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Sleep-disordered breathing in adolescents with obesity: When does it start to affect cardiometabolic health?

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Abstract *Background and aims:* Pediatric obesity and sleep-disordered breathing (SDB) are associated with cardiometabolic risk (CMR), but the degree of severity at which SDB affects cardiometabolic health is unknown. We assessed the relationship between the CMR and the apnea-hypopnea index (AHI), to identify a threshold of AHI from which an increase in the CMR is observed, in adolescents with obesity. We also compared the clinical, cardiometabolic and sleep characteristics between adolescents presenting a high (CMR+) and low CMR (CMR-), according to the threshold of AHI.

Methods and results: 114 adolescents with obesity were recruited from three institutions specialized in obesity management. Sleep and SDB as assessed by polysomnography, anthropometric parameters, fat mass (FM), glucose and lipid profiles, and blood pressure (BP) were measured at admission. Continuous ($MetScore_{FM}$) and dichotomous (metabolic syndrome, MetS) CMR were determined. Associations between $MetScore_{FM}$ and AHI adjusted for BMI, sex and age were assessed by multivariable analyses.

Data of 82 adolescents were analyzed. Multivariable analyses enabled us to identify a threshold of AHI = 2 above which we observed a strong and significant association between CMR and AHI (Cohen's d effect-size = 0.57 [0.11; 1.02] p = 0.02). Adolescents with CMR+

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exhibited higher MetScore$_{FM}$ ($p < 0.05$), insulin resistance ($p < 0.05$), systolic BP ($p < 0.001$), sleep fragmentation ($p < 0.01$) and intermittent hypoxia than CMR- group ($p < 0.0001$). MetS was found in 90.9% of adolescents with CMR+, *versus* 69.4% in the CMR- group ($p < 0.05$).
Conclusions: The identification of a threshold of AHI ≥ 2 corresponding to the cardiometabolic alterations highlights the need for the early management of SDB and obesity in adolescents, to prevent cardiometabolic diseases.
Clinical trials: NCT03466359, NCT02588469 and NCT01358773

Introduction

The prevalence of pediatric overweight and obesity has been increasing over the last few decades, and is now reaching alarming proportions [1]. Pediatric obesity is accompanied by many complications and comorbidities, such as metabolic disorders, amongst others [2]. It is also closely associated with sleep-disordered breathing (SDB) which is observed in 33–61% of obese youths [2–4] *versus* 1–3% in the general pediatric population [5]. Obesity and SDB are both known as independent pro-inflammatory factors [6,7], promoting endothelial and metabolic dysfunctions [7,8] and favoring cardiovascular mortality [6]. Indeed, breathing disorders during sleep are associated with sleep fragmentation [9] and intermittent hypoxia [10], leading to sympathetic overactivity [11] and over-production of radical oxygen species [12]. This inflammatory cascade is involved in the development of numerous cardiometabolic disorders [13]. Concomitantly, adipose tissue dysfunction, observed in pediatric obesity, has been incriminated in the development of insulin resistance [14] which, in turn, has a major impact on the metabolism of triglyceride-rich lipoproteins and free-fatty acids, favoring a pro-atherogenic state [15].

While several studies reported contradictory results regarding the effects of SDB on the development of dyslipidemia [16–18] and insulin resistance [19,20] in youth with obesity, a recent meta-analysis showed that SDB favors increased metabolic impairments in adolescents independently of the effects of obesity [21]. SDB has indeed been shown to be associated with higher systolic blood pressure (SBP), higher triglyceride (TG) and insulin concentrations, as well as reduced levels of high-density lipoprotein-cholesterol (HDL-C) in adolescents with obesity. These variables correspond to the parameters currently retained for the diagnosis of metabolic syndrome (MetS) [22], and there is a body of evidence suggesting a positive association between MetS and the presence of SDB in youth with obesity [17,23].

As a substitute for the MetS, a continuous metabolic score named MetScore [24,25] can be used to overcome the limits of dichotomous definitions. Indeed, in 2009, Thivel and colleagues [26] assessed CMR in children and adolescents with obesity comparing the use of a classical MetS diagnosis based on cut-offs [27], and the MetScore. According to these authors [26], the standard dichotomous definition of the MetS did not adequately diagnose patients at risk of metabolic disorders, and the MetScore could propose a better and accurate alternative. Mostly, our group [28] recently reported an association between this MetScore and the severity of SDB in children with obesity, despite the absence of any significant difference in the rate of children diagnosed with MetS as per the classical definition, confirming its limited clinical significance.

Finally, if it is recognized that SDB has deleterious effects on cardiometabolic health in adolescents with obesity [21], the degree of severity at which SDB affects cardiometabolic health is unknown.

In that context, the objectives of the present study were, first, to assess the relationship between the MetScore$_{FM}$ and the apnea-hypopnea index (AHI) in order to identify a threshold of AHI from which an increase in the severity of the CMR is observed, in a population of adolescents with obesity. Second, we compared the clinical, cardiometabolic and sleep characteristics between adolescents presenting a high (CMR+) and low CMR (CMR-), according to the threshold of AHI. We hypothesized that participants with CMR+ would exhibit greater fat mass (FM) and waist circumference (WC), along with higher dyslipidemia, insulin resistance and SBP, as well as greater nocturnal intermittent hypoxia and fragmented sleep, compared to participants with CMR-.

Methods

Participants

One-hundred fourteen adolescents (69 girls and 45 boys) with obesity were recruited from three institutions specialized in the management of adolescent obesity; 39 adolescents were recruited through the pediatric obesity center of Clermont-Ferrand, France, 29 adolescents from the pediatric obesity center of Besançon, France, and 46 adolescents were recruited from the institution of Saõ Paulo, Brazil. Obesity was defined as age-specific BMI greater than the IOTF-30 according to the International Obesity Task Force (IOTF) references [29].

The flow chart of the study is presented in Fig. 1.

Protocol overview

The present analyses were performed as part of a collaborative project focusing on sleep and cardiometabolic health in adolescents with obesity, combining identical data from Clermont-Ferrand (ethical agreement of the University Hospital of Clermont-Ferrand, France: 2017-A00817-46, registered with ClinicalTrials. Gov under the identifier NCT03466359), Besançon (ethical agreement of the University Hospital of Besançon, France: 2015-A00763-46, registered with ClinicalTrials. Gov under the identifier NCT02588469), and Saõ Paulo (ethical agreement of the Universidade Federal of Saõ Paulo, Brazil: #0135/04, registered with ClinicalTrials. Gov under the identifier NCT01358773). Any potential experimental center effects have been tested on the outcome studies by comparing data between the three experimental sites. Since no effect was observed, pooling of the data from all three centers was possible.

The studies were performed in accordance with the Declaration of Helsinki. All participants and their parents or legal guardians were fully informed of the experimental procedures and provided written informed consent before enrollment in the study.

Experimental procedures

At enrollment in the institutions, clinical evaluation, blood pressure measurement, nocturnal recordings and fasting blood sample collection the following day were performed for all participants.

Clinical evaluations

Body weight was measured to the nearest 0.1 kg using a calibrated scale and height was determined to the nearest 0.01 m using a standing stadiometer for each child. BMI was calculated as body mass divided by height in meters squared ($kg.m^{-2}$). Waist circumference (WC) was measured to the nearest 0.5 cm in a standing position with a standard non-elastic tape that was applied horizontally midway between the last rib and the superior iliac crest.

BMI *z*-score was calculated for age and sex reference values adapted to the international pediatric population [30]. Body composition was assessed by three different techniques depending on the center: In Clermont-Ferrand, body composition was assessed by dual-energy X-ray absorptiometry (DXA) following standardized procedures (QDR4500A scanner, Hologic, Waltham, MA, USA). In Besançon, body fat mass (FM)

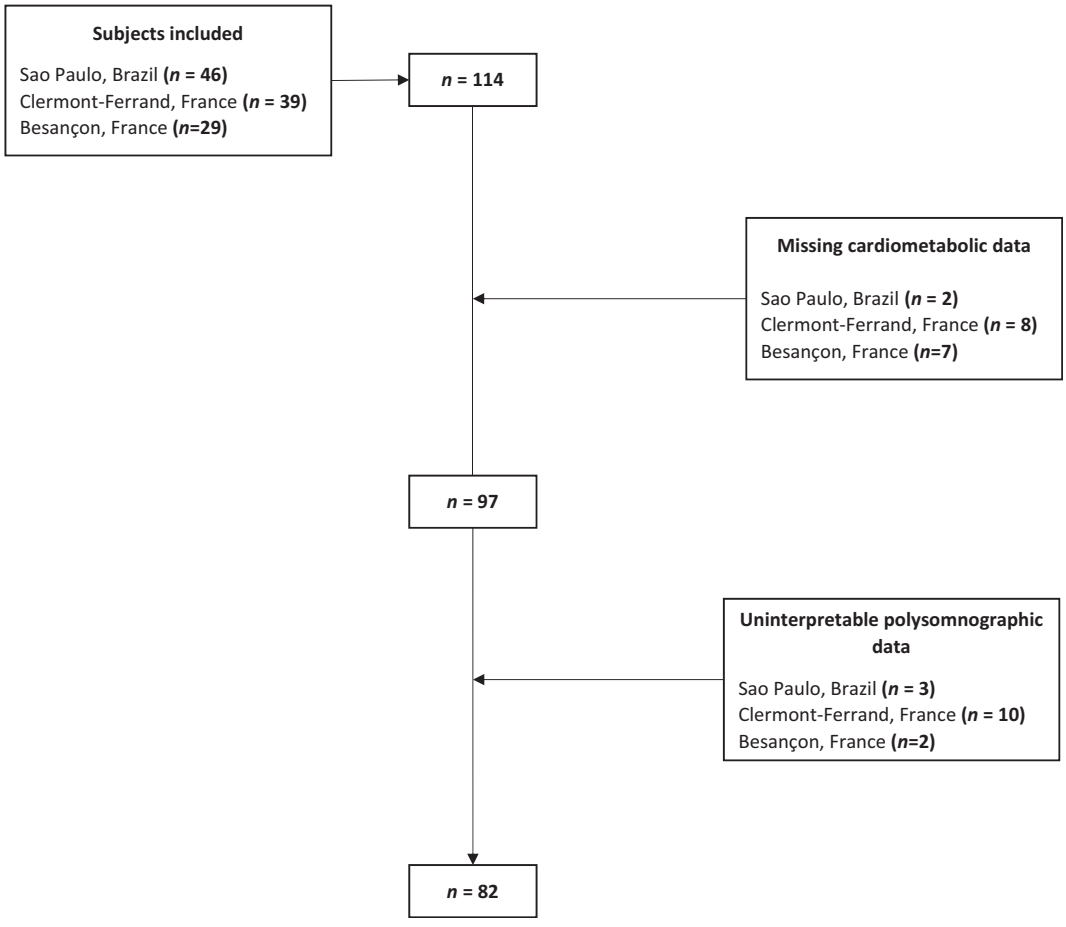

Figure 1 Flow chart of the study population.

and fat-free mass (FFM) were measured by multi-frequency bioelectrical impedance analysis (MF-BIA, SFB7 model, Impedimed Limited, Pinkenba, Queensland, Australia) using four body surface electrodes in the supine position. BIA was performed in a fasting state after voiding the bladder. Finally, in Saõ Paulo, body composition was measured by plethysmography in a BOD POD body composition system (version 1.68; Life Measurement Instruments, Concord, CA, USA).

Both multi-frequency bioelectrical impedance analysis and air plethysmography have shown good agreement with DXA for body composition assessment in children and adolescents [31–34].

Blood pressure measurement

Systolic and diastolic blood pressures (SBP and DBP, respectively) were measured in a seated position after 20min resting using an auditory stethoscope with a blood pressure cuff adapted to the arm circumference (Column Trimline graduated in mmHg, blood pressure cuff Welch Allyn).

Nocturnal recordings

All participants underwent a standard polysomnography (PSG) on a weekday and during the school period, under the same conditions. Recordings were performed in the specialized residential nursing institution with an ambulatory polysomnograph (Morpheus, Micromed, Italy and Medatec, DREAM, Belgium) or in the sleep laboratory following an adaptation night (EMBLA S7000, Embla Systems Inc., Broomfield, CO., USA). Sleep was assessed with standard PSG techniques using the 10–20 system [35] and the following variables were also continuously measured and recorded for at least 6 h: Fz, Cz, F4-M1, C4-M1, O2-M1, F3-M2, C3-M2 and O1-M2, left and right electrooculogram, chin electromyogram, left and right anterior tibialis electromyogram and electrocardiogram.

Respiratory efforts were studied by thoracic and abdominal inductance plethysmography. Airflow was measured with a thermistor and nasal pressure cannula. Peripheral oxygen saturation (SpO_2) and heart rate were both recorded by pulse oximetry (Nonin medical, Inc. Plymouth, Minnesota, USA).

The electroencephalogram (EEG) recordings were visually scored in 30-s periods by an experienced board-certified sleep physician using the American Academy of Sleep Medicine's standard rules to obtain the overnight pattern of sleep stages [36].

The following sleep parameters were recorded: sleep latency (time from lights out to sleep onset, defined as the first epoch of any sleep stage, min), total sleep time (TST, min), arousal index (number of arousals/TST, %), percentage of stage 1 sleep in TST (N1, %), percentage of stage 2 sleep in TST (N2, %), percentage of stage 3 sleep in TST (N3, %) and percentage of rapid-eye movement sleep stage in TST (REM, %).

Respiratory events, were scored in 3-min periods for airflow, according to the pediatric criteria, by an experienced board-certified sleep physician according to the criteria of the American Academy of Sleep Medicine [37]. Apnea was defined as $\geq$ 90% reduction in airflow for a duration of at least 2 breaths, associated with the presence of respiratory effort for obstructive apnea (OA), or associated with absent respiratory effort during one portion of the event and the presence of inspiratory effort in another portion for mixed apnea (MA). Central apnea (CA) was defined as $\geq$ 90% reduction in airflow, for at least 20 s with absent inspiratory effort throughout the entire event, or for at least the duration of 2 breaths associated with $\geq$3% fall in oxygen saturation and/or arousal. Hypopnea was defined as $\geq$ 30% reduction in airflow for at least 2 breaths associated with $\geq$3% fall in oxygen saturation and/or arousal. Respiratory Effort-Related Arousal (RERA) was defined as increasing respiratory effort for at least 2 breaths, characterized by a flattening of the inspiratory portion of the nasal pressure, and leading to arousal from sleep [37]. Apnea, obstructive apnea, central apnea, mixed apnea, hypopnea and RERA index (AI, OAI, CAI, MAI, HI and RERA-I, respectively; events per hour) were determined by dividing the number of apnea, obstructive apnea, central apnea, mixed apnea, hypopnea and RERA events, respectively, by hours of sleep. Obstructive apnea-hypopnea index (OAHI; events per hour) was determined by dividing the number of obstructive apnea plus mixed apnea and hypopnea events by hours of sleep. Apnea-hypopnea index (AHI; events per hour) was determined by dividing the number of apneas plus hypopneas by hours of sleep. Respiratory Disturbance Index (RDI) was defined by the sum of AHI and RERA-I indices. Oxygen Desaturation Index (ODI) was determined by dividing the number of oxygen desaturation $\geq$ 3% by hours of sleep.

Blood sample collection

Blood was collected via an antecubital vein after an overnight fast (12-h). Samples were centrifuged (4000 g for 10 min at 4 °C) and plasma was transferred into plastic tubes and kept at −80 °C until analysis. Plasma glucose, total cholesterol, HDL-C, low-density lipoprotein cholesterol (LDL-C) and TG concentrations were determined by enzymatic methods. Plasma insulin concentrations were measured by chemoluminescence. Homeostatic model assessment for insulin resistance ($HOMA_{IR}$) was calculated using the following formula: fasting insulin (mIU/L) *fasting glucose (mmol/L)/22.5 [38]. The intra-assay coefficients of glucose, HDL-C, LDL-C, TG and insulin were 1.8%, 0.8%, 1.0%, 1.0% and 2.3%, respectively.

Metabolic syndrome detection

The presence or absence of MetS was based on the criteria of Chen et al. using thresholds adapted to the pediatric population [39,40]. MetS was considered to be present when a child presented at least 3 of the following criteria: (1) BMI $\geq$ IOTF-30 [29]; (2) SBP or DBP $\geq$ 90th percentile [41]; (3) HDL-C $\leq$ 0.4 g L^{-1} [40]; (4) TG $\geq$ 1.3 g L^{-1} [40] and (5) $HOMA_{IR} \geq$ 75th percentile [42].

Cardiometabolic risk scores

In the absence of site differences, a continuous CMR score ($MetScore_{FM}$) [24,25] was calculated in the whole sample, according to previous studies [26,28,43]. *Z*-scores of the 6 following variables were calculated: fasting insulin and glucose, TG, HDL-C, FM_{kg}, and SBP and DBP average. Each z-score was obtained by subtracting the sample mean from the individual value divided by the standard deviation (SD) of the sample mean: z-score = (individual value − sample mean)/SD.

The 6 z-scores were then summed, except for HDL-C z-score which was deducted because of its decreased health risk with higher values, and then divided by 6 to create a continuous CMR score; $MetScore_{FM}$.

Statistical analysis

Statistical analysis was performed using STATA software (version 13, StataCorp, College Station, Texas, USA). The statistical tests were two-sided, with type I error at 0.05. Data are presented as mean ± standard deviation (SD) and as median (25−75% ranges). The Kolmogorov-Smirnov test was used to test the assumption of distribution normality for quantitative parameters.

First, a sensitivity analysis was conducted to determine the best threshold of AHI from which CMR is increased using (i) Hedges' effect size (ES) for univariate analysis and (ii) regression coefficients (β) for multivariable analysis. More precisely, for each value of AHI between 1 and 3, $MetScore_{FM}$ was compared among $<$ or $\geq$ of each value of AHI. The results were expressed as ES and 95% confidence interval (95%CI), and were interpreted according to Cohen's rules of thumb which defined effect-size bounds as: small (ES: 0.2), medium (ES: 0.5) and large (ES: 0.8: grossly perceptible and therefore large). Multivariable analysis was then performed to take into account possible cofounders covariates as sex, age and BMI. Results were expressed as β coefficients and 95%CI. The range fixed for the sensitivity analysis (AHI between 1 and 3) was determined according to statistical AHI distribution.

Finally, unpaired t test, Welch's test or Chi^2 test were performed as appropriate, to compare data between participants exhibiting CMR+ and CMR-

Results

Characteristics of the population

One-hundred fourteen adolescents (69 girls and 45 boys) were eligible at admission. Seventeen participants (12 girls, 5 boys) were excluded because they did not undergo blood sample collections or blood pressure assessments, and 15 (8 girls, 7 boys) because they presented poor quality of polysomnographic data.

In total, 82 participants (49 girls, 33 boys) with a mean age (±SD) of 15.03 ± 1.68 years were then considered for analysis. Participants presented a median BMI (25−75% range) of 35.43 (33.45−42.11). MetS was observed in 64 participants (78%). Overall, AHI ranged from to 0 to 22.9 events per hour, with a median AHI (25−75% range) of 1.40 (0.40−3.23). Results are presented in Table 1.

Sensitivity analysis to determine the threshold of AHI from which CMR is increased

As presented in the statistical analysis section, for each value of AHI between 1 and 3, $MetScore_{FM}$ was compared among $<$ or $\geq$ of each value of AHI. Results are presented in Fig. 2, with effect sizes and 95% CI for univariate analyses, and with regression coefficients and 95% CI for multivariable analyses adjusted for age, BMI and sex. For AHI between 1.50 and 2.40, $MetScore_{FM}$ was statistically associated with AHI. Specifically, for AHI = 2, ES = 0.57 [0.11; 1.02] ($p = 0.02$) and $\beta = 0.25$ [0.04; 0.47] ($p = 0.02$).

Comparison of participants of the CMR+ group (AHI ≥2) and the CMR- group (AHI < 2)

Accordingly, the 33 participants who exhibited an AHI ≥2 were allocated to the CMR+ group (40.2%), while the 49 participants with an AHI < 2 were allocated to the CMR- group (59.8%).

Clinical characteristics

Adolescents with CMR+ and CMR- presented similar age, body weight, height, BMI and body composition, while a greater waist circumference was observed in the CMR+ group ($p < 0.05$, Table 1).

Cardiometabolic data

Total cholesterol, LDL-C, HDL-C and TG concentrations were similar between the two groups, despite a trend towards lower HDL-C in participants with CMR+ ($p = 0.08$). Insulin concentrations and $HOMA_{IR}$ were significantly higher in the CMR+ group ($p < 0.05$) with no difference in glucose concentrations. SBP was higher in the CMR + group ($p < 0.001$) while DBP was not different between groups.

As expected, $MetScore_{FM}$ was higher in the group of participants with CMR+ ($p < 0.05$). A higher prevalence of MetS was found in participants with CMR+ compared to participants with CMR- (90.9% *vs* 69.4%, $p < 0.05$, Table 1).

Sleep data

TST and sleep latency were similar between the two groups. Regarding sleep architecture, only N1% was found in higher proportions in participants with CMR+ ($p < 0.05$) and N2%, N3% and REM% were similar between groups.

Arousal index was greater in the CMR+ group ($p < 0.01$). Regarding the respiratory events, AHI, AI, OAI, CAI, OAHI and HI were higher in the CMR+ group ($p < 0.001$), while MAI did not differ between groups. RERA and RDI were greater in the group of CMR+ participants ($p < 0.01$ and $p < 0.0001$, respectively). Finally, both nadir SpO_2 and ODI were higher in the group of participants with CMR+ (respectively; $p < 0.001$ and $p < 0.0001$, Table 1).

Table 1 Clinical, cardiometabolic and sleep characteristics of participants with CMR- and CMR+, depending of the AHI threshold (AHI < or ≥ 2).

	Whole population	CMR- (AHI < 2)	CMR+ (AHI ≥ 2)	*p*
n (%)	82 (100)	49 (59.8)	33 (40.2)	
Clinical characteristics				
Boys/Girls	33/49	15/34	18/15	<***0.05***
Age (yrs)	15.03 ± 1.68	15.18 ± 1.72	14.79 ± 1.61	*0.30*
Body weight (kg)	101.30 (91.51–118.00)	100.60 (89.77–111.40)	104.50 (93.27–122.50)	*0.21*
Height (cm)	1.67 ± 0.07	1.67 ± 0.07	1.67 ± 0.07	*0.65*
BMI (kg/m^2)	35.43 (33.45–42.11)	35.34 (33.02–40.40)	36.45 (33.65–42.75)	*0.27*
BMI z-score	2.39 ± 0.32	2.34 ± 0.28	2.47 ± 0.36	*0.07*
Waist Circumference (cm)	102.00 (94.63–112.00)	100.00 (93.00–109.80)	103.50 (96.00–123.00)	<***0.05***
Fat mass (%)	42.43 ± 6.26	43.10 ± 6.25	41.43 ± 6.23	*0.25*
Fat mass (kg)	41.25 (35.15–54.95)	41.25 (35.27–54.95)	41.43 (35.08–55.06)	*0.99*
Fat-free mass (kg)	57.65 (52.56–64.77)	56.34 (52.05–62.90)	59.11 (53.44–69.41)	*0.06*
Cardiometabolic data				
Total Cholesterol (g/L)	1.45 (1.26–1.77)	1.45 (1.32–1.73)	1.44 (1.17–1.88)	*0.97*
LDL-C (g/L)	0.89 ± 0.30	0.90 ± 0.28	0.88 ± 0.34	*0.81*
HDL-C (g/L)	0.43 ± 0.09	0.45 ± 0.09	0.41 ± 0.08	*0.08*
Triglycerides (g/L)	0.92 (0.67–1.13)	0.88 (0.66–1.11)	0.95 (0.69–1.27)	*0.42*
Glucose (g/L)	0.86 (0.80–0.90)	0.86 (0.81–0.90)	0.85 (0.80–0.88)	*0.70*
Insulin (μUI/mL)	17.40 (13.20–23.43)	16.2 (12.4–22.45)	20.6 (15.2–26.2)	<***0.05***
$HOMA_{IR}$	3.80 (2.72–4.86)	3.60 (2.50–4.50)	4.40 (3.27–4.93)	<***0.05***
Systolic blood pressure (mmHg)	120 (110–130)	120 (110–120)	130 (120–130)	<***0.001***
Diastolic blood pressure (mmHg)	70 (70–80)	70 (70–80)	70 (65–80)	*0.9*
$MetScore_{FM}$	−0.01 (−0.35-0.22)	−0.13 (−0.45-0.15)	0.05 (−0.19-0.40)	<***0.05***
Metabolic syndrome *n* (%)	64 (78.0)	34 (69.4)	30 (90.9)	<***0.05***
Sleep data				
Total sleep time (min)	433 (401.9–465.3)	437 (400.5–474.3)	428 (406.5–461.5)	*0.58*
Sleep latency (min)	14.50 (8.30–28.00)	14.20 (9.00–27.50)	14.80 (6.15–30.05)	*0.93*
Stage N1 (% TST)	6.65 ± 3.59	5.99 ± 2.94	7.63 ± 4.24	<***0.05***
Stage N2 (% TST)	50.56 ± 6.97	51.15 ± 7.44	49.67 ± 6.20	*0.35*
Stage N3 (% TST)	24.37 ± 6.67	24.59 ± 7.32	24.03 ± 5.67	*0.70*
REM (% TST)	18.40 ± 4.95	18.23 ± 5.07	18.64 ± 4.85	*0.72*
Arousal index (nb/h)	7.40 (5.05–9.65)	6.20 (4.45–8.60)	8.40 (6.30–11.90)	<***0.01***
AHI (nb/h)	1.40 (0.40–3.23)	0.50 (0.10–1.10)	4.30 (2.65–7.40)	<***0.0001***
AI (nb/h)	0.10 (0.00–0.53)	0.00 (0.00–0.20)	0.60 (0.20–1.45)	<***0.0001***
OAI (nb/h)	0.00 (0.00–0.40)	0.00 (0.00–0.00)	0.30 (0.00–0.85)	<***0.0001***
MAI (nb/h)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	*0.08*
CAI (nb/h)	0.00 (0.00–0.93)	0.00 (0.00–0.01)	0.10 (0.00–0.65)	<***0.001***
OAHI (nb/h)	1.25 (0.30–3.53)	0.40 (0.05–1.00)	3.80 (2.55–6.85)	<***0.0001***
HI (nb/h)	1.10 (0.30–2.50)	0.40 (0.00–0.90)	3.60 (2.15–5.40)	<***0.0001***
RERA-I (nb/h)	1.10 (0.00–5.85)	0.00 (0.00–4.25)	5.00 (0.00–8.35)	<***0.01***
RDI (nb/h)	5.20 (0.50–10.13)	1.00 (0.25–4.30)	10.40 (7.40–12.35)	<***0.0001***
Nadir SpO_2 (%)	90.00 (85.00–92.00)	91.00 (87.70–93.00)	87.50 (80.75–90.00)	<***0.001***
ODI ≥3% (nb/h)	2.40 (0.80–4.50)	1.85 (1.10–2.83)	4.35 (2.75–5.68)	<***0.0001***

Values are presented as mean ± sd and as median (25–75% range). Comparison between groups with CMR- (AHI < 2) and CMR+ (AHI ≥ 2); Unpaired *t* test for parametric data, Welch's test for non-parametric data. Chi^2 for qualitative data. AHI = apnea-hypopnea index; AI = apnea index; BMI = body mass index; CAI = central apnea index; CMR = cardiometabolic risk; HDL-C = high-density lipoprotein cholesterol; $HOMA_{IR}$ = homeostatic model assessment for insulin resistance; LDL-C = low-density lipoprotein cholesterol; MAI = mixed apnea index; OAHI = obstructive apnea-hypopnea index; OAI = obstructive apnea index; ODI = oxygen desaturation index; RDI = respiratory disturbance index; REM = rapid-eye movements sleep; RERA-I = respiratory-related arousal index; SpO_2 = peripheral oxygen saturation.

Discussion

The prevalence of pediatric obesity continues to grow worldwide [1], associated with an alarming prevalence of SDB [2–4], promoting systemic inflammation [6,7] and increased risks for cardiovascular and metabolic diseases [6]. If the management of SDB in adolescents with obesity is challenging [2,4], its relationship with cardiometabolic health deserves to be clarified, and it remains especially unclear when SDB starts affecting cardiometabolic health. Then, the main objective of the present study was to assess the relationship between the $MetScore_{FM}$ and the AHI, in order to identify a threshold of AHI from which an increase in the severity of the CMR is observed, in a population of adolescents with obesity. Second, we aimed to assess the differences, in terms of clinical, cardiometabolic and sleep parameters, between the adolescents identified with high (CMR+) and low CMR (CMR-), according to the threshold of AHI.

In our population of adolescents with severe obesity, AHI ranged from 0 to 22.9 events/hour, and we found an alarming rate of MetS at around 78%. This prevalence, although high, is consistent with that previously reported by our research group in children with obesity [28] and

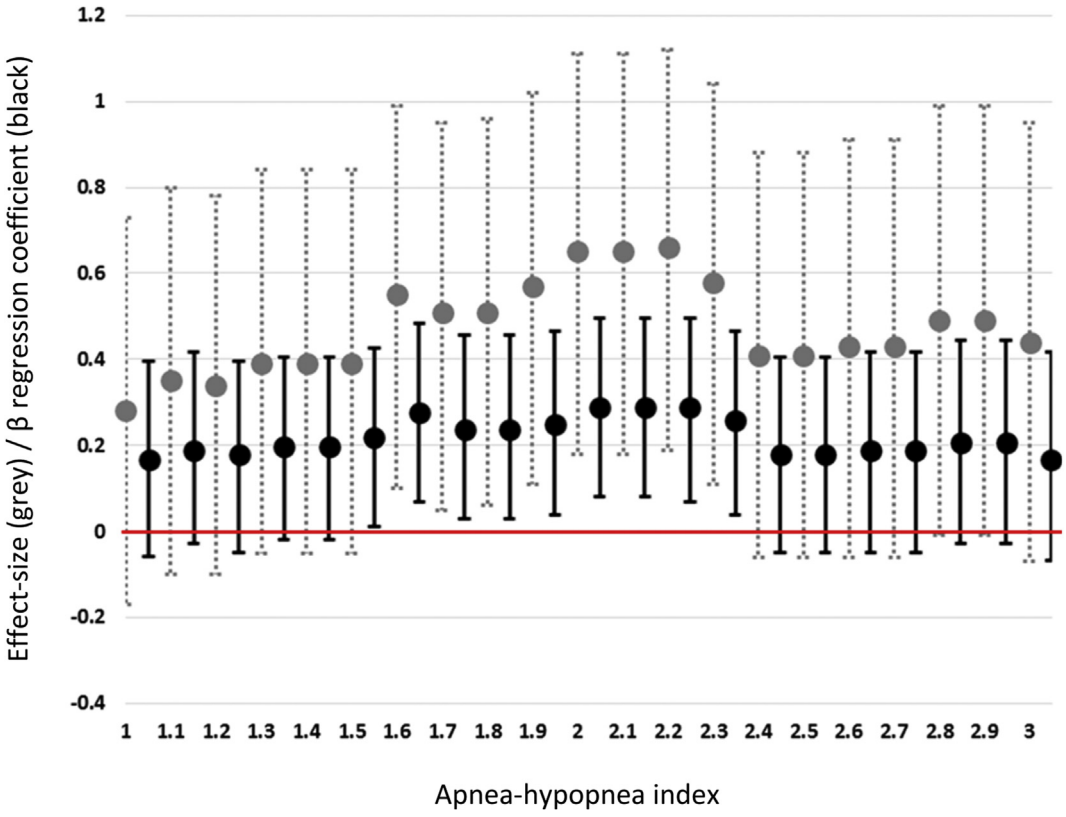

Figure 2 Sensitivity analysis studying the relationship between $MetScore_{FM}$ and AHI. Grey: Effect-size and 95% CI (univariate analysis), Black: β regression coefficient from linear regression and 95% CI (multivariable analysis).

emphasizes the deleterious effects of obesity and SDB on cardiometabolic health. The detection of MetS, although commonly used to identify patients at risk for cardiovascular disease [44], is based on a dichotomous approach that presents several limitations [26], also leading us to investigate the association between CMR and SDB using continuous score ($MetScore_{FM}$).

Multivariable analyses adjusted for BMI, sex and age enabled us to identify a range of thresholds of AHI above which we observed a strong and significant association with CMR. Indeed, significant associations were found between $1.5 \leq$ AHI <2.4. Beyond the threshold of AHI $= 2.4$, the thresholds were less sensitive to discriminate participants who exhibited CMR+ from those exhibiting CMR- (i.e. there was no significant association between CMR status and SDB status as defined by an AHI above a certain threshold). Importantly, the strongest association between the $MetScore_{FM}$ and AHI was observed around a clinically useable threshold of AHI $= 2$. This threshold corresponds to the one commonly used, arbitrarily, to determine SDB in the adolescents with obesity [45], and the present result seems then to confirm its clinical relevance. To the best of our knowledge, this study is the first to propose a threshold of SDB from which CMR seems to be significantly increased in adolescents with obesity.

Based on our analysis, adolescents in the present study were then classified as CMR+ (AHI ≥ 2) or CMR- (AHI < 2), enabling us to report an alarming prevalence of MetS in adolescents with CMR+ (90.9%) as compared with participants with CMR- (69.4%). Additionally, the classification according to an AHI $\geq$2 allowed us to report a prevalence of SDB of 40.2% in our sample, which is consistent with the current literature [2–4].

Despite similar age, BMI, BMI z-score and percentage of fat mass and fat-free mass, the adolescents with CMR+ showed higher WC, indicating greater abdominal obesity, compared with participants with CMR-. In the literature, inconsistent results regarding the relation between SDB and abdominal obesity assessed by WC in adolescents are reported [4,28]. For instance, Verhulst and colleagues [46], in a study assessing 104 youths with overweight or obesity, reported that SDB was independent of WC. In 2011, Canapari and colleagues [47] however showed that visceral adiposity, as measured by magnetic resonance imaging (MRI) at L4, was a significant predictor of the SDB severity in adolescents with obesity independently of BMI. Our results seem to be in line with those of Canapari et al. [47], noting however that simple WC assessment does not make it possible to distinguish between visceral and subcutaneous abdominal fat mass. On the other hand, the same authors [47] reported that AHI was associated with insulin resistance.

In the current study, we reported higher levels of insulin and greater $HOMA_{IR}$ for similar glucose levels, along with greater SBP, and a trend for lower concentrations of HDL-C in the group of adolescents with CMR+, compared to adolescents with CMR-. These three parameters of

cardiometabolic health seem to be the first affected by SDB in this population.

Indeed, the association between insulin resistance, which is characterized by elevated levels of insulin and high $HOMA_{IR}$, and SDB, is well documented in the literature [20,47] and may be explained through numerous pathways. Among others, sympathetic overactivity induced by intermittent hypoxia and sleep fragmentation leads to the release of catecholamines which, in turn, decrease the peripheral absorption of glucose by insulin and increase insulin resistance [48]. Also, gluconeogenesis, induced by sympathetic overactivity would contribute to high fasting glycemia, promoting type 2 diabetes [49]. Moreover, intermittent hypoxia may attenuate the glucose-induced secretion from pancreatic β-cells through the downregulation of the CD38 gene that is implicated in insulin release [50]. In 2012, Lesser and colleagues [20] reported that sleep fragmentation and intermittent hypoxia were associated with decreased insulin sensitivity in a population of obese adolescent males. As expected, in our study, we observed substantial sleep fragmentation and intermittent hypoxia in adolescents with CMR+ compared to their counterparts with CMR-, and these alterations might have promoted the observed insulin resistance.

Moreover, higher SBP was observed in adolescents with CMR+ while no difference in DBP was found. Similar results have recently been reported by Horne and colleagues [51] in a population of adolescents with SDB compared to their counterparts without SDB and to normal-weight adolescents with SDB. In their study, Horne et al. reported that obese youth with SDB exhibited impaired autonomic control in addition to elevated BP. As for insulin resistance, high SBP may be explained by recurrent nocturnal sympathetic overactivity. Additionally, intermittent hypoxia may lead to over-reactivity of peripheral chemoreceptors, leading to diurnal hypertension [11,52].

Although we did not report any difference in TG and LDL-C concentrations between our two groups, we found a trend towards lower HDL-C concentrations in the CMR+ group, as already reported in similar groups of subjects [21,53]. HDL-C has anti-atherogenic and antioxidant properties [54] which might be disturbed by SDB. Tan and colleagues reported in a controlled study focusing on adults with SDB that, despite having similar concentrations of TG, LDL-C and HDL-C to controls, subjects with SDB had a greater degree of HDL-C dysfunction [55]. In fact, HDL-C was dysfunctional in preventing the formation and inactivation of oxidized lipids. Interestingly, the authors [55] outlined that HDL-C dysfunction was strongly associated with markers of oxidative stress, itself induced by intermittent hypoxia [56]. Additionally, Li and colleagues, in an animal study assessing the effects of moderate and severe chronic intermittent hypoxia on lipid metabolism, reported that even mild to moderate SDB might increase lipid peroxidation, a consequence of oxidative stress, promoting atherosclerosis [57].

Insulin resistance, elevated BP and low HDL-C concentrations are among the criteria for MetS. The association between MetS and SDB in adolescents with obesity remains controversial [16,58–60]. There are at least probable explanations for this: firstly, discrepancies regarding the retained parameters, and their thresholds, for MetS definition and secondly, discrepancies regarding the retained cut-off for SDB diagnosis, making it difficult to compare results between studies. In 2015, Erdim and colleagues [59] investigated this relationship and failed to observe any difference in MetS prevalence between adolescents with and without SDB, the latter being diagnosed as AHI $\geq$1. By contrast, Redline and colleagues [60] reported a prevalence of MetS of 59% in adolescents with SDB, using a cut-off of AHI $\geq$5, while it reached 16% in adolescents without SDB. In the present study, we proposed to assess the relationship between the CMR severity and the AHI, in order to identify a threshold of AHI from which we observe an increase in the severity of the CMR. Following this method, we found that cardiometabolic health was affected from AHI = 2 and we reported an alarming prevalence of MetS in adolescents with CMR+ (90.9%) as compared with participants with CMR- (69.4%). The high rates of MetS reported in our overall population (78%), compared to the previously cited studies, might be explained by the severity of obesity of our population.

In light of these results, the identification of a threshold of AHI corresponding to the cardiometabolic alterations in adolescents with obesity seems of major importance since it highlights the need for the early management of both SDB and obesity in this population.

This study has some limitations that deserve to be underlined. First, body composition was assessed using three different methods, and this potentially introduced bias in comparing participants. Despite the fact that both multi-frequency bioelectrical impedance analysis and air plethysmography have shown good agreement with DXA for body composition assessment in children and adolescents [31–34], it would have been preferable to use a single method, ideally DXA. This was unfortunately not possible due to the availability of different facilities between sites. Obviously, the use of MRI would have been relevant in order to assess visceral fat mass in our population. Second, it would have been relevant to propose a MetScore including a measure of central obesity, since this parameter has been found to be associated with SDB. While the measurement of WC was part of our clinical evaluation, this remains a multi-center study, and different experimentators assessed WC, increasing the potential inter-experimentator variability of its measure, which explains why we did not prefer to include WC in the calculation of the MetScore.

Third, despite insulin, glucose and lipid profiles were measured following the same methodology, different kits were used among the sites, and the analyses were performed at different time and by different experimentators. As such, we cannot ignore the inter-assay variability, which must be taken into account when interpreting the present findings.

Fourth, the present study exclusively included participants with obesity, and so, at risk for metabolic abnormalities. As such, the present findings cannot be generalized to populations that include normal-weight individuals.

Finally, two out of three centers proposed an adaptation night before the recording used for analysis. Nevertheless, as we did not discuss sleep stages in the present study and since respiratory events were presented in the form of indices, the lack of an adaptation night does not reduce the significance of our results. Finally, the measurement of carbon dioxide concentrations by capnometry during the night would have been interesting for the assessment of the obesity hypoventilation syndrome, as often found in individuals with obesity, but it was not possible for practical reasons.

In conclusion, this study is, to the best of our knowledge, the first to propose a threshold of SDB from which affected CMR is found. Multivariable analyses adjusted for BMI, sex and age enabled us to identify a threshold of AHI = 2 above which we observed a strong and significant association between CMR and AHI. Secondary, we were able to compare the clinical and cardiometabolic parameters of participants identified with CMR+ and CMR-.

According to this classification, we reported that adolescents with CMR+ and AHI ≥2, presented substantial insulin resistance and high SBP, certainly mediated through sleep fragmentation, intermittent hypoxia and sympathetic overactivity. An alarming prevalence of MetS was found in our overall population (78%), and more specifically, in the participants identified to have AHI ≥2 (90.9%), emphasizing the additive deleterious effects of SDB on cardiometabolic health in adolescents with obesity.

In the current context of the continued increase in pediatric obesity worldwide, the identification of a threshold of AHI ≥ 2 corresponding to the cardiometabolic alterations in adolescents with obesity seems of major importance since it highlights the need for the early diagnosis and management of SDB, even when considered as mild, and of obesity in adolescents, in order to prevent cardiometabolic diseases. The results of this study provide new insights, and further studies in larger samples of participants are warranted to better explore the relationships between CMR and SDB in adolescents with severe obesity.

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