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REGULAR ARTICLE

Nocturnal blood pressure non-dipping is prevalent in severely obese, prepubertal and early pubertal children

M Westerståhl (maria.westerstahl@ki.se)[1,2], P Hedvall Kallerman[2], E Hagman[2], A E Ek[2], S M Rössner[3], C Marcus[2,4]

1.Division of Clinical Physiology, Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden
2.Division of Paediatrics, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden
3.Department of Woman and Child Health, Karolinska Institutet, Stockholm, Sweden
4.National Childhood Obesity Centre, Karolinska University Hospital Huddinge, Stockholm, Sweden

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Correspondence
Maria Westerståhl, Karolinska Institutet, Clinical Physiology, C188, Karolinska University Hospital Huddinge, SE-141 86 Stockholm.
Tel: +46858586509 |
Fax: +4687748082 |
Email: maria.westerstahl@ki.se

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ABSTRACT

Aim: To investigate the prevalence of nocturnal blood pressure dipping among obese prepubertal and early pubertal children and to analyse the relationship between dipping and measures of insulin-glucose metabolism or sleep-disordered breathing.

Methods: We studied 76 obese children (41% girls) under clinical care, with an average age of 10.4 ± 1.7 and a body mass index Z-score (BMI Z-score) of 6.2 ± 1.6. We performed a 24-h ambulatory blood pressure measurement. Non-dipping was defined as a nocturnal blood pressure reduction of <10%. We calculated measures of insulin-glucose metabolism from the performed frequently sampled intravenous glucose-tolerance test and from fasting blood samples. Overnight sleep polygraph recordings were performed to assess sleep-disordered breathing.

Results: Forty-two percent of the children were systolic non-dippers, and 17% were diastolic non-dippers. There were no associations between systolic or diastolic dipping and measures of insulin-glucose metabolism after adjustments for BMI Z-score, gender and pubertal status. There were no associations between dipping and measures of sleep-disordered breathing.

Conclusion: Nocturnal non-dipping was two times higher among severely obese, prepubertal and early pubertal children, compared to previous reports among children in general. There were no associations between nocturnal dipping and insulin-glucose metabolism or measures of sleep-disordered breathing in this group.

INTRODUCTION

Ambulatory blood pressure monitoring provides the opportunity to study blood pressure (BP) patterns during the day and night. Children's night-time (sleep) systolic BP normally drops by >10% from daytime (awake) BP, in other words 'dipping' (1). A nocturnal BP dip of less than 10% is defined as non-dipping. A non-dipping pattern seems to increase the risk of BP-related complications in children with diabetes or in adults, compared to those with a normal dipping pattern. A high nocturnal BP in children and adolescents with type 1 diabetes is associated with cardiac hypertrophy (2), subclinical atherosclerosis (3) and renal dysfunction (4). Among adults, non-dipping is associated with an increased risk of all-cause mortality (5).

Children with type 1 diabetes (6) and renal disease (7) have a higher prevalence of non-dipping than healthy children. There is also a high risk of non-dipping (8–10) among otherwise healthy obese adolescents (11) and mixed groups including obese children and adolescents. The prevalence of non-dipping in young obese children has been studied less (12).

Abbreviations
BMI, Body mass index; BP, Blood pressure; FSIVGTT, Frequently sampled intravenous glucose tolerance test; HOMA, Index homeostatic model assessment; SDB, Sleep-disordered breathing.

Key notes

- Non-dipping patterns of nocturnal blood pressure can increase the risk of cardiovascular complications.
- Our study of 76 obese children showed that nocturnal blood pressure non-dipping was two times higher among severely obese prepubertal and early pubertal children than what has been reported for the general child population.
- Non-dipping was not associated with insulin-glucose metabolism or sleep-disordered breathing, indicating that the mechanisms for non-dipping seem to be different in young children compared to adolescents and adults.

The physiological mechanisms behind nocturnal dipping disturbances in obesity are unclear and probably multifactorial. Insulin-glucose metabolism seems to affect nocturnal dipping in adults and adolescents: experimentally evoked hyperinsulinemia has been found to decrease dipping among healthy, normal-weight adults (13) and patients with impaired glucose tolerance were non-dippers more often than healthy controls (14). The high fasting insulin level and low insulin sensitivity in obese adolescents, assessed by the homeostatic model assessment (HOMA) index, are associated with impaired dipping (11) or night-time systolic BP (15). The results are inconsistent, however, among mixed groups of obese children and adolescents. Night-time BP has been reported to be positively correlated with fasting insulin levels and the HOMA index (16), but others found no association between dipping and the HOMA index (8,10) or two-hour glucose in a glucose tolerance test (10). Because insulin-glucose metabolism varies with the progress of puberty (17), the inconsistent results could be because of the large age ranges in these studies, including both prepubertal and pubertal children. Little is known about how insulin-glucose metabolism affects dipping in young children. Only one earlier study has exclusively investigated prepubertal children; it found no correlation between night-time BP and the HOMA index (12).

Another reason for non-dipping in obesity could be a sympathetic activation due to sleep-disordered breathing (SDB) causing sleep fragmentation and arousals. In some studies (18), but not all (19), children with SDB have been found to have impaired dipping compared to controls. However, the impact of disturbed sleep on dipping in obese children with no complaints of SDB has been studied less (20).

This study's purpose was to investigate the prevalence of nocturnal blood pressure dipping among obese prepubertal and early pubertal children and to analyse the relationship between nocturnal dipping and measures of insulin-glucose metabolism or sleep-disordered breathing in these children. Also, we studied the association between nocturnal dipping and cardiac hypertrophy as a measure of end-organ damage.

MATERIALS AND METHODS

Subjects

In this retrospective study, we reviewed a cohort of obese children aged between 5.5 and 12.9 years, enrolled at the National Childhood Obesity Centre of the Karolinska University Hospital, Huddinge, Sweden, between May 1997 and June 2007. All patients at the centre are registered in a national quality registry for childhood obesity treatment called BORIS. Patients with severe obesity come to the centre from all parts of Sweden, but mainly from the Stockholm region. The ethnicity of the patients is poorly registered in the BORIS register but experience indicates they are predominately Caucasians. During the study period, ambulatory BP monitoring, along with the other examinations described below, was part of the routine co-morbidity check-up in children with severe obesity. All children in the registry classified as prepubertal or early pubertal (see below), and having available data on 24-h ambulatory BP monitoring and body mass index (BMI), were eligible for the study. We extracted 115 prepubertal and early pubertal children from the register. Of these children, 39 who lacked data on ambulatory BP monitoring because of technical problems or poor compliance were not included in the study. There were no differences between the children included in the study and those who were not in age, percentage total body fat, percentage abdominal fat, length of time they were obese and glucose or insulin levels. However, the children included in the study had lower BMI Z-Scores (21) (6.3 vs. 7.0, $p < 0.05$), an indication of the number of standard deviations the age-adjusted and gender-adjusted BMI is above or below the 50th percentile. Thus, the subjects in the study are not selected but are representative of the severely obese children at the centre.

The local Ethics Committee in Stockholm, Sweden, approved the study protocol. The study was performed in accordance with the ethical standards of the committee and with the Helsinki Declaration of 1975, as revised in 1983.

Anthropometric assessments

Trained nurses made the anthropometric assessments. A calibrated wall-mounted scale (Ulmer Stadiometer, Ulm, Germany) measured height, and a calibrated electronic scale (Vetek Model T1-2001, Stockholm, Sweden) measured weight. We calculated BMI (kg/m^2). We used the equation developed by Rolland-Cachera and colleagues (21) to calculate a BMI standard deviation score (BMI Z-score) that would enable comparisons of obesity levels between different ages and genders. Dual X-ray Absorptiometry (Lunar Prodigy; software version 8; GE Lunar Corporation, Madison, WI, USA) measured body fat. A paediatric endocrinologist assessed sexual maturity with the five stage Tanner criteria of pubertal development (22), using the subscales of testicular volume (boys) and breast development (girls). Tanner stage one was defined as prepubertal and Tanner stage two to three were defined as early pubertal.

BP measurements

Each study participant underwent 24-h ambulatory BP monitoring (Space Labs 90 217; Space Labs, Wokingham, UK). An appropriate-sized cuff was attached around the upper non-dominant arm during a hospital visit. During the ambulatory BP monitoring, systolic BP and diastolic BP were measured every 20 min from eight a.m. to 10 p.m., and every 30 min from 10 p.m. to eight am. The participants were instructed to live as usual but to not move their arm during measurements. The participants also reported their bedtime and waking time. For the data analysis, the whole 24-h period and the daytime (eight a.m. to eight p.m.) and night-time (12 p.m. to 6 a.m.) periods were calculated. When needed, we corrected these static periods according to participant-reported awake and sleep periods. The percentage of night-time BP dipping was calculated as (daytime BP − night-time BP) × 100/daytime BP. Non-dipping

was defined as a nocturnal blood pressure reduction of <10%. When expressed as 'measures of blood pressure' in the text, all the following variables are indicated: 24-h, daytime, night-time and percentage dipping for systolic BP and diastolic BP respectively.

Frequently sampled intravenous glucose tolerance test (FSIVGTT)

According to our standard protocol (11), the FSIVGTT was performed at eight a.m. following an overnight fast. Briefly, at time zero minutes, glucose was administered intravenously for one minute. At 20 min, insulin was administered as an intravenous bolus dose. We drew frequent blood samples for glucose and insulin determinations over a period of 180 min. We calculated the insulin sensitivity index, glucose effectiveness, acute insulin response and disposition index from the glucose and insulin values using the minimal model computer program Minimal Model Millennium, developed by Boston *et al.* (23). The FSIVGTT investigates different aspects of insulin and glucose metabolism: the ability of glucose to stimulate glucose disposal at basal insulin levels (glucose efficiency), the adequacy of insulin secretion in the individual (acute insulin response), the ability of insulin to enhance glucose disposal and inhibit glucose production (insulin sensitivity) and the ability of β-cells to compensate for insulin resistance (disposition index).

Assays

Blood samples were drawn in the morning after overnight fasting from midnight and were subsequently analysed by the hospital's accredited chemistry laboratory (Karolinska University Hospital). Serum insulin was analysed using radioimmunoassay, Insulin RIA 100 (Pharmacia Diagnostics AB, Uppsala, Sweden), or, starting in February 26, 2003, by electrochemiluminescense immunoassay, ECLIA (Elecsys, Roche Diagnostics, Scandinavia AB, Bromma, Sweden). Plasma glucose was measured by the hexokinase method. HOMA index was calculated using the formula serum insulin (pmol/L) x plasma glucose (mmol/L)/156.26. Glycosylated haemoglobin A1c was determined by high-performance liquid chromatography.

When expressed as 'measures of insulin-glucose metabolism' in the text, all the following variables are indicated: fasting glucose, fasting insulin, HOMA index, glycosylated haemoglobin A1c and all measures of the FSIVGTT.

Polygraph recordings

The overnight sleep polygraph recordings were performed in-hospital and sampled by the Micro Digitrapper SAS (Synectics Medical AB, Stockholm, Sweden). The recordings included airflow, respiratory movements and oxygen saturation. Apnoea was defined as a complete cessation of airflow for at least 10 sec, and hypopnoea as a decrease in flow greater than 40% and lasting for at least 10 sec. An apnoea-hypopnoea index was calculated as the number of apnoeas plus hypopnoeas per hour of sleep. Obstructive sleep-disordered breathing was classified as mild obstructed sleep apnoea if the apnoea-hypopnoea index was between 1.5 and 4.9, and as moderate to severe obstructed sleep apnoea if the apnoea-hypopnoea index was five or more. This classification is used only for describing the group. Oxygen desaturation index was calculated as the average number of desaturation dips per hour of sleep. The lowest oxygen saturation (%) was monitored. When expressed as 'measures of sleep-disordered breathing' in the text, all three variables are indicated (apnoea-hypopnoea index, oxygen desaturation index and lowest oxygen saturation).

Echocardiogram

An experienced biomedical scientist performed echocardiography using a GE Vingmed System FiVe (Horten, Norway) or Siemens. We used a standard phased array 2.5 MHz multi-frequency transducer. All recordings were done at the end of expiration from apical four-chamber and two-chamber views with the subjects in the left lateral position. Cine loops of two consecutive heartbeats with a high temporal resolution were acquired in each case. M-mode was used to measure end-diastolic and end-systolic left ventricular diameters and intraventricular septum and posterior wall thicknesses according to the method established by the American Society of Echocardiography. Left ventricular mass was then calculated by using the Devereux equation (24). The left ventricular mass index was calculated by dividing left ventricular mass by the 2.7th power of height ($g \times m^{-2.7}$).

Analysis and statistics

The statistical analysis was performed using the STATISTICA 10 data analysis software system, StatSoft, Inc., (www.statsoft.com).

Either the Student's *t*-test or the Mann–Whitney U-test was used to analyse group differences between subjects that were included and excluded because of missing data. The Student's *t*-test was used to analyse differences between prepubertal and early pubertal children in normally distributed anthropometric and clinical variables, and the Mann–Whitney U-test was used for skewed variables. The chi-squared test was used to analyse differences between gender in distribution of prepubertal/early pubertal children and distribution of dippers/non-dippers respectively. An analysis of variance (ANOVA) was used to evaluate the gender difference in normally distributed anthropometric variables, and an analysis of variance with covariates (ANCOVA) was used to evaluate the gender difference, adjusted for pubertal status, in normally distributed clinical variables.

ANCOVA was used to analyse associations with nocturnal dipping (systolic and diastolic) (daytime BP – night-time BP) or left ventricular mass index. We included gender and pubertal status (prepubertal/early pubertal) as fixed factors. Daytime BP and BMI Z-score were included as covariates in the model. The two-way interaction effect was tested between the fixed-factor pubertal status and the independent variables. Beta (ß) and p values are presented from these analyses. The ß value is the estimate of the partial correlation between the dependent variable and the independent variables.

In the ANCOVA and *t*-test analysis, square-root transformed data were used for the variables HOMA index and serum insulin to obtain normally distributed data. Log-transformed data were used for the variables insulin sensitivity, acute insulin response, and the disposition index. p values <0.05 were regarded as significant.

RESULTS

Characteristics of the study group

Table 1 presents anthropometric and clinical characteristics of the study population. Forty-one percent (n = 33) were girls and there was a higher proportion of prepubertal boys (72%) than girls (33%) (p < 0.001). There was no gender difference in any anthropometric or clinical characteristics, after adjustment for differences in pubertal status, except for higher plasma glucose among boys (5.4 ± 0.4 mmol/L) compared to girls (5.1 ± 0.6 mmol/L) (p = 0.01).

Prepubertal children were younger, weighed less, and were shorter compared to early pubertal children. Prepubertal children had more favourable serum insulin, HOMA indexes, and insulin sensitivity. Prepubertal and early pubertal children did not differ in other variables (Table 1).

Twenty-three percent (four girls, 13 boys) of the children had a high daytime and/or night-time BP, defined as >95th percentile according to Wühl et al. (25). All children were non-diabetic (26). Of the children with polygraph measurements, 66% (n = 29) had no signs of obstructive sleep, 16% (n = 7) had mild obstructed sleep apnoea, 11% (n = 5) had moderate or severe obstructed sleep apnoea.

Prevalence of non-dipping

Forty-two percent of the children (n = 32) were systolic non-dippers and 17% (n = 13) were diastolic non-dippers. Eleven percent of the children were both systolic and diastolic non-dippers (n = 8). There was no difference in prevalence between prepubertal and early pubertal children (p = 0.71) or between genders (p = 0.64).

Associations with dipping

We evaluated the relationship between nocturnal dipping and anthropometrics, measures of insulin-glucose metabolism or polygraphic measurements. BMI Z-score, gender or pubertal status was not associated with systolic BP or diastolic BP dipping in these obese children (ß = −0.16–0.06 p < 0.1–0.8). There was an association or tendency for an association between BMI Z-score and daytime systolic BP (p < 0.01), night-time systolic BP (p = 0.08), and night-time diastolic BP (p < 0.04), but not with daytime diastolic BP (p = 0.20). There were no associations between systolic or

Table 1 Anthropometric and clinical characteristics of prepubertal and early pubertal obese children*

	n	All	n	Prepubertal	n	Early pubertal	$P^{\dagger}$
Age (years)	76	10.4 ± 1.7	42	9.9 ± 1.7	34	11.2 ± 1.3	<0.001
Weight (kg)	76	73.1 ± 15.9	42	67.7 ± 15.4	34	79.9 ± 14.0	<0.001
Height (cm)	62	151.2 ± 11.4	37	147.2 ± 10.5	27	157.1 ± 10.1	<0.001
BMI Z-score	76	6.2 ± 1.6	42	6.5 ± 1.8	34	5.9 ± 1.3	0.06
% Body fat	69	47.6 ± 3.9	38	47.5 ± 3.9	31	47.7 ± 4.0	0.80
% Abdominal fat	68	45.6 ± 5.2	37	45.2 ± 5.2	31	46.0 ± 5.3	0.51
Gender (%) (girls/boys)	76	43/57	42	26/74	34	65/35	0.01
24 h systolic BP (mmHg)	75	113.9 ± 6.8	41	115 ± 6.9	34	112 ± 6.6	0.09
24 h diastolic BP (mmHg)	75	63.2 ± 5.0	41	64.3 ± 4.5	34	62.0 ± 5.4	0.05
Daytime systolic BP (mmHg)	76	118.8 ± 7.5	42	120.1 ± 7.3	34	117.1 ± 7.4	0.08
Daytime diastolicBP (mmHg)	73	68.3 ± 5.8	39	69.5 ± 5.2	34	67.6 ± 6.6	0.17
Night-time systolic BP (mmHg)	76	106.3 ± 7.4	42	107.5 ± 7.1	34	105.0 ± 7.5	0.14
Night-time diastolic BP (mmHg)	76	55.4 ± 5.6	42	55.8 ± 5.5	34	54.9 ± 5.8	0.51
Systolic dipping (%)	76	10.4 ± 5.2	42	10.4 ± 5.4	34	10.3 ± 5.1	0.91
Diastolic dipping (%)	76	18.7 ± 7.6	42	19.6 ± 7.7	34	17.5 ± 7.4	0.25
Plasma glucose (mmol L^{-1})	70	5.3 ± 0.5	38	5.3 ± 0.4	32	5.3 ± 0.6	0.64
Serum Insulin (pmol L^{-1})‡	57	89.2 (26.0–290.0)	28	72.4 (26.0–245.2)	28	111.5 (29.7–290.0)	<0.01
HOMA index‡	60	2.73 (0.13–19.20)	31	2.52 (0.58–8.10)	29	3.31 (0.13–19.20)	0.01
Glycosylated haemoglobin A1c (%)	56	4.3 ± 0.3	33	4.3 ± 0.3	23	4.4 ± 0.3	0.54
Insulin sensitivity ($\times 10^{-5}$ pM^{-1} min^{-1})‡	56	2.71 (0.75–9.47)	28	3.11 (1.00–9.47)	28	2.49 (0.75–4.83)	0.02
Glucose efficiency (min^{-1})	56	0.020 ± 0.01	28	0.020 ± 0.01	28	0.020 ± 0.01	0.56
Acute insulin response (pM)‡	57	1023 (195–5021)	28	944 (207–5021)	29	1162 (195–3817)	0.45
Disposition index ($\times 10^{-5}$ min^{-1})‡	56	2817 (838–10044)	28	2850 (1292–10044)	29	2743 (838–7778)	0.13
Apnoea-hypopnoea index (apneas/hour)‡	44	0.8 (0–21.3)	20	1.15 (0–6,7)	24	0.65 (0–21.3)	0.40
Oxygen desaturation index (desaturations/hour)‡	44	1.95 (0.2–22.3)	21	2.0 (0.2–5.6)	23	1.8 (0.3–22.3)	0.90
Lowest oxygen saturation (%)	46	88 (68–95)	21	89 (80–94)	25	86.0 (68–95)	0.05
Left ventricular mass index (g/$height^{2.7}$)	60	40.8 ± 8.1	35	40.7 ± 9.1	25	40.9 ± 6.6	0.90

*Data shown as the mean ± SD unless indicated otherwise.
†Significance level for the group difference between prepubertal and early pubertal children.
‡Skewed variable presented as median (range).

diastolic dipping and measures of insulin-glucose metabolism after adjustments for BMI Z-score, gender, and pubertal status (ß = −0.13–0.13, p < 0.3–1.0). Nor were there any associations between dipping and the sleep measurements apnoea-hypopnoea index, oxygen desaturation index or lowest oxygen saturation (ß = −0.13–0.12, p < 0.4–0.7).

Associations with left ventricular mass index

The association between left ventricular mass index and BMI Z-score, measures of blood pressure, insulin-glucose metabolism or polygraph measurements was evaluated as an indication of end-organ affect. There was an association between left ventricular mass index and BMI Z-score (ß = 0.45–0.51, p < 0.001) adjusted for gender, pubertal status and measures of systolic BP or diastolic BP. There were no associations between left ventricular mass index and measures of blood pressure (ß = −0.15–0.11, p = 0.2–0.9), insulin-glucose metabolism (ß = −0.16–0.19, p < 0.2–0.9), or measures of SDB (ß = −0.15–0.0, p = 0.3–1.0) adjusted for BMI Z-score, gender and pubertal status.

DISCUSSION

We found a high prevalence of non-dipping among severely obese prepubertal and early pubertal children. The prevalence of non-dipping in this study is almost identical to the data Marcovecchio and colleagues reported previously (12) in a small group of children with the same degree of obesity and within the same age range. In this study, the prevalence of non-dipping was similar among prepubertal and early pubertal children. The prepubertal children also were similar to the early pubertal children in measurements of glucose levels and BP. However, the prepubertal children had a more favourable insulin metabolism, which could be expected because of their prepubertal status (17). Thus, the prevalence of non-dipping among severely obese prepubertal and early pubertal children is found to be around 40%; in other words, it is two times higher than among children in general (1). We were worried to find that already in these young obese children, there was an association between the obesity level and cardiac hypertrophy, an association previously shown in young adults (27).

It can be assumed that SDB affects night-time blood pressure due to frequent arousals and sympathetic activation. Some previous studies have found elevated night-time BP among children initially seeking treatment for SDB (18). We studied the impact of SDB on non-dipping in a group of severely obese children without previous complaints of SDB, and found no associations between dipping and apnoea-hypopnoea index, oxygen desaturation index and lowest oxygen saturation. This is in line with recent findings indicating that SDB does not impair dipping in young children (19). However, the lack of an association could be because of the small number of children with SDB in our study, where only 11% of the children suffered from moderate to severe obstructed sleep apnoea.

The mechanisms behind impaired dipping are not fully known. Compared to lean or overweight children, obese children have a reduced vagal function and an imbalance between the parasympathetic and sympathetic nervous system, especially at night (28,29). This imbalance is suggested to be especially marked in young children with a shorter history of obesity (29). Hyperinsulinemia is suggested as one mechanism causing this imbalance. Petrova and colleagues (13) found that experimentally evoked hyperinsulinemia decreased dipping in healthy, normal-weight adults by disrupting the sympathetic/parasympathetic balance in the autonomic nervous system. Also, we (11) and others (15) have found an association between night-time BP and elevated insulin levels among obese adolescents. In this study, we were the first to investigate this association in younger children using an advanced method for measuring insulin-glucose metabolism (FSIVGTT) (23), and we found no associations. This is in line with the findings of Marcovecchio (12), who found no difference between dippers and non-dippers in a cruder measure of insulin sensitivity, the HOMA index. Our finding that dipping in obese children was not associated with insulin-glucose metabolism could indicate the occurrence of a primary sympathovagal imbalance, caused by the obesity per se. We speculate that as the obese child grows older and hyperinsulinemia develops, the high insulin levels add to the imbalance. Therefore, an association between dipping and a high insulin level appears in adolescents and adults (9,11,13) but not in children.

One strength of this study is that we have used patient-reported awake and sleep periods as a complement to static periods for the classification of day and night-time blood pressure. Also, we used gold standard methods for measuring insulin-glucose metabolism. We performed the blood pressure measurements and polygraphy on different nights in order not to disturb the children's sleep more than necessary. However, this could have negatively affected the possibility of finding associations between dipping and SDB.

The clinical consequences of non-dipping in prepubertal obese children are presently unknown because of the absence of prevalence and long-term follow-up studies. In children with diabetes, a high nocturnal BP is associated with cardiac hypertrophy (2) and renal dysfunction (4). In this study, we found no association between dipping and cardiac hypertrophy. However, considering the high prevalence of non-dipping already in these young obese children, and the suggestion that non-dipping is an early marker of cardiovascular dysregulation (30) and subclinical atherosclerosis (3), it would be important to monitor the diurnal blood pressure variation already occurring in obese prepubertal children.

CONCLUSION

We found a two times higher prevalence of nocturnal non-dipping among severely obese, prepubertal as well as early pubertal children, compared to what has previously been reported among children in general. There were no associations between nocturnal dipping and insulin-glucose metabolism or measures of sleep-disordered breathing in this group.

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DISCLOSURE

There is no conflict of interest to report.

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