vs primary snoring in systolic BP; and effect of SDB on dBP)”.**

In the revised manuscript, odds ratios for non-significant results were deleted.

2. **“Most p-values are reported in 3 digits. This is overkill, probably 2 digits are alright”.**

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This comment is very reasonable. However, few p-values of the present manuscript are close to 0.05 and three digits are necessary to indicate that the respective comparisons are significant (e.g.  $p=0.046$ ). Thus, for consistency all p-values are presented in 3 digits.

3. **“The conclusive statement on pg 9, ‘Elevated FEna...snoring...related to intermittent upper airway obstruction...’ is unclear and unrelated”**

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The conclusion in the revised manuscript has been modified.

4. **“Table 2 is redundant. Either you may combine both tables 2 and 3 or you can drop table 2.”**

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Table 2 was deleted.

5. **“Figure 1 is uninformative. Please drop it. In addition, the description of axis and figure is unclear.”**

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Figure 1 may help the reader to have an overall impression of the numeric data presented in the manuscript. We have made the figure more self-explanatory according to the reviewer's suggestion

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14 Konstantinos Evangelopoulos MD<sup>1</sup>, Eleni Kostadima MD<sup>2</sup>,  
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45 Funded by the University of Thessaly Research Committee

46 **None of the authors has any conflict of interest to disclose**  
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48 **Key words:** blood pressure, natriuresis, obstructive sleep apnea, snoring  
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## Abstract

**Background:** Nocturnal urinary sodium excretion is related to blood pressure (BP) levels. Elevated BP and increased nocturnal natriuresis have been demonstrated in adults with sleep apnea. Although evidence indicates increased BP in children with obstructive sleep-disordered breathing (SDB), it is unknown whether these children have also enhanced urinary sodium excretion.

**Objective:** To evaluate the effects of SDB and morning BP on urinary sodium excretion.

**Methods:** Consecutive children with snoring (n=95) underwent polysomnography and morning BP measurement. Fractional excretion of sodium ( $FE_{Na}$ ) was the primary outcome measure and was calculated using sodium and creatinine concentrations in early morning serum and urine specimens.

**Results:** Subjects with moderate-to-severe SDB had similar log-transformed  $FE_{Na}$  to that of children with mild SDB and higher than children with primary snoring:  $-0.13 \pm 0.53$  vs.  $-0.28 \pm 0.41$  vs.  $-0.61 \pm 0.65$  ( $p=0.657$  and  $p=0.003$ ). Obstructive apnea-hypopnea index was significantly related to  $FE_{Na}$  after adjustment for age, gender and body mass index z-score ( $p=0.002$ ). Children with moderate-to-severe SDB had similar systolic BP z-scores to those of subjects with mild SDB and higher than participants with primary snoring:  $0.7 \pm 1.2$  vs.  $0.1 \pm 1.0$  vs.  $-0.02 \pm 1.0$  ( $p=0.074$  and  $p=0.046$ ). In addition, participants with diastolic BP z-scores in the upper quartile of measured values had higher  $FE_{Na}$  than subjects with z-scores in the lower quartiles:  $-0.08 \pm 0.39$  vs.  $-0.41 \pm 0.57$  ( $p=0.007$ ).

**Conclusions:** Morning natriuresis is related to severity of SDB in children and this association may be mediated in part by elevated BP. (249 words)

## Introduction

Obstructive sleep apnea-hypopnea is an established risk factor for cardiovascular disease in adults.<sup>1</sup> Elevated blood pressure (BP) and increased BP variability are some of the mechanisms that may contribute to cardiovascular morbidity.<sup>1-4</sup> Obstructive events during sleep are accompanied by episodically increased sympathetic output, intermittent peripheral vasoconstriction and repeated BP surges.<sup>5</sup> The baroreflex system, which should regularly smooth these BP fluctuations, has reduced sensitivity in sleep apneic adults.<sup>4</sup>

Renal excretion of sodium and water is an additional protective mechanism against elevated BP.<sup>6</sup> The rate of nocturnal natriuresis in healthy adults and children is positively associated with BP levels, a phenomenon described by the term “pressure natriuresis”.<sup>7,8</sup> Indeed, increased nocturnal diuresis and natriuresis have been reported in adults with obstructive sleep apnea-hypopnea compared to healthy controls.<sup>9-11</sup> Renal sodium excretion correlates with diastolic BP levels and diminishes after treatment of sleep apnea with nasal continuous positive airway pressure (nCPAP).<sup>9-11</sup> Hence, it has been proposed that increased BP in adults with sleep apnea may be responsible for the enhanced nocturnal natriuresis in these patients.<sup>10</sup>

Although recent evidence suggests that similar to adults, children with obstructive sleep-disordered breathing (SDB) have high levels of sympathetic activity, increased BP levels and BP variability and reduced sensitivity of the baroreflex system,<sup>12-16</sup> no pediatric studies have explored the potential relationship between severity of intermittent upper airway obstruction during sleep and natriuresis. Thus, in the current investigation

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2 it was hypothesized that there is a positive association of urine excretion of sodium with  
3 severity of SDB.  
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## 6 Patients and Methods

### 7 Participants and clinical evaluation

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9 The study protocol was approved by the Larissa University Hospital Ethics  
10 Committee and parents of participants provided informed consent. Consecutive children  
11 with snoring (> 3 nights/week) for the last six months who were referred to the Sleep  
12 Disorders Laboratory for polysomnography were recruited in the study. *Exclusion*  
13 *criteria* for participation were: i) symptoms of respiratory tract infection or acute  
14 gastroenteritis; ii) history of renal disease or use of diuretics or antihypertensive  
15 medications; and iii) history of cardiovascular, neuromuscular or genetic disorders.  
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18 All subjects underwent physical examination. Body mass index (BMI) and BMI  
19 z-score were calculated.<sup>17</sup> Obesity was defined as BMI z-score > 1.645.<sup>17</sup> Participants  
20 voided in the evening prior to polysomnography and none of them had urine loss or  
21 voided overnight. Upon morning arousal from sleep and after the child had been sitting  
22 quietly for about 5 minutes, BP was measured three times using the right arm and a cuff  
23 of appropriate size (Dinamap Pro 100; Criticon; Tampa, FL, USA). To adjust for the  
24 effects of age, gender and height, BP z-scores were determined.<sup>18</sup>  
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27 Shortly after BP measurement and without having drunk any water, children were  
28 instructed to empty their bladder in a container and venipuncture was also performed.  
29 Urine and venous blood samples were collected and processed immediately in the Central  
30 Biochemistry Laboratory. Serum and urine sodium and creatinine concentrations were  
31 measured using standard laboratory methods.  
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## Polysomnography

Overnight polysomnography in a single night was performed under the supervision of trained personnel.<sup>19</sup> The following parameters were recorded: electroencephalogram (C3/A2, C4/A1, O1/A2); right and left oculogram; submental and tibial electromyogram; body position; electrocardiogram; thoracic and abdominal wall motion; oronasal airflow; and oxygen saturation of hemoglobin.

Obstructive apnea was defined as the presence of chest/abdominal wall motion in the absence of airflow for at least two breaths in duration.<sup>20</sup> Hypopnea was: i) a reduction in the airflow signal amplitude of at least 50% compared to baseline; ii) in the presence of chest/abdominal wall motion; and iii) associated with oxygen desaturation of hemoglobin equal to or greater than 4% or with an arousal. Obstructive apnea-hypopnea index (OAHI) was equal to the number of obstructive and mixed apneas (apneas with both central and obstructive components) and hypopneas per hour of sleep.

## Primary outcome measure

Fractional urinary excretion of sodium ( $FE_{Na}$ ) was the primary outcome measure.

$FE_{Na}$  was calculated as:

$$FE_{Na} = \frac{\text{(urine sodium concentration X serum creatinine concentration)}}{\text{(urine creatinine concentration X serum sodium concentration)}}$$

All concentrations were measured in early morning urine and serum specimens, and were expressed in mg/dL.  $FE_{Na}$  values were log-transformed (natural logarithm) to approach a normal distribution.

## Data analysis

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Severity of SDB was classified as: i) primary snoring (OAH1 < 1 episode/hour);  
ii) mild SDB (OAH1 1-5 episodes/h); and iii) moderate-to-severe SDB (OAH1 > 5  
episodes/hour). The three groups of children were compared in terms of age, gender,  
obesity status, BP and polysomnography indices using  $\chi^2$  for categorical characteristics  
and one-way analysis of variance (ANOVA), followed by post-hoc tests (Bonferroni), for  
continuous variables.

BP measurements were categorized as those: i) in the upper quartile of values for  
all participants; or ii) in the lower three quartiles of BP values for all participants.  
Univariate logistic regression analysis was applied to assess the risk for having systolic or  
diastolic BP in the upper quartile of measurements, in children with moderate-to-severe  
or mild SDB compared to those with primary snoring (reference group).

Two general linear models (GLM) were tested to describe the potential effects on  
FE<sub>Na</sub> of: i) severity of SDB; ii) systolic or diastolic BP; and iii) the interaction of SDB  
severity with systolic or diastolic BP, after adjustment for age, gender and obesity (SPSS  
version 16.0; SPSS, Chicago, IL). In order to assess whether natriuresis was increasing  
linearly to severity of SDB, linear regression analysis was carried out using FE<sub>Na</sub> as the  
dependent variable and OAH1, age, gender and BMI z-score as independent variables.

## Results

### Subjects' characteristics

A total of 95 children were recruited. Subjects' characteristics and  
polysomnography findings are summarized in Table 1. There were no significant

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3 differences in terms of age, female-to-male ratio, body mass index z-score or proportion  
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5 of obese subjects between the three study groups. Children with moderate-to-severe SDB  
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7 had similar morning systolic BP z-score to those of subjects with mild SDB and higher  
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9 than subjects with primary snoring ( $p=0.074$  and  $p=0.046$ , respectively). A non-  
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11 significant trend for higher diastolic BP with higher OAHl was noted (Table 1).

### 12 **Effects of SDB severity and BP on $FE_{Na}$**

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15 The cut-off value separating the upper quartile from the lower quartiles for  
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17 systolic BP z-score was 0.78. The respective cut-off value for diastolic BP z-score was  
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19 1.14. Children with moderate-to-severe SDB-but not with mild SDB-were at increased  
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21 risk for having systolic BP in the upper quartile of measured values compared to subjects  
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23 with primary snoring [odds ratios (95% confidence intervals): 4.12 (1.12-15.16);  $p =$   
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25 0.033 and 1.33 (0.36-4.97);  $p=0.669$ ]. The association between severity of SDB and  
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27 diastolic BP was not significant ( $p>0.05$ ).

**Deleted:** The respective odds ratios for diastolic BP in the upper quartile of measured values were: 1.51 (0.47-4.82;  $p = 0.488$  and 0.56 (0.17-1.83);  $p=0.337$ ).

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30 SDB and diastolic BP had significant effects on  $FE_{Na}$  ( $p<0.05$  and  $p=0.007$ ,  
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32 respectively), whereas systolic BP had no effect on  $FE_{Na}$  ( $p=0.715$ ) (Table 2 and Figure  
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34 1). More specifically, subjects with moderate-to-severe SDB had similar log-transformed  
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36  $FE_{Na}$  to that of children with mild SDB ( $p=0.657$ ) and higher than participants with  
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38 primary snoring ( $p=0.003$ ). The interactions between SDB and systolic or diastolic BP  
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40 were not significant ( $p=0.246$  and  $p=0.225$ , respectively). In linear regression analysis,  
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42 OAHl was significantly associated with  $FE_{Na}$  after adjustment for age, gender and BMI z-  
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44 score ( $p=0.002$ ) (Table 3).

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## Discussion

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7 children have significant effect on renal excretion of sodium. Since sleep apnea in  
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9 childhood has been related to elevated BP,<sup>15,21</sup> the association between SDB and  
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11 natriuresis may be mediated in part by BP elevation.  
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14 According to traditional physiology teaching, systemic BP and blood volume are  
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16 tightly regulated.<sup>6</sup> Any increase in systemic BP is buffered by activation of the  
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18 baroreflex system (arterial, venous and cardiac baroreceptors, brainstem, sympathetic and  
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20 parasympathetic neurons) that decreases heart rate, cardiac output and systemic vascular  
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22 resistance. BP elevation promotes renal excretion of sodium and water both directly, by  
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24 decreased renal tubular reabsorption of sodium (pressure natriuresis), and indirectly via  
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26 reduced activity of the renin-angiotensin-aldosterone system.<sup>6-8</sup> Moreover, any blood  
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28 volume expansion leads to atrial and ventricular distention, and release of ANP and BNP.  
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30<sup>22,23</sup> Natriuretic peptides inhibit renal tubular reabsorption of sodium and accentuate  
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32 renal sodium filtration.<sup>24</sup>  
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35 Studies in adults and children with sleep apnea indicate that at the termination of  
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37 obstructive events repetitive increases in systemic BP take place.<sup>25-27</sup> Although the  
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39 baroreflex system should normally attenuate excessive BP variability, both adults and  
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41 children with obstructive sleep apnea have reduced nighttime baroreflex gain and  
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43 increased BP variability.<sup>4,16</sup> Therefore, reduction of the intravascular volume by renal  
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45 excretion of sodium and water could be another defense mechanism to or biomarker of  
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47 SDB-related BP fluctuations. Studies in sleep apneic adults have consistently shown  
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49 increased nocturnal renal excretion of sodium that diminishes after treatment with  
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2 nCPAP. <sup>9-11,28</sup> Results of the present investigation extend the observations from adults to  
3 children with obstructive SDB. Of note, children with obstructive sleep apnea or primary  
4 snoring have increased prevalence of nocturnal enuresis that frequently resolves after  
5 adenotonsillectomy or treatment of adenoidal hypertrophy and SDB with nasal  
6 corticosteroids. <sup>29-32</sup> Increased nocturnal natriuresis and diuresis could conceivably  
7 contribute to nocturnal urine loss.  
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15 The exact pathophysiologic mechanisms underlying increased renal excretion of  
16 sodium in sleep apnea have not been elucidated. Similarly to the current report, Gjorup et  
17 al have found that diastolic BP and  $FE_{Na}$  in sleep apneic adults were positively correlated.  
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19 <sup>10</sup> Hence, the investigators proposed that this association may be due to pressure  
20 natriuresis. Other studies have revealed increased levels of ANP and BNP that could  
21 represent the pathophysiologic link between sleep apnea and nocturnal diuresis and  
22 natriuresis. <sup>33,34</sup>  
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30 A few methodologic issues should be discussed. First, sodium and creatinine  
31 concentrations in an early morning urine specimen were used to calculate  $FE_{Na}$ . Since the  
32 recruited children have not voided overnight, we speculate that the calculated  $FE_{Na}$   
33 reflects nocturnal urinary excretion of sodium. Second, hydration status and sodium  
34 losses via the sweat glands and the gastrointestinal system and daily sodium intake may  
35 influence  $FE_{Na}$ . Nevertheless, none of the study participants was dehydrated, was  
36 exposed to high temperatures or had symptoms or signs of gastroenteritis. Third, recent  
37 studies have documented significant associations between systolic or diastolic BP and  
38 severity of SDB using ambulatory BP monitoring. <sup>15,21</sup> A trend for higher morning  
39 diastolic BP with increasing OAH1 was identified in the present report and the absence of  
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2 statistical significance may be attributed to the fact that overnight BP monitoring was not  
3 performed in the current report. Finally, a healthy control group including children  
4 without SDB, who were of normal weight or overweight, was not included. The absence  
5 of such a group possibly limited the statistical comparisons and the delineation of an  
6 interaction effect between SDB, obesity and BP in natriuresis. Furthermore, the use of a  
7 control group with OAH  $< 1$  episode/hour may be suboptimal, since even primary  
8 snoring could be associated with BP elevation.<sup>35</sup>

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17 In conclusion, severity of obstructive SDB and diastolic BP are positively  
18 associated with urinary excretion of sodium in childhood. Natriuresis may be a defense  
19 mechanism to systemic blood pressure fluctuations related to intermittent upper airway  
20 obstruction during sleep.

Deleted: Elevated  $FE_{Na}$  in children with snoring could possibly separate those subjects with hemodynamically significant effects related to i

## REFERENCES

1. Somers VIKKI, White DP, Amin R, Abraham WT, Costa F, Culebras A, Daniels S, Floras JS, Hunt CE, Olson LJ, Pickering TG, Russell R, Woo M, Young T. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. *J Am Coll Cardiol* 2008;52:686-717.
2. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000;342:1378-1384.
3. Narkiewicz K, Montano N, Cogliati C, van de Borne PJ, Dyken ME, Somers VK. Altered cardiovascular variability in obstructive sleep apnea. *Circulation* 1998;98:1071-1077.
4. Bonsignore MR, Parati G, Insalaco G, Marrone O, Castiglioni P, Romano S, Di Rienzo M, Mancina G, Bonsignore G. Continuous positive airway pressure treatment improves baroreflex control of heart rate during sleep in severe obstructive sleep apnea syndrome. *Am J Respir Crit Care Med* 2002;166:279-286.
5. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest* 1995;96:1897-1904.

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2  
3 6. Vander A, Sherman J, Luciano D. Human Physiology: The mechanisms of body  
4 function. New York: Mc Graw Hill; 2001.
- 5  
6  
7 7. Lurbe E, Alvarez V, Liao Y, Torro I, Cremades B, Redon J, Cooper R. Obesity  
8 modifies the relationship between ambulatory blood pressure and natriuresis in  
9 children. *Blood Press Monit* 2000;5:275-280.
- 10  
11  
12 8. Staessen JA, Birkenhager W, Bulpitt CJ, Fagard R, Fletcher AE, Lijnen P, Thijs  
13 L, Amery A. The relationship between blood pressure and sodium and potassium  
14 excretion during the day and at night. *J Hypertens* 1993;11:443-447.
- 15  
16  
17 9. Zhang L, Huang X, Li X, Wu Q. Alterations in renal function in patients with  
18 obstructive sleep apnea syndrome and effects of continuous positive airway  
19 pressure. *Chin Med J (Engl)* 1997;110:915-918.
- 20  
21  
22 10. Gjorup PH, Sadauskiene L, Wessels J, Nyvad O, Strunge B, Pedersen EB.  
23 Increased nocturnal sodium excretion in obstructive sleep apnoea. Relation to  
24 nocturnal change in diastolic blood pressure. *Scand J Clin Lab Invest* 2008;68:11-  
25 21.
- 26  
27  
28 11. Rodenstein DO, D'Odemont JP, Pieters T, Aubert-Tulkens G. Diurnal and  
29 nocturnal diuresis and natriuresis in obstructive sleep apnea. Effects of nasal  
30 continuous positive airway pressure therapy. *Am Rev Respir Dis* 1992;145:1367-  
31 1371.
- 32  
33  
34 12. Amin RS, Carroll JL, Jeffries JL, Grone C, Bean JA, Chini B, Bokulic R, Daniels  
35 SR. Twenty-four-hour ambulatory blood pressure in children with sleep-  
36 disordered breathing. *Am J Respir Crit Care Med* 2004;169:950-956.
- 37  
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13. Kaditis AG, Alexopoulos EI, Damani E, Hatzi F, Chaidas K, Kostopoulou T, Tzigeroglou A, Gourgoulialis K. Urine levels of catecholamines in Greek children with obstructive sleep-disordered breathing. *Pediatr Pulmonol* 2009;44:38-45.
  14. Snow AB, Khalyfa A, Serpero LD, Capdevila OS, Kim J, Buazza MO, Gozal D. Catecholamine alterations in pediatric obstructive sleep apnea: effect of obesity. *Pediatr Pulmonol* 2009;44:559-567.
  15. Li AM, Au CT, Sung RY, Ho C, Ng PC, Fok TF, Wing YK. Ambulatory blood pressure in children with obstructive sleep apnoea: a community based study. *Thorax* 2008;63:803-809.
  16. McConnell K, Somers VK, Kimball T, Daniels S, VanDyke R, Fenchel M, Cohen A, Willging P, Shamsuzzaman A, Amin R. Baroreflex gain in children with obstructive sleep apnea. *Am J Respir Crit Care Med* 2009;180:42-48.
  17. Ogden CL, Kuczmarski RJ, Flegal KM, Mei Z, Guo S, Wei R, Grummer-Strawn LM, Curtin LR, Roche AF, Johnson CL. Centers for Disease Control and Prevention 2000 growth charts for the United States: improvements to the 1977 National Center for Health Statistics version. *Pediatrics* 2002;109:45-60.
  18. National High Blood Pressure Education Program Working Group. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics* 2004;114:555-576.
  19. Li AM, Wing YK, Cheung A, Chan D, Ho C, Hui S, Fok TF. Is a 2-night polysomnographic study necessary in childhood sleep-related disordered breathing? *Chest* 2004;126:1467-1472.

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20. American Thoracic Society. Standards and indications for cardiopulmonary sleep studies in children. *Am J Respir Crit Care Med* 1996;153:866-878.
  21. Amin R, Somers VK, McConnell K, Willging P, Myer C, Sherman M, McPhail G, Morgenthal A, Fenchel M, Bean J, Kimball T, Daniels S. Activity-adjusted 24-hour ambulatory blood pressure and cardiac remodeling in children with sleep disordered breathing. *Hypertension* 2008;51:84-91.
  22. Dietz JR. Release of natriuretic factor from rat heart-lung preparation by atrial distension. *Am J Physiol* 1984;247:R1093-1096.
  23. Nakagawa O, Ogawa Y, Itoh H, Suga S, Komatsu Y, Kishimoto I, Nishino K, Yoshimasa T, Nakao K. Rapid transcriptional activation and early mRNA turnover of brain natriuretic peptide in cardiocyte hypertrophy. Evidence for brain natriuretic peptide as an "emergency" cardiac hormone against ventricular overload. *J Clin Invest* 1995;96:1280-1287.
  24. Yoshimura M, Yasue H, Morita E, Sakaino N, Jougasaki M, Kurose M, Mukoyama M, Saito Y, Nakao K, Imura H. Hemodynamic, renal, and hormonal responses to brain natriuretic peptide infusion in patients with congestive heart failure. *Circulation* 1991;84:1581-1588.
  25. Leuenberger U, Jacob E, Sweer L, Waravdekar N, Zwillich C, Sinoway L. Surges of muscle sympathetic nerve activity during obstructive apnea are linked to hypoxemia. *J Appl Physiol* 1995;79:581-588.
  26. Ringler J, Basner RC, Shannon R, Schwartzstein R, Manning H, Weinberger SE, Weiss JW. Hypoxemia alone does not explain blood pressure elevations after obstructive apneas. *J Appl Physiol* 1990;69:2143-2148.

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27. O'Driscoll DM, Foster AM, Ng ML, Yang JS, Bashir F, Nixon GM, Davey MJ, Anderson V, Walker AM, Trinder J, Horne RS. Acute cardiovascular changes with obstructive events in children with sleep disordered breathing. *Sleep* 2009;32:1265-1271.
  28. Baruzzi A, Riva R, Cirignotta F, Zucconi M, Cappelli M, Lugaresi E. Atrial natriuretic peptide and catecholamines in obstructive sleep apnea syndrome. *Sleep* 1991;14:83-86.
  29. Alexopoulos EI, Kostadima E, Pagonari I, Zintzaras E, Gourgoulianis K, Kaditis AG. Association between primary nocturnal enuresis and habitual snoring in children. *Urology* 2006;68:406-409.
  30. Sans Capdevila O, Crabtree VM, Kheirandish-Gozal L, Gozal D. Increased morning brain natriuretic peptide levels in children with nocturnal enuresis and sleep-disordered breathing: a community-based study. *Pediatrics* 2008;121:e1208-1214.
  31. Weider DJ, Sateia MJ, West RP. Nocturnal enuresis in children with upper airway obstruction. *Otolaryngol Head Neck Surg* 1991;105:427-432.
  32. Alexopoulos EI, Kaditis AG, Kostadima E, Gourgoulianis K. Resolution of nocturnal enuresis in snoring children after treatment with nasal budesonide. *Urology* 2005;66:194.
  33. Krieger J, Follenius M, Sforza E, Brandenberger G, Peter JD. Effects of treatment with nasal continuous positive airway pressure on atrial natriuretic peptide and arginine vasopressin release during sleep in patients with obstructive sleep apnoea. *Clin Sci (Lond)* 1991;80:443-449.

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34. Kita H, Ohi M, Chin K, Noguchi T, Otsuka N, Tsuboi T, Itoh H, Nakao K, Kuno K. The nocturnal secretion of cardiac natriuretic peptides during obstructive sleep apnoea and its response to therapy with nasal continuous positive airway pressure. *J Sleep Res* 1998;7:199-207.
35. Li AM, Au CT, Ho C, Fok TF, Wing YK. Blood pressure is elevated in children with primary snoring. *J Pediatr* 2009;155:362-368 e361.

### Figure legends

**Figure 1.** Mean log-transformed fractional urinary excretion of sodium ( $\ln FE_{Na}$ ) in the three groups of children with SDB according to morning diastolic blood pressure (BP) level (diastolic BP in the upper quartile vs. in the lower quartiles). Less negative  $\ln FE_{Na}$  values indicate higher excretion of sodium.

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## Tables

**Table 1.** Subjects' characteristics, polysomnography findings and fractional urinary excretion of sodium ( $FE_{Na}$ ) values.

Variables	Primary snoring	Mild SDB	Moderate-to-severe SDB
	n = 26	n = 41	n = 28
Age (years)	6.6 ± 2.8	6.6 ± 2.7	5.7 ± 2.0
Female gender (%)	9 (34.6)	24 (58.5)	11 (39.3)
Body mass index z-score	0.8 ± 1.1	0.7 ± 1.4	1.1 ± 1.6
Obese (%)	7 (26.9)	9 (22)	10 (35.7)
Systolic BP (mmHg)	97.1 ± 11.0	97.9 ± 12.2	103.1 ± 13.5
Systolic BP z-score *	-0.02 ± 1.0	0.1 ± 1.0	0.7 ± 1.2
Diastolic BP (mmHg)	61.4 ± 8.8	62.3 ± 7.3	64.1 ± 7.6
Diastolic BP z-score	0.5 ± 0.8	0.6 ± 0.7	0.8 ± 0.8
OAH index † (episodes/hour)	0.6 ± 0.2	2.5 ± 1.2	15.4 ± 10.0
Respiratory arousal index † (episodes/hour)	0.3 ± 0.1	1.4 ± 0.8	5.5 ± 3.6
Oxygen desaturation of hemoglobin ( $\geq 4\%$ ) index † (episodes/hour)	0.8 ± 0.5	3.0 ± 1.7	17.3 ± 11.9
SpO <sub>2</sub> nadir † (%)	92.6 ± 1.5	88.9 ± 3.1	81.2 ± 6.6
$FE_{Na}^{\ddagger}$	0.65 ± 0.35	0.81 ± 0.28	1.02 ± 0.61

\* p = 0.046 for comparison of moderate-to-severe SDB group vs. primary snoring group

† p &lt; 0.001 for comparisons of moderate-to-severe SDB group vs. mild SDB or vs. primary snoring groups

‡ p=0.005 for comparison of moderate-to-severe SDB group vs. primary snoring group

**Abbreviations****BP** Blood pressure

**Table 2.** Effects of severity of sleep-disordered breathing (SDB) and diastolic blood pressure (BP) on log-transformed fractional urinary excretion of sodium ( $\ln\text{FE}_{\text{Na}}$ ) adjusted for age, gender and obesity. Less negative  $\ln\text{FE}_{\text{Na}}$  values indicate higher excretion of sodium.

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**Deleted: Table 2.** Effects of severity of sleep-disordered breathing (SDB) and systolic blood pressure (BP) on log-transformed fractional urinary excretion of sodium ( $\ln\text{FE}_{\text{Na}}$ ) adjusted for age, gender and obesity. Less negative  $\ln\text{FE}_{\text{Na}}$  values indicate higher excretion of sodium.¶

	Primary snoring	Mild SDB	Moderate-to-severe SDB	Overall effect of diastolic BP <sup>†</sup>
<b>Diastolic BP in the upper quartile</b>	-0.15 ± 0.37 n = 7	-0.02 ± 0.30 n = 7	-0.06 ± 0.48 n = 10	-0.08 ± 0.39 n = 24
<b>Diastolic BP in the lower quartiles</b>	-0.78 ± 0.66 n = 19	-0.34 ± 0.41 n = 34	-0.17 ± 0.56 n = 18	-0.41 ± 0.57 n = 71
<b>Overall effect of SDB<sup>*</sup></b>	-0.61 ± 0.65 n = 26	-0.28 ± 0.41 n = 41	-0.13 ± 0.53 n = 28	

\* p = 0.043 for the effect of severity of SDB on  $\ln\text{FE}_{\text{Na}}$

† p = 0.007 for the effect of diastolic BP on  $\ln\text{FE}_{\text{Na}}$ ; the interaction between SDB and diastolic BP was not significant (p=0.225).

**Table 3.** Multiple linear regression analysis model assessing the association of log-transformed fractional urinary excretion of sodium ( $\ln\text{FE}_{\text{Na}}$ ) with OAHl adjusted for age, gender and BMI z-score.

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Parameters	$\beta$ standardized coefficient	p values
Age	0.004	0.964
Gender	0.002	0.982
BMI z-score	0.103	0.305
OAHl	0.329	0.002

**Abbreviations**

<b>BMI</b>	Body mass index
<b>OAHl</b>	Obstructive apnea-hypopnea index

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**Table 2.** Effects of severity of sleep-disordered breathing (SDB) and systolic blood pressure (BP) on log-transformed fractional urinary excretion of sodium ( $\ln\text{FE}_{\text{Na}}$ ) adjusted for age, gender and obesity. Less negative  $\ln\text{FE}_{\text{Na}}$  values indicate higher excretion of sodium.

	<b>Primary snoring</b>	<b>Mild SDB</b>	<b>Moderate-to-severe SDB</b>	<b>Overall effect of systolic BP</b>
<b>Systolic BP in the upper quartile</b>	-0.70 ± 0.61 n = 4	-0.35 ± 0.41 n = 8	-0.15 ± 0.47 n = 12	-0.19 ± 0.49 n = 24
<b>Systolic BP in the lower quartiles</b>	-0.59 ± 0.67 n = 22	-0.01 ± 0.27 n = 33	-0.11 ± 0.58 n = 16	-0.37 ± 0.56 n = 71
<b>Overall effect of SDB *</b>	-0.61 ± 0.65 n = 26	-0.28 ± 0.41 n = 41	-0.13 ± 0.53 n = 28	

\*  $p = 0.01$  for the effect of severity of SDB on  $\ln\text{FE}_{\text{Na}}$ ; the effect of systolic BP and the interaction between SDB and systolic BP were not significant ( $p=0.715$  and  $p=0.246$ , respectively).

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