

ORIGINAL ARTICLE

The effect of iron deficiency on quality of life outcomes after surgery for obstructive sleep apnoea

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Aim: This study aimed to assess the effect of iron deficiency on parent-reported changes in quality of life (QOL) among children receiving an adenotonsillectomy for paediatric obstructive sleep apnoea (OSA).

Methods: This was a retrospective review study that recruited children under 16 years of age undergoing an adenotonsillectomy, adenoidectomy, or tonsillectomy for clinically diagnosed paediatric OSA between June 2020 and January 2021 inclusive, in Western Australia. The main outcome measures for this study were changes in QOL by age group and iron status, defined by an absolute change of more than 3 points on OSA-18 survey domains.

Results: About 249 participants had iron studies performed on perioperative blood samples drawn at operation and completed both pre-operative and post-operative OSA-18 QOL questionnaires at initial consultation and 8–12 weeks post-surgery, respectively. 41.8% were iron deficient, 53.8% were borderline iron deficient and 4.4% had normal iron levels. Following surgery, a decrease was observed for all OSA-18 score domains in post-operation scores compared to pre-operation scores in both iron-deficient and borderline iron-deficient cohorts. ‘Daytime Problems’ in the <2 years group, within the iron-deficient cohort, was the only domain that found to be non-superior (i.e. ‘not better’) following surgery.

Conclusions: Following adenotonsillectomy, patients with paediatric OSA reported significant improvements in QOL regardless of their iron status. Those undergoing an adenotonsillectomy for paediatric OSA had a high prevalence of iron deficiency at operation, especially those under 6 years of age.

Key words: adenotonsillectomy; iron deficiency; obstructive sleep apnoea; paediatrics; quality of life.

What is already known on this topic

- 1 Among children with paediatric obstructive sleep apnoea (OSA), quality of life (QOL) improves after receiving an adenotonsillectomy.
- 2 Information on the QOL of children receiving an adenotonsillectomy for OSA in an Australian cohort is limited.

What this paper adds

- 1 Iron deficiency does not impact reported changes in quality of life (QOL) among children receiving an adenotonsillectomy for obstructive sleep apnoea (OSA) apart from the iron-deficient under 2-year-old group who may have persistent daytime symptoms.
- 2 Children receiving an adenotonsillectomy for OSA in Australia have a high prevalence of iron deficiency.

Sleep-disordered breathing (SDB) is a condition characterised by breathing problems when asleep.¹ The most severe expression of SDB, obstructive sleep apnoea (OSA), is a common childhood condition with a prevalence of 1.2–5.7%.² Clinically, OSA is defined by repeated episodes of prolonged partial upper airway obstruction and/or intermittent complete upper airway

obstruction that interferes with normal ventilation during sleep,² reducing oxygen saturation levels of arterial blood and consequently inducing sleep arousal.³ Children with untreated OSA incur significant health-related consequences including growth failure, cardiovascular complication, and neurocognitive deficits such as attention-deficit/hyperactivity disorders, behavioural problems and poor learning.⁴

Within the paediatric population, adenotonsillar hypertrophy is the most commonly identified risk factor for OSA.⁵ Enlargement of the adenoid and tonsillar tissue, in conjunction with relaxation of the pharyngeal muscles during sleep, can cause partial or complete airway obstruction and therefore may lead to OSA.⁶ Surgery in the form of adenoidectomy, tonsillectomy, or

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both, remains as the first-line therapy for the management of OSA in this population.⁷ In Australia alone, 38 575 tonsillectomies were performed on those aged 17 years and under between 2012 and 2013.⁸

Iron deficiency is also common in the paediatric population, occurring in approximately 8% of Australian children under the age of 5 years.⁹ Iron is essential to many biological processes including growth, immunity and erythropoiesis.¹⁰ Consequently, a deficiency of iron can manifest clinically in children with common signs and symptoms such as fatigue, lethargy and reduced concentration, as well as poor feeding and irritability in infants.¹¹ Iron has also been implicated in child neurocognitive development.¹² It is thought that the components of the brain involved in the metabolism of neurotransmitters, myelin synthesis and oligodendrocyte functioning are all impaired as a result of iron deficiency.¹³

The OSA-18 survey is a validated disease-specific QOL measure for paediatric OSA comprising of 18 items categorised into five domains: sleep disturbance, physical suffering, emotional distress, daytime problems and caregiver concerns.¹⁴ Previous findings have demonstrated that children diagnosed with OSA have a quality of life (QOL) similar to that of children with chronic diseases.¹⁵ However, it has been reported that those who received an adenotonsillectomy for paediatric OSA, as opposed to watchful waiting, had reduced symptoms and improved QOL and behaviour.⁵ Despite the existing body of literature measuring the changes in QOL following adenotonsillectomy for paediatric OSA, to the best of our knowledge, few have considered the effect of iron deficiency. Therefore, the aim of this study was to¹ evaluate the impact of adenotonsillectomy on the QOL in those with paediatric OSA and² to compare the changes in domain scores of those in different iron subgroups. We hypothesised that in children receiving an adenotonsillectomy for OSA, those with a co-existing iron deficiency at operation will have no observed improvement in mood, behaviour, or attention at follow-up compared to baseline OSA-18 QOL questionnaire (OSA-18) scores.

Methods

Ethics approval for this study was obtained via the St John of God Hospital Human Research Ethics Committee (Reference number 1671). Participants were recruited from June 2020 to January 2021 inclusive. There was no commercial support for this study.

The study population included children aged 16 years that underwent adenoidectomy, tonsillectomy, or both for clinically diagnosed OSA. Pre-operative OSA-18 surveys were completed by caregivers at the initial consultation. A single surgeon performed all procedures using the same surgical technique: coblation, both intracapsular and extracapsular techniques were used but not recorded for the purposes of this study. A peri-operative blood sample was withdrawn from the intravenous cannula used by the anaesthetist and sent for iron studies: ferritin, iron, and transferrin saturation. Post-operative OSA-18 surveys were either completed by caregivers, 8–12 weeks post-surgery, at the patient's routine follow-up appointment or returned completed via email. Furthermore, it was at this post-operative appointment that patients were informed of the results of the iron studies, and if found to be iron deficient, were advised to commence iron supplementation.

Data recorded included the date, patient demographics, indication for surgery, surgical procedure, iron study results, and pre-

operative and post-operative OSA-18 survey domain and total scores, see Table A1. Retrospective analysis of data was conducted by authors separate from those responsible for either performing the surgical procedure or collecting the data.

Statistical analysis

Statistical analyses were performed using the R statistical computation software *via* the RStudio IDE. Although the peri-operative blood samples withdrawn included a full panel of iron studies, ferritin is noted to be the best marker of iron stores and as a result a reflection of iron deficiency. Therefore, in accordance with the Royal College of Pathologists Australasia (RCPA), iron deficiency was defined as a ferritin concentration of <20 µg/L, a borderline iron deficiency was defined as a ferritin concentration of 20–60 µg/L, and a ferritin concentration >60 µg/L represented a normal iron status.¹⁶

Participants were further divided based upon age and iron status for subgroup analysis. Age categories were defined as: under 2, 2–6 and over 6 years old. These categories were based on previous literature in addition to physiological and clinical reasons such as growth spurts, surgical patterns and diet.^{9,17}

Paired *t*-tests were used to calculate mean change estimates and 95% confidence intervals (CIs) between pre-operation and post-operation OSA-18 surveys by OSA-18 domain and age group. Lower OSA-18 scores indicating an improved QOL, thus superiority, or a 'better' outcome, post-operation was established when the 95% CI of the change in OSA-18 scores included a range that was less than, but did not include the superiority margin, which was defined as a 3 points decrease on the OSA-18 scale; non-superiority, or 'not better', was defined as the 95% CI including a range that was greater than the superiority margin (–3 points). An inconclusive result was observed if the 95% CI included the superiority margin. CIs that include the superiority margin by only a, subjectively, small amount could indicate superiority/non-superiority in a larger cohort, which would yield a more precise estimate; results are discussed here under this assumption.

Results

The collection of OSA-18 surveys from caregivers pre- and post-adenotonsillectomy operations began in June 2020 and concluded in January 2021, at which time 249 caregivers had completed both surveys and were included for analysis, see Table 1. Of the 249 respondents, 104 (41.8%) children were iron deficient, 134 (53.8%) had a borderline iron deficiency and 11 (4.4%) had normal iron levels, see Table 2. Analysis by age group revealed that in those <2 years, 15 (36.6%) children were iron deficient, 23 (56.1%) were borderline iron deficient and 3 (7.3%) had normal iron levels. In the 2 to <6 years group, 75 (47.8%) children were iron deficient, 79 (50.3%) were borderline iron deficient and 3 (1.9%) had normal iron levels. While in those aged 6 to <16 years, 14 (27.5%) children were iron deficient, 32 (62.7%) were borderline iron deficient and 5 (9.8%) had normal iron levels.

In the iron-deficient cohort, 15 (14.4%) were aged <2 years, 75 (72.1%) were aged 2 to <6 years and 14 (13.5%) were aged 6 to <16 years. Among the borderline iron-deficient cohort, 23 (17.2%) were aged <2 years, 79 (59.0%) were aged 2 to <6 years and 32 (23.9%) were aged 6 to <16 years. Following

surgery, a decrease was observed for all OSA-18 score domains in post-operation scores compared to pre-operation scores in both cohorts, see Figure 1.

Table 1 Cohort clinical characteristics

	Clinical characteristics
<i>n</i>	249
Age, mean (SD) [†]	3.91 (2.60)
Male sex, <i>n</i> (%)	142 (57.0)
Surgical procedure	
Adenotonsillectomy, <i>n</i> (%)	173 (71.9)
Adenoidectomy, <i>n</i> (%)	58 (23.3)
Tonsillectomy, <i>n</i> (%)	12 (4.8)
Ferritin (µg/L) (median) (IQR) [‡]	22 (18)
Iron (µmol/L) (median) (IQR) [‡]	11 (7)
Transferrin saturation (%) (median) (IQR) [‡]	17 (10)

[†] SD, standard deviation. [‡] IQR, interquartile range.

Iron-deficient cohort

For the <2 years group, the ‘Daytime problems’ domain was found to be, on average non-superior (i.e. ‘not better’, 95% CI: -2.801 to 0.001) in post-operative OSA-18 scores when compared to pre-operation, ‘Sleep disturbance’ (95% CI: -10.957 to -2.910, noting that the CI does include the superiority margin) and ‘Physical suffering’ (95% CI: -9.514 to -3.953) were found to be superior, and ‘Caregiver concerns’ (95% CI: -6.318 to 1.251) and ‘Emotional distress’ (95% CI: -3.753 to 1.886) were inconclusive, see Table 3. Within the 2 to <6 years group, superiority was observed for ‘Caregiver concerns’ (95% CI: -7.844 to -5.236), ‘Physical suffering’ (95% CI: -8.095 to -5.465) and ‘Sleep disturbance’ (95% CI: -9.108 to -7.026), with ‘Daytime problems’ and ‘Emotional distress’ yielding inconclusive results. Among the 6 to <16 years group, ‘Sleep disturbance’ (95% CI: -10.546 to -3.739) and ‘Caregiver concerns’ (95% CI: -10.043 to -2.814) were superior in post-operative scores (*P* < 0.05), with the other domains inconclusive, see Figure 2.

Table 2 Prevalence of iron deficiency by age group; Count (%)

Age group	Iron deficiency (ferritin < 20 µg/L)	Borderline iron deficiency (ferritin 20–60 µg/L)	Normal iron (ferritin > 60 µg/L)
<2 years, <i>n</i> (%)	15 (36.6)	23 (56.1)	3 (7.3)
2 to <6 years, <i>n</i> (%)	75 (47.8)	79 (50.3)	3 (1.9)
6 to <16 years, <i>n</i> (%)	14 (27.5)	32 (62.7)	5 (9.8)
Total, <i>n</i> (%)	104 (41.8)	134 (53.8)	11 (4.4)

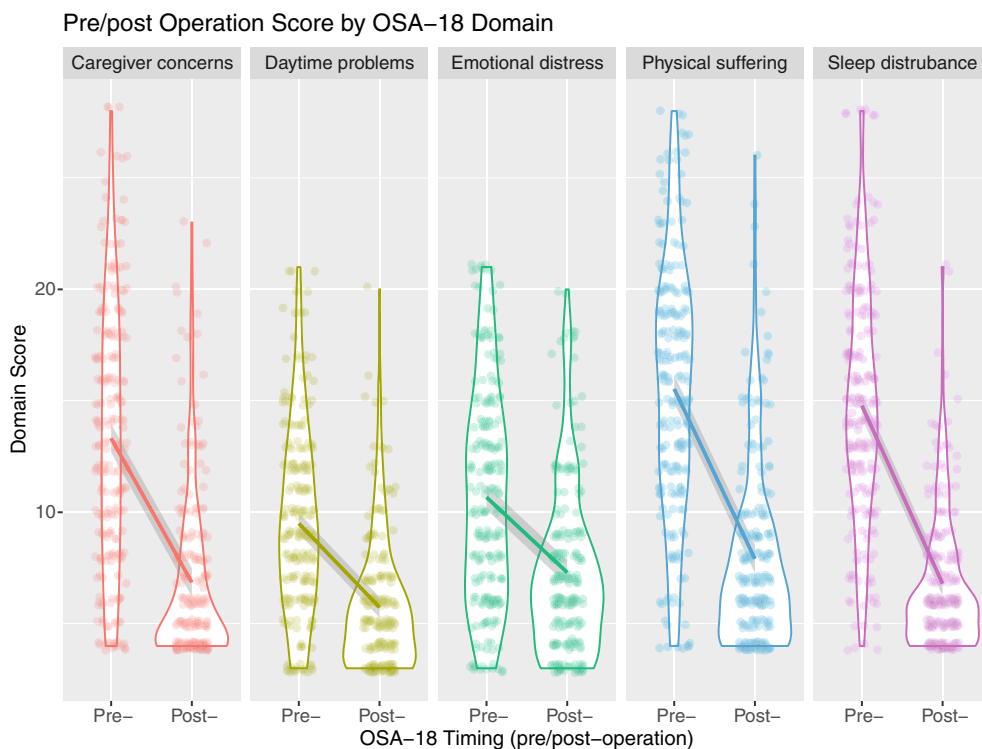


Fig. 1 Pre- and post-operation score difference by OSA-18 domain for iron deficient and borderline iron-deficient cohorts.

Table 3 Mean change (95% CI) OSA-18 domain score changes in the iron-deficient cohort

OSA-18 domain	<2 years	2 to <6 years	6 to <16 years
Caregiver concerns	-2.533 (-6.318 to 1.251)	-6.540 (-7.844 to -5.236)**	-6.429 (-10.043 to -2.814)
Daytime problems	-1.400 (-2.801 to 0.001)*	-3.613 (-4.508 to -2.718)	-4.071 (-6.913 to -1.230)
Emotional distress	-0.933 (-3.753 to 1.886)	-3.160 (-4.246 to -2.704)	-4.643 (-7.251 to -2.035)
Physical suffering	-6.733 (-9.514 to -3.953)*	-6.780 (-8.095 to -5.465)**	-4.571 (-8.800 to -0.342)
Sleep disturbance	-6.933 (-10.957 to -2.910)	-8.067 (-9.108 to -7.026)**	-7.143 (-10.546 to -3.739)*

* $P < 0.05$. ** $P < 0.001$.

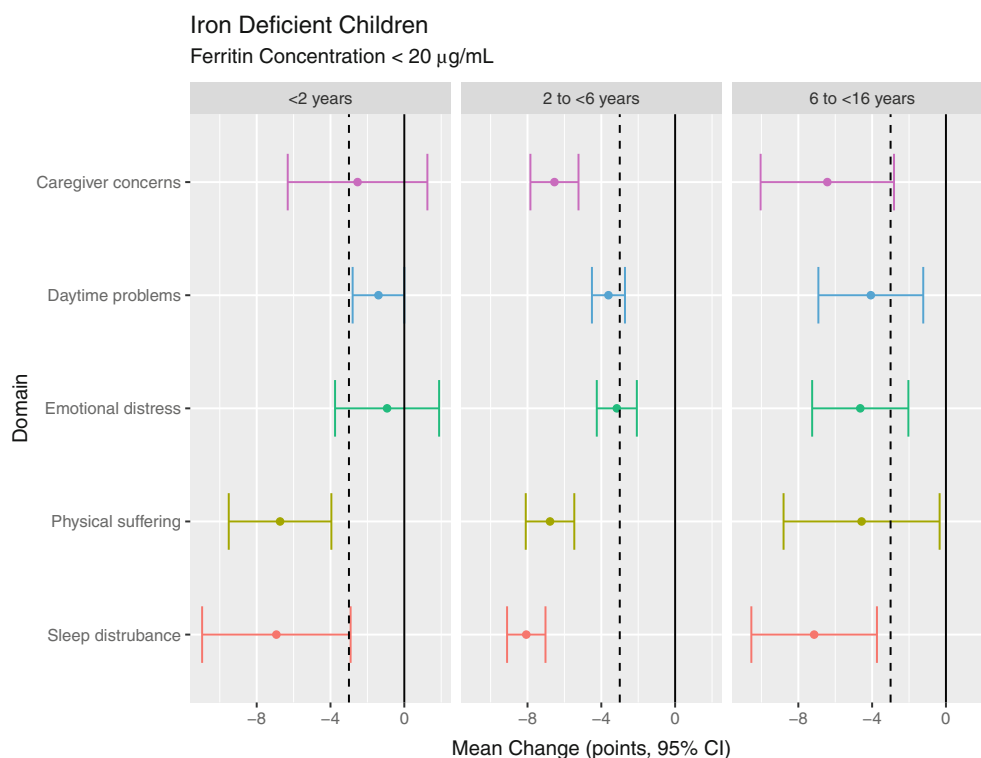


Fig. 2 Mean OSA-18 domain score changes in the iron-deficient cohort. The figure illustrates the mean change estimate and the 95% confidence intervals from paired *t*-tests for each OSA-18 domain. The solid vertical line represents a change of 0 points, while the dashed line indicates a clinically significant change of 3 points.

Table 4 Mean change (95% CI) OSA-18 domain score changes in the borderline iron-deficient cohort

OSA-18 domain	<2 years	2 to <6 years	6 to <16 years
Caregiver concerns	-7.870 (-10.488 to -5.251)***	-6.962 (-8.301 to -5.623)***	-5.969 (-8.218 to -3.719)*
Daytime problems	-2.217 (-4.047 to -0.388)	-4.500 (-5.406 to -3.594)**	-4.406 (-5.957 to -2.855)
Emotional distress	-3.261 (-5.252 to -1.270)	-4.165 (-5.118 to -3.211)*	-2.594 (-4.076 to -1.112)
Physical suffering	-9.391 (-11.780 to -7.002)***	-8.911 (-10.168 to -7.655)***	-6.969 (-9.352 to -4.585)**
Sleep disturbance	-7.543 (-10.399 to -4.688)**	-8.747 (-9.907 to -7.586)***	-7.156 (-9.396 to -4.917)***

* $P < 0.05$. ** $P < 0.01$. *** $P < 0.001$.

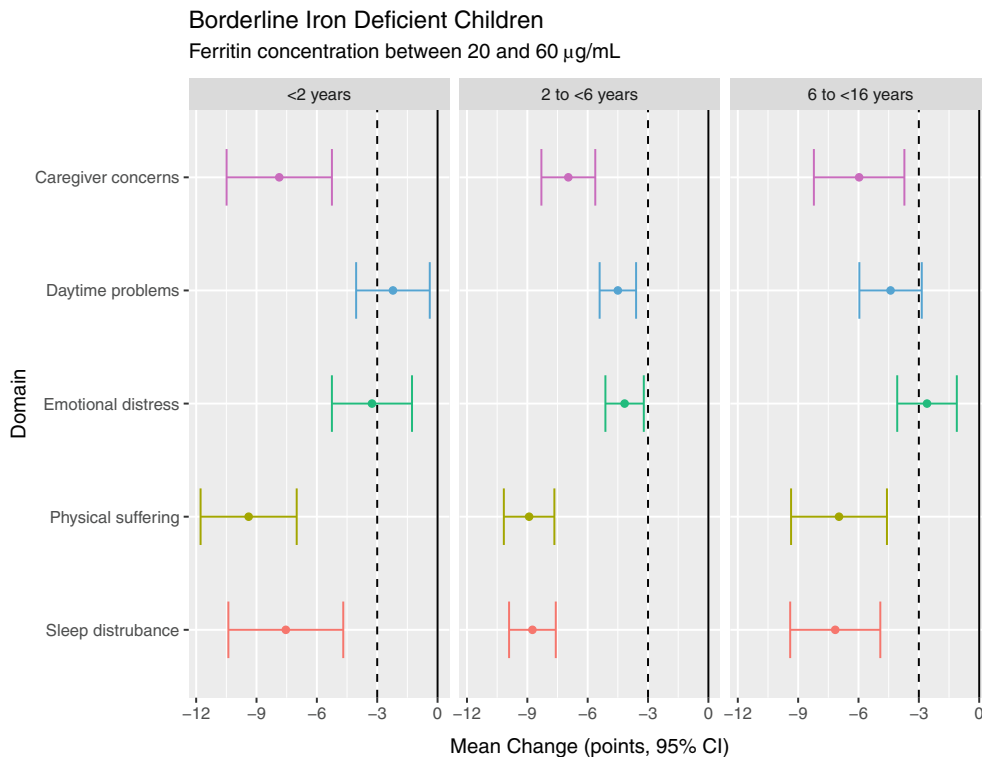


Fig. 3 Mean OSA-18 domain score changes in the borderline iron-deficient cohort. The figure illustrates the mean change estimate and the 95% confidence intervals from paired t-tests for each OSA-18 domain. The solid vertical line represents a change of 0 points, while the dashed line indicates a clinically significant change of 3 points.

Borderline iron-deficient cohort

For the <2 years group, superiority of the post-operation OSA-18 scores was observed in the ‘Caregiver concerns’ (95% CI: -10.488 to -5.251), ‘Physical suffering’ (95% CI: -11.780 to -7.002) and ‘Sleep disturbance’ (95% CI: -10.399 to -4.688) domains, while ‘Daytime problems’ and ‘Emotional distress’ were inconclusive, see Table 4. Within the 2 to <6 years group, superiority was observed in all domains: ‘Caregiver concerns’ (95% CI: -8.301 to -5.623), ‘Daytime problems’ (95% CI: -5.406 to -3.594), ‘Emotional distress’ (95% CI: -5.118 to -3.211), ‘Physical suffering’ (95% CI: -10.168 to -7.655) and ‘Sleep disturbance’ (95% CI: -9.907 to -7.586). Among the 6 to <16 years group, superiority was observed for ‘Caregiver concerns’ (95% CI: -8.218 to -3.719), ‘Physical suffering’ (95% CI: -9.352 to -4.585) and ‘Sleep disturbance’ (95% CI: -9.396 to -4.917), and ‘Daytime problems’ (95% CI: -5.957 to -2.855), with ‘Emotional distress’ observed as inconclusive, see Figure 3.

Discussion

Results from this study have shown improvements (absolute change of more than 3 points) in QOL, following adenotonsillectomy, across several OSA-18 domains in all age groups for both cohorts.

Iron-deficient cohort

For the iron-deficient cohort, improvements in sleep disturbance were significant for all age groups. Such improvements were also observed in the caregiver concerns domain in the 2- to <6-year-old group, and the physical suffering domain in the <2-year-old, and the 2- to <6-year-old group.

Caregiver concerns in the 6 to <16 years old, daytime problems in the 2 to <6 years old, and sleep disturbance in the <2 years old, the 95% CI only just included -3 and a larger sample size might indicate statistical significance.

Only daytime problems in the <2 years old were found to be non-superior in the post-operation surveys than in the pre-operation surveys, while emotional distress in the same cohort might have sufficient evidence to support a claim of ‘not better’ with a larger sample size.

Borderline iron-deficient cohort

In the borderline iron-deficient cohort, significant decreases were observed in all domains for the 2 to <6 years old. For both the <2-year-old and 6- to <16-year-old age groups, significant improvements were observed in caregiver concerns, physical suffering, and sleep disturbance domains.

Kerstein *et al.* performed a retrospective analysis on 94 children undergoing adenotonsillectomy for clinically diagnosed SDB to

determine if low iron stores were associated with, and a possible contributing factor to paediatric SDB.¹⁷ They found an association between children undergoing adenotonsillectomy for clinically diagnosed SDB and low iron status, identifying a higher incidence of low iron stores in this population when compared to the normal paediatric population, with deficiencies most pronounced in those under 6 years old. Our results demonstrate that in children undergoing an adenotonsillectomy for clinically diagnosed OSA, the prevalence of iron deficiency is also high, especially in those under 6 years old. Of the 249 participants, 104 were iron deficient (41.8%), and this is likely an underestimate of the true prevalence of iron deficiency in this population. As ferritin is an acute-phase reactant, it can be elevated in certain conditions that cause co-existing inflammation, potentially including recurrent infections such as tonsillitis.¹⁸ This, in part, contributes to the broad definition of the borderline iron-deficient cohort, 20–60 µg/L, and it is likely that some children in this cohort are also iron deficient.

The domains that demonstrated the most improvement following adenotonsillectomy were sleep disturbance, physical suffering, and caregiver concerns while emotional distress and daytime problem domains showed smaller magnitudes of improvement. These findings are in concordance with other studies. Mitchell *et al.* performed a prospective study of 60 children with OSA, diagnosed by polysomnography, to examine the changes in QOL following adenotonsillectomy.¹⁹ They reported that the domains with the greatest change in mean score following surgery were sleep disturbance and caregiver concerns, while the smallest mean change was in the domain of emotional distress. Similarly, Sohn *et al.* reported that the largest improvements in QOL following surgical intervention occurred in the domains of sleep disturbance, physical suffering, and caregiver concerns.²⁰ Moreover, in our study, within the 2- to <6-year-old age group, clinically and statistically significant improvements in emotional distress and daytime problem domain scores were observed in the borderline iron-deficient cohort but not in the iron-deficient cohort. As such, a high prevalence of iron deficiency in children receiving an adenotonsillectomy for paediatric OSA may provide a possible explanation for small magnitudes of improvement in the domains of emotional distress and daytime problems within this population.

It is important to note however that QOL measures are intrinsically subjective, and in the environment of a surgical intervention trial, where there is an inability to blind participants, it is possible that improvements in QOL could reflect a surgical placebo effect.²¹ Furthermore, the completion of OSA-18 surveys is reliant on a caregiver proxy to assess a child's symptoms and behaviour and therefore scores are subject to caregiver variability. Bergeron *et al.* evaluated the impact of treatment for persistent paediatric OSA on QOL and documented differences in self- and caregiver-reported patient outcomes.²² They found that patient and caregiver-reported estimates of the patient's QOL were similar at baseline, however, following treatment only patient-reported QOL improved significantly, indicating that parents underestimated the improvement in patient QOL. Conversely, the findings from a study by Garetz *et al.* did not demonstrate an improvement in child-reported 'Pediatric Quality of Life' following adenotonsillectomy.²¹ The authors suggested this may be because children either have difficulty in discerning feelings of sleepiness, irritability and reduced concentration, or they do not consider those as problematic as feelings of pain and immobility.

This study has limitations. First, paediatric OSA was diagnosed clinically in the absence of a polysomnography (PSG). PSG is recognised as the gold standard for diagnosing OSA in children by using physiological parameters in sleep to quantify the presence and severity of OSA. However, it is also expensive, time-consuming, and frequently unavailable, as such clinical criteria are commonly used for diagnosis.²³ Furthermore, there was a lack of demographic data concerning patient body mass index and ethnicity. It has been reported that following adenotonsillectomy, obese children are more likely to have poor QOL scores and develop persistent OSA compared to normal-weight children.²⁴ Additionally, it has been demonstrated that OSA is more common in some ethnicities, with one study reporting that OSA was more common in African-American children.¹⁹ The sample size in some of the age subgroups was too small, and therefore the study was underpowered to detect an absolute change of greater than 3 points in these groups, limiting the utility of these findings.

Conclusions

This retrospective review study found that following adenotonsillectomy, patients with paediatric OSA reported significant improvements in QOL regardless of their iron status; 'Daytime problems' in the <2 years group, within the iron-deficient cohort, was the only domain that was 'not better' following surgery. The high prevalence of iron deficiency in those undergoing an adenotonsillectomy for paediatric OSA, especially those under 6 years, is in support of findings from prior prevalence studies. This study warrants further research into investigating the relationship between iron, adenotonsillar hypertrophy and paediatric OSA.

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Appendix A

Table A1 OSA-18 quality of life survey

Domain	None of the time	Hardly any of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
Sleep disturbance							
During the past 4 weeks, how often has your child had...							
<i>Loud snoring?</i>	1	2	3	4	5	6	7
<i>Breath holding spells or pauses in breathing at night?</i>	1	2	3	4	5	6	7
<i>Choking or gasping sounds while asleep?</i>	1	2	3	4	5	6	7
<i>Restless sleep or frequent awakenings from sleep?</i>	1	2	3	4	5	6	7
Physical suffering							
During the past 4 weeks, how often has your child had...							
<i>Mouth breathing because of nasal obstruction?</i>	1	2	3	4	5	6	7
<i>Frequent colds or upper respiratory infections?</i>	1	2	3	4	5	6	7
<i>Nasal discharge or runny nose?</i>	1	2	3	4	5	6	7
<i>Difficulty in swallowing foods?</i>	1	2	3	4	5	6	7
Emotional distress							
During the past 4 weeks, how often has your child had...							
<i>Mood swings or temper tantrums?</i>	1	2	3	4	5	6	7
<i>Aggressive or hyperactive behaviour?</i>	1	2	3	4	5	6	7
<i>Discipline problems?</i>	1	2	3	4	5	6	7
Daytime problems							
During the past 4 weeks, how often has your child had...							
<i>Excessive daytime drowsiness or sleepiness?</i>	1	2	3	4	5	6	7
<i>Poor attention span or concentration?</i>	1	2	3	4	5	6	7
<i>Difficulty getting out of bed in the morning?</i>	1	2	3	4	5	6	7
Caregiver concerns							
During the past 4 weeks, how often have the above problems...							
<i>Caused you to worry about your child's general health?</i>	1	2	3	4	5	6	7
<i>Created concern that your child is not getting enough air?</i>	1	2	3	4	5	6	7
<i>Interfered with your ability to perform daily activities?</i>	1	2	3	4	5	6	7
<i>Made you frustrated?</i>	1	2	3	4	5	6	7