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Original Article

A multidisciplinary weight loss intervention in obese adolescents with and without sleep-disordered breathing improves cardiometabolic health, whether SDB was normalized or not

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ABSTRACT

Objectives: Pediatric obesity and sleep-disordered breathing (SDB) are strongly associated, and both promote metabolic impairments. However, the effects of a lifestyle intervention on the overall metabolic syndrome (MetS) are unknown. The objectives were i) to evaluate the effects of a lifestyle intervention on cardiometabolic risk (CMR), assessed with a dichotomous (MetS) and a continuous ($MetScore_{FM}$) instrument, in obese adolescents with and without SDB and ii) to compare the post-intervention cardiometabolic responses between adolescents with persistent (apnea-hypopnea index; AHI≥2) or normalized-SDB (AHI<2).

Methods: Seventy-six adolescents with obesity recruited from two specialized institutions underwent a 9–12month diet and exercise intervention. Sleep and SDB (AHI≥2) were studied by polysomnography. Anthropometric parameters, fat mass (FM), glucose, insulin, lipid and leptin profiles, blood pressure (BP), $MetScore_{FM}$ and MetS were assessed pre- and post-intervention. We performed comparisons between Non-SDB and SDB groups and between Normalized-SDB and Persistent-SDB subgroups.

Results: Fifty participants completed the study. Pre-intervention, twenty youth had SDB (40%) with higher insulin concentrations and systolic BP than Non-SDB participants ($p < 0.01$), for a similar degree of obesity. Post-intervention, $MetScore_{FM}$ ($p < 0.001$) and MetS prevalence ($p < 0.05$) were decreased in both groups. Eleven participants (55%) normalized SDB along with a decrease in insulin concentrations and BP ($p < 0.05$). Triglycerides, total cholesterol and LDL-cholesterol concentrations ($p < 0.01$) improved equally in the Normalized and Persistent-SDB subgroups.

Conclusion: SDB was associated with lower insulin sensitivity and higher BP but did not affect the lipid profile. A diet and exercise lifestyle intervention is effective in decreasing the CMR whether or not SDB was normalized in obese adolescents.

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1. Introduction

Pediatric obesity is a chronic pro-inflammatory disease, whose prevalence is still dramatically elevated worldwide [1]. In addition to its well-described relationship with respiratory [2] or functional impairments [3], pediatric obesity is also closely associated with sleep-disordered breathing (SDB), which affects 33–61% of obese youth [4–8] compared to 1–3% in the general pediatric population [9–11].

Obesity and SDB have been recognized as independent risk factors in the development of metabolic disorders and cardiovascular disease [12,13]. Indeed, breathing disorders during sleep are associated with sleep fragmentation [14] and intermittent hypoxia [15], leading to sympathetic overactivity [16,17] and an overproduction of radical oxygen species [18]. These disturbances are involved in the development of type 2 diabetes, hypertension and dyslipidemia [19]. Concomitantly, adipose tissue dysfunction, currently observed in pediatric obesity, has been incriminated in the development of insulin resistance [20,21] which, in turn, has a major impact on the metabolism of triglycerides-rich lipoproteins and free-fatty acids [22]. These disorders represent those assessed for the diagnosis of metabolic syndrome (MetS), and despite contradictive results within scientific literature [23,24], our group reported a positive association between SDB severity and a continuous MetS ($MetScore_{FM}$) [25]. Additionally, Patinkin and colleagues [19] confirmed that SDB was independently associated with the components of the MetS, highlighting the necessity for early screening and care of SDB in this population.

Management of SDB by weight loss in adolescents is challenging since SDB induces sleepiness [26], lower daily physical activity and poor diet [27]. These behaviors can worsen obesity which, in turn, aggravates SDB severity and, finally, complicates the care process [26]. Nevertheless, studies assessing the effects of multidisciplinary interventions associating physical exercise and a balanced diet on SDB severity in adolescents with obesity reported convincing results, SDB being normalized in 46.2–79.7% of the participants at the end of those interventions [8,28–31]. Among these studies, only three investigated the impact of those multidisciplinary interventions on metabolic health, and discordant results were found [8,32,33]. Moreover, none of them assessed all the parameters required for the diagnosis of the MetS and, consequently, none of these studies allow to conclude that multidisciplinary interventions are effective in decreasing cardiometabolic risk in obese adolescents with SDB. Finally, current reports do not allow to distinguish whether metabolic improvement were attributable to SDB normalization, a decrease in obesity severity, or both. For this purpose, comparisons between youth with persistent and normalized SDB post-intervention are of interest.

In that context, the objectives of the present study were to: i) evaluate the effects of a multidisciplinary weight loss intervention on cardiometabolic risk (assessed using both a dichotomous (MetS) and a continuous ($MetScore_{FM}$) instrument) in obese adolescents with and without SDB and; ii) to compare the post-intervention cardiometabolic responses between adolescents with persistent or normalized SDB.

We hypothesized that the multidisciplinary intervention would have beneficial effects on cardiometabolic risk in participants without SDB, and in the ones whose SDB would be normalized post-intervention.

2. Material and methods

2.1. Participants

Seventy-six adolescents (44 girls and 32 boys) with obesity were recruited from two institutions specialized in the management of adolescent obesity; one was located in Besançon, France, and the second one in São Paulo, Brazil. Participants had a Tanner stage of 4–5 in Besançon France, and of 5 in São Paulo, Brazil, assessed by the physician of each institution. Obesity was defined as age-specific BMI greater than the IOTF-30 according to the International Obesity Task Force (IOTF) references [34].

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

2.2. Protocol overview

The analyses have been performed as part of a collaborative project focusing on sleep and cardiometabolic health in adolescents with obesity, combining data from Besançon, France (ethical agreement of the University Hospital of Besançon, France: 2015-A00763-46, Clinical Trial: NCT02588469) and São Paulo, Brazil (ethical agreement of the Universidade Federal of São Paulo, Brazil: #0135/04, Clinical Trial: NCT01358773).

These 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 enrolment in the study. Since no site effect was observed regarding the variable "apnea-hypopnea index" (AHI) and no site × time interaction among any of the measured variables were found, we pooled the data from the two centers (see Supplementary Table S1).

2.3. Experimental procedures

Clinical evaluations, blood pressure measurements, maximal exercise testing's, nocturnal recordings and blood sample collections were performed for all participants at admission and within two weeks before the end of each intervention (9 and 12 months, respectively).

2.3.1. Clinical evaluations

We measured body weight to the nearest 0.1 kg using a calibrated scale and height to the nearest 0.01 m using a standing stadiometer. BMI was calculated for each child. Waist circumference (WC) was measured to the nearest 0.5 cm in a standing position with a standard non-elastic tape that was applied midway between the last rib and the superior iliac crest. BMI *z*-score was calculated for age and sex reference values adapted to the pediatric population [35]. Body composition was assessed by two different techniques depending on the center:

In Besançon France, body fat mass (FM) and fat-free mass (FFM) were measured by multi-frequency bioelectrical impedance analysis (MF-BIA, SFB7 model, Impedimed Limited, Pinkenba, Queensland, Australia) by using four body surface electrodes in the supine position. BIA was performed in a fasting state after voiding the bladder. In São Paulo Brazil, 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

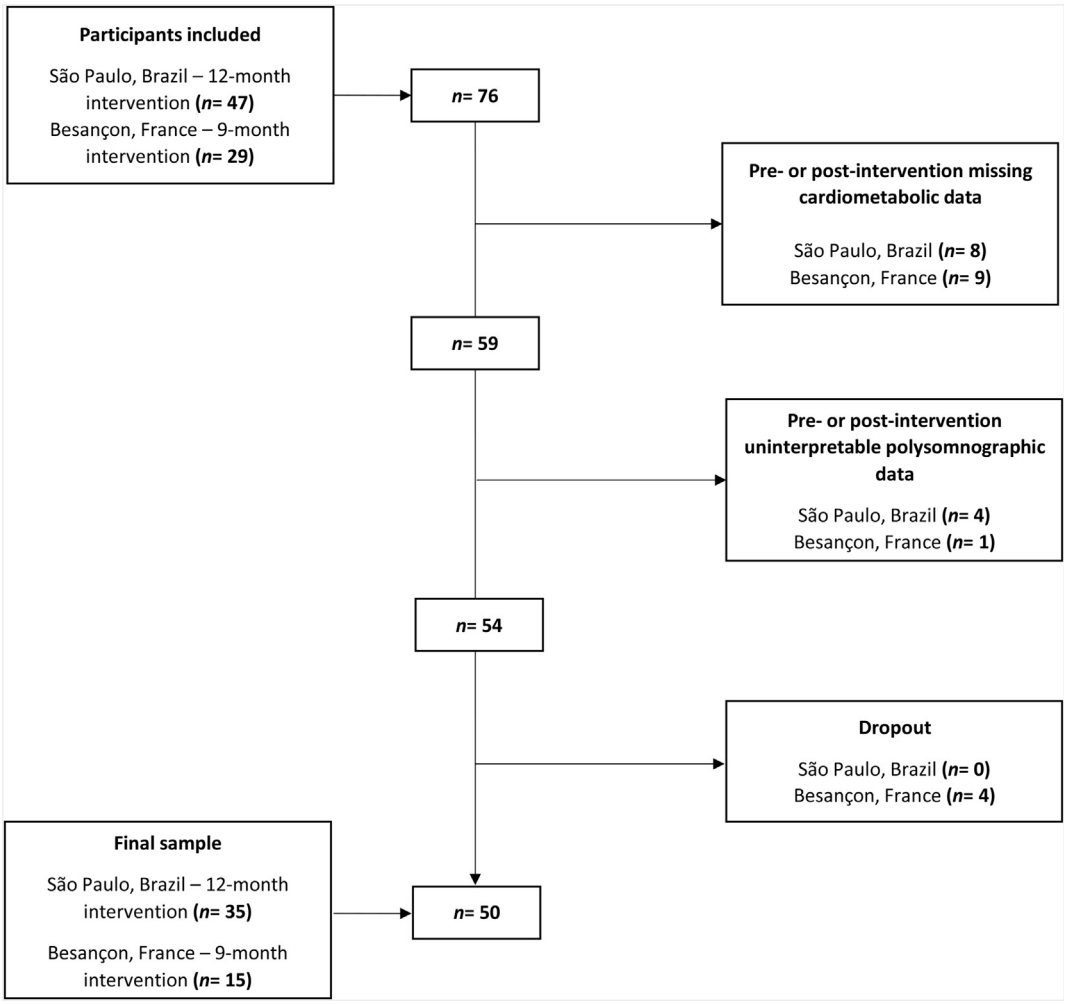

Fig. 1. Flow chart of the study population.

plethysmography have shown a good agreement with the gold standard technique (Dual-energy X-ray absorptiometry, DXA) for body composition assessment in children and adolescents [36–39]. In addition, a recent study showed that body impedance could be used as a surrogate of BOD POD for group estimate of FM% and FFM in adults with obesity [40].

2.3.2. Blood pressure measurements

Systolic and diastolic blood pressures (SBP and DPB, respectively) were measured in a seated position using an auditory stethoscope with a blood pressure cuff adapted to the arm circumference (Column Trimline graduated in mmHg, blood pressure cuff Welch Allyn) after 5 min rest.

2.3.3. Maximal exercise tests

Maximal exercise test was performed at least 2 days before nocturnal polysomnography, because of possible modifications in sleep architecture the night following intense exercise. Peak oxygen uptake (VO_{2peak}) was measured during a graded exhaustive cycling test on a fixed cycle ergometer (Ergoselect 200 K, Ergoline GmbH, Bitz, Germany) with gas exchange measurement (MetaMax®, Matsport, France). The initial power of 30 watts was maintained for 3 min and followed by 10 watts increments every minute. Adolescents were strongly encouraged by experimenters throughout the test to perform a maximal effort. Maximal criteria were peak respiratory exchange ratio (RER: VCO_2/VO_2) >1.1, leveling-off of VO_2 with increased work rate, heart rate (HR) > 90% of the age-predicted maximum heart rate (210−0.65 × age), and/or subjective exhaustion of the participant. Cardiorespiratory fitness, measured through $VO_{2peak,}$ was reported in absolute value (L/min) and then expressed relative to the body weight ($VO_{2peakBW;}$ mL/min/kg), and to the fat-free mass ($VO_{2peakFFM}$; mL/min/kg_{FFM}).

2.3.4. Nocturnal recordings

All participants underwent, under the same conditions, a standard polysomnography (PSG) on a weekday and during the school period. In France, recordings were performed in the specialized residential nursing institution with an ambulatory polysomnograph (Morpheus, Micromed, Italy). In Brazil, they were performed in the sleep laboratory following an adaptation night (EMBLA S7000, Embla Systems Inc., CO, USA). Sleep was assessed with standard PSG techniques using the 10–20 system [41] and the following variables were continuously recorded: 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, and airflow with a thermistor and nasal pressure cannula. Peripheral oxygen saturation (SpO_2) and heart rate were both recorded by pulse oximetry.

The electroencephalogram (EEG) recordings were visually scored in 30-s periods by two experienced board-certified sleep physicians using the American Academy of Sleep Medicine's standard rules to obtain the overnight pattern of sleep stages [42].

The following sleep parameters were recorded: sleep latency (min), total sleep time (TST, min), arousal index (events/h of 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 [obstructive apnea (OA), central apnea (CA), mixed apnea (MA), hypopnea, and respiratory effort-related arousal (RERA)] were scored in 3-min periods for airflow by two experienced board-certified sleep physicians, according to the pediatric criteria of the American Academy of Sleep Medicine [43]. Apnea, OA, CA, MA, hypopnea and RERA index (AI, OAI, CAI, MAI, HI and RERA-I respectively; events/h of TST) were determined. Obstructive apnea-hypopnea index (OAHI, (OA + MA + hypopneas)/h of TST), AHI (events/h of TST), respiratory disturbance index (RDI, events/h of TST) and oxygen desaturation ≥ 3% index (ODI; events/h of TST) were determined.

The diagnosis of SDB was defined by the presence of an AHI ≥2/h of TST [28], and participants were thus classified as SDB group (AHI ≥ 2) or non-SDB group (AHI < 2). At the end of the intervention, two subgroups within the SDB group were defined according to the change of the AHI: Normalized (AHI < 2) and Persistent-SDB subgroups (AHI ≥ 2) [44].

2.3.5. Blood sample collections

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 kept at −80 °C until analysis. Plasma leptin concentrations were assessed by radioimmunoassay. Plasma total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG) and glucose concentrations were determined by enzymatic methods. Plasma insulin concentrations were measured by chemoluminescence. Homeostasis model-assessment of insulin resistance ($HOMA_{IR}$) was calculated using the following formula: fasting insulin (mUI/L)*fasting glucose (mmol/L)/22.5 [45]. 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.

2.4. Multidisciplinary weight loss interventions

The 9-to-12month interventions were respectively performed in two institutions specialized in the management of adolescent obesity; one was located in Besançon, France [7], and the second one in São Paulo, Brazil [32].

2.4.1. 9-Month intervention (Besançon, France)

2.4.1.1. Psychological support. The adolescents were submitted to weekly psychological orientation group sessions and to weekly individual meetings with a trained psychologist. In case of a behavioral disorder, the frequency of individual appointments was adjusted.

2.4.1.2. Diet and nutritional education. Changes in dietary habits included the consumption of a balanced diet and nutritional education sessions. Total daily calorie intake was controlled at about 2300–2500 kcal including 30% fat, 15% proteins and 55% carbohydrates, according to age and recommended French allowances [46]. Individual and group nutritional education sessions, consisting in promoting healthy cooking methods, portion size control and food labelling were held twice a week. Finally, special attention was paid to the subjective feelings of hunger and satiety, and the pleasure of eating.

2.4.1.3. Exercise program. Over the duration of the program, participants exercised 4–5 times/week for 45–60min: interval training program 2 times/week, including 9 sessions of 5 min each (4 min at 50% of VO_{2peak} and 1 min at 85% of VO_{2peak}. Workload was readjusted monthly to maintain target HR over time), moderate and high intensity activities (walking, swimming, cycling, climbing and team sports), and muscle strengthening 3 times/week. Adolescents also had physical education lessons on how to incorporate exercise into their daily life and how to reduce sedentary behaviors.

2.4.2. 12-Month intervention (São Paulo, Brazil)

2.4.2.1. Psychological support. The adolescents were submitted to weekly psychological orientation group sessions based on the psychodynamic approach with a trained psychologist. Individual psychological therapy was recommended when behavioral disorders were found.

2.4.2.2. Diet and nutritional education. Energy intake was set at the levels recommended by the dietary reference intake for subjects with low levels of physical activity of the same age and gender, following a balanced diet [47]. Once a week, adolescents had nutritional lectures for 1 h in small groups by trained nutritionists. The major purpose of the group intervention was to improve knowledge for better choosing meals as well to discuss main difficulties on succeeding in the new healthy lifestyle.

2.4.2.3. Exercise program. Over the duration of the program, participants exercised 3 times/week for 60 min, including 30 min of aerobic training (running on a treadmill at a ventilatory threshold of 1) and 30 min of resistance training per session. The exercises targeted each of the main muscle groups. After an introductory period (2 weeks for adaptation to the training to learn the movements), the training load was adjusted, and each 8-week volume and intensity were adjusted inversely, decreasing the number of repetitions from 15 to 20 to 10–12 and 6–8, respectively, for 3 sets.

2.5. Metabolic syndrome (MetS) detection

The presence or absence of MetS was based on the criteria of Chen et al. using thresholds adapted to the pediatric population [48,49]. MetS was considered when a child presented at least 3 of the following criteria: (1) BMI ≥ IOTF-30 [34]; (2) SBP or DBP ≥ 90th percentile [50]; (3) HDL-C ≤ 0.4 g L^{-1} [49]; (4) TG ≥ 1.3 g L^{-1} [49]; and (5) $HOMA_{IR}$ ≥ 75th percentile [51].

2.6. Cardiometabolic risk scores

A continuous CMR score ($MetScore_{FM}$) was calculated in the whole sample, following the same methods as reported in previous studies [25,52,53]. *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 cardiometabolic risk score; $MetScore_{FM}$.

Post-intervention, Z-scores were calculated as follow: (final individual value − basal sample mean)/basal SD. Then, the 6 z-scores were summed as presented above.

2.7. Statistical analysis

Statistical analysis was performed using STATA software (version 13, StataCorp, College Station, Texas, USA). Data are presented as mean ± standard deviation (SD), with a level of significance set at $p < 0.05$. The Kolmogorov–Smirnov test was used to test the assumption of distribution normality for quantitative parameters. Paired Student's t-tests and Wilcoxon matched pair's tests were used, as appropriate, to compare data in the whole population at admission and post-intervention. Fisher's exact tests were performed to assess qualitative data. A McNemar's test was performed to assess the frequency differences in MetS pre- and post-intervention.

Random-effects models for repeated data were performed to study the evolution between pre- and post-intervention (time effect) for clinical, biological, sleep parameters and cardiorespiratory fitness among participants with or without SDB and with persistent or normalized SDB (group effect). When an interaction between the group and time effects was observed, post-hoc paired Student's t tests were performed.

Changes (Δ) in anthropometric parameters, body composition, cardiorespiratory fitness, sleep parameters and cardiometabolic parameters were calculated using the following formula: [final value − initial value]. Multivariable analyses adjusted for sex and age were performed to examine associations between changes (Δ) in cardiometabolic parameters and anthropometric, body composition, sleep and/or cardiorespiratory parameters. To meet the condition of parsimony in model building, we chose the model with the highest adjusted r^2 and the lowest number of independent variables. In case of collinearity between two variables, we chose the most significant variable in the model adjusted for sex and age. Nonparametric data were log transformed as appropriate.

In supplementary material (Table S1), random-effects models for repeated data were performed to study the evolution between pre- and post-intervention (time effect) for all of the variables, among participants from Brazil (12-month intervention) and from France (9-month intervention), (site effect).

3. Results

3.1. Characteristics of the whole population (n = 50), pre- and post-intervention

Out of the 76 participants recruited, 26 (13 boys, 13 girls) were excluded from the study; 17 participants did not undergo anthropometric measures, blood sample collections or blood pressure assessments, 5 participants presented poor quality of polysomnographic data, and 4 dropped out of the lifestyle intervention program. In total, 50 participants (19 boys, 31 girls) with a mean age ± SD of 15.8 ± 1.5 years were considered for analysis. Participants had a mean BMI of 38.0 ± 6.1 kg m^{-2}.

Pre-intervention mean AHI was 2.7 ± 4.2. MetS was observed in 36 participants (72%), mean $VO_{2peakFFM}$ was 47.4 ± 10.2 ml/min/kg_{FFM}. Results are presented in Table 1.

The intervention significantly reduced body weight, BMI, BMI z-score, WC and FM% ($p < 0.001$), and FFM_{kg} was not changed.

Leptin concentrations ($p < 0.001$), total cholesterol ($p < 0.01$) and TG concentrations were decreased ($p < 0.001$) while HDL-cholesterol concentrations were increased ($p < 0.05$). Glucose and LDL-cholesterol levels were not modified while insulin concentrations and $HOMA_{IR}$ were decreased ($p < 0.01$). SBP and DBP ($p < 0.01$) and $MetScore_{FM}$ decreased ($p < 0.001$) post-intervention. Prevalence of MetS decreased to 36% ($p < 0.001$).

TST, N1, N2 and N3 were not modified by the intervention, whereas REM sleep was increased ($p < 0.05$).

AHI was not modified despite a trend for a decrease ($p = 0.052$). HI was decreased ($p < 0.05$) and AI, RDI, OAHI and ODI were not affected by the intervention.

Finally, absolute VO_{2peak} ($p < 0.05$) and $VO_{2peakBW}$ ($p < 0.001$) were improved by the intervention, while $VO_{2peakFFM}$ remained unchanged (Table 1).

3.2. SDB and non-SDB groups

Among the 50 participants described above, 20 (40%) were diagnosed with SDB, defined as AHI≥2. Those 20 participants made up the 'SDB group' as shown in Table 1. The other 30 participants (with AHI <2) made up the 'Non-SDB group'. The group effect in the analyses below was defined using these two groups, and the time effect was defined using pre- *vs.* post-intervention.

3.2.1. Clinical characteristics

Using mixed models' analyses, for weight, BMI, BMI z-score or FM, we found no significant main effect of group, a significant main effect of time ($p < 0.001$) whereby the intervention significantly reduced all these parameters, and no interaction between the main effects. FFM_{kg} was higher in the SDB group (group effect; $p < 0.05$) and no time effect or time × group interaction was found. Considering WC, a group effect ($p < 0.01$) whereby WC was higher in the SDB group, a time effect ($p < 0.001$) whereby WC significantly decreased post-intervention in the two groups, and a time × group interaction ($p < 0.01$) whereby a greater decrease in WC was observed in the SDB group were found.

3.2.2. Cardiometabolic data

No differences in concentrations of leptin, total cholesterol, HDL-C and TG were found between the SDB and non-SDB groups, and the intervention significantly improved these parameters (time effects: $p < 0.001$, $p < 0.01$, $p < 0.05$ and $p < 0.01$, respectively). There was no interaction between the main effects found for these variables.

LDL-C and glucose concentrations were similar between groups and were not affected by the intervention. Considering insulin and $HOMA_{IR}$, higher values were observed in the SDB group (group effect; $p < 0.001$ and $p < 0.05$, respectively), and the intervention decreased insulin concentrations and $HOMA_{IR}$ severity in both groups (time effect; $p < 0.01$ in both cases). We found no significant interaction between the main effects for insulin and $HOMA_{IR}$ severity.

Group and time effects ($p < 0.05$ and $p < 0.01$) were observed for SBP (higher in the SDB group and an overall decrease after the intervention), while a time effect, only, was found for DBP (decrease post-intervention, $p < 0.001$, see Table 1).

The $MetScore_{FM}$ was not different between the SDB and Non-SDB groups and was decreased by the intervention (time effect; $p < 0.001$) without an interaction between the main effects. Prevalence of MetS was significantly decreased in both groups (time effect: $p < 0.05$, see Table 1).

3.2.3. Sleep data

TST, N1%, N2% and N3% were not different between the two groups, and not modified by the intervention. Regarding REM%, a group and time effects were found ($p < 0.05$), whereby REM% was higher in the SDB group and increased overall post-intervention. The SDB group had a higher arousal index (group effect; $p < 0.01$) but it was not modified after the intervention.

Both a group effect ($p < 0.001$) and a time × group interaction ($p < 0.001$) were found for AHI (higher AHI overall in the SDB group and significant decrease from 6.2 ± 4.9 pre-intervention to 3.0 ± 3.9

Table 1
Clinical parameters, cardiometabolic data, sleep and cardiorespiratory fitness at admission and post-intervention in the whole population and in participants with (SDB group) and without SDB (Non-SDB group).

	Whole population (n = 50, 100%)		SDB Group (n = 20, 40%)		Non-SDB Group (n = 30, 60%)		Group effect	Time effect	Interaction
	Admission	Post-intervention	Admission	Post-intervention	Admission	Post-intervention			
Boys/Girls n (%)	19/31 (38/62)		11/9 (55/45)		8/22 (27/73) ^{ns}				
Clinical parameters									
Age (years)	15.8 ± 1.5	16.7 ± 1.6†††	15.4 ± 1.5	16.3 ± 1.6	16.0 ± 1.5	16.9 ± 1.6	ns	***	**
Height (cm)	167.9 ± 8.0	169.2 ± 8.2†††	168.7 ± 7.9	170.2 ± 8.3	167.3 ± 8.1	168.6 ± 8.2	ns	***	ns
Weight (kg)	107.3 ± 20.1	95.7 ± 18.8†††	113.0 ± 23.1	100.7 ± 22.1	103.6 ± 16.7	92.3 ± 15.7	ns	***	ns
BMI (kg.m^{-2})	38.0 ± 6.1	33.4 ± 5.8†††	39.6 ± 7.3	34.7 ± 7.0	37.0 ± 5.2	32.5 ± 4.8	ns	***	ns
BMI z-score	2.4 ± 0.3	2.0 ± 0.5†††	2.5 ± 0.4	2.1 ± 0.6	2.3 ± 0.3	1.9 ± 0.4	ns	***	ns
WC (cm)	107.4 ± 15.3	95.6 ± 12.2†††	116.4 ± 17.5	98.1 ± 13.3§§§	102.0 ± 11.0	93.2 ± 11.0§§§	**	***	**
FM (%)	44.0 ± 6.0	37.0 ± 6.1†††	42.8 ± 6.5	36.2 ± 6.5	44.7 ± 5.6	37.5 ± 5.9	ns	***	ns
FFM (kg)	58.8 ± 10.5	59.9 ± 11.0 ^{ns}	62.1 ± 12.0	63.8 ± 13.1^{ns}	56.7 ± 9.0	57.4 ± 8.6 ^{ns}	*	ns	ns
Cardiometabolic data									
Leptin (ng/mL)	61.40 ± 28.31	35.08 ± 21.80†††	54.14 ± 20.37	35.45 ± 22.34	65.91 ± 31.78	34.85 ± 21.85	ns	***	ns
Total cholesterol (g/L)	1.61 ± 0.38	1.54 ± 0.32††	1.64 ± 0.46	1.52 ± 0.39	1.59 ± 0.33	1.55 ± 0.26	ns	**	ns
LDL-C (g/L)	0.95 ± 0.31	0.91 ± 0.31 ^{ns}	0.99 ± 0.36	0.91 ± 0.32	0.92 ± 0.28	0.92 ± 0.30	ns	ns	ns
HDL-C (g/L)	0.44 ± 0.09	0.46 ± 0.09†	0.41 ± 0.09	0.49 ± 0.09	0.45 ± 0.10	0.48 ± 0.09	ns	*	ns
TG (g/L)	1.12 ± 0.70	0.89 ± 0.40†††	1.22 ± 0.91	0.89 ± 0.43	1.06 ± 0.52	0.89 ± 0.39	ns	**	ns
Glucose (g/L)	0.87 ± 0.09	0.89 ± 0.10 ^{ns}	0.87 ± 0.11	0.87 ± 0.13	0.88 ± 0.08	0.90 ± 0.08	ns	ns	ns
Insulin (µIU/mL)	17.73 ± 9.58	15.35 ± 12.85††	21.99 ± 12.85	20.75 ± 18.21 ^{ns}	14.89 ± 5.12	11.75 ± 5.31§§	**	**	ns
$HOMA_{IR}$	3.8 ± 2.3	3.5 ± 3.3††	4.8 ± 3.2	4.8 ± 4.8 ^{ns}	3.2 ± 1.1	2.6 ± 1.2§§	*	**	ns
SBP (mmHg)	120.9 ± 11.1	114.9 ± 8.7††	125.3 ± 11.9	116.8 ± 8.5§	118.0 ± 9.6	113.7 ± 8.8$^{0.057}$	*	**	ns
DBP (mmHg)	74.2 ± 7.0	71.0 ± 7.1††	74.0 ± 8.2	69.5 ± 8.6§	74.3 ± 6.3	72.0 ± 6.0$^{0.078}$	ns	**	ns
$MetScore_{FM}$	0.00 ± 0.58	−0.37 ± 0.59†††	0.17 ± 0.67	−0.24 ± 0.80	−0.13 ± 0.48	−0.45 ± 0.39	ns	***	ns
MetS n (%)	36 (72)	18 (36)‡‡‡	17 (85)	8 (40)	19 (63)	10 (33)	ns	*	ns
Sleep parameters									
TST (min)	414.7 ± 69.4	432.7 ± 54.1 ^{ns}	413.4 ± 58.2	440.9 ± 64.4	415.6 ± 76.9	427.5 ± 46.9	ns	ns	ns
N1 (%TST)	6.0 ± 3.6	6.1 ± 2.8 ^{ns}	6.7 ± 3.8	6.4 ± 2.5	5.5 ± 3.4	5.9 ± 3.0	ns	ns	ns
N2 (%TST)	49.9 ± 6.9	48.7 ± 6.8 ^{ns}	48.1 ± 5.4	48.5 ± 6.8	51.1 ± 7.5	48.8 ± 6.9	ns	ns	ns
N3 (%TST)	24.9 ± 6.8	23.9 ± 7.1 ^{ns}	24.8 ± 5.8	22.5 ± 5.1	25.0 ± 7.5	24.7 ± 8.0	ns	ns	ns
REM (%TST)	19.2 ± 4.8	21.2 ± 5.4†	20.4 ± 4.0	22.7 ± 5.0	18.4 ± 5.1	20.3 ± 5.5	*	*	ns
Arousal Index (events/h)	8.7 ± 3.8	9.3 ± 4.9 ^{ns}	9.9 ± 4.3	11.2 ± 5.7	7.8 ± 3.2	8.0 ± 4.0	**	ns	ns
AHI (events/h)	2.7 ± 4.2	1.6 ± 2.8$^{0.052}$	6.2 ± 4.9	3.0 ± 3.9 $^{\$\$}$	0.5 ± 0.5	0.7 ± 0.9 ^{ns}	***	ns	***
AI (events/h)	0.5 ± 0.8	0.3 ± 0.5	1.0 ± 1.0	0.5 ± 0.6 ^{ns}	0.1 ± 0.2	0.2 ± 0.4 ^{ns}	***	ns	**
HI (events/h)	2.3 ± 3.9	1.3 ± 2.5†	5.2 ± 4.8	2.5 ± 3.6 $^{\$\$}$	0.4 ± 0.4	0.5 ± 0.7 ^{ns}	***	ns	***
RDI (events/h)	5.0 ± 6.5	4.0 ± 5.6 ^{ns}	10.8 ± 6.8	7.5 ± 6.8$^{0.056}$	1.1 ± 1.9	1.7 ± 3.0 ^{ns}	***	ns	**
OAHI (events/h)	2.5 ± 4.0	1.5 ± 2.8 ^{ns}	5.7 ± 4.9	3.0 ± 39 $^{\$\$}$	0.4 ± 0.4	0.6 ± 0.8 ^{ns}	***	ns	***
ODI (events/h)	3.5 ± 4.7	2.6 ± 3.7 ^{ns}	7.2 ± 5.6	4.8 ± 4.9 ^{ns}	1.0 ± 1.0	1.1 ± 1.3 ^{ns}	***	*	**
Cardiorespiratory fitness									
VO_{2peak} (L/min)	2.8 ± 0.7	3.0 ± 0.7†	2.9 ± 0.7	3.1 ± 0.7	2.7 ± 0.7	2.9 ± 0.7	ns	**	ns
$VO_{2peakBW}$ (mL/min/kg)	26.1 ± 5.5	31.5 ± 6.7†††	25.7 ± 5.4	31.1 ± 6.0	26.3 ± 5.6	31.7 ± 7.2	ns	***	ns
$VO_{2peakFFM}$ (mL/min/kg_{FFM})	47.4 ± 10.2	50.2 ± 10.4 ^{ns}	46.2 ± 11.4	49.3 ± 10.6	48.3 ± 9.4	50.8 ± 10.5	ns	*	ns

BMI = body mass index; FM = fat mass; FFM = fat-free mass; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides; $HOMA_{IR}$ = homeostatic model assessment for insulin resistance; SBP = systolic blood pressure; DBP = diastolic blood pressure; $MetScore_{FM}$ = cardiometabolic risk score; MetS = metabolic syndrome; TST = total sleep time; N1 = stage N1 sleep; N2 = stage N2 sleep; N3 = stage N3 sleep; REM = rapid eye movement sleep; AHI = apnea-hypopnea index; AI = apnea index; HI = hypopnea index; RDI = respiratory disturbance index; OAHI = obstructive apnea-hypopnea index; ODI = oxygen desaturation index; SDB = sleep-disordered breathing; VO_{2peak} = absolute peak oxygen uptake (L/min); $VO_{2peakBW}$ = peak oxygen uptake expressed relative to body weight (mL/min/kg); $VO_{2peakFFM}$ = peak oxygen uptake expressed relative to fat-free mass (mL/min/kg_{FFM}).
Values are presented as mean ± standard deviation. Paired Student t test for parametric data and Wilcoxon matched pairs test for non-parametric data for comparison in the whole population between admission and post-intervention; ^{ns} not significant, $^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.01$, $^{\dagger\dagger\dagger}p < 0.001$. Random-effects models with effects of group (SDB vs. non SDB), time (post− vs. pre-intervention) and interaction group x time, non-parametric data are log transformed; ^{ns} not significant, *p < 0.05, **p < 0.01, ***p < 0.001. Paired Student's t test for post-hoc comparison between admission and post-intervention for each group; ^{ns} not significant, $^{\S}p < 0.05$, $^{\S\S}p < 0.01$, $^{\S\S\S}p < 0.001$. Fisher's exact test for sex distribution in the two groups; ^{ns} not significant. McNemar's test to assess the frequency differences in MetS pre- and post-intervention; $^{\ddagger\ddagger\ddagger}p < 0.001$.

events/h post-intervention in the SDB group, post hoc t test; $p < 0.01$). Complete results are shown in Table 1.

3.2.4. Cardiorespiratory fitness

Absolute VO_{2peak} ($p < 0.01$), $VO_{2peakBW}$ ($p < 0.001$) and $VO_{2peakFFM}$ all improved after the intervention in both groups (time effect $p < 0.05$; Table 1).

3.3. Normalized and Persistent-SDB subgroups

3.3.1. Clinical characteristics

We found the same proportion of girls and boys in the Normalized and Persistent-SDB subgroups. Within the SDB group, weight, BMI, BMI z-score, WC and FM% were not different in the normalized and persistent-SDB subgroups and were decreased overall by the intervention (time effect; $p < 0.001$, Table 2), while FFM_{kg} was not modified.

3.3.2. Cardiometabolic data

Leptin concentrations, total cholesterol, LDL-C and TG concentrations ($p < 0.001$) were decreased (time effect; $p < 0.01$, $p < 0.01$, $p < 0.01$ and $p < 0.05$, respectively) while HDL-C concentrations were not affected.

Considering glucose concentrations, a time × group interaction effect ($p < 0.05$) was found however post-hoc paired Student's t tests showed that glucose was not modified in the Normalized-SDB subgroup, nor in the Persistent-SDB subgroup.

As for insulin concentrations and $HOMA_{IR}$, a trend for a time × group interaction was found ($p = 0.063$ and $p = 0.053$, respectively). Accordingly, we applied post-hoc paired Student's t

tests and found that insulin concentrations and $HOMA_{IR}$ were decreased for the participants from the Normalized-SDB subgroup, only (both $p < 0.05$).

SBP was decreased by the intervention (time effect; $p < 0.01$). As for DBP, a trend for a time × group interaction was found ($p = 0.08$). Accordingly, we applied a post-hoc paired Student's t test and found that DBP was decreased for the participants from the Normalized-SDB subgroup, only ($p < 0.05$).

A time effect was found for the $MetScore_{FM}$ ($p < 0.01$) and a trend for a time × group interaction was found ($p = 0.057$). Accordingly, we applied a post-hoc paired Student's t test and found that $MetScore_{FM}$ was decreased for both the participants from the Normalized-SDB subgroup ($p < 0.01$) and for those from the Persistent-SDB subgroup ($p < 0.001$), with a greater decrease for the Normalized-SDB subgroup. Finally, the prevalence of the MetS went from 90 to 36% in the Normalized-SDB subgroup, and from 78 to 44% in the Persistent-SDB subgroup but this was non-significant (Table 2).

3.3.3. Sleep data

Regarding AHI, HI and OAHI, time effect, group effect and time × group interaction were observed. A time effect and a time × group interaction was also observed for RDI and ODI (time effect: $p < 0.01$, interaction; $p < 0.001$ for both). Post-hoc paired Student's t tests revealed that AHI ($p < 0.01$), HI ($p < 0.01$), OAHI ($p < 0.01$), RDI ($p < 0.05$) and ODI ($p < 0.05$) were decreased in the Normalized-SDB subgroup, while no modifications were observed in the Persistent-SDB subgroup. As for AI, a group effect ($p < 0.01$) was found, whereby AI was greater in the Persistent-SDB subgroup. Considering arousal index, a time × group interaction effect ($p < 0.05$) was found however post-hoc paired Student's t

Table 2
Clinical parameters, cardiometabolic data, sleep and cardiorespiratory fitness at admission and post-intervention in participants with Normalized and Persistent SDB.

	Normalized SDB ($n = 11$)		Persistent SDB ($n = 9$)		Group effect	Time effect	Interaction
	Admission	Post-intervention	Admission	Post-intervention			
Boys/Girls *n* (%)	7/4 (64/36)		4/5 (44/56) ^{ns}				
Clinical parameters							
Age (years)	15.8 ± 1.8	16.6 ± 1.8	15.0 ± 1.0	15.9 ± 1.1	ns	***	ns
Weight (kg)	119.0 ± 23.5	103.0 ± 17.4	105.6 ± 23.1	97.9 ± 27.6	ns	***	ns
BMI ($kg.m^{-2}$)	40.0 ± 8.3	33.9 ± 6.1	39.0 ± 6.3	35.7 ± 8.3	ns	***	ns
BMI z score	2.5 ± 0.4	2.1 ± 0.5	2.5 ± 0.4	2.2 ± 0.6	ns	***	ns
WC (cm)	116.5 ± 19.4	100.2 ± 15.9	116.3 ± 15.6	96.0 ± 10.8	ns	***	ns
FM (%)	42.1 ± 5.9	34.7 ± 6.2	43.6 ± 7.4	38.2 ± 6.8	ns	***	ns
FFM (kg)	65.9 ± 11.4	67.6 ± 13.2	57.9 ± 11.8	59.3 ± 12.2	ns	ns	ns
Cardiometabolic data							
Leptin (ng/mL)	48.9 ± 18.51	29.41 ± 14.78	60.68 ± 21.88	43.01 ± 28.52	ns	**	ns
Total cholesterol (g/L)	1.59 ± 0.48	1.46 ± 0.41	1.71 ± 0.45	1.60 ± 0.36	ns	**	ns
LDL-C (g/L)	0.95 ± 0.39	0.87 ± 0.33	1.03 ± 0.33	0.96 ± 0.31	ns	**	ns
HDL-C (g/L)	0.40 ± 0.10	0.41 ± 0.09	0.43 ± 0.07	0.46 ± 0.09	ns	ns	ns
TG (g/L)	1.20 ± 1.15	0.88 ± 0.44	1.24 ± 0.54	0.90 ± 0.45	ns	*	ns
Glucose (g/L)	0.88 ± 0.12	0.83 ± 0.10 ^{ns}	0.86 ± 0.11	0.91 ± 0.15 ^{ns}	ns	ns	*
Insulin (μIU/mL)	19.16 ± 7.04	13.15 ± 6.25†	25.44 ± 17.48	30.05 ± 23.71 ^{ns}	*	ns	0.063
$HOMA_{IR}$	4.1 ± 1.5	3.0 ± 1.2†	5.6 ± 4.5	7.1 ± 6.6 ^{ns}	ns	ns	0.053
SBP (mmHg)	125.0 ± 9.2	115.0 ± 8.1†	125.6 ± 15.1	118.9 ± 8.9	ns	**	ns
DBP (mmHg)	74.6 ± 6.9	67.7 ± 6.1†	73.3 ± 10.0	71.7 ± 10.9 ^{ns}	ns	**	0.08
$MetScore_{FM}$	0.16 ± 0.47	−0.46 ± 0.42††	0.18 ± 0.88	0.01 ± 1.07†††	ns	**	0.057
MetS *n* (%)	10 (90)	4 (36)	7 (78)	4 (44)	ns	ns	ns
Sleep data							
AHI (events/h)	6.3 ± 6.0	0.7 ± 0.2††	6.0 ± 3.5	5.9 ± 4.3 ^{ns}	***	***	***
HI (events/h)	5.5 ± 5.8	0.5 ± 0.2††	4.8 ± 3.6	5.0 ± 4.3 ^{ns}	**	***	***
AI (events/h)	0.8 ± 0.9	0.2 ± 0.2	1.2 ± 1.1	0.9 ± 0.7	**	ns	ns
OAHI (events/h)	5.9 ± 6.0	0.6 ± 0.3††	5.6 ± 3.3	5.7 ± 4.3 ^{ns}	***	***	**
RDI (events/h)	12.4 ± 8.4	5.1 ± 5.3†	8.8 ± 3.6	10.5 ± 7.4 ^{ns}	ns	**	**
Arousal index (events/h)	11.5 ± 4.1	10.4 ± 3.8 ^{ns}	8.0 ± 3.9	12.4 ± 7.7 ^{ns}	ns	ns	*
ODI (events/h)	7.8 ± 6.9	2.7 ± 3.4†	6.5 ± 3.7	7.3 ± 5.3 ^{ns}	0.055	**	**
TST (min)	412.5 ± 75.7	438.9 ± 72.0	414.4 ± 29.8	443.5 ± 57.0	ns	*	ns
N1 (%TST)	6.5 ± 4.1	6.6 ± 2.3	7.1 ± 3.6	6.1 ± 3.0	ns	ns	ns
N2 (%TST)	49.4 ± 4.7	50.0 ± 7.1	46.5 ± 6.0	46.4 ± 6.2	ns	ns	ns
N3 (%TST)	24.2 ± 5.7	21.3 ± 4.9	25.5 ± 6.1	24.2 ± 5.2	ns	*	ns
REM (%TST)	20.0 ± 4.4	22.1 ± 6.0	20.9 ± 3.8	23.4 ± 3.3	ns	ns	ns
Cardiorespiratory fitness							
VO_{2peak} (L/min)	3.0 ± 0.6	3.2 ± 0.7	2.7 ± 0.7	2.9 ± 0.8	ns	*	ns
$VO_{2peakBW}$ (mL/min/kg)	25.2 ± 4.1	32.0 ± 6.1	26.3 ± 6.9	30.2 ± 6.2	ns	***	ns
$VO_{2peakFFM}$ (mL/min/kg_{FFM})	44.1 ± 7.9	48.9 ± 9.5	48.3 ± 14.2	49.6 ± 12.1	ns	0.055	ns

BMI = body mass index; FM = fat mass; FFM = fat-free mass; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides; $HOMA_{IR}$ = homeostatic model assessment for insulin resistance; SBP = systolic blood pressure; DBP = diastolic blood pressure; $MetScore_{FM}$ = cardiometabolic risk score; MetS = metabolic syndrome; TST = total sleep time; N1 = stage N1 sleep; N2 = stage N2 sleep; N3 = stage N3 sleep; REM = rapid eye movement sleep; AHI = apnea-hypopnea index; AI = apnea index; HI = hypopnea index; RDI = respiratory disturbance index; OAHI = obstructive apnea-hypopnea index; ODI = oxygen desaturation index; SDB = sleep-disordered breathing; VO_{2peak} = absolute peak oxygen uptake (L/min); $VO_{2peakBW}$ = peak oxygen uptake expressed relative to body weight (mL/min/kg); $VO_{2peakFFM}$ = peak oxygen uptake expressed relative to fat-free mass (mL/min/kg_{FFM}).
Values are presented as mean ± standard deviation. Random-effects models, non-parametric data are log transformed; ^{ns} not significant, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Paired Student's t test for post hoc comparison between admission and post-intervention; ^{ns} not significant, $^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.01$, $^{\dagger\dagger\dagger}p < 0.001$. Fisher's exact test for sex distribution in the two groups.

tests showed that it was not modified in the Normalized-SDB subgroup, nor in the Persistent-SDB subgroup.

TST was improved by the intervention, while N3 was decreased (time effect: $p < 0.05$, respectively, Table 2).

3.3.4. Cardiorespiratory fitness

Absolute VO_{2peak} ($p < 0.05$) and $VO_{2peakBW}$ increased significantly in both subgroups ($p < 0.001$), while no modifications were found for $VO_{2peakFFM}$ ($p = 0.055$).

3.4. Associations of changes (Δ) in cardiometabolic parameters with sex, and changes (Δ) in BMI, in sleep and in cardiorespiratory parameters among participants with SDB

Decrease in glucose concentrations from pre to post-intervention among participants with SDB was significantly associated with decrease in BMI (adjusted $r^2 = 0.41$, β Coefficient = 0.012, $p = 0.0375$) and decrease of AHI (β Coefficient = 0.012, $p = 0.0102$), independently of age ($p = 0.2487$) and sex ($p = 0.5652$). Decrease in insulin concentrations from pre to post-intervention was associated with decrease in BMI (adjusted $r^2 = 0.16$, β Coefficient = 2.462, $p = 0.0375$), independently of age ($p = 0.8586$ and sex ($p = 0.3398$).

Change in SBP was associated with the age only (adjusted $r^2 = 0.29$, β Coefficient = 5.479, $p = 0.0375$), independently of sex ($p = 0.7245$).

No significant models for Δ total cholesterol, Δ LDL-C, Δ HDL-C, ΔTG and Δ DBP were found.

4. Discussion

Despite current campaigns of primary prevention, the prevalence of pediatric obesity remains alarming worldwide, and is associated with an increased risk of developing SDB [54]. While public policies recommend the implementation of multidisciplinary weight loss intervention in adolescents with obesity [55], the effects of such behavioral interventions on the components of MetS and the CMR in adolescents with SDB deserve more attention. In the present study, we aimed at assessing the effects of a multidisciplinary weight loss intervention program on cardiometabolic risk assessed using both a dichotomous (MetS) and continuous ($MetScore_{FM}$) instruments in obese adolescents with and without SDB. We also compared these cardiometabolic responses to the intervention in the SDB group between the subgroups with persistent and normalized SDB post-intervention.

At baseline, 40% of the adolescents had SDB (determined as AHI $\geq$ 2) and had a clinically greater CMR score ($MetScore_{FM}$) than their counterparts without SDB, despite a similar degree of obesity. As expected, this result highlights the deleterious effects of SDB on cardiometabolic health in adolescents with obesity. While divergent results regarding the association between SDB and MetS in youth with obesity were reported in the literature [23,24,32,56], our research group previously found that SDB started to affect cardiometabolic health from an AHI of 2 in adolescents with obesity [44]. In the present study, the prevalence of the MetS was about 85% in the group of participants with SDB, *vs.* 63% in those without SDB, and this result supports our previous findings, whereby SDB, even mild, affects cardiometabolic health in this population.

Post-intervention, the overall prevalence of the MetS decreased from 72 to 36%, mainly through an improvement in the lipid profile, but also through a decrease in insulin resistance and in systolic and diastolic BP. The beneficial effects of the combination of long-term diet and exercise on cardiometabolic health and MetS in adolescents with obesity are already well established [20,57–59]. However, and to the best of our knowledge, this study is the first to assess this parameter in obese adolescents with SDB. Previous works in similar populations already reported promising effects of comparable interventions on insulin resistance [33] and lipid profile [32,33], but none assessed all the components of the MetS.

According to our results, SDB was normalized (AHI<2) among 55% of the adolescents initially diagnosed with SDB even though mean post-intervention AHI did not improve to normal in the SDB group. In a systematic review and meta-analysis of the literature, our group already reported the effectiveness of such interventions on SDB prevalence and severity in this population [31]. The present result confirms that behavioral interventions may benefit adolescents with obesity who have SDB. Interestingly, prevalence of the MetS was decreased in the SDB group from 85 to 40%, whether SDB was normalized post-intervention or not. When comparing participants with persistent SDB to those whose SDB was normalized, we first observed that they exhibited similar weight loss and cardiorespiratory improvements. However, although improvements regarding the continuous $MetScore_{FM}$ and the prevalence of the MetS were found in both subroups, $MetScore_{FM}$ values remained greater in the Persistent-SDB subgroup than in the Normalized-SDB subgroup.

Considering the lipid profile, we found that lipids concentrations were equally improved in the two groups. This result is in accordance with Van Hoorenbeeck et al., who found similar post-intervention lipid profile in their Normalized and Persistent-SDB participants following a 3-to-6 month lifestyle intervention [33]. In addition, in the present work, participants with SDB at baseline did not exhibit a worst lipid profile than their counterparts without SDB. Given that, it seems that the lipid profile is not primarily affected by SDB in the present sample. Rather, improvements in the concentrations of total cholesterol, LDL-C and TG are more probably explained by the combination of diet and exercise in adolescents with obesity [60]. It has indeed been reported that chronic exercise has a positive impact on lipoprotein lipase expression and activity, resulting in a higher TG hydrolysis [61]. In addition, it decreases the release of the Proprotein convertase subtilisin/kexin type 9 (PCSK9), an enzyme involved in lipoprotein homeostasis. Less PCSK9 increases LDL-C absorption from the blood and excretion in the gastrointestinal tract by the liver [62]. Through the HDL-C pathway, chronic exercise also improves the reverse cholesterol transport; an anti-atherogenic mechanism by which excess cholesterol is removed from peripheral tissues and delivered to the liver, where it is then redistributed to other tissues or removed from the body by the gallbladder [62,63].

There is a known reciprocal relationship between lipid and glucose profiles, whereby insulin resistance leads to higher adipose tissue lipolysis and thus, dyslipidemia [22], and whereby dyslipidemia promotes insulin resistance [64]. We had therefore hypothesized that improvements in the lipid profile would be associated with higher insulin sensitivity. However, we found that the insulin-glucose axis was only improved in participants whose SDB was normalized post-intervention, and that adolescents with persistent SDB had post-intervention insulin concentrations twice as high as their counterparts.

Insulin resistance has already been shown to be strongly associated with SDB in youth, independently of obesity, through numerous pathways [19,65,66]. For instance, sympathetic overactivity induced by intermittent hypoxia and sleep fragmentation leads to the release of catecholamines which, in turn, decreases the peripheral absorption of glucose by insulin and increase insulin resistance [67]. It has also been suggested that gluconeogenesis, induced by sympathetic overactivity contributes to high fasting glycemia, promoting type 2 diabetes [68]. Moreover, it has been suggested that SDB-associated intermittent hypoxia attenuates the glucose-induced secretion of insulin from pancreatic β-cells

through the downregulation of CD38, which is involved in insulin release [69].

When performing multivariable analyses in our SDB group, we found that decrease in insulin concentrations was associated with a decrease in BMI, while decrease in glucose concentrations was associated with both decreased BMI and AHI. This suggests that improvements in glucose homeostasis result from 1) the decrease in intermittent hypoxia and improvement in sleep duration resulting from SDB normalization, and 2) fat mass loss resulting from the diet and chronic exercise intervention.

Chronic exercise is known to improve adipose tissue function by altering systemic levels of inflammatory adipokines, such as leptin [20,70,71]. Although normalized-SDB and persistent-SDB subgroups had comparable proportions of fat mass and comparable AHI at baseline, both pre- and post-intervention leptin concentrations were unexpectedly lower in the normalized-SDB participants, compared to their counterparts with persistent SDB. Leptin, which is an hormone secreted by the adipose tissue, is involved in satiety signaling and energy balance [72], but also in central and peripheral breath control [73] and glucose-insulin homeostasis [74]. In individuals with obesity, as illustrated in the present sample, elevated concentrations of leptin, namely leptin resistance, reflect adipose tissue dysfunction and promote insulin resistance [75]. This last decade, authors have suggested that leptin resistance may be involved in the pathogenesis of SDB through its effects on central and peripheral breath control [76,77]. In our study, persistent SDB, despite comparable weight loss, was associated with high leptin levels at baseline, suggesting that high leptin concentration might be a predictor of the persistence of SDB, to be further investigated in future studies. The high leptin concentration may also explain, at least in part, the remaining of insulin resistance in participants with persistent SDB. Recently, Alonso-Àlvarez and colleagues, in a study assessing the effects of different treatments on obstructive sleep apnea (OSA) in children with obesity, suggested that insulin resistance was a predictor of the incidence and persistence of OSA [78]. We suggest that leptin resistance, which also promotes insulin resistance, may be a predictor of the persistence of SDB in our sample, rather than insulin resistance itself.

Finally, systolic and diastolic BP among participants with SDB were only improved for participants whose SDB was normalized post-intervention. In a study performed in a population of obese adolescents with SDB compared to their counterparts without SDB and to normal-weight adolescents with SDB, Horne and colleagues reported that obese youth with SDB exhibited impaired autonomic control in addition to elevated BP [79]. Similar to the mechanisms that explain insulin resistance in SDB, high SBP may be explained by recurrent nocturnal sympathetic overactivity [17]. Additionally, intermittent hypoxia may lead to overreactivity of peripheral chemoreceptors, promoting diurnal hypertension as well [16,80]. Thus, improvements in BP are probably mediated by the decrease in intermittent hypoxia found among participants with normalized SDB.

This study has some limitations that deserve to be underlined. First, body composition was assessed using two different methods in the two institutions, and this potentially introduced bias in comparing participants. It would have been preferable to use a single method, ideally DXA. This was unfortunately not possible due to the availability of different equipment between the two study sites. The use of MRI would also have been relevant in order to assess visceral fat mass in our population.

Also, São Paulo, Brazil proposed an adaptation night before the recording used for analysis, and as shown in Supplementary Material (Table S1), participants from Brazil had a shorter TST, less N2 and a greater proportion of N3 compared to participants from France. Given this, these comparisons between the two sites (Table S1) deserve to be interpreted with caution. Nevertheless, since respiratory events were presented in the form of indices, the lack of an adaptation night does not reduce the significance of our results regarding the effects of the intervention on respiratory parameters. Plus, 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.

Finally, we were not able to measure habitual sleep duration chronically among our participants. It is recognized that chronic sleep deprivation is common among adolescents [81] and affects cardiometabolic health [82,83]. Even though we did not find changes in sleep duration in the overall population, this parameter may have played a role in maintaining or improving cardiometabolic disorders at an individual level. Future studies should include measures of sleep patterns (eg, actigraphy or sleep diaries) in order to address this limitation.

To conclude, adolescents with obesity and SDB have a higher CMR compared to their counterparts without SDB, due to higher insulin and blood pressure values. To the best of our knowledge, this study is the first to report that a multidisciplinary weight loss intervention with diet and exercise improves the prevalence of the MetS and the severity of the CMR in adolescents with obesity and SDB, whether SDB was normalized or not. Thus, SDB was normalized for 55% of the participants. Cardiometabolic improvements in participants with persistent SDB were mainly mediated by weight loss and improved lipid profile, which does not seem to be primarily affected by the sleep respiratory disorders. In contrast insulin-glucose homeostasis and high blood pressure among participants initially diagnosed with SDB were improved along with SDB normalization.

The results of this study provide new insights and highlight the necessity of such interventions in youth with obesity and SDB in order to prevent future cardiovascular morbidities. Further studies in larger samples of participants are warranted to better explore the relationships between lipid, insulin-glucose homeostasis and SDB, and in particular to investigate the role of leptin resistance in SDB pathogenesis and persistence, as well as in insulin resistance in the population of adolescents with severe obesity.

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Conflict of interest

The authors report no conflicts of interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2020.06.030.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2020.06.030.

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