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Sex-Stratified Associations Between Sleep-Stage-Specific Respiratory Indices and Metabolic Parameters in Children with Obstructive Sleep Apnea

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Highlights

What are the main findings?

- Triglycerides (TG) were positively associated with whole-night and sleep-stage-specific respiratory indices in both boys and girls.
- Formal interaction analyses identified stronger positive associations of TG with whole-night and non-rapid eye movement (NREM) obstructive apnea–hypopnea index (OAHI) in girls than in boys.

What are the implications of the main findings?

- Overall-cohort estimates may obscure sex-related differences in respiratory–metabolic associations, particularly the stronger positive associations of triglycerides with whole-night and NREM-specific OAHI observed in girls.
- These findings suggest that sex and the distribution of respiratory burden across sleep stages may be relevant when interpreting the relationship between Obstructive Sleep Apnea (OSA) severity and triglyceride levels in children.

Abstract

Objectives: To examine whether sex modifies associations between whole-night and sleep-stage-specific respiratory indices and metabolic parameters in children with obstructive sleep apnea (OSA). Methods: This retrospective cross-sectional secondary analysis included a previously reported cohort of 514 children (330 boys, 184 girls) referred for suspected sleep-disordered breathing. Whole-night, rapid eye movement (REM), and non-rapid eye movement (NREM) obstructive apnea–hypopnea index (OAHI) and oxygen desaturation index (ODI) were examined in sex-stratified and pooled interaction models adjusted for age and body mass index z-score. Benjamini–Hochberg correction was applied across 30 interaction tests. Sleep architecture was also assessed. Results: After false discovery rate (FDR) correction, triglycerides (TG) were positively associated with all six respiratory indices in both sexes. Sex interactions were significant for TG with whole-night OAHI (standardized $\beta = -0.509$; 95% CI, −0.737 to −0.281) and NREM OAHI ($\beta = -0.582$; 95% CI, −0.813 to −0.350; both $q < 0.001$), indicating stronger associations in girls (boys minus girls). No other interactions survived FDR correction. Conclusions: Sex-related heterogeneity was confined to selected TG–OAHI associations. Independent prospective validation is needed to assess reproducibility and clinical relevance.

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Keywords: obstructive sleep apnea; children; sex-stratified analysis; sleep stages; metabolic parameters; triglycerides

1. Introduction

Obstructive sleep apnea (OSA) is characterized by recurrent upper airway obstruction, intermittent hypoxia, and sleep fragmentation [1]. Estimates of its prevalence in children range between 1.2% and 5.7% [2]. A community-based study in Chinese children reported a prevalence of 5.8% in boys and 3.8% in girls, and identified an independent association between male sex and OSA [3]. Pediatric OSA has been associated with altered lipid metabolism [4,5], and childhood lipid concentrations are associated with cardiovascular events in adulthood [6].

Polysomnography (PSG) provides whole-night respiratory indices and allows respiratory events to be assessed separately during rapid eye movement (REM) and non-rapid eye movement (NREM) sleep. Obstructive respiratory-event frequency is expressed by the obstructive apnea–hypopnea index (OAHI), while the oxygen desaturation index (ODI) expresses oxygen-desaturation frequency. Upper airway muscle activity and autonomic regulation vary between these stages and may influence the frequency and physiological consequences of respiratory events [7,8]. For example, REM-related events may involve greater oxygen desaturation [9,10]. Therefore, whole-night respiratory indices may not fully capture stage-specific differences in respiratory burden, highlighting the need to assess REM- and NREM-specific respiratory indices [11–13].

Sex-related differences in pediatric OSA may vary with age and developmental stage [3,14,15], and differences in lipid profiles and metabolic associations have been reported before puberty [16–18]. However, whether sex modifies the association between respiratory burden and metabolic parameters in younger children with suspected OSA remains unclear.

Our previous exploratory analysis of this same 514-child cohort, reported by Wan et al., identified associations between OAHI and lipid parameters during both REM and NREM sleep. ODI showed a broader pattern of lipid associations during REM sleep [19]. Whether these respiratory–metabolic associations differed between boys and girls remained unclear. We therefore proposed an exploratory hypothesis that the associations between whole-night and sleep-stage-specific respiratory indices and metabolic parameters might differ between boys and girls. To test this hypothesis, we used sex-stratified models and formal interaction tests in this exploratory secondary analysis.

2. Materials and Methods

2.1. Study Participants

This retrospective cross-sectional analysis included the same cohort of 514 children previously reported by Wan et al. [19]. Participants were aged 3 to 14 years and had been referred for suspected sleep-disordered breathing at Capital Children's Medical Center, Capital Medical University, between 2022 and 2023. On the assessment day, trained physicians measured neck length, neck circumference, height, and weight. We obtained measurements twice and recorded the mean values. We calculated BMI and the neck-to-height ratio from these measurements. Ethical approval was granted on 22 September 2025 by the Ethics Committee of Capital Institute of Pediatrics, Capital Medical University (Approval No. SHERLL2025108). Parents or legal guardians provided written informed consent permitting the use of their children's existing clinical data.

Biochemical tests were requested by the treating physicians during routine care on clinical grounds, including metabolic risk factors, obesity-related concerns, or abnormal physical findings. No additional blood samples were collected for research purposes. PSG and biochemical assessments were performed during the same clinical evaluation. Children without available biochemical measurements were excluded from the metabolic analyses. Participant flow and exclusion criteria are provided in Figure 1.

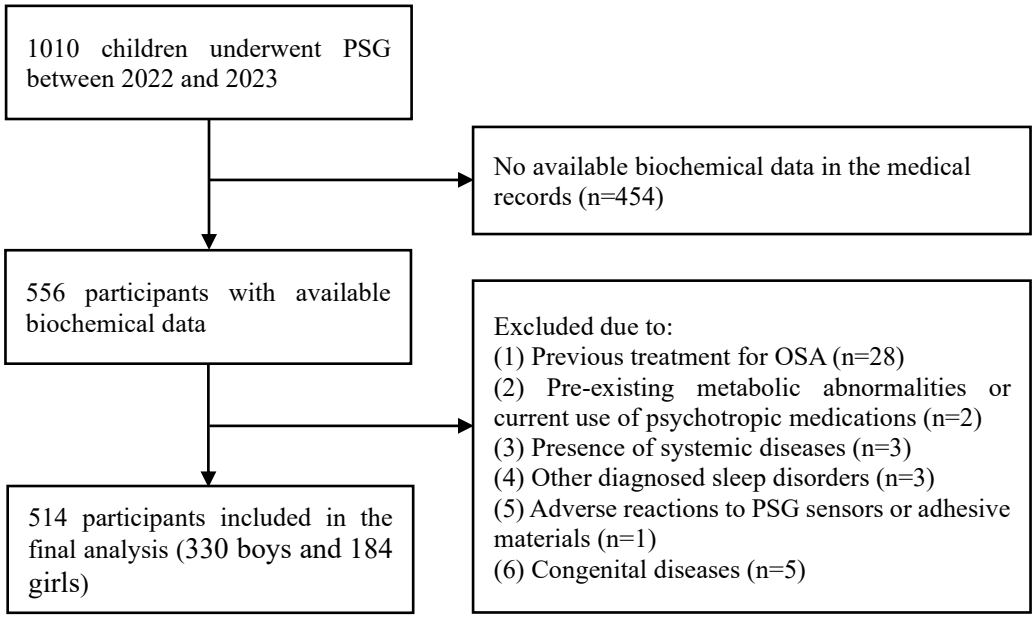


Figure 1. Participant selection.

2.2. Polysomnographic Assessment

Overnight PSG was recorded at the sleep medicine center with the Alice 6 system (Philips Respironics, Murrysville, PA, USA). During routine clinical evaluation, each child underwent a single recording of ≥6 h while accompanied by a caregiver in a dark, quiet room maintained at approximately 24 °C. Recordings included electrocardiogram, electrooculogram, electroencephalogram, pretibial and submental electromyogram, oronasal airflow, thoracic and abdominal movements, and pulse oximetry (SpO_2), body position sensor (analog output) and sidestream end-tidal carbon dioxide capnography.

For each examination, registered PSG technologists applied the American Academy of Sleep Medicine (AASM) scoring criteria. The rule was used to classify arousals, respiratory events and sleep stages [20]. Recordings were reviewed for technical adequacy.

OAHI expressed the hourly frequency of hypopneas, mixed apneas, and obstructive apneas during sleep. The diagnostic threshold for OSA was a whole-night OAHI of >1 event/h. ODI expressed the hourly frequency of oxygen desaturations of ≥3% during sleep. Separate OAHI values were also derived for REM and NREM sleep ($OAHI_{REM}$ and $OAHI_{NREM}$, respectively), using the corresponding sleep-stage. REM- and NREM-specific ODI values were calculated in the same way. Indices calculated over total sleep time (TST) represented whole-night measurements. Sleep architecture was characterized using the available PSG summary measures. Sleep continuity and latency measures included TST, sleep efficiency, REM latency, time in bed (TIB), wake after sleep onset (WASO), and sleep onset latency (SOL). We characterized sleep-stage composition using the proportion of TST spent in each of the N1, N2, N3, and REM stages. Within NREM sleep, stages 1, 2, and 3 are designated N1, N2, and N3, respectively. Estimated durations of individual sleep

stages were calculated by multiplying TST by the corresponding stage proportion; NREM duration was calculated as TST minus REM duration.

For exploratory categorical analyses, whole-night, REM-specific, and NREM-specific OAHI were each categorized as follows: ≤1, >1 to ≤5, >5 to ≤10, and >10 events/h. Clinical OSA severity was classified according to whole-night OAHI [21]. ODI was categorized as ≤1, >1 to ≤5, and >5 events/h.

2.3. Metabolic Parameters

Laboratory analyses were performed in the core laboratory. Venous blood was collected on the morning immediately following overnight PSG after an 8–12 h fasting period. Samples were separated by centrifugation at 3000 rpm for 15 min. Analyses used a Siemens ADVIA 2400 automated biochemistry analyzer (Siemens Healthcare, Erlangen, Germany). The biochemical parameters included: AST: aspartate aminotransferase, ALT: alanine aminotransferase, TBil: total bilirubin, DBil: direct bilirubin, IBil: indirect bilirubin, TBA: total bile acids, TC: total cholesterol, TG: triglycerides, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, VLDL-C: very low-density lipoprotein cholesterol, urea, SCr: serum creatinine, UA: uric acid, TP: total protein, albumin, and FPG: fasting plasma glucose. Derived measures included the AST/ALT, LDL-C/HDL-C, urea-to-creatinine (UCR), and albumin-to-globulin (A/G) ratios. To maintain consistency with our earlier analysis, we calculated BMI z-scores using the 2000 Growth Charts published by the Centers for Disease Control and Prevention (CDC). We calculated the triglyceride–glucose (TyG) index as follows [22]: $\mathrm{TyG} = \ln\left[\frac{\mathrm{TG(mg/dL)} \times \mathrm{FPG(mg/dL)}}{2}\right]$.

2.4. Statistical Analyses

We used R software (version 4.5; R Foundation for Statistical Computing, Vienna, Austria) to perform the analyses. The distribution of continuous variables was evaluated using the Shapiro–Wilk test. Descriptive statistics were reported as mean ± standard deviation (SD) or median with interquartile range. Depending on the distribution, baseline comparisons between boys and girls used independent-samples *t*-tests or Mann–Whitney U tests (Table 1). Comparisons with children without biochemical measurements used two-sided Mann–Whitney U tests with asymptotic approximation and continuity correction. Pearson's chi-square test, without continuity correction, was used to compare sex distributions (Supplementary Table S1).

Table 1. Characteristics of the participants.

	All Participants (*N* = 514)	**Boys (*N* = 330)**	**Girls (*N* = 184)**	***p* Value**
Age (years)	6.15 ± 2.46	6.14 ± 2.41	6.16 ± 2.55	0.393
BMI (kg/m^2)	16.89 ± 3.65	17.45 ± 4.03	15.9 ± 2.55	<0.001
BMI z-score	0.13 ± 1.60	0.33 ± 1.70	−0.22 ± 1.34	0.003
Neck-to-height ratio	0.23 ± 0.02	0.23 ± 0.02	0.22 ± 0.02	0.226
Mean SaO_2 (%)	98 (97, 98)	98 (97, 98)	98 (98, 98)	0.883
Minimum SaO_2 (%)	92 (88, 94)	92 (88, 94)	92 (89, 94.75)	0.097
NREM Mean SaO_2 (%)	98 (97, 98)	98 (97, 98)	98 (97, 98)	0.613
REM Mean SaO_2 (%)	98(97, 98)	98 (97, 98)	98 (97, 98)	0.994
$OAHI_{TST}$ (events/h)	2.5 (1.2, 6.2)	2.6 (1.2, 7.35)	2 (1.025, 5.175)	0.109
$OAHI_{NREM}$ (events/h)	2 (0.8, 5.425)	2.05 (0.9, 6.125)	1.8 (0.7, 3.925)	0.618
$OAHI_{REM}$ (events/h)	2.85 (0.8, 8.325)	3.15 (0.9, 10.65)	2.35 (0.7, 5.775)	0.021
ODI_{TST} (events/h)	1.3 (0.5, 3.7)	1.5 (0.5, 4.425)	1 (0.3, 2.7)	0.015
ODI_{NREM} (events/h)	0.9 (0.2, 2.6)	1.1 (0.3, 3.075)	0.6 (0.2, 1.8)	0.010

Table 1. *Cont.*

	All Participants (*N* = 514)	**Boys (*N* = 330)**	**Girls (*N* = 184)**	***p* Value**
ODI_{REM} (events/h)	2.2 (0.6, 6.9)	2.25 (0.7, 8.25)	2 (0.525, 5.175)	0.885
WASO (min)	43.5 (23, 81)	46 (22.85, 82.88)	39.2 (23.50, 75.75)	0.422
Sleep efficiency (%)	90.2 (83.4, 93.8)	90 (82.62, 93.88)	91 (84.88, 93.60)	0.724
N1 sleep (%)	11.1 (7.73, 14.9)	11.1 (7.73, 15.17)	11.05 (7.77, 14.4)	0.538
N2 sleep (%)	43.1 (38.4, 48)	43.3 (38.30, 47.48)	43.3 (38.98, 49.08)	0.116
N3 sleep (%)	25.42 ± 6.50	25.36 ± 6.58	25.54 ± 6.38	0.756
REM sleep (%)	19.50 ± 4.66	19.77 ± 4.86	19.02 ± 4.23	0.069
TP (g/L)	70.65 ± 4.50	70.74 ± 4.61	70.49 ± 4.28	0.357
Albumin (g/L)	43.9 ± 2.24	43.9 ± 2.4	43.9 ± 1.91	0.986
A/G	1.7 ± 0.27	1.68 ± 0.26	1.72 ± 0.29	0.593
TG (mmol/L)	0.8 ± 0.42	0.78 ± 0.35	0.85 ± 0.51	0.022
TC (mmol/L)	4.13 ± 0.66	4.18 ± 0.71	4.04 ± 0.55	0.002
HDL-C (mmol/L)	1.54 ± 0.32	1.56 ± 0.33	1.51 ± 0.3	0.230
LDL-C (mmol/L)	2.15 ± 0.46	2.14 ± 0.48	2.16 ± 0.42	0.041
LDL-C/HDL-C	1.46 ± 0.45	1.44 ± 0.46	1.49 ± 0.43	0.238
VLDL-C (mmol/L)	0.16 ± 0.09	0.16 ± 0.09	0.16 ± 0.1	0.804
FPG (mmol/L)	4.95 ± 0.47	5 ± 0.47	4.84 ± 0.45	0.546
TyG	7.95 ± 0.46	7.94 ± 0.45	7.97 ± 0.48	0.879
AST (U/L)	29.89 ± 11.82	30.50 ± 14.08	28.78 ± 5.76	0.223
ALT (U/L)	14.56 ± 7.31	15.48 ± 8.58	12.93 ± 3.67	0.004
AST/ALT	2.25 ± 1.10	2.2 ± 1.28	2.34 ± 0.63	0.333
TBil (μmol/L)	10.55 ± 3.47	10.35 ± 3.49	10.92 ± 3.43	0.654
DBil (μmol/L)	1.28 ± 0.62	1.25 ± 0.66	1.33 ± 0.53	0.590
IBil (μmol/L)	9.48 ± 5.22	9.43 ± 6.1	9.57 ± 3.07	0.641
TBA (μmol/L)	2.5 ± 2.17	2.56 ± 2.3	2.41 ± 1.93	0.117
Urea (mmol/L)	4.47 ± 1.02	4.55 ± 1.03	4.33 ± 0.99	0.601
SCr (μmol/L)	31.73 ± 7.41	31.7 ± 7.50	31.79 ± 7.26	0.796
UCR	0.27 ± 2.00	0.23 ± 1.43	0.35 ± 2.75	0.181
UA (μmol/L)	278.86 ± 69.59	283.88 ± 75.12	269.8 ± 57.40	0.014

Data are presented as mean ± standard deviation (SD) or median (interquartile range [IQR]), as appropriate. Comparisons between boys and girls were performed using independent-samples *t*-tests or Mann–Whitney U tests, as appropriate. Abbreviations: BMI, body mass index; SaO_2, arterial oxygen saturation; OAHI, obstructive apnea–hypopnea index; TST, total sleep time; NREM, non-rapid eye movement; REM, rapid eye movement; ODI, oxygen desaturation index; WASO, wake after sleep onset; N1, stage 1 of NREM sleep; N2, stage 2 of NREM sleep; N3, stage 3 of NREM sleep; TP, total protein; A/G, albumin-to-globulin ratio; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol; FPG, fasting plasma glucose; TyG, triglyceride–glucose index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AST/ALT, aspartate aminotransferase-to-alanine aminotransferase ratio; TBil, total bilirubin; DBil, direct bilirubin; IBil, indirect bilirubin; TBA, total bile acids; SCr, serum creatinine; UCR, urea-to-creatinine ratio; UA, uric acid.

Exploratory multivariate analysis of covariance (MANCOVA) was performed separately in boys and girls to examine differences in metabolic parameters across categories of whole-night, REM-specific, and NREM-specific respiratory indices, adjusting for age and BMI z-score. Each model included one categorical respiratory index as a fixed factor and multiple metabolic parameters as dependent variables. Adjusted analyses also explored associations between sleep architecture parameters and metabolic outcomes. Nominal *p* values for individual metabolic outcomes are reported in Table 2, with the corresponding F statistics and partial η^2 provided in Supplementary Table S2. Based on the exploratory findings, five metabolic outcomes with nominal signals were carried forward to continuous-index regression: TC, TG, LDL-C, ALT, and UA.

Table 2. Sex-stratified associations of respiratory indices and sleep architecture parameters with metabolic parameters.

Sex	Parameter	$OAHI_{TST}$	$OAHI_{NREM}$	$OAHI_{REM}$	ODI_{TST}	ODI_{NREM}	ODI_{REM}	TIB	WASO	TST	SE	SOL	REM latency	N1 (%)	N2 (%)	N3 (%)	REM (%)
Boys	TC (mmol/L)	**0.003**	**0.004**	**0.001**	0.232	0.189	**0.001**	0.411	0.442	0.762	0.677	0.848	0.238	0.108	0.436	0.870	0.424
	TG (mmol/L)	**<0.001**	**<0.001**	**<0.001**	**0.010**	0.054	**<0.001**	0.445	0.525	0.237	0.689	0.976	0.168	0.174	0.540	0.064	0.791
	LDL-C (mmol/L)	**<0.001**	**<0.001**	**<0.001**	**0.002**	**0.003**	**<0.001**	0.434	0.725	0.559	0.988	0.996	0.059	**0.025**	0.160	0.679	0.137
	ALT (U/L)	**<0.001**	**<0.001**	**0.035**	**0.037**	0.168	0.132	0.834	0.950	0.881	0.834	0.490	0.181	0.311	0.356	0.909	0.883
	Albumin (g/L)	0.639	0.168	0.524	0.995	0.981	0.845	0.905	0.301	0.399	0.345	0.176	0.324	0.658	0.523	0.573	0.260
	UA (µmol/L)	**0.003**	**0.031**	**0.002**	0.060	0.658	**0.013**	0.687	0.904	0.623	0.751	0.452	**0.043**	0.903	0.289	0.351	0.593
Girls	TC (mmol/L)	0.056	**0.019**	0.813	0.833	0.882	0.566	0.377	0.754	0.166	0.526	0.297	0.692	0.084	0.210	0.154	**0.039**
	TG (mmol/L)	**<0.001**	**<0.001**	**0.027**	**0.038**	0.170	0.396	0.904	0.104	0.289	0.118	0.525	0.622	**0.006**	0.771	0.133	0.546
	LDL-C (mmol/L)	**0.012**	**0.002**	0.929	0.476	0.674	0.762	0.776	0.501	0.260	0.307	0.650	0.567	**0.004**	0.248	0.093	**0.004**
	ALT (U/L)	**0.011**	0.068	0.380	0.609	0.445	0.699	**0.018**	0.213	**<0.001**	0.057	0.657	0.503	0.219	**0.046**	**0.023**	0.116
	Albumin (g/L)	0.691	0.897	0.586	0.316	0.162	0.292	0.329	0.527	0.594	0.592	0.849	0.642	0.756	0.950	0.794	0.509
	UA (µmol/L)	0.325	0.253	0.084	0.109	0.994	0.618	0.237	0.555	0.188	0.614	0.670	0.434	0.617	0.680	0.888	0.769

Values are nominal p values for the corresponding respiratory index or sleep architecture parameter in separate multivariable regression models, with each metabolic parameter as the dependent variable. Models were fitted separately for boys and girls and adjusted for age and BMI z-score. p values were not adjusted for multiple comparisons. Bold values indicate nominal $p < 0.05$. Corresponding F statistics and partial η^2 values are provided in Supplementary Table S2. Subscripts TST, NREM, and REM denote whole-night, NREM-specific, and REM-specific respiratory indices, respectively. Abbreviations: OAHI, obstructive apnea-hypopnea index; TST, total sleep time; NREM, non-rapid eye movement; REM, rapid eye movement; ODI, oxygen desaturation index; TIB, time in bed; WASO, wake after sleep onset; SE, sleep efficiency; SOL, sleep onset latency; N1, stage 1 of NREM sleep; N2, stage 2 of NREM sleep; N3, stage 3 of NREM sleep; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; UA, uric acid; BMI, body mass index.

Sex-stratified ordinary least squares (OLS) regression models included one continuous respiratory index, age, and BMI z-score. Five outcomes and six respiratory indices (whole-night OAHI, REM-specific OAHI, NREM-specific OAHI, whole-night ODI, REM-specific ODI, and NREM-specific ODI) yielded 60 models. Selected metabolic regression results are presented in Table 3, and all 60 models are reported in Supplementary Table S3. Standardized coefficients, 95% confidence intervals (CIs), nominal *p* values, and adjusted R^2 were reported. Within each sex–outcome family, the Benjamini–Hochberg procedure controlled the false discovery rate (FDR) over the six respiratory-index tests.

Sex-related effect modification was assessed in pooled models containing sex, one continuous respiratory index, their interaction, age, and BMI z-score. Interaction coefficients were expressed as boys minus girls. Coefficients and CIs were standardized using the pooled respiratory-index standard deviation divided by the outcome standard deviation. FDR correction covered all 30 respiratory-index interaction tests jointly (Table 4; Supplementary Figure S1).

Table 3. Multiple linear regression analyses of associations between respiratory indices and metabolic parameters stratified by sex.

Sex	Parameter	Respiratory Index	Std β (95% CI)	*p* Value	AdjR²	Sig. F Change
Boys	TC (mmol/L)	$OAHI_{TST}$	0.090 (−0.021,0.202)	0.112	−0.001	0.466
		$OAHI_{NREM}$	0.069 (−0.041,0.180)	0.219	−0.004	0.675
		$OAHI_{REM}$	0.108 (−0.004,0.220)	0.059	0.002	0.309
		ODI_{REM}	0.098 (−0.015,0.210)	0.088	<0.001	0.402
	TG (mmol/L)	$OAHI_{TST}$	0.169 (0.061,0.276)	**0.002**	0.073	<0.001
		$OAHI_{NREM}$	0.135 (0.028,0.242)	**0.014**	0.063	<0.001
		$OAHI_{REM}$	0.229 (0.122,0.336)	**<0.001**	0.095	<0.001
		ODI_{TST}	0.155 (0.046,0.264)	**0.006**	0.068	<0.001
		ODI_{REM}	0.198 (0.090,0.306)	**<0.001**	0.082	<0.001
	LDL-C (mmol/L)	$OAHI_{TST}$	0.175 (0.065,0.284)	**0.002**	0.038	0.001
		$OAHI_{NREM}$	0.139 (0.030,0.248)	**0.013**	0.028	0.007
		$OAHI_{REM}$	0.186 (0.077,0.296)	**0.001**	0.042	0.001
		ODI_{TST}	0.164 (0.053,0.275)	**0.004**	0.034	0.003
		ODI_{NREM}	0.130 (0.020,0.241)	**0.021**	0.025	0.010
		ODI_{REM}	0.202 (0.092,0.312)	**<0.001**	0.047	<0.001
	ALT (U/L)	$OAHI_{TST}$	0.047 (−0.060,0.155)	0.387	0.070	<0.001
		$OAHI_{NREM}$	0.034 (−0.072,0.141)	0.526	0.069	<0.001
		$OAHI_{REM}$	0.098 (−0.009,0.206)	0.073	0.077	<0.001
		ODI_{TST}	0.034 (−0.075,0.143)	0.542	0.069	<0.001
	UA (μmol/L)	$OAHI_{TST}$	0.088 (−0.014,0.191)	0.089	0.161	<0.001
		$OAHI_{NREM}$	0.055 (−0.046,0.157)	0.287	0.156	<0.001
		$OAHI_{REM}$	0.161 (0.060,0.263)	**0.002**	0.178	<0.001
		ODI_{TST}	0.053 (−0.051,0.157)	0.316	0.156	<0.001
		ODI_{REM}	0.123 (0.021,0.226)	**0.019**	0.168	<0.001
Girls	TC (mmol/L)	$OAHI_{NREM}$	0.203 (0.057,0.348)	**0.007**	0.030	0.037
	TG (mmol/L)	$OAHI_{TST}$	0.338 (0.201,0.475)	**<0.001**	0.127	<0.001
		$OAHI_{NREM}$	0.359 (0.221,0.496)	**<0.001**	0.138	<0.001
		$OAHI_{REM}$	0.256 (0.115,0.397)	**<0.001**	0.077	0.001
		ODI_{TST}	0.198 (0.051,0.344)	**0.008**	0.049	0.008

Table 3. *Cont.*

Sex	Parameter	Respiratory Index	Std β (95% CI)	*p* Value	AdjR²	Sig. F Change
Girls	LDL-C (mmol/L)	$OAHI_{TST}$	0.135 (−0.010,0.280)	0.067	0.021	0.078
		$OAHI_{NREM}$	0.155 (0.009,0.301)	**0.038**	0.026	0.050
	ALT (U/L)	$OAHI_{TST}$	0.032 (−0.113,0.177)	0.662	0.017	0.108

Each model was fitted separately within each sex stratum and included one continuous respiratory index, age, and body mass index (BMI) z-score. Standardized regression coefficients (β) are presented with 95% confidence intervals (CIs). Adjusted R^2 (Adj R^2) describes the fit of the full model. The *p* value for the respiratory-index coefficient is unadjusted. Bold values indicate nominal $p < 0.05$. "Sig. F change" denotes the *p*-value from the hierarchical F-test comparing the model adjusted for age and BMI z-score with the model additionally including the respiratory index. The Benjamini–Hochberg procedure was applied to the six respiratory-index coefficient *p* values within each sex stratum and metabolic outcome; an FDR-adjusted q value < 0.05 was considered statistically significant. Abbreviations: TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; UA, uric acid; OAHI, obstructive apnea–hypopnea index; TST, total sleep time; NREM, non-rapid eye movement; REM, rapid eye movement; ODI, oxygen desaturation index; CI, confidence interval; BMI, body mass index; FDR, false discovery rate.

Sleep architecture comparisons between boys and girls used two-sided Wilcoxon rank-sum tests (Supplementary Table S4). Comparisons across the four whole-night OAHI categories used Kruskal–Wallis tests (Supplementary Table S5). FDR correction covered the 15 sleep architecture parameters separately for each set of comparisons. These comparisons were unadjusted for age, BMI z-score, or other covariates.

Separate exploratory analyses treated ten sleep architecture parameters as predictors of six metabolic outcomes, including albumin (Table 2; Supplementary Table S6). Predictors comprised the six continuity and latency measures and four stage proportions. Each sex-stratified model included one sleep parameter, age, and BMI z-score. This produced 120 models, with FDR correction across ten sleep parameters within each sex–outcome family. Coefficients and CIs were standardized using the sleep parameter SD divided by the outcome SD within each sex-specific model sample.

Table 4. Sex-by-Respiratory-Index Interactions in Multivariable Linear Regression Models.

Parameter	Respiratory Index	Interaction β (95% CI)	*p* Value	FDR-Adjusted q Value
TC (mmol/L)	$OAHI_{TST}$	−0.140 (−0.380, 0.101)	0.254	0.586
	$OAHI_{NREM}$	−0.195 (−0.439, 0.050)	0.118	0.355
	$OAHI_{REM}$	−0.018 (−0.249, 0.213)	0.880	0.955
	ODI_{TST}	−0.006 (−0.215, 0.204)	0.958	0.984
	ODI_{NREM}	−0.014 (−0.217, 0.189)	0.892	0.955
	ODI_{REM}	0.002 (−0.230, 0.235)	0.984	0.984
TG (mmol/L)	$OAHI_{TST}$	−0.509 (−0.737, −0.281)	<0.001	<0.001
	$OAHI_{NREM}$	−0.582 (−0.813, −0.350)	<0.001	<0.001
	$OAHI_{REM}$	−0.277 (−0.498, −0.055)	0.014	0.143
	ODI_{TST}	−0.182 (−0.385, 0.021)	0.079	0.355
	ODI_{NREM}	−0.168 (−0.365, 0.029)	0.094	0.355
	ODI_{REM}	−0.221 (−0.445, 0.003)	0.053	0.355

Table 4. *Cont.*

Parameter	Respiratory Index	Interaction β (95% CI)	*p* Value	FDR-Adjusted q Value
LDL-C (mmol/L)	$OAHI_{TST}$	−0.019 (−0.257, 0.219)	0.877	0.955
	$OAHI_{NREM}$	−0.071 (−0.314, 0.172)	0.568	0.777
	$OAHI_{REM}$	0.066 (−0.163, 0.295)	0.570	0.777
	ODI_{TST}	0.171 (−0.037, 0.378)	0.107	0.355
	ODI_{NREM}	0.160 (−0.041, 0.361)	0.118	0.355
	ODI_{REM}	0.128 (−0.101, 0.357)	0.274	0.587
ALT (U/L)	$OAHI_{TST}$	0.039 (−0.193, 0.271)	0.741	0.954
	$OAHI_{NREM}$	0.036 (−0.200, 0.272)	0.763	0.954
	$OAHI_{REM}$	0.069 (−0.153, 0.292)	0.540	0.777
	ODI_{TST}	0.103 (−0.099, 0.304)	0.318	0.612
	ODI_{NREM}	0.090 (−0.105, 0.285)	0.367	0.612
	ODI_{REM}	0.106 (−0.117, 0.329)	0.352	0.612
UA (μmol/L)	$OAHI_{TST}$	0.132 (−0.090, 0.353)	0.242	0.586
	$OAHI_{NREM}$	0.104 (−0.122, 0.329)	0.367	0.612
	$OAHI_{REM}$	0.171 (−0.040, 0.382)	0.112	0.355
	ODI_{TST}	0.066 (−0.127, 0.258)	0.501	0.777
	ODI_{NREM}	0.023 (−0.164, 0.209)	0.812	0.955
	ODI_{REM}	0.137 (−0.075, 0.350)	0.205	0.559

Note: β denotes the standardized sex-by-respiratory-index interaction coefficient (boys minus girls). All models were adjusted for age and BMI z-score. *p* values and 95% confidence intervals were obtained from conventional ordinary least squares regression. The Benjamini–Hochberg procedure was applied across all 30 interaction tests. Statistical significance was defined as FDR $q < 0.05$. Abbreviations: CI, confidence interval; FDR, false discovery rate; TC, total cholesterol; OAHI, obstructive apnea–hypopnea index; TST, total sleep time; NREM, non-rapid eye movement; REM, rapid eye movement; ODI, oxygen desaturation index; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; UA, uric acid; BMI, body mass index.

Pooled models additionally included sex and its interaction with the mean-centered sleep parameter (Supplementary Table S7). The interaction coefficients represented differences in slopes between boys and girls (boys minus girls). Interaction coefficients and CIs were standardized using the same SD ratio in each model's pooled complete-case sample. FDR correction covered all 60 sleep-parameter interaction tests jointly. Analyses in Supplementary Tables S6 and S7 used conventional OLS inference and model-specific complete cases without imputation.

Within-child REM–NREM differences were calculated as REM minus NREM and tested using two-sided Wilcoxon signed-rank tests. FDR correction covered the three comparisons of OAHI, ODI, and stage-specific mean oxygen saturation (Supplementary Table S8).

Sensitivity analyses examined REM-specific OAHI and ODI associations with TG in the pooled sample (Supplementary Table S9). The initial models included age, sex, and BMI z-score as covariates. Further models restricted the sample to children with at least 60 min of REM sleep or additionally adjusted for REM duration. The 60 min threshold was an exploratory restriction rather than a validated minimum recording requirement. Unstandardized coefficients and 95% CIs were reported, with nominal *p* values.

Sample size was determined by the available clinical data; no a priori calculation was performed. All association analyses were exploratory. *p* values for regression coefficients and two-group comparisons were two-sided. An FDR-adjusted $q < 0.05$ defined significance within each corrected test family. Unadjusted $p < 0.05$ was considered nominal evidence for the remaining analyses.

3. Results

3.1. Participant Characteristics by Sex

Among the 1010 children who underwent PSG, 454 had no available biochemical measurements and 42 were excluded for other eligibility reasons. The final sample included 514 children, comprising 330 boys and 184 girls (Figure 1; Table 1). Mean age was 6.15 ± 2.46 years. OSA was mild in 247 children (48.1%), moderate in 73 (14.2%), and severe in 87 (16.9%). The remaining 107 children (20.8%) had a whole-night OAHI ≤ 1 event/h.

Boys had higher BMI z-scores than girls (0.33 ± 1.70 vs. −0.22 ± 1.34; $p = 0.003$) but lower TG (0.78 ± 0.35 vs. 0.85 ± 0.51 mmol/L; $p = 0.022$). TC, ALT, and UA were higher in boys, whereas LDL-C was lower (p all < 0.05). REM-specific OAHI, whole-night ODI, and NREM-specific ODI were also higher in boys (Table 1).

Compared with children without biochemical measurements, the analytic sample was younger (6.15 ± 2.46 vs. 6.64 ± 3.15 years; $p = 0.011$). Whole-night and stage-specific OAHI values were higher in the analytic sample (all $p < 0.05$). Sex distribution did not differ significantly between the groups ($p = 0.458$; Supplementary Table S1).

3.2. Exploratory Adjusted Analyses

In models adjusted for age and BMI z-score, associations reached nominal significance for TG, TC, LDL-C, ALT, and UA in boys, and for TG, TC, LDL-C, and ALT in girls. No significant association was observed for UA in girls or for albumin in either sex (Table 2; Supplementary Table S2). p-values in these exploratory analyses were not corrected for multiple comparisons.

3.3. Respiratory Indices and Metabolic Parameters

TG was positively associated with all six respiratory indices in both sexes after within-family FDR correction. In boys, the REM-specific OAHI coefficient was β = 0.229 (95% CI, 0.122–0.336; q < 0.001). The corresponding whole-night and NREM-specific coefficients were 0.169 and 0.135, respectively. In girls, β was 0.338 for whole-night OAHI (95% CI, 0.201–0.475; q < 0.001). The NREM-specific estimate was 0.359 (95% CI, 0.221–0.496; q < 0.001), and the REM-specific estimate was 0.256 (95% CI, 0.115–0.397; q < 0.001).

LDL-C was positively associated with all six respiratory indices in boys after correction. UA was associated with REM-specific OAHI (β = 0.161; 95% CI, 0.060–0.263; q = 0.012). No TC or ALT association in boys met the FDR threshold. In girls, TC was associated with NREM-specific OAHI (β = 0.203; 95% CI, 0.057–0.348; q = 0.040). The nominal LDL-C association with NREM-specific OAHI did not remain significant after correction ($p = 0.038$; q = 0.200). Selected results are presented in Table 3, with all 60 metabolic models in Supplementary Table S3.

3.4. Sex-Related Differences in Respiratory–Metabolic Associations

Interaction tests showed stronger positive associations of TG with whole-night and NREM-specific OAHI in girls than in boys. With the sex contrast defined as boys minus girls, the standardized interaction coefficients were −0.509 (95% CI, −0.737 to −0.281) for whole-night OAHI and −0.582 (95% CI, −0.813 to −0.350) for NREM-specific OAHI. Both interactions remained significant after FDR correction across 30 tests (q < 0.001; Table 4; Supplementary Figure S1).

For the association between REM-specific OAHI and TG, the sex interaction was nominally significant but did not remain significant after correction ($p = 0.014$; q = 0.143). No interaction involving TC, LDL-C, ALT, or UA was significant after correction.

3.5. Sleep Architecture

None of the 15 sleep architecture parameters differed significantly between boys and girls after FDR correction (all $q \geq 0.435$; Supplementary Table S4). Across the four OSA categories, unadjusted comparisons identified differences in WASO, sleep efficiency, and N1, N2, and REM proportions. Estimated durations of N1, N2, N3, and REM sleep also differed across categories (all $q < 0.05$; Supplementary Table S5). Mean N1 proportion was 9.30% in children with OAHI ≤ 1 and 17.49% in those with severe OSA; the corresponding mean REM proportions were 20.47% and 18.11%.

Exploratory models linking sleep architecture to metabolic parameters identified three associations in girls after within-family FDR correction. N1 proportion was positively associated with LDL-C ($\beta = 0.210$; 95% CI, 0.066–0.354; $q = 0.022$). REM proportion was inversely associated with LDL-C ($\beta = -0.211$; 95% CI, −0.354 to −0.068; $q = 0.022$). TST was inversely associated with ALT ($\beta = -0.252$; 95% CI, −0.398 to −0.106; $q = 0.008$). No association in boys met the corrected threshold (Supplementary Table S6). None of the 60 sex-by-sleep-parameter interactions remained significant after correction (all $q \geq 0.806$; Supplementary Table S7).

3.6. REM–NREM Comparisons and Sensitivity Analyses

Paired comparisons showed higher OAHI and ODI during REM than NREM sleep. The median within-child differences were 0.60 and 1.10 events/h, respectively. Mean stage-specific oxygen saturation was lower during REM, with a mean paired difference of −0.28 percentage points (all $q < 0.001$; Supplementary Table S8).

In the pooled analysis restricted to 453 children with at least 60 min of REM sleep, both REM-specific OAHI and ODI were positively associated with TG. The unstandardized coefficient for REM-specific OAHI was 0.00538 mmol/L per event/h (95% CI, 0.00325–0.00751). Additional adjustment for REM duration changed the estimates little (Supplementary Table S9). All six sensitivity models had nominal $p < 0.001$.

4. Discussion

In this cohort of children referred for suspected sleep-disordered breathing, TG was positively associated with several whole-night and sleep-stage-specific respiratory indices after adjustment for age and BMI z-score. These associations differed by sex. Formal interaction analyses showed that the positive associations of TG with whole-night and NREM-specific OAHI were stronger in girls than in boys. Both interactions remained significant after correction for multiple comparisons. No other sex-by-respiratory-index interaction remained significant after the same correction. Although associations in-volving LDL-C, TC, and UA were also observed in selected sex-stratified models, the corresponding interactions with sex were not significant after correction. These findings suggest that sex-related heterogeneity in pediatric respiratory–metabolic associations may be concentrated in specific metabolic outcomes and respiratory measures rather than reflecting a generalized difference across all metabolic parameters.

Longitudinal cohort studies have linked childhood TG concentrations to cardiovascular events in adulthood [6], highlighting the importance of understanding factors associated with TG levels early in life. Previous pediatric studies have investigated the association between sleep-disordered breathing and metabolic alterations, although the findings have been inconsistent. Tauman et al. found that lipid abnormalities were associated with obesity, whereas lipid levels were not significantly correlated with measures of sleep-disordered breathing severity [23]. Lei et al. reported higher TG, TC, and LDL-C levels in children with OSA than in those with primary snoring or controls, together with an inverse association between TG and lowest oxygen saturation [24]. Our previous study of

514 children examined metabolic differences across OSA severity groups and respiratory–metabolic associations in the overall cohort [19]. The present secondary analysis of the same cohort extends that work by formally testing whether these associations differ by sex. After adjustment for age and BMI z-score, the positive associations of TG with whole-night and NREM-specific OAHI were stronger in girls than in boys, and both interactions remained significant after correction for multiple comparisons. These findings suggest that overall-cohort estimates may obscure sex-related differences in selected respiratory–metabolic associations. Intermittent hypoxia offers a plausible biological pathway linking obstructive respiratory events to altered TG metabolism. Mouse studies have shown that intermittent hypoxia can increase circulating and hepatic TG levels, upregulate hepatic lipid biosynthetic pathways, and impair the clearance of TG-rich lipoproteins [25,26]. Another mouse study found that metabolic responses to intermittent hypoxia were influenced by sex and estradiol [27], providing a rationale for investigating sex-related variation in these responses. The extent to which these experimental findings explain the stronger TG–OAHI associations observed in girls remains uncertain. Differences in body composition or developmental stage that are incompletely captured by age and BMI z-score may also contribute to the observed heterogeneity. Clinically, these findings raise the question of whether considering sex alongside PSG-derived respiratory indices and conventional metabolic risk factors could improve the identification of children with elevated TG. Prospective studies are needed to evaluate this possibility and determine whether such information can inform metabolic assessment and follow-up in children undergoing evaluation for OSA.

Previous pediatric studies examined sex differences in REM- and NREM-related OSA phenotypes [28,29], but did not assess whether the associations between respiratory in-dices and metabolic parameters differed by sex. Our analysis extends this work by identifying a sex difference in the strength of the association between NREM-specific OAHI and TG in this referral cohort. This finding adds a metabolic perspective to research on sleep-stage-related OSA phenotypes. Exploratory analyses of sleep architecture pro-vided additional information on sleep–metabolic associations. After adjustment for age and BMI z-score, total sleep time was inversely associated with ALT in girls. N1 sleep proportion was positively associated with LDL-C, whereas REM sleep proportion was inversely associated with LDL-C. These associations remained significant after FDR correction within each sex-outcome family. However, neither the multivariate omnibus tests nor the sex-by-sleep-parameter interactions remained significant after their respective FDR corrections. Thus, although selected associations were observed in girls, these analyses provided no statistically significant evidence of sex-related heterogeneity in the associations between the examined sleep architecture measures and metabolic parameters.

The potential clinical relevance of these findings is whether sex and more detailed PSG information can help identify children who may warrant further metabolic assessment. Future studies could combine sex, whole-night OAHI, and REM- and NREM-specific respiratory indices with conventional risk factors, including age, adiposity, and family history of metabolic disease. This would allow researchers to assess whether adding sex and PSG information improves the identification of children at increased risk of dyslipidemia. Such an approach may help identify metabolic abnormalities earlier in childhood and inform subsequent clinical assessment, follow-up, and management.

This study has several limitations. The single-center, retrospective cross-sectional design precludes causal inference and assessment of treatment-related metabolic changes. The clinically selected cohort consisted predominantly of young children, which limits generalizability. Furthermore, biochemical testing was performed according to clinical indications, which may have introduced selection bias toward children with greater metabolic risk. The smaller female subgroup may also have yielded less precise estimates. Single-night PSG and the absence

of detailed sleep-cycle and quantitative EEG data limit the characterization of habitual sleep and sleep architecture. Despite adjustment for age and BMI z-score, residual confounding by adiposity, lifestyle, and pubertal development remains possible. The use of US CDC growth references in Chinese children also warrants consideration. Finally, all association analyses were exploratory. Although FDR correction was applied within defined test families, it did not account for the initial selection of regression outcomes. The observed TG–OAHI interactions therefore require replication in independent prospective cohorts.

5. Conclusions

In this clinical pediatric cohort, TG was positively associated with several whole-night and sleep-stage-specific respiratory indices after adjustment for age and BMI z-score. Formal interaction analyses further identified stronger positive associations of TG with whole-night and NREM-specific OAHI in girls than in boys, with both interactions remaining significant after correction for multiple comparisons. These findings suggest that sex-related heterogeneity may be relevant to the relationship between respiratory burden and lipid metabolism in children, although it was not evident across all metabolic parameters or sleep-stage-specific indices. The clinical implications of these exploratory associations remain to be established. Independent prospective studies are warranted to determine their reproducibility, prognostic relevance, and potential implications for the longitudinal assessment and management of cardiometabolic health in children with OSA.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/children13111590/s1, Figure S1: Sex-by-respiratory-index interactions for metabolic parameters; Table S1: Comparison of the analytic sample and children without available biochemical measurements; Table S2: Sex-stratified associations between respiratory indices and metabolic parameters: F statistics and partial η^2; Table S3: Complete sex-stratified respiratory–metabolic regression results; Table S4: Sleep architecture characteristics by sex; Table S5: Sleep architecture characteristics across OSA severity categories; Table S6: Sex-stratified multivariable linear regression of metabolic parameters on sleep architecture; Table S7: Sex-by-sleep-parameter interactions in multivariable linear regression models; Table S8: Paired Comparisons of Respiratory Indices and Mean Oxygen Saturation Between REM and NREM Sleep; Table S9: Sensitivity Analyses of the Associations Between REM-Specific Respiratory Indices and Triglyceride Levels.

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Abbreviations

The following abbreviations are used in this manuscript:

OSA	Obstructive sleep apnea
PSG	Polysomnography
OAHI	Obstructive apnea–hypopnea index
ODI	Oxygen desaturation index
TST	Total sleep time
REM	Rapid eye movement
NREM	Non-rapid eye movement
BMI	Body mass index
TG	Triglycerides
TC	Total cholesterol
UA	Uric acid
ALT	Alanine aminotransferase
MANCOVA	Multivariate analysis of covariance
FDR	False discovery rate
CI	Confidence interval
OLS	Ordinary least squares

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