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Original Article

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Ferritin is a potential marker of cardiometabolic risk in adolescents and young adults with sleep-disordered breathing

Esther T. W. Cheng[1], Chun T. Au[1,2], Raymond N. C. Chan[1], Joey W. Y. Chan[3,4], Ngan Y. Chan[3,4], Yun K. Wing[3,4], Albert M. Li[1,5,6], Ethan Lam[1], Kate C. Chan[1,5,6,*]

[1]Department of Paediatrics, Faculty of Medicine, Chinese University of Hong Kong, Hong Kong SAR, China
[2]Translational Medicine, Research Institute, Hospital for Sick Children, Toronto, Ontario, Canada
[3]Li Chiu Kong Family Sleep Assessment Unit, Department of Psychiatry, Faculty of Medicine, Chinese University of Hong Kong, Hong Kong SAR, China
[4]Department of Psychiatry, Faculty of Medicine, Chinese University of Hong Kong, Hong Kong SAR, China
[5]Laboratory for Paediatric Respiratory Research, Li Ka Shing Institute of Health Sciences, Faculty of Medicine, Chinese University of Hong Kong, Hong Kong SAR, China
[6]Hong Kong Hub of Paediatric Excellence, Chinese University of Hong Kong, Hong Kong SAR, China

*Corresponding author: Kate Ching-ching Chan, Department of Paediatrics, Chinese University of Hong Kong, 6/F, Clinical Sciences Building, Prince of Wales Hospital, Shatin, Hong Kong Special Administrative Region, China. Email: katechan@cuhk.edu.hk.

Abstract

Objective: To explore markers that reflect sleep-disordered breathing (SDB) severity and investigate their associations with cardiometabolic risk factors in adolescents and young adults.

Methods: Participants were recruited from our SDB epidemiological cohort. They underwent overnight polysomnography and ambulatory blood pressure (BP) monitoring. Complete blood count, ferritin, high-sensitivity C-reactive protein (hs-CRP), fasting blood glucose, and lipid profile were measured. Multiple linear regression was used to examine the association between red cell indices (RCIs), ferritin, and obstructive apnea-hypopnea index (OAHI). Subgroup analyses on participants with SDB were performed for the association of RCIs and ferritin with lipid profile, hs-CRP, and BP.

Results: There were 88 participants with SDB and 155 healthy controls aged 16–25 years. Hemoglobin (Hb; $p < .001$), hematocrit (HCT; $p < .001$), and ferritin ($p < .001$) were elevated with increasing SDB severity and were independently associated with OAHI (β=1.06, $p < .001$; β=40.2, $p < .001$; β=4.89 × 10^{-3}, $p = .024$, respectively). In participants with SDB, after adjusting for age, sex, and BMI, significant associations were found between ferritin with low-density lipoprotein (LDL; β=0.936 × 10^{-3}, $p = .008$) and triglyceride (TG; β =1.08 × 10^{-3}, $p < .001$), as well as between Hb (β=1.40, $p = .007$), HCT (β=51.5, $p = .010$) and mean arterial pressure (MAP). Ferritin (β=0.091, $p = .002$), Hb (β=0.975, $p = .005$), and HCT (β=38.8, $p = .004$) were associated with hs-CRP independent of age, sex, BMI, plasma LDL, and MAP. OAHI was not associated with LDL and TG in the multivariable models.

Conclusions: Serum ferritin, but not OAHI, was associated with LDL and TG in participants with SDB, suggesting it is a potential marker of cardiometabolic risk in patients with SDB.

Key words: obstructive sleep apnea; sleep-disordered breathing; serum ferritin; low-density lipoprotein; triglyceride; cardiometabolic risk

Statement of Significance

This study explored whether red cell indices and serum ferritin could be potential biomarkers to reflect cardiometabolic risk in adolescents and young adults with sleep-disordered breathing (SDB). We observed independent associations between serum ferritin and lipid traits including low-density lipoprotein and triglyceride; as well as between hemoglobin, hematocrit and mean arterial pressure after adjusting for age, sex, and body mass index in patients with SDB. Serum ferritin is also associated with high-sensitivity C-reactive protein, a risk factor of long-term cardiovascular events especially in the moderate risk group. Our findings suggest that serum ferritin may reflect SDB severity and serve as a potential marker for lipid traits and cardiometabolic risk stratification.

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Introduction

Sleep-disordered breathing (SDB) encompasses a range of clinical and subclinical conditions characterized by snoring and/or recurrent episodes of upper airway obstruction during sleep. It is known to be an independent risk factor for cardiometabolic morbidity, including hypertension and dyslipidemia [1–4]. Findings from animal models also demonstrated that SDB confers independent cardiovascular (CV) risk through hypoxia-induced endothelial injury [5]. In adults, a number of studies have shown that treatment with continuous positive airway pressure (CPAP) can improve blood pressure (BP), glucose metabolism, and lipid profile in patients with obstructive sleep apnea (OSA) [6, 7], supporting that OSA is a potential cause of increased cardiometabolic risk (CMR). Identifying individuals with a higher CMR is clinically essential to personalize treatment approaches.

Lipid traits, especially low-density lipoprotein (LDL), are the most significant prognosticators of CV events [8], as well as the most commonly requested investigation for CV risk stratification in both SDB and non-SDB patients [9, 10]. Notably, dyslipidemia is a long-term consequence of chronic intermittent hypoxia (IH) and manifests only in the later course of the disease [11, 12]. Studies suggested that the apnea-hypopnea index (AHI), the most commonly used marker for OSA severity, failed to correlate significantly with lipid traits [13–15]. Animal studies suggest that ferritin and red cell indices (RCIs), which have been found to be associated with OSA and their severity, may reflect the long-term hypoxic burden and systemic inflammation [16–18]. Hence, we hypothesized that ferritin and RCIs were early markers of lipid derangement in patients with SDB/OSA, reflecting their CV risk. This study aimed to (1) evaluate the differences in RCIs/serum ferritin in adolescents/young adults with and without SDB; (2) investigate the association of RCIs/serum ferritin and obstructive apnea-hypopnea index (OAHI), the recommended marker for severity in the Chinese population [19]; and (3) explore whether OAHI, RCIs, and serum ferritin are independently associated with lipid profile, BP, glucose, and high-sensitivity C-reactive protein (hs-CRP) in adolescents/young adults with SDB.

Methods

Study participants and sleep study

This was a cross-sectional study with participants recruited from our childhood OSA epidemiological cohort when they attended the 10-year follow-up [20, 21]. Details of recruitment can be found in our previous publications [20, 21]. Participants were pooled from 13 randomly selected primary schools in Hong Kong. For this study, all participants from the original cohort were invited to complete a set of validated SDB screening questionnaires and were preliminarily assigned to the high-risk or low-risk group according to a composite system score (summations of the scores of the screening questionnaire) [22]. All participants belonging to the high-risk group and half of the randomly selected participants from the low-risk group were invited to undergo standard overnight polysomnography (PSG) in the Department of Paediatrics sleep laboratory in the Prince of Wales Hospital. Individuals were excluded from participation if they had (1) cardiovascular, renal, and neuromuscular diseases, (2) chromosomal abnormalities, or (3) acute illness within two weeks of PSG. Written informed consent and assent were obtained from the parents and participants, respectively.

Polysomnography and definitions

PSG took place in a dedicated sleep laboratory at the Prince of Wales Hospital. A model Siesta ProFusion III PSG monitor (Compumedics Telemed, Abbotsford, Victoria, Australia) was used to record the following parameters: electroencephalogram (F4/A1, C4/A1, and O2/A1), bilateral electrooculogram, and electromyogram of mentalis activity and bilateral anterior tibialis. Respiratory movements of the chest and abdomen were measured by inductance plethysmography. Electrocardiogram and heart rate (HR) were continuously recorded from two anterior chest leads. Arterial oxyhemoglobin saturation (SaO_2) was measured by an oximeter with a finger probe. Respiratory airflow pressure signal was obtained via a nasal catheter placed at the anterior nares and connected to a pressure transducer. An oronasal thermal sensor was used to detect the absence of airflow. Snoring was measured by a snoring microphone placed near the throat. Body position was monitored via a body position sensor. Respiratory events including obstructive apneas, mixed apneas, central apneas, and hypopneas were scored based on the AASM Manual for the Scoring of Sleep and Associated Events [23]. A respiratory event was scored when it lasted ≥10 seconds. All computerized sleep data were scored manually, as described in our previous publications based on the standard criteria [21, 23]. OSA was defined by an OAHI ≥ 5 events/hour as the participants (aged 16–25) had already reached late adolescence or early adulthood [24]. Participants were classified into 4 groups according to their PSG and questionnaire results: (1) healthy controls if OAHI < 5 and snoring less than 3 nights per week, (2) snorers if self-reported or parent-reported snoring more than or equal to 3 nights per week but with an OAHI < 5, (3) mild OSA if OAHI ≥ 5 but < 15, and (4) moderate-to-severe OSA if OAHI ≥ 15 [24].

Anthropometric data, blood biochemistry, and ABP

On the day of PSG, anthropometric parameters such as weight and height were measured. Standing height without shoes was documented using a Harpenden stadiometer (Holtain, UK) to the nearest 0.1 cm. Body weight, estimated to the nearest 0.1 kg, was obtained by an electronic weighing scale (Tanita BF-522, Japan). Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Blood was taken and sent to the laboratory for complete blood count, serum ferritin, lipid profile, fasting blood glucose (FBG), and hs-CRP.

Ambulatory blood pressure (ABP) was monitored on the same day as the overnight PSG using an oscillometer (SpaceLabs 90217; SpaceLabs Medical). The participants arrived at the sleep laboratory at 09:00, and ABP recordings began at arrival until they were discharged home upon finishing PSG the next day. The correct size cuff was placed on the nondominant arm. Systolic (SBP), diastolic (DBP), and mean arterial (MAP) were measured every 30 minutes during the nocturnal sleep period (i.e., 21:30 to 07:30) and every 15 minutes outside of this period (i.e., daytime wake period). The exact cutoff dividing wake and sleep BP was defined according to the PSG tracings. Individual mean SBP and DBP were calculated for wake and sleep periods. Recordings were accepted if there were at least 40 successful readings for the entire 24-hour period, with at least one successful reading per hour [25]. The HR was measured using cardiac monitors.

Statistical analysis of baseline demographics and disease severity

Data were analyzed using RStudio 2022.02.3. D'Agostino-Pearson and Anscombe-Glynn tests were performed to assess the Skewness and Kurtosis of the data. Descriptive statistics for

categorical variables were presented as frequencies and percentages, while for continuous variables, they were presented as mean and SD or median and interquartile range (IQR) for normally distributed and skewed data, respectively. Analysis of variance test was used to evaluate the baseline difference across different severity of SDB. Multiple linear regression was performed to examine the association between RCIs/serum ferritin and OAHI in all participants, adjusting for age, sex, and BMI.

Statistical analysis of cardiometabolic traits

Subgroup analysis was performed by excluding all healthy controls. As SDB is associated with cardiometabolic traits in the long term, i.e., plasma LDL, TG, FBG, and MAP, we evaluated their potential relations with RCIs/serum ferritin after adjustment for age, sex, and BMI ± OAHI. We further assessed the association between RCIs/serum ferritin and hs-CRP, with the additional adjustment for LDL and MAP, given that previous studies identified hs-CRP as one of the most significant independent risk factors of CV events, especially in individuals with moderate CV risk [26]. LDL and MAP were also adjusted as they were known CV risk factors. A value of $p < .05$ was considered statistically significant for all analyses.

Results

A total of 243 participants, aged 16–25 with a mean age of 20.2 ± 1.93, 148 male, were included in this analysis. There were 155 healthy controls and 88 participants with SDB. Among those with SDB, 28 were primary snorers, and 60 were diagnosed with OSA. Forty of them had mild OSA, and 20 had moderate-to-severe OSA. The mean ages of the healthy control, snorers, patients with mild OSA, and those with moderate-to-severe OSA were similar, but there appeared to be more male participants and higher BMI/BMI Z-score in the more severe end of the SDB spectrum. Participants with moderate-to-severe OSA had higher red blood cells (RBC), hemoglobin (Hb), hematocrit (HCT), serum ferritin, BP, triglyceride (TG), and hs-CRP (Supplementary Table S1). Table 1 summarizes the demographics, PSG parameters, RCI, as well as cardiometabolic traits of the participants according to their SDB severity group.

Association between RCIs, serum ferritin, and severity of SDB

Using multiple linear regression, we first explored the correlation between RCIs/serum ferritin and the severity of SDB. We included all participants, i.e. both the healthy controls and those with SDB, and then performed a subgroup analysis in only those with SDB, both with adjustment for age, sex, and BMI. The results are summarized in Table 2. Amongst all the RCIs, only Hb ($\beta = 1.06$, $p < .001$) and HCT ($\beta = 40.2$, $p < .001$) were significantly associated with OAHI. A positive relationship was also demonstrated between serum ferritin ($\beta = 4.89 \times 10^{-3}$, $p = .0244$) and OAHI. No significant associations were identified for other RCIs, including RBC, mean corpuscular volume, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and red cell distribution width (RDW). Similar results were reproduced in the subgroup analysis, where only participants with SDB were included (Table 2). Sensitivity analyses with AHI yielded similar results (Supplementary Table S2).

Associations of RCIs/serum ferritin and cardiometabolic traits/hs-CRP

Table 3 summarizes the correlation between RCIs/serum ferritin and cardiometabolic traits, i.e. plasma LDL, TG, FBG, and MAP, among participants with SDB after adjusting for age, sex, and BMI. Serum ferritin was positively correlated with plasma LDL ($\beta = 0.936 \times 10^{-3}$, $p = .00836$) and TG ($\beta = 1.08 \times 10^{-3}$, $p < .001$). Hb ($\beta = 1.40$, $p = .00697$) and HCT ($\beta = 51.5$, $p = .0102$) were associated with MAP. Interestingly, all of the above three markers, i.e. Hb, HCT, and serum ferritin ($\beta = 0.975$, $p = .005$; $\beta = 38.8$, $p = .004$; $\beta = 0.091$, $p = .002$) were shown to correlate with hs-CRP after adjusting for age, sex, BMI, plasma LDL, and MAP (Table 3). Sensitivity analyses with AHI yielded similar results (Supplementary Table S3).

Serum ferritin is associated with cardiometabolic traits/hs-CRP independent of SDB severity

We then evaluated the independent relationship between serum ferritin and cardiometabolic traits/hs-CRP by further adjusting for OAHI. In linear models including serum ferritin, age, sex, BMI, LDL, MAP, and OAHI, both serum ferritin ($\beta = 5.37 \times 10^{-3}$, $p = .006$) and OAHI ($\beta = 0.127$, $p = .012$) were significantly associated with hs-CRP. Meanwhile, only serum ferritin was significantly associated with plasma LDL ($\beta = 0.865 \times 10^{-3}$, $p = .019$) and TG ($\beta = 1.03 \times 10^{-3}$, $p < .001$) but not OAHI, suggesting that serum ferritin may better correlate with lipid traits in patients with SDB compared to OAHI (Table 4). Sensitivity analyses with AHI yielded similar results (Supplementary Table S4).

Discussion

Our study explored the associations between RCI, serum ferritin, and CMRs independent of age, sex, BMI, and OAHI in patients with SDB. First, Hb, HCT, and serum ferritin were significantly elevated in patients with SDB compared to those without SDB. Second, Hb, HCT, and serum ferritin were positively correlated with OAHI in all participants and across the SDB spectrum after adjusting for age, sex, and BMI. Third, serum ferritin was associated with lipid traits after adjusting for age, sex, and BMI in patients with SDB, while Hb and HCT were associated with MAP. No associations were observed between RCIs/serum ferritin and FBG, while all the three mentioned markers were positively correlated with hs-CRP. Fourth, in linear models of serum ferritin, OAHI, age, sex, and BMI, OAHI was not associated with LDL and TG while the positive associations between these lipid traits and serum ferritin remained significant.

Our findings suggested that serum ferritin was associated with SDB severity and serves as a potential marker for lipid traits and CV risk stratification in this study population. Individuals with SDB are at a higher risk of developing cardiometabolic complications, namely elevated BP, increased adiposity, insulin resistance, and deranged lipid profile [9, 27–29]. Although the epidemiological link between SDB and the untoward cardiometabolic phenotypes has been consistent, potential markers that can predict these traits are yet to be found, especially in adolescents and young adults. The present study provided real-world evidence that certain RCIs and serum ferritin may be associated with lipid traits in adolescents/young adults with SDB.

Hb, HCT, and serum ferritin are associated with SDB and its severity

Currently, PSG remains the gold standard for diagnosis and determination of severity in patients suspected to have SDB, despite the high cost and the inconvenience it causes to patients. Our study demonstrated that simple and routine blood markers, namely Hb, HCT, and serum ferritin, may reflect disease severity and carry clinical implications given that they are readily available in clinical

Table 1. Baseline Demographics

	Healthy controls	Snorer	Mild OSA	Moderate-to-severe OSA	*p* value
Demographics					
Total	155	28	40	20	
Male sex	88 (56.8%)	15 (53.6%)	28 (70%)	17 (85%)	.046
Age, years	20.1 ± 1.97	20.4 ± 1.98	20.4 ± 1.94	20.0 ± 1.56	.69
Weight, kg	60.1 ± 13.1	59.2 ± 11.8	63.9 ± 11.6	77.7 ± 17.6	<.001
Height, cm	167 ± 9.19	164 ± 8.49	168 ± 7.44	173 ± 5.65	.005
BMI, kg/m^2	21.2 ± 3.52	21.9 ± 3.61	22.6 ± 4.03	25.9 ± 5.19	<.001
BMI Z-score	0.133 ± 1.04	0.279 ± 1.14	0.469 ± 0.960	1.09 ± 0.995	.001
Sleep parameters					
AHI*	2.56 (1.53, 4.27)	3.51 (7.54, 13.2)	9.78 (20.4, 27.4)	22.6 (30.4, 27.4)	<.001
OAHI*	0.6 (0.0, 1.9)	0.9 (5.65, 9.33)	7.50 (18.4, 25.3)	20.2 (18.4, 25.3)	<.001
CAHI*	1.36 (1.13, 1.91)	1.51 (1.14, 1.73)	1.26 (1.41, 2.96)	1.58 (1.41, 2.96)	.001
ODI*	1.76 (1.23, 3.41)	1.99 (4.53, 11.8)	7.69 (6.71, 19.3)	11.7 (6.71, 19.3)	<.001
ARI*	12.4 (9.97, 15.5)	11.6 (13.6, 20.3)	17.5 (27.1, 40.2)	29.7 (27.1, 40.2)	<.001
RAI*	1.83 (1.29, 2.81)	1.96 (4.39, 8.08)	5.47 (15.1, 21.0)	16.9 (15.1, 21.0)	<.001
RCI and ferritin					
RBC	5.05 ± 0.607	5.13 ± 0.657	5.10 ± 0.594	5.45 ± 0.490	.063
Hb	14.2 ± 1.53	13.8 ± 1.68	14.4 ± 1.63	15.7 ± 1.42	<.001
HCT	0.431 ± 0.041	0.419 ± 0.044	0.437 ± 0.045	0.473 ± 0.036	<.001
MCV	85.9 ± 8.37	82.8 ± 11.9	86.3 ± 8.22	87.0 ± 4.50	.338
MCH	28.3 ± 3.29	27.3 ± 4.55	28.5 ± 3.14	28.9 ± 2.09	.401
MCHC	32.9 ± 0.992	32.8 ± 1.02	32.9 ± 0.811	33.2 ± 0.994	.608
RDW*	13.1 (12.7, 13.7)	13.1 (12.8, 14.0)	13.1 (12.8, 13.9)	13.3 (13.0, 13.5)	.629
Ferritin*	236 (107, 443)	246 (139, 305)	268 (134, 428)	509 (348, 659)	<.001
Cardiometabolic traits					
SBP	112 ± 8.65	109 ± 10.9	115 ± 8.72	120 ± 8.63	<.001
DBP	69.6 ± 5.46	69.4 ± 7.49	70.6 ± 5.91	74.1 ± 5.08	.014
MAP	84.1 ± 5.44	83.1 ± 7.72	85.9 ± 5.63	89.7 ± 5.27	<.001
HR	68.6 ± 7.93	67.5 ± 6.81	68.5 ± 7.75	71 ± 7.16	.515
FBG*	5.1 (4.9, 5.3)	4.9 (4.8, 5.1)	5.1 (4.8, 5.4)	5.4 (5.2, 5.7)	.118
TC	4.09 ± 1.14	3.81 ± 1.61	4.15 ± 0.701	4.36 ± 1.77	.47
HDL	1.61 ± 0.338	1.5 ± 0.318	1.60 ± 0.385	1.52 ± 0.428	.456
LDL	2.29 ± 0.674	2.4 ± 0.734	2.12 ± 0.649	2.68 ± 0.889	.0389
TG*	0.8 (0.6, 1.0)	0.8 (0.600, 1.03)	0.8 (0.675, 1.10)	1.05 (0.800, 1.58)	<.001
hs-CRP*	0.5 (0.2, 1.1)	0.4 (0.200, 0.625)	0.5 (0.25, 1.15)	2.2 (1.1, 4.0)	<.001

Categorical variables were presented as frequency (percentage); continuous variables were presented as mean ± standard deviation (SD) unless specified otherwise.
*Data were presented as median (IQR).
Abbreviations: BMI, body mass index; AHI, apnea-hypopnea index; OAHI, obstructive apnea-hypopnea index; CAHI, central apnea-central hypopnea index; ODI, oxygen desaturation index; ARI, arousal index; RAI, respiratory arousal index; RBC, red blood cell; Hb, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width; SBP, systemic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; FBG, fasting blood glucose; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; hs-CRP, high-sensitivity C-reactive protein.

practice. We showed that Hb, HCT, and serum ferritin were significantly elevated in participants with SDB and increased with disease severity/OAHI, independent of well-recognized risk factors of SDB, including obesity. Whilst two meta-analyses including adult patients and several smaller-scale studies have demonstrated similar differences in HCT and Hb between patients with SDB and control [30–36], we extended and validated these findings in a large cohort of youth patients. Such findings are likely of substantial clinical value, as several studies have shown that successful treatment of OSA by CPAP was associated with lower HCT and Hb [6, 7]. Although these RCIs and serum ferritin are unlikely to replace PSG for an accurate diagnosis of SDB/OSA, they may serve as surrogate markers of disease severity or treatment response, especially when overnight PSGs are not readily available [6, 7].

At the same time, we provided evidence that in addition to HCT and Hb which are known to rise in hypoxic lung diseases, serum

Table 2. Association Between RCIs/Serum Ferritin and OAHI After Adjusting for Age, Gender, and BMI

	β	95% CI		SE	*p* value
In all participants					
RBC	0.237	−1.37	1.85	0.817	.772
Hb	1.06	0.323	1.79	0.371	<.001
HCT	40.2	11.6	68.8	14.5	<.001
MCV	0.061	−0.037	0.159	0.050	.222
MCH	0.167	−0.084	0.419	0.128	.191
MCHC	0.546	−0.336	1.43	0.448	.224
RDW	−0.112	−0.883	0.660	0.392	.776
Serum ferritin	4.89×10^{-3}	0.638×10^{-3}	9.15×10^{-3}	2.16×10^{-3}	.024
In SDB participants					
RBC	0.580	−2.95	4.12	1.76	.745
Hb	1.92	0.511	3.33	0.709	<.001
HCT	74.2	19.8	129	27.3	<.001
MCV	0.153	−0.068	0.373	0.111	.173
MCH	0.398	−0.170	0.966	0.285	.167
MCHC	1.16	−0.959	3.27	1.06	.280
RDW	−0.606	−2.34	1.13	0.871	.489
Serum ferritin	9.02×10^{-3}	0.608×10^{-3}	0.0174	4.23×10^{-3}	.036

Abbreviations: RBC, red blood cell; Hb, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width.

ferritin, a marker of iron metabolism and systemic inflammation, may reflect SDB severity. This added to the recent literatures exploring alternative markers which were more readily available than PSG in measuring disease severity [37, 38]. However, there are conflicting results on the serum ferritin level in patients with SDB [18, 39–42]. A study published by Kerstein et al. [39] reported a lower-than-normal serum ferritin level in children with SDB. In contrast, several other studies showed that serum ferritin level was higher in adults with moderate-to-severe OSA [18, 40–42]. Indeed, Kerstein et al. included only 94 pediatric patients without description of disease severity. The absence of healthy control limited the comparison with the local reference range only.

Serum ferritin is associated with lipid traits and hs-CRP

Hypertension, dyslipidemia, and insulin resistance are more prevalent amongst patients with SDB, while there is a lack of potential markers of these cardiometabolic traits. Although chronic and severe OSA appeared to contribute to cardiometabolic risk factors and CV risks, previous studies suggested that sleep study parameters, including OAHI, failed to predict such traits/outcomes [43]. In this study, we identified that serum ferritin was associated with TG and LDL, which might confer CMRs to these patients whereas OAHI did not correlate with these lipid traits.

Traditionally, serum ferritin is believed to be a surrogate marker of total iron body storage and a positive acute phase reactant in systemic inflammation [44]. Previous literature demonstrated increased chronic inflammation in patients with SDB, and it has been shown to correlate with dyslipidemia, potentially explaining our findings [45]. Meanwhile, it is also likely that other pathways related to iron metabolism are involved. There is evidence that SDB, with the hallmark of nocturnal IH, resembles ischemic-reperfusion injury [46], which results in oxidative stress through the production of iron-derived reactive oxidative species [47, 48]. In this process, serum ferritin is upregulated as a cellular defense mechanism against heme-mediated cytotoxicity [49].

Of note, serum ferritin, independent of traditional risk factors of CVD including age, sex, BMI, LDL, and MAP, was strongly associated with hs-CRP, suggesting that it may indicate CV risk beyond the conventional factors in SDB patients. Indeed, hs-CRP is a well-established marker for predicting CV morbidity beyond traditional risk factors. According to the 2019 ACC/AHA Guideline on the Primary Prevention of CVD, hs-CRP is recommended for screening in patients with intermediate risk of CVD, and studies are highlighting an elevated level of serum ferritin in SDB patients who develop coronary artery disease [50]. We hypothesized that serum ferritin, associated with LDL, TG, and hs-CRP, may predict CV morbidities in the long term. Arguably, as an acute phase reactant, serum ferritin is likely to be associated with another stable marker of inflammation, i.e. hs-CRP. Whether or not such association is related to long-term outcomes remains unclear and warrants further investigation.

Limitations

Although the present study shed light on the association of certain RCIs/serum ferritin and the severity/cardiometabolic traits in patients with SDB/OSA, it is not without limitations. First, the present study is of cross-sectional design, an exploratory effort to investigate the potential clinical implication of elevated RCIs/serum ferritin in patients with SDB. Further confirmation, especially with longitudinal studies, is needed. Second, although the well-balanced proportion of patients in each severity group with the inclusion of a healthy control group allowed fairer comparison, the relatively modest sample size of the study limits the statistical power. Third, future longitudinal study will help identify whether a meaningful cutoff of serum ferritin could serve as

Table 3. Association Between RCIs/Serum Ferritin and Cardiometabolic Traits Amongst Patients with SDB After Adjusting for Age, Gender, and BMI

	β	95% CI		SE	*p* value
LDL					
RBC	−0.011	−0.307	0.285	0.149	.941
Hb	0.056	−0.067	0.179	0.062	.368
HCT	2.09	−2.67	6.85	2.39	.385
MCV	3.10×10^{-3}	−0.016	0.0217	9.36×10^{-3}	.742
MCH	8.44×10^{-3}	−0.040	0.056	0.024	.727
MCHC	0.042	−0.137	0.221	0.090	.641
RDW	−0.013	−0.158	0.132	0.073	.859
Serum ferritin	0.936×10^{-3}	0.248×10^{-3}	1.62×10^{-3}	0.346×10^{-3}	.008
Triglyceride					
RBC	0.097	−0.128	0.321	0.113	.394
Hb	0.042	−0.052	0.135	0.047	.379
HCT	1.67	−1.96	5.29	1.82	.362
MCV	-2.66×10^{-3}	−0.017	0.012	7.13×10^{-3}	.710
MCH	-5.01×10^{-3}	−0.042	0.032	0.018	.786
MCHC	0.017	−0.119	0.154	0.068	.800
RDW	0.040	−0.071	0.150	0.055	.475
Serum ferritin	1.08×10^{-3}	0.586×10^{-3}	1.57×10^{-3}	0.247×10^{-3}	<.001
Fasting blood glucose					
RBC	0.062	−0.168	0.293	0.116	.592
Hb	0.038	−0.058	0.134	0.048	.433
HCT	1.65	−2.05	5.35	1.86	.377
MCV	0.721×10^{-3}	−0.014	0.015	7.33×10^{-3}	.922
MCH	1.31×10^{-3}	−0.036	0.039	0.019	.945
MCHC	9.30×10^{-3}	−0.130	0.149	0.070	.895
RDW	−0.054	−0.167	0.060	0.057	.349
Serum ferritin	0.430×10^{-3}	-0.127×10^{-3}	0.988×10^{-3}	0.280×10^{-3}	.128
Mean arterial pressure					
RBC	−0.558	−3.08	1.97	1.27	.661
Hb	1.40	0.395	2.41	0.505	.007
HCT	51.5	12.6	90.5	19.6	.010
MCV	0.149	-6.58×10^{-3}	0.306	0.078	.060
MCH	0.378	−0.024	0.780	0.202	.065
MCHC	1.11	−0.398	2.61	0.755	.147
RDW	−0.528	−1.77	0.711	0.622	.399
Serum ferritin	4.02×10^{-3}	-2.13×10^{-3}	0.010	3.09×10^{-3}	.197
hs-CRP*					
RBC	0.681	−0.909	2.27	0.798	.396
Hb	0.975	0.309	1.64	0.334	.005
HCT	38.8	13.1	64.4	12.9	.004
MCV	0.049	−0.054	0.252	0.051	.347
MCH	0.135	−0.047	0.251	0.132	.310
MCHC	0.509	−0.460	1.48	0.486	.299
RDW	−0.131	−0.917	0.655	0.394	.741
Serum ferritin	0.091	2.43×10^{-3}	0.010	0.002	.002

*Association between RCIs/serum ferritin and hs-CRP amongst patients with SDB after adjusting for age, gender, BMI, plasma LDL, and MAP.
Abbreviations: LDL, low-density lipoprotein; RBC, red blood cell; Hb, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width; hs-CRP, high-sensitivity C-reactive protein.

Table 4. Association Between Serum Ferritin and Cardiometabolic Traits Amongst Patients with SDB After Adjusting for Age, Gender, BMI, LDL, MAP, and OAHI

	β	95% CI		SE	*p* value
LDL					
Serum ferritin	0.865×10^{-3}	0.147×10^{-3}	1.58×10^{-3}	0.360×10^{-3}	.019
OAHI	4.53×10^{-3}	−0.015	0.024	9.72×10^{-3}	.643
Triglyceride					
Serum ferritin	1.03×10^{-3}	0.528×10^{-3}	1.53×10^{-3}	0.251×10^{-3}	<.001
OAHI	-3.10×10^{-3}	−0.017	0.010	6.78×10^{-3}	.649
hs-CRP					
Serum ferritin	5.37×10^{-3}	1.61×10^{-3}	9.12×10^{-3}	1.88×10^{-3}	.006
OAHI	0.127	0.029	0.224	0.049	.012

Abbreviations: LDL, low-density lipoprotein; OAHI, obstructive apnea-hypopnea index; hs-CRP, high-sensitivity C-reactive protein.

an important clinical tool in predicting cardiometabolic consequences of OSA. Fourth, information on lifestyle and sleep habits were not available, which could also be potential confounders. ABP was measured on the same day as the overnight PSG for patient's convenience, which may also have influence on the PSG results.

Conclusion

Hb, HCT, and serum ferritin are elevated in patients with SDB and correlate with OAHI. Serum ferritin is associated with plasma LDL and TG, while HCT and Hb are associated with BP. All three mentioned markers show a positive association with hs-CRP in patients with SDB. Only serum ferritin, not OAHI, is associated with TG and LDL. Serum ferritin and certain RCIs may serve as potential markers of cardiometabolic risks in adolescents/young adults with SDB.

Supplementary Material

Supplementary material is available at *SLEEP Advances* online.

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Author Contributions

Esther Tin Wing Cheng (Conceptualization [lead], Formal analysis [lead], Investigation [lead], Visualization [lead], Writing—original draft [lead], Writing—review & editing [lead]), Chun Ting Au (Data curation [equal], Funding acquisition [equal], Methodology [equal], Project administration [equal], Supervision [equal], Writing—review & editing [equal]), Raymond N.C. Chan (Conceptualization [equal], Formal analysis [equal], Visualization [equal], Writing—original draft [equal], Writing—review & editing [equal]), Joey Chan (Data curation [equal], Funding acquisition [equal], Methodology [equal], Project administration [equal], Supervision [equal], Writing—review & editing [equal]), Ngan Yin Chan (Data curation [equal], Funding acquisition [equal], Methodology [equal], Project administration [equal], Supervision [equal], Writing—review & editing [equal]), Yun-Kwok Wing (Data curation [equal], Funding acquisition [equal], Methodology [equal], Project administration [equal], Supervision [equal], Writing—review & editing [equal]), Albert Martin Li (Data curation [equal], Funding acquisition [lead], Methodology [equal], Project administration [equal], Resources [equal], Supervision [equal], Writing—review & editing [equal]), Ethan Lam (Data curation [equal], Project administration [equal]), and Kate Ching-ching Chan (Conceptualization [equal], Data curation [lead], Funding acquisition [lead], Methodology [lead], Project administration [lead], Resources [equal], Supervision [lead], Writing—review & editing [lead])

Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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