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Persistent sleep-disordered breathing independently contributes to metabolic syndrome in prepubertal children

Pablo Armañac-Julián MSc[1,2] | Adrián Martín-Montero MSc[1,3] | Jesús Lázaro PhD[1,2] | Roberto Hornero PhD[1,3] | Pablo Laguna PhD[1,2] | Leila Kheirandish-Gozal MD, MSc[4] | David Gozal MD, MBA, PhD (Hon)[5] | Eduardo Gil PhD[1,2] | Raquel Bailón PhD[1,2] | Gonzalo Gutiérrez-Tobal PhD[1,3]

[1]CIBER-BBN, Instituto de Salud Carlos III, Madrid, Spain

[2]BSICoS Group, University of Zaragoza, Zaragoza, Aragon, Spain

[3]GIB Group, University of Valladolid, Valladolid, Spain

[4]Department of Neurology, University of Missouri School of Medicine, Columbia, Missouri, United States

[5]Office of the Dean, Joan C. Edwards School of Medicine, Marshall University, Huntington, Virginia, United States

Correspondence

Pablo Armañac-Julián, MSc, University of Zaragoza, I3A, C/María de Luna, Ed. Ada Byron, Lab. 3.07-50018 Zaragoza, Spain.
Email: parmanac@unizar.es

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Abstract

Background: Obstructive sleep apnea (OSA) is a risk factor for metabolic syndrome (MetS) in adults, but its association in prepubertal children is still questionable due to the relatively limited cardiometabolic data available and the phenotypic heterogeneity.

Objective: To identify the role of OSA as a potential mediator of MetS in prepubertal children.

Methods: A total of 255 prepubertal children from the Childhood Adenotonsillectomy Trial were included, with standardized measurements taken before OSA treatment and 7 months later. MetS was defined if three or more of the following criteria were present: adiposity, high blood pressure, elevated glycemia, and dyslipidemia. A causal mediation analysis was conducted to assess the effect of OSA treatment on MetS.

Results: OSA treatment significantly impacted MetS, with the apnea–hypopnea index emerging as mediator (p = .02). This mediation role was not detected for any of the individual risk factors that define MetS. We further found that the relationship between MetS and OSA is ascribable to respiratory disturbance caused by the apnea episodes, while systemic inflammation as measured by C-reactive protein, is mediated by desaturation events and fragmented sleep. In terms of evolution, patients with MetS were significantly more likely to recover after OSA treatment (odds ratio = 2.56, 95% confidence interval [CI] 1.20–5.46; risk ratio = 2.06, 95% CI 1.19–3.54) than the opposite, patients without MetS to develop it.

Conclusion: The findings point to a causal role of OSA in the development of metabolic dysfunction, suggesting that persistent OSA may increase the risk of MetS in prepubertal children. This mediation role implies a need for developing screening for MetS in children presenting OSA symptoms.

KEYWORDS

cardiovascular risk and obesity, metabolic syndrome, obstructive sleep apnea, sleep-disordered breathing

URL: https://bsicos.i3a.es/

1 | INTRODUCTION

Obstructive sleep apnea (OSA), along with other sleep disorders resulting in fragmented sleep, has emerged as a risk factor for cardiometabolic comorbidities.[1,2] When persistent over time, particularly when excessive daytime sleepiness is manifest, OSA promotes the risk of cardiovascular diseases (CVD), such as hypertension or hypercholesterolemia.[3–6] In the pediatric population, OSA is also associated with an increased risk of obesity (OB), insulin resistance, and systemic inflammation.[7–9]

Metabolic syndrome (MetS) is a cluster of conditions encompassing central OB, impaired fasting glucose, dyslipidemia, and hypertension.[10] In adults, the criteria and definition of MetS are well established.[10–12] Furthermore, MetS is directly associated with CVD risk, insulin resistance, type 2 diabetes mellitus, and overall mortality.[6,13] In studies that assessed the association of MetS in childhood with adult CVD years later,[13,14] children with MetS were significantly more likely to manifest an increased risk of CVD in adulthood.

Compared to the abundant body of adult data, very few experimental studies examining metabolic sequelae of sleep perturbations have been conducted in children and adolescents.[15–17] In general, OSA seems to be associated with increased risk of metabolic dysfunction in overweight and obese children.[18,19] Metabolic dysfunction is more prevalent in pediatric patients with known insulin resistance and dyslipidemia,[20] and in those with one of the individual components of MetS, either the presence of elevated systemic blood pressure or higher blood.[21,22] However, the extant studies have yielded inconsistent findings at times, and the divergence from the findings in adults may be due in part to the several competing definitions of MetS in children, but also to longer lags between disease onset and development of MetS-related sequelae.[23–26] From this point of view, an important study (IDEFICS) by Ahrens et al.,[27] classified children according to different definitions of MetS in a population-based survey of 18,745 healthy European children, aged 2–11 years, which resulted in the proposal of standard specific cut-off values for each of the MetS components according to percentiles in nonobese children.

Here, we hypothesized that there is an interaction between pediatric OSA and MetS, especially in children with higher OSA severity. Consequently, screening for MetS components may be indicated in children with OSA. Causal mediation analysis (CMA) is a powerful technique that enables determination of mediators affecting a particular disease.[28] Of relevance to the current study, CMA allows for assessing whether a treatment has a measurable effect, while also detecting possible causal pathways through which a treatment influences changes in an outcome. However, CMA has not been systematically employed to study the mediators of OSA and their interactions with MetS outcomes.

In addition to MetS, OB and C-reactive protein levels (CRP) are also frequently used as biomarkers for CVD. CRP is a well-established marker of systemic inflammation and has been found to be a reliable indicator of cardiovascular morbidity in adults.[19,29] In addition, OB is also known to be strongly related to the development of OSA and MetS in adults, but different studies disagree on their results in children.[15,19,30] Consequently, the main novelty of the study focuses on the evaluation of both the causality of OSA in the development of MetS and the interactions between OSA, MetS, CRP, and OB in prepubertal children from the Childhood Adenotonsillectomy Trial (CHAT).

2 | MATERIALS AND METHODS

The methodological approaches used herein are divided into three stages. First, we conducted analysis of MetS in the cohort based on the IDEFICS cutoff values.[27] Then, we applied CMA to assess the putative causal pathways between pediatric OSA and the development of MetS.[31] Finally, the prevalence of MetS was studied and related to the prevalence of OSA.

2.1 | Sleep data

The CHAT sleep study was a multicentric prospective randomized trial, designed to evaluate the efficacy of adenotonsillectomy surgery (early adenotonsillectomy [eAT]) versus a strategy of watchful waiting with supportive care (WWSC) for pediatric OSA treatment.[32] The rationale, design, and primary outcomes for the CHAT study have been previously reported.[32] All data are publicly available at https://sleepdata.org/datasets/chat. The study recruited prepubertal children between 5 and 10 years of age with OSA symptoms who were scheduled for a baseline nocturnal polysomnography in a clinical laboratory. After allocation to the corresponding therapeutic strategy, eAT or WWSC, children completed a follow-up polysomnographic study 7 months later. The legal caretakers of each patient provided the informed consent, and the CHAT study was judged ethical and approved by all relevant independent review boards. For more details on the protocol, inclusion-exclusion criteria, and ethical considerations, see Marcus et al.[32]

The study investigators relied on the apnea–hypopnea index (AHI) to establish OSA severity according to the American Academy of Sleep Medicine rules.[32] Children were assigned to one of four common severity groups for pediatric OSA, as follows: no OSA (AHI < 1 events per hour of sleep, *e/h*), mild OSA (1 ≤ AHI < 5 *e/h*), moderate OSA (5 ≤ AHI < 10 *e/h*), and severe OSA (AHI ≥ 10 *e/h*). The distribution of patients according to OSA severity is shown in Table 1. OSA resolution was considered for those patients with both AHI ≤ 2 *e/h* and apnea index (AI) ≤ 1 *e/h* at follow-up[33] (103 patients resolved vs. 152 unresolved). Note that this criterion considers both obstructive and central apneas, thus defining stringent rules for disease resolution than the criterion proposed in the original CHAT study.[32] Owing to the study design, all subjects at baseline were diagnosed as suffering from pediatric OSA (Table 1), such that at baseline none of the subjects could be considered with OSA Resolution (AHI ≤ 2 *e/h* and AI ≤ 1 *e/h*) or No OSA (AHI ≤ 1 *e/h*).

TABLE 1 OSA severity definition and prevalence at baseline and follow-up, including OSA resolution at follow-up.

	OSA severity (e/h)	Baseline (*n*)	Follow-up (*n*)	OSA resolution % (*n*)
No OSA	AHI < 1	-	63	-
Mild OSA	1 < AHI ≤ 5	107	135	48% (52)
Moderate OSA	5 < AHI ≤ 10	90	30	33% (30)
Severe OSA	10 ≤ AHI	58	27	36% (21)
		(255)	(255)	[AHI ≤ 2 and AI ≤ 1] at follow-up[a]

Abbreviations: AHI, apnea–hypopnea index; AI, apnea index; OSA, obstructive sleep apnea.

[a]All subjects at baseline were diagnosed as suffering from pediatric OSA, such that at baseline, none of the subjects could be considered as OSA resolution (AHI ≤ 2 e/h and AI ≤ 1 e/h) or No OSA (AHI ≤ 1 e/h).

From the CHAT database, we included 255 subjects who had all the necessary information to define MetS, both at baseline and follow-up. Among these, 127 subjects were assigned to eAT and 128 were assigned to WWSC. Table 2 shows the demographic and relevant clinical data at baseline, separated into two groups considering OSA status at follow-up.

2.2 | Definition of MetS

MetS consists of a cluster of metabolic disorders that are often associated with chronic inflammation or with insulin resistance.[34] The specific criteria for MetS in adults have been defined by the National Cholesterol Education Program (NCEP), the Adult Treatment Panel III, and the World Health Organization.[11,12] MetS in adults is defined if three or more of the following risk factors are present[1]: central OB,[2] hypertension,[3] dyslipidemia, and[4] hyperglycemia. However, there are different competing definitions of MetS in children, and each of such proposed criteria has significant limitations. For example, the definition by Cook et al.[23] corresponds to the NCEP criteria, adapted to adolescents, which restricts its applicability in younger children.

In the IDEFICS study, the investigators applied and compared three commonly used definitions of the pediatric MetS, along with a new definition criterion.[23–25,27] Based on the most recent age- and sex-specific percentiles derived from the study, they suggested an updated definition of pediatric MetS,[27] which is shown in Table 3, and summarily consists of percentiles cutoffs based on statistical criteria adapted for age and sex. Using the IDEFICS criteria, a considerable proportion of prepubertal children will be designated as MetS compared to other definitions.[27]

Finally, there is also relevance in evaluating the association between OB, OSA, and MetS.[15,19,30,35] Therefore, children with body mass index (BMI) z-score values exceeding the 95th percentile were classified as fulfilling the criteria for OB, following the recommendations of the Centers for Disease Control and Prevention (https://www.cdc.gov/obesity/basics/childhood-defining.html).

2.3 | Statistical analysis

The commonly reported total causal effect (TE) of an intervention evaluates whether a treatment modifies the outcome of interest. In this work, we implement a CMA, which further identifies the causal pathways, namely mediators, through which the treatment affects the outcome. A mediator is an intermediate variable that resides within the causal pathway between an independent variable (in this case, OSA treatment), and a dependent variable (outcome of the study, e.g., MetS). It helps to clarify how and why a treatment influences a given outcome. In other words, the mediator is influenced by the independent variable (OSA treatment), which in turn influences the dependent variable (outcome). For example, with a CMA, we can evaluate whether variations in MetS are causally attributable to OSA treatment,[28] influenced by AHI as mediator/pathway of the disease. Then, CMA allows to split the TE of the OSA treatment into two components (see Figure 1):

1. First, the average causal mediation effect (ACME), represents the indirect effects. ACME measures the changes in the outcome particularly attributable to changes in a given mediator, which changed due to the treatment.
2. Second, the average direct effect (ADE), reflects the direct effects of the treatment. ADE measures the changes in the outcome unlinked to the mediator under study.

On the one hand, ACME evaluates the relationships between the after-treatment variations occurring in the outcome, that is, the variations of the clinical indicators such as MetS, z-scored BMI (BMIz), systolic blood pressure (SBP), and so on, and the variations in the indicators representing the disease severity, that is, the mediators, such as AHI, oxygen desaturation index (ODI), and so on. The MetS criteria represent an outcome from the disease. On the other hand, ADE evaluates how treatment affects the outcome through any other (and possibly unknown) factor(s) different from the mediator. ACME and ADE jointly form the TE.

CMA utilizes regression models to estimate the effects and associations between the variables: one model is constructed examining the mediator-outcome relationship, other assessing the treatment-mediator relationship, and a final one exploring the treatment-outcome relationship. One additional model is calculated to conduct the mediation analysis, which combines the estimated coefficients from the previous models to calculate the ACME and the ADE. The software used for the assessment of causal mediation has been extensively validated in R language.[36]

In this study, the intervention is represented by one of the treatment arms (either eAT or WWSC). Five different mediators are included:

1. AHI, AI, and hypopnea index (HI), as measures of the possible different number of apneic events, in e/h.
2. ODI: oxygen desaturations with events >3% desaturation per hour of sleep, related to OSA and intermittent hypoxemia.[32]
3. Total Arousal Index (TAI), as the measure reflecting sleep disturbance and sleep fragmentation associated with OSA.[37]

As outcomes for the analysis, we consider MetS, but also each of the individual variables included in MetS criteria, namely adiposity: waist circumference (WC); blood pressure: SBP and diastolic blood pressure (DBP); blood glucose: homeostatic model assessment (HOMA) and glucose levels (GLUC); blood lipids: triglycerides levels and high-density lipoprotein levels. In addition, for comparative purposes, BMIz and CRP levels were also included.[19,29]

Finally, to formulate an accurate interpretation of the ACME, all confounders must be controlled based on their potential associations with both the exposure (OSA treatment) and any outcome (MetS, CRP, SBP, etc.). The baseline values of age, race, sex, BMIz, average overnight heart rate, tonsil size, and OSA severity group are included in the statistical adjustment procedures.[15,33,38] For example, age, sex, and race-related variations in the metabolic outcomes are incorporated to ensure that any observed effects are not solely driven by demographic factors.[27] In particular, the rationale for including average overnight heart rate is

TABLE 2 Clinical and demographic characteristics at baseline in CHAT subjects for whom complete metabolic information was available.

	Patients who resolved OSA (baseline values)	Patients with persistent OSA (baseline values)	*p* Value
Patients (*n*)	40% (103)	60% (152)	–
Treatment arm (eAT)	65% (67)	39% (60)	<.001*
Age (years)	6 (1)	7 (1)	.1908
Sex (females)	57% (59)	50% (76)	.2544
Race			.8455
White	35% (36)	33% (50)	
Black	52% (54)	59% (90)	
Other	13% (13)	8% (12)	
BMIz	0.52 (1.34)	1.03 (1.26)	.0019*
WC (cm)	60 (12)	64 (13)	.0045*
SBP (mmHg)	96 (8)	98 (9)	.0805
DBP (mmHg)	62 (7)	64 (8)	.0167*
CHOL (mg/dL)	159 (27)	158 (23)	.6012
HDL (mg/dL)	50 (12)	52 (12)	.1044
LDL (mg/dL)	95 (22)	92 (21)	.5922
TRIG (mg/dL)	71 (29)	72 (30)	.7580
GLUC (mg/dL)	81 (8)	81 (6)	.3725
HOMA	1.58 (1.77)	1.76 (1.66)	.0637
CRP (μg/mL)	1.33 (2.21)	2.36 (5.66)	.0913
AHI (e/h)	6.9 (5.6)	8.0 (5.7)	.0114*
AI (e/h)	2.9 (2.5)	3.3 (3.1)	.2596
HI (e/h)	4.0 (4.0)	4.7 (4.1)	.0182*
ODI (e/h)	6.5 (7.0)	7.2 (6.2)	.0305*
TAI (e/h)	8.4 (3.1)	8.2 (3.1)	.6509
Epworth Sleepiness Scale	6.7 (4.8)	7.1 (4.7)	.4526
Obese (*n*)	28% (29)	42% (64)	.0235*
HR (bpm)	85 (8)	84 (9)	.5000
Tonsil size, >2+ (*n*)	78% (80)	70% (107)	.1986
MetS, ≥3 (*n*)	11% (11) [AHI ≤ 2 and AI ≤ 1] at follow-up	19% (29)	.0711

Note: Subjects are separated into two groups considering OSA status at follow-up, namely those with resolution of OSA and those with persistent OSA at follow-up. Data are shown as mean (σ) or % (*n*) for each subgroup. Statistically significant differences for the Wilcoxon rank sum test ($p < .05$) are marked with asterisks (*), comparing values of patients with OSA resolution against values of patients with OSA at follow. OSA resolution for patients with AHI ≤ 2 e/h and an AI ≤ 1 e/h at follow-up.

Abbreviations: AHI, apnea-hypopnea; AI, apnea index; BMIz: z-scored body mass index; CHOL, total cholesterol level; CRP, C-reactive protein level; DBP, diastolic blood pressure; eAT, early adenotonsillectomy; GLUC, serum glucose level; HDL, high-density lipoprotein level; HI, hypopnea index; HOMA, homeostatic model assessment; HR, heart rate; LDL, low-density lipoprotein level; MetS, metabolic syndrome; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; SBP, systolic blood pressure; TAI, total arousal index; TRIG, triglycerides level; WC, waist circumference; WWSC, watchful waiting with supportive care.

TABLE 3 Definition of pediatric metabolic syndrome.[27]

Excess adiposity	Blood pressure	Blood lipids	Blood glucose/insulin
WC ≥ 90th PCT	SBP ≥ 90th PCT	TRIG ≥ 90th PCT	HOMA ≥ 90th PCT
	DBP ≥ 90th PCT	HDL ≤ 10th PCT	GLUC ≥ 90th PCT

Note: All cut-off reference PCT values are dependent on age and sex, but the blood pressure cut-off reference values are also dependent on height. MetS is present if three or more clusters of risk factors are met. If one of two conditions exceeds cut-off criteria, the cluster is considered to be present. PCT reference values were obtained in nonobese healthy children population, which can be found in the IDEFICS study.[27]

Abbreviations: DBP, diastolic blood pressure; GLUC, fasting plasma glucose; HDL, high-density lipoprotein cholesterol; HOMA, homeostatic model assessment, for insulin resistance; PCT, percentile; SBP, systolic blood pressure; TRIG, triglycerides; WC, waist circumference.

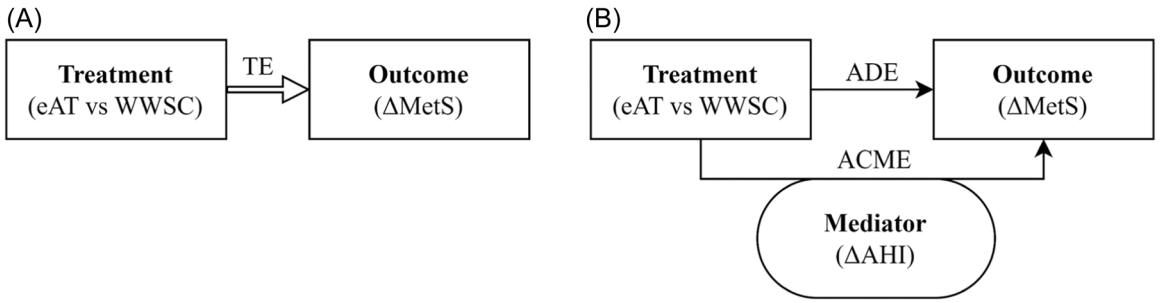

FIGURE 1 (a) Typical estimation of the total causal effect.[33] (b) Causal mediation analysis performed in the present study.

based on previous research suggesting that increased overnight heart rate is associated with OSA,[39] and that it may be also influenced by many other factors such as age, sex, physical condition, and so on,[40] ensuring too that any observed effects on causal mediation are not solely attributable to heart rate variations. We additionally computed the Fisher combined probability, which primarily addresses the potential for Type I errors (false positives) in multiple independent testing.

3 | RESULTS

3.1 | Baseline values: Comparing OSA resolution versus persistent OSA

Table 2 summarizes the baseline data from children included in the CHAT study, comparing the baseline values for subjects whose OSA resolved at follow-up and those with persistent OSA after treatment. Significant differences were found for treatment arm (eAT vs. WWSC), for BMIz, WC, DBP, AHI, and OB. No significant differences emerged for all other clinical and demographic parameters, such as age, sex, race, GLUCs, HR, tonsil size, and MetS.

3.2 | Causality results

Regarding CMA, statistical significance results of causal mediation are reported in Table 4. Those *p* values that preserved statistical significance after correcting for multiple testing with the combined probability of Fisher are marked in bold with asterisks (*). Mainly, CMA exhibits no significant ACME with the single constitutive criteria for MetS. Nonetheless, there was a significant causal mediation effect on MetS with AHI as mediator. Furthermore, significant ACME was detected for CRP with AHI and ODI as mediators, and for BMIz with TAI as mediator. With TAI as mediator, there was also significant ACME on DBP and WC. Specific values obtained for ACME and ADE can be found in Supporting Information: Table S1. Of note, statistically significant differences were found in the change in BMIz from baseline to follow-up ($\Delta BMIz = BMIz^{follow\text{-}up} - BMIz^{baseline}$), with TAI as a mediator. However, CMA performed considers BMIz levels at baseline as confounder, thus revealing a robust causal mediation effect of TAI on changes in BMIz, after OSA treatment.

No differences in analytical outcomes were detected when only obstructive apnea and hypopnea events were analyzed with respect to when both central and obstructive events were included. Therefore, the results for AHI, AI, and HI are shown considering both central and obstructive events. The significant ADE obtained with different mediators and, for example, HOMA as outcome, means that OSA treatment significantly affected HOMA through mediators other than those evaluated in the present study.

The original CHAT study found high OSA resolution rates in both treatment arms.[32] These findings have led researchers to analyze CHAT based on OSA resolution rather than relying on treatment arm.[33,38,41] However, for CMA, it is mandatory to conduct an initial preliminary analysis, to ascertain if there are interactions between the type of treatment and the outcomes. In general, no significant effects of interactions between treatment types on the outcomes were detected, and therefore the average joint effect (ACME) for the two treatment

TABLE 4 *p* values and statistical significance from the causal mediation analysis, assessing treatment effects on change in clinical variables (follow-up−baseline) through different mediators.

	ΔAHI		ΔAI		ΔHI		ΔODI		ΔTAI	
Mediators	**ACME**	**ADE**	**ACME**	**ADE**	**ACME**	**ADE**	**ACME**	**ADE**	**ACME**	**ADE**
ΔMetS	**0,02**[a]	0,88	0,03	0,91	0,43	0,80	0,41	0,77	0,17	0,88
ΔWC	0,12	0,60	0,83	0,96	0,12	0,86	0,18	0,76	**« 0.01**[a]	0,52
ΔSBP	0,93	0,95	0,35	1,00	0,97	0,44	0,83	0,95	0,20	0,86
ΔDBP	0,41	0,41	0,73	0,83	0,76	0,91	0,75	0,84	**0,02**[a]	0,77
ΔTRIG	0,42	0,28	0,22	0,24	0,97	0,36	0,68	0,23	0,06	0,33
ΔHDL	0,32	0,95	0,77	0,66	0,15	0,60	0,51	0,83	0,41	0,82
ΔHOMA	0,09	0,08	0,40	**0,02**[a]	0,21	0,03	0,14	0,04	0,99	**0,02**[a]
ΔGLUC	0,65	0,36	0,09	0,47	0,85	0,26	**0,02**[a,b]	0,44	0,41	0,22
ΔCRP	**0,02**[a]	0,43	0,13	0,57	0,046	0,56	**0,02**[a]	0,39	0,03	0,40
ΔBMIz	0,10	0,08	0,65	0,046	0.07	**0,02**[a]	0,48	0,06	**0,02**[a]	0,12

Note: Statistically significant effects ($p < .05$) are highlighted with blue and green color for ACME and ADE, respectively.

Abbreviations: ACME, average causal mediation effect; ADE, average direct effect; AHI, apnea–hypopnea index; AI, apnea index; BMIz: z-scored body mass index; CRP, C-reactive protein levels; DBP, diastolic blood pressure; GLUC, serum glucose levels; HDL, high-density lipoprotein levels; HI, hypopnea index; HOMA, homeostasis model assessment; MetS, metabolic syndrome; ODI, oxyhemoglobin desaturation index 3%; SBP, systolic blood pressure; TAI, total arousals index; TRIG, triglycerides levels; WC, waist circumference; WWSC, watchful waiting with supportive care.

[a]Significant effect after correcting for multiple testing with the combined probability of Fisher.

[b]Significant effect only for WWSC arm.

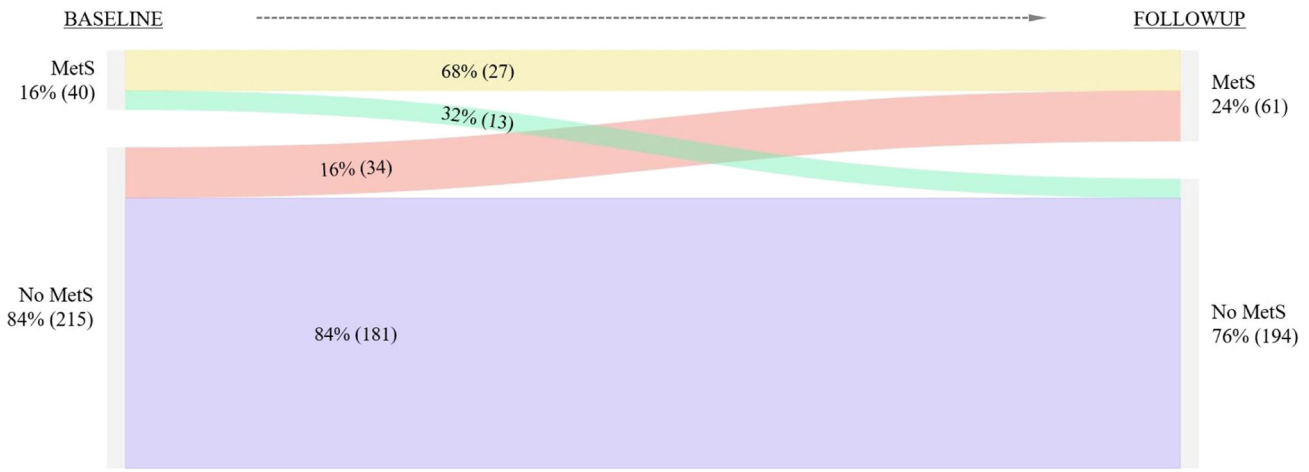

FIGURE 2 Proportion plot showing prevalence and evolution of metabolic syndrome (MetS) from baseline to follow-up. Units are % (*N*). Prevalence is summarized by having or not MetS (number of risk factors ≥ 3).

arms is reported.[36] Only ODI-GLUC results in an interaction effect, and causal mediation effect is provided for the treatment arm for which there is significant effect.

3.3 | Prevalence, odds ratio (OR), and risk ratio (RR) of MetS

To further explain the relationship between OSA and MetS, Figure 2 presents a proportion plot with the prevalence and evolution of MetS from baseline to follow-up. At first glance, we can see that the number of patients with MetS increased from baseline to follow-up (61 subjects at follow-up with at least three cardiovascular risk factors compared to 40 subjects at baseline). However, note that the two categories (MetS vs. no MetS) are not balanced. Upon closer examination, patients with MetS at baseline were more likely to recover at follow-up (32%, 13 patients) as compared to those without MetS at baseline developing MetS at follow-up (16%, 34 patients). As shown in Supporting Information: Table S2 (b), there is evidence that among the children who did not recover from MetS after OSA

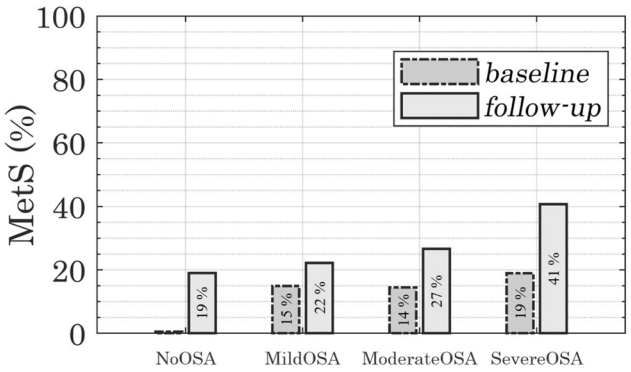

FIGURE 3 Prevalence of metabolic syndrome (MetS) according to obstructive sleep apnea (OSA) severity categories based on apnea–hypopnea index (AHI) criteria at baseline and at follow-up.

treatment, the number of MetS risk factors decreased. Only two out of the 27 patients worsened in terms of the number of risk factors at follow-up, while 17 patients improved.

As such, the OR of changing the health state after OSA treatment from having MetS at baseline to not having MetS at follow-up, with respect to worsening from no MetS to MetS was 2.56 (confidence interval [CI] 95%: 1.2031–5.4606); and the RR was 2.06 (95% CI: 1.1943–3.5364). Accordingly, despite the increased total number of subjects with MetS after treatment for OSA (40 vs. 61, respectively), the probability of recovering from MetS was significantly higher (2.06-fold), than the probability of developing MetS. Similarly, the odds of not having MetS after OSA treatment if the patient had MetS at baseline were also significantly higher (2.56-fold), than the odds of having MetS after OSA treatment if the patient did not have MetS at baseline.

3.4 | MetS and OSA severity

The prevalence of MetS in our sample is presented in Figure 3 according to OSA severity groups and baseline or follow-up. As mentioned above, a higher MetS presence was found after OSA treatment. However, Figure 3 shows that its prevalence increases with OSA severity: no-OSA (19%), mild-OSA patients (22%), moderate-OSA (27%), and severe-OSA patients (41%), thus suggesting persistent OSA as a risk factor for MetS and gradual relationship with OSA severity.

Further detailed results and analysis, including OSA prevalence, results by treatment strategy, and the proportion of different combinations of MetS, can be found in the Supporting Information. In particular, Supporting Information: Table S3 shows the evolution of MetS for children with and without OB at baseline and at follow-up further illustrating the known impact of OB on prevalence of MetS over time. Supporting Information: Table S4 exhibits the relationships between OSA severity and the evolution of MetS from baseline to follow-up.

4 | DISCUSSION

Using CMA, we assessed and established the putative causal pathways and the contribution of various OSA mediators to the development of MetS in prepubertal children. Furthermore, the present study revealed improvements in MetS as being causally attributable to OSA treatment. In fact, causal mediation was found only for MetS, but not for any of the constitutive elements used to define MetS. In particular, an improvement trend in MetS after OSA treatment can be ascribed to a reduction in the frequency of apnea events during sleep (AI). In addition, a trend of greater presence of systemic inflammation, as illustrated by CRP levels, was causally attributable to the HI, thereby corroborating previous studies.[42] Furthermore, our findings support the existence of an interrelationship between MetS, OSA, and OB in children, although such associations are less robust than in adults. These novel results may help enhance the putative and unique value of phenotyping pediatric OSA patients with the designated goals of improving patient selection and treatment along with their overall short-term and long-term outcomes.

Fundamentally, CMA revealed that the changes in the number of cardiovascular risk factors of MetS are causally attributable to the changes in the frequency of respiratory events after OSA treatment. Indeed, the causal contribution of OSA to metabolic dysfunction in prepubertal children persisted even after adjusting for confounders. Thus, the association between OSA and MetS is consistent, independent, and not influenced by age, sex, BMIz at baseline, or by other confounders. The mediation results are significant for MetS as outcome when AHI ($p = .02$*), is examined as OSA mediator. However, no causal effects emerged for MetS as outcome and ODI as a mediator. Contrary to what has been reported in adults, intermittent hypoxia as reflected by the ODI does not appear to be a causal contributor for MetS in children. This could be due to the relatively minor hypoxic burden frequency found in pediatric OSA when compared to adults with OSA. In contrast, causal mediation effects were found for AHI ($p = .02$*), and ODI ($p = .02$*) as mediators of CRP levels. As compared to adults with OSA, prepubertal children with OSA have less pronounced and less severe desaturation profiles likely related to the decreased collapsibility of their upper airway.[43] These differences may explain why desaturation events do not directly impact on MetS in prepubertal children and may count for children requiring increased OSA treatment duration before they exhibit cardiovascular risk symptoms.

Redline et al. quantified the association between MetS and sleep-disordered breathing (SDB, AHI ≥ 5) in adolescents.[15] They found that MetS is significantly more prevalent in subjects with SDB (59% in SDB vs. 16% if no SDB). Our current findings in prepubertal children are closely aligned with the results reported by Redline and colleagues, suggesting the need for MetS screening not only in adults and adolescents but also in children.[27] Of note, the criteria for MetS in children should be implemented using IDEFICS normative reference values to avoid discrepancies across different ages.[27]

In Supporting Information: Table S4, we exhibit how OSA and MetS interactions are less prominent in children with persistent OSA at

follow-up. However, we should also remark that those children with persistent OSA are more likely to develop MetS, especially when residual OSA remains moderate to severe (Figure 3). As such, it seems likely that although treatment of OSA in these instances did not result in normalization of respiratory parameters, although the latter were improved relative to the baseline disease severity, and as such their impact on MetS may have consequently been mitigated leading to a reduced effect size that nevertheless persists over time and ultimately promotes the emergence of MetS. Notwithstanding, it is suggested that children presenting any of the conditions of MetS, OSA, or OB should be screened and if needed, comprehensively evaluated.

As shown by Redline et al.,[15] OB is a strong risk factor for adult OSA, and is also a major risk factor for snoring or OSA in pediatric populations.[35,44,45] Accordingly, as illustrated in Table 2, we found significant differences between the OB prevalence of children with resolved OSA after treatment and those with persistent disease. However, CMA did not uncover a causal mediation effect of OSA over the changes in BMIz.

In the extant literature, there is conflicting evidence about the relationship between OB with OSA and MetS in children.[15,19,30] In the current study, OB children were more likely to exhibit MetS at baseline as well as at follow-up (as depicted in Supporting Information: Table S3), further emphasizing the interdependencies between OB and OSA as causal mediators contributing either additively or synergistically to the risk of MetS. It is also likely that the conflictive findings may be due to the different definitions of MetS. Therefore, we strongly endorse the need for general adoption of the percentile approaches to MetS criteria proposed in the IDEFICS study.[27]

As discussed above, one of the important strengths of the current analyses is the utilization of the IDEFICS criteria to define MetS in children[27] along with the implementation of CMA. Another important observation in this study is the fact that isolated components of MetS do not emerge as being causally mediated by OSA and that only when these elements are coalesced into MetS criteria, does the causal mediation then become significant. Thus, MetS appears to be an independent and complementary biomarker of pediatric OSA, which may provide insights into long-term cardiometabolic risk in these children. The major limitation of the present study is that it included sufficient representation of only some ethnic groups, and that no complementary population cohort was available for confirmatory purposes. Therefore, prospective studies similar to CHAT in larger cohorts are needed. In addition, the original study (CHAT) has not been designed for the hypothesis of this reanalysis, therefore, different sources of bias cannot be excluded.

5 | CONCLUSION

We found that treating OSA in prepubertal children causally reduces the probability of developing MetS and its severity. This effect was independent of age, sex, BMI, and other confounding factors, and was mediated by the decrease in the frequency of respiratory events. Causal mediation effects were not significant for each of the components of MetS and only became apparent when these elements were combined into the definition of MetS, using more epidemiologically robust approaches (i.e., IDEFICS-derived percentiles[27]).

AUTHOR CONTRIBUTIONS

Study design: Gonzalo Gutiérrez-Tobal, Raquel Bailón, Roberto Hornero, David Gozal, Pablo Armañac-Julián, P. Laguna, and Eduardo Gil. *Implementation*: Pablo Armañac-Julián and Adrián Martín-Montero. *Data analysis*: Pablo Armañac-Julián. *Manuscript writing*: Pablo Armañac-Julián, Gonzalo Gutiérrez-Tobal, Eduardo Gil, and David Gozal. *Manuscript review*: Adrián Martín-Montero, Jesús Lázaro, Leila Kheirandish-Gozal, David Gozal, Pablo Laguna, Gonzalo Gutiérrez-Tobal, Eduardo Gil, Raquel Bailón, and Roberto Hornero. *Funding acquisition*: David Gozal, Raquel Bailón, Pablo Laguna, Roberto Hornero, and Gonzalo Gutiérrez-Tobal. All authors gave their final approval of this version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in CHAT at https://sleepdata.org/datasets/chat, reference number NCT00560859.

ETHICS STATEMENT

In all children, the informed consent from caretakers was acquired.

ORCID

Pablo Armañac-Julián https://orcid.org/0000-0001-5918-1043
Roberto Hornero https://orcid.org/0000-0001-9915-2570
Gonzalo Gutiérrez-Tobal https://orcid.org/0000-0002-1237-3424

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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