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RESEARCH

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Pilot study to investigate sleep and breathing related complications in children and young people with osteogenesis imperfecta

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Abstract

Background Children with the rare bone disease osteogenesis imperfecta (OI) suffer from difficulty sleeping, and breathing problems during sleep, which can affect their long-term physical and mental health, and consequently their quality of life. In addition, children and young people with OI have structural and soft tissue changes which could affect breathing both during sleep and in relation to lung function.
Although commonly reported, we do not fully understand how many children are affected, the specific causes (and hence the most effective treatment) and how best to identify these sleep related breathing problems.
Our aim was to assess the feasibility of undertaking a clinical study that would investigate the frequency, severity and potential causes of sleep and breathing related problems in children with OI.

Methods Twelve children aged 4 to 16 years with a diagnosis of osteogenesis imperfecta attending Sheffield Children's Hospital were recruited to a prospective observational study. All participants underwent demographic history, quality of life questionnaires, spirometry and overnight in-laboratory polysomnography (PSG) during a 20-month period.

Results Recruitment targets were reached, and all investigational procedures were well tolerated by children and young people with OI. Clinically abnormal findings from polysomnography (sleep disordered breathing, excessive leg movements and delayed sleep latency) and from spirometry (restrictive airways disease) were identified in seven out of twelve participants who were referred on for further sleep and respiratory investigations. In addition, quality of life of children and young people with OI was lower than the population norms and children with other long-term conditions. These findings justify the need for a larger study, and highlighted some areas for improvement to the methodology for incorporation into future study designs.

Conclusion It is feasible to carry out a study investigating sleep and breathing problems safely in children with all severities of OI. This feasibility study supports the need for a multicentre trial to investigate this further, with the potential to improve clinical care.

Keywords Osteogenesis imperfecta, Sleep-disordered breathing, Spirometry, Quality of life

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Background

Osteogenesis imperfecta (OI) is a hereditary condition, caused by mutations within particular genes, affecting approximately 1 in 20,000 births [1]. It is a disease which varies in severity and affects the physical, social and emotional well-being of the child and their family. Children with OI have low bone mass, recurrent fractures (often with minimal trauma), varying degrees of short stature and long bone deformity, spinal deformity, pain, and respiratory failure in the severest types which can be fatal.

There is currently no cure for OI and hence the disease is managed rather than cured [2]. Treatment aims to provide pain relief, reduce fractures, prevent deformity, improve mobility, and facilitate independent function. OI can have a significant impact on the lives of children and their families. Children with mild and moderate OI may achieve independent walking with or without equipment, but some will use wheelchairs for longer distances [3]. Some severely affected children may achieve household walking or therapeutic walking, but many will not walk at all.

Children with OI and their families however also report problems with tiredness, stiffness, pain, headaches, reduced mobility and poor concentration, all of which can be caused by or lead to poor sleep and/or breathing difficulties [4]. These problems affect social functioning as well as cognitive and physical development through mechanisms such as difficulty concentrating at school and behavioural problems. We know that there are many possible causes of these problems which include poor sleep quality, bone structural changes and soft tissue changes [5, 6]. Whilst much research is carried out into strategies for preventing and treating fractures in children with OI [7–9], to date little research has been carried out in children investigating sleep and breathing related complications.

Arponen et al. [10] prospectively examined the prevalence of sleep disordered breathing (SDB) in the adult OI population. SDB is characterised by repetitive pauses in breathing during sleep, leading to desaturations in blood oxygen levels and brief arousals from sleep. The pauses in breathing tend to be classified as either obstructive or central in pattern. Obstructive sleep apnoea is described as repetitive complete (apnoea) or partial (hypopnoea) collapse of the upper airway, and central sleep apnoea is the repetitive cessation of respiratory effort [11]. Changes to the craniofacial structure, lung structure, airway passages and tightening at the foramen magnum junction may all play potential causative roles in SDB and hypoventilation in the OI population [10–12]. Arponen et al. [10] found a higher prevalence of SDB in 24 adults with OI, with 52% of their cohort having SDB classified as an apnoea/hypopnoea index (AHI) ≥ 5/hr. Leotard et al. [12] retrospectively examined the prevalence of SDB in children with OI and found obstructive sleep apnoea (OSA) in 6.4% of their OI clinic sample. However, only those with suspected SDB underwent a sleep study.

The purpose of this prospective pilot study was to evaluate the feasibility of a clinical trial investigating sleep and breathing related complications in children with OI. The findings of which will inform the future design of a multicentre clinical trial to investigate the prevalence, severity, and potential causes of sleep and breathing related complications. The multicentre trial would also aim to identify factors indicating when a sleep and breathing assessment should be performed and the most time and cost-effective way of doing this.

The objectives of this pilot study were therefore to investigate recruitment strategy, rate and retention of participants; the suitability and characteristics of chosen outcome measures; the acceptability of the investigational techniques; data collection, management and timescale to inform the design of a larger study.

We report the pilot data from our feasibility study.

Method

Setting

Sheffield Children's Hospital (SCH) is a regional specialist centre for OI caring for over 400 patients with OI who regularly visit SCH for planned clinical treatments. Participants were assessed for eligibility and then screened for around the time of their next clinical visit to SCH by a member of the clinical care team.

Eligibility criteria

Children had a clinical diagnosis of osteogenesis imperfecta and were aged 4 years to 16 years. Exclusion criteria included patients who were already treated for diagnosed sleep disorders; parent not fluent in written or spoken English; a cast that would affect sleep; a bone fracture within 1 week of the study; coexisting medical conditions with a known high risk of sleep disordered breathing (e.g. Trisomy 21, cerebral palsy).

Recruitment/Selection

Children were recruited between November 2017 and July 2019 from the OI cohort of patients at SCH. Patients and parents were approached during clinics or hospital admissions by a member of the clinical care team and given study information, or study information with an accompanying invitation letter was sent out in the post to suitable patients who had up and coming hospital appointments. In addition, patients were also identified as potential participants in the study when a clinical referral was made for a sleep study. Participants therefore comprised a non-probabilistic convenience sample. In all

cases, there was a minimum of 24 hours' notice between first approach and enrolment.

Ethics and consent

The research study was approved by the National Research Ethics Committee (London – Queen Square Research Ethics Committee, reference: 17/LO/0733). Clinical trial number: not applicable. Parents provided written informed consent on behalf of their child (as legal representatives), and wherever possible informed written assent was also obtained from the child. Each participant received £20 as a thank you for participating in the study.

All participants followed a set schedule of events, as shown in Fig. 1.

Demographics and medical data.

Data were recorded on age; sex; height and/or arm span; weight; ethnicity; OI disease severity and relevant medical history.

Questionnaires

Following informed consent, parents and children completed the following questionnaires/scales. The questionnaires were self-completed by the child where appropriate. For younger children, the parent completed the questionnaire on the child's behalf. Parents self-completed the parent questionnaires. All questionnaires were attempted, even if their age was outside the currently validated age range for the questionnaire. All questionnaires were reprinted with permission of the copyright holder and completed in the presence of a study team member.

PedsQL generic module

The PedsQL (generic) is a 23-item questionnaire that measures participant and parent proxy reports of generic health related quality of life in the four domains of physical, emotional, social, and school functioning. The questionnaire is validated for use in 2-18 year olds [13]. Scores range from 0-100 with a higher score indicating better quality of life [13].

PedsQL fatigue module

The PedsQL Multidimensional Fatigue Scale is a generic symptom-specific instrument to measure fatigue in patients with acute and chronic health conditions. It is an 18-item questionnaire with participant and parent report versions. The questionnaire is validated for use in 2-18 year olds [14]. Scores range from 0-100 with higher scores indicating better quality of life [14].

OIQoL

To measure child self-report of disease specific quality of life in the areas of being safe and careful; reduced function; pain; fear; and independence and isolation. The questionnaire is validated for use in 6-18 year olds [15]. Scores range from 0-100 with higher scores indicating better quality of life [15].

Paediatric Daytime Sleepiness Scale (PDSS)

The PDSS is an 8-item questionnaire that measures daytime sleepiness in school aged children, in the past week. The questionnaire is validated for use in 7-17 years [16; 17] Scores range from 0-32 with higher scores indicating higher daytime sleepiness [16].

Pittsburgh Sleep Quality Index (PSQI)

This questionnaire measures sleep parameters over the past month. Sleep measures include quality; latency; duration; efficiency and disturbance. A global PSQI score is calculated and the global score ranges from 0-21 with higher scores indicating higher levels of sleep quality issues [18, 19]. The questionnaire is validated for use in 3-16 year olds [20].

Pain Assessment

A visual analogue scale (VAS) of 100 mm was used to measure the level of pain experienced by an individual, with higher scores indicating higher pain levels.

Lung function testing (spirometry)

Each participant over the age of 5 years underwent spirometry (Jaeger Vyntus Pneumo, Vyaire Medical Inc, Chicago) using a pneumotachograph. All children had their height and arm span measured (as a surrogate for height), and this information, along with ethnicity and sex, was entered into the spirometer to enable comparison of their lung function with the 2012 global lung index reference values [21]. Spirometry was performed as per standard protocol [22] with the child seated, wearing a nose clip and with the test repeated until there were three test results within 5% agreement. Measurements of forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and FVC/FEV_1 ratio were recorded.

Polysomnography

All children underwent polysomnography (PSG). PSG is the gold standard diagnostic test for sleep disordered breathing and measures both sleep and breathing variables in an overnight recording in a sleep laboratory.

PSG was performed using the SOMNOscreen device (SOMNOmedics, Germany) and the following channels were measured: sleep was assessed using electroencephalogram, electro-oculogram and submental electromyogram; movement via leg electromyogram, body position and video; respiratory parameters by chest and abdominal respiratory inductance bands, oronasal thermistor, nasal pressure flow, throat microphone, echocardiogram and pulse oximetry for oxygen saturations,

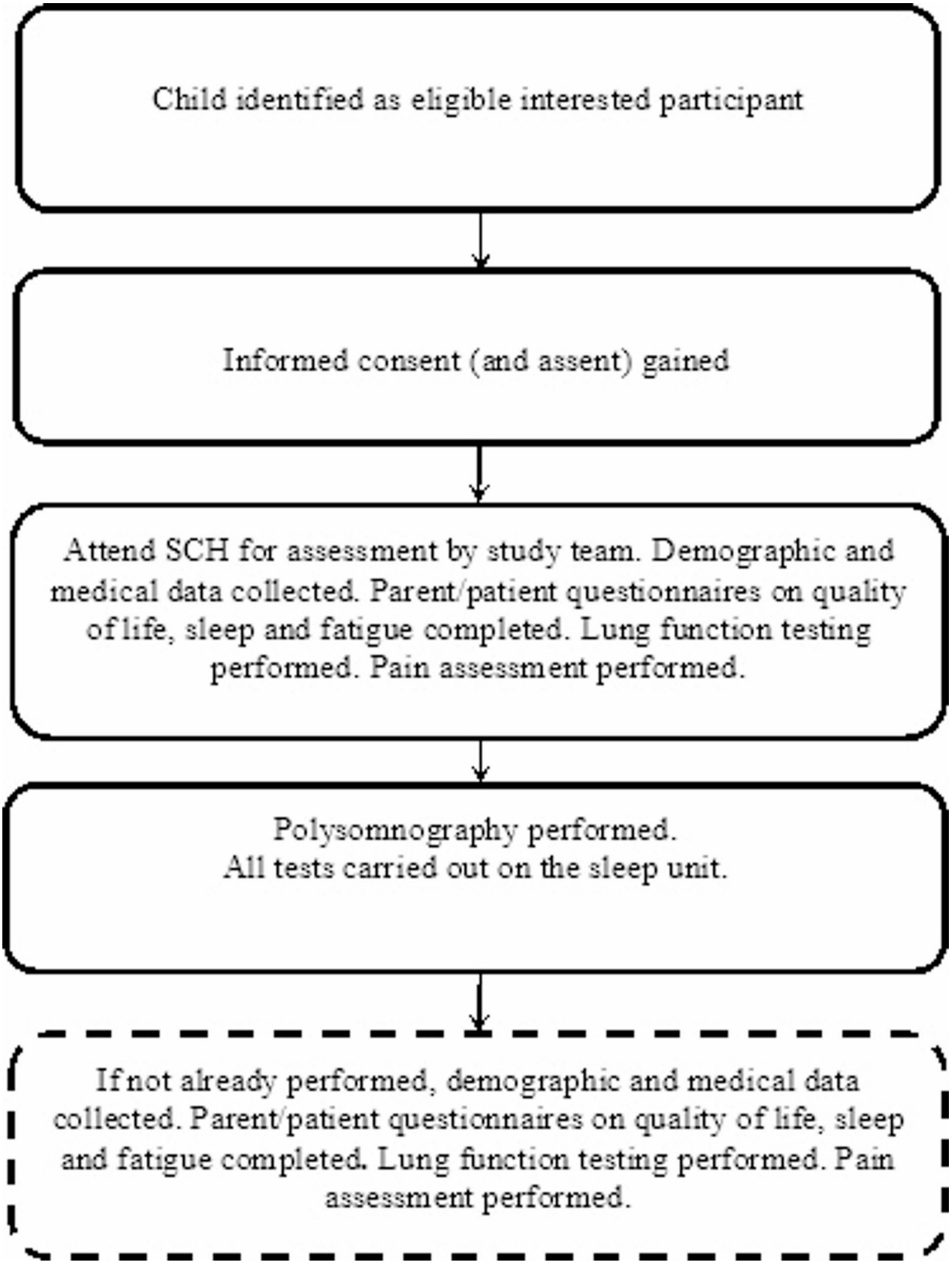

Fig. 1 Schedule of Events

plethysmography and pulse rate. An integrated transcutaneous carbon dioxide monitor was also attached (TOSCA 500, Radiometer, UK).

Quality and analysis

Questionnaires

All questionnaires were completed by the parent/child (as appropriate) and checked by the research team afterwards for missing data. Each questionnaire was scored manually, using questionnaire scoring guidelines where appropriate, and rechecked to make sure all scores were compiled and correct.

Spirometry

All spirometry was performed by trained staff who have undertaken paediatric spirometry certification. Spirometry was conducted using standard methods and tests were repeated to obtain repeatability within 5% [22]. For those patients with scoliosis or an inability to stand; arm span was used instead of height.

Polysomnography

In-laboratory PSGs were set up by experienced specialist sleep physiologists, with sensor placement as per standards [23]. Studies were monitored overnight by specialist sleep nurses. PSG studies were scored by an experienced sleep physiologist (RNK) who was blind to the questionnaire data and therefore did not know if the participants had any features or symptoms of sleep disordered breathing. Studies were manually scored on the Domino sleep software (SOMNOmedics, Germany) using the American Academy of Sleep Medicine (AASM) guidelines (Version 2; 2012) using paediatric rules for sleep staging and the scoring of respiratory events, and periodic limb movements for all participants [23]. Sleep efficiency (%) was calculated as follows: [Total sleep time (mins)/time in bed (mins)] * 100 and the sleep onset latency was calculated as the time (in minutes) from when sleep was attempted (lights out) until the first page of sleep. SDB was classified into three levels of severity: Mild SDB (AHI of 1.5-5/hr); Moderate SDB (AHI of 5–10/hr); Severe SDB (AHI > 10/hr) based on previous OI and SDB literature [12].

Data from all sources were entered into a spreadsheet and checked on a separate occasion to reduce human error.

Statistical analysis

As this was a pilot study, a full descriptive analysis of all variables collected was performed. Significance testing is minimised in line with recommendations for pilot studies [24]. Continuous variables are summarised with the mean and standard deviation, or median and interquartile range when not normally distributed. Categorical variables are summarised as proportions observed in each category. Where population norms are available, results were compared to these values. The outcomes measured were PSG sleep and breathing variables of 3% oxygen saturation dips, breathing pauses per hour of sleep, arousal frequency overnight, % slow wave sleep and sleep efficiency. The variation of these outcomes needs to be estimated to inform the design of a larger multicentre study. The statistics were estimated from a sample size of twelve which is the minimum sample size recommended for a pilot study [25]. It is anticipated that for a larger multicentre study, an age and sex matched control group would be measured for comparison over population norms.

Results

Twenty-five out of the first 26 children identified were eligible on screening and, of these, twelve agreed to take part. Recruitment rate was slower than anticipated with recruitment taking over 20 months rather than the five months as originally planned. The retention rate was 100% for the children who enrolled; all completed the study.

Baseline characteristics

Twelve children consented to the study and all twelve completed the study. The group consisted of six females and six males. Median age (25th –75th percentiles) was 9.45yrs (6.85–13.5). Participants were classified as White British (10); White Irish (1); Any other mixed background (1). The demographics of the individual participants are presented in Table 1 below. This was a small convenience sample and therefore not representative of the total OI cohort for severity of disease. Median pain score (25th –75th percentiles) was 29.3 (3.5,40.3).

Spirometry

Spirometric data was successfully collected for ten children. One child was too young to attempt spirometry and one data set was discounted due to a technical equipment error. One of the children had performed spirometry prior to taking part in the study, all other participants had never performed spirometry before. Results are summarised in Table 2. Seven of the ten children had values within normal range for FEV_1, FVC and FEV_1/FVC ratio. Two children recorded values indicating obstructive airways disease and one child had values indicating severe restrictive airways disease.

Polysomnography findings

All participants successfully underwent polysomnography. Results are summarised in Table 3. The median obstructive AHI (25th –75th percentile) was 0.4/hr (0.3, 0.55) and the median central AHI (25th –75th percentile)

Table 1 Baseline Characteristics

	Height (cm)	Weight (Kg)	BMI (value)	OI severity	Co-morbidities	Ethnicity
1	97.5 91 *	14.8	15.6	Severe	None	White British
2	139.9 137 *	44.5	22.7	Moderate	None	White British
3	138.4 134.5 *	46.7	24.4	Moderate	None	White British
4	84.4	14.4	20.2	Severe	None	White British
5	104 *	18.4	17	Severe	None	White Irish
6	147.6	43.0	19.7	Mild	None	White British
7	110 108 *	19.0	15.7	Mild	None	White British
8	140.6 147 *	41.6	19.3	Severe	None	Any other mixed background
9	100.6 101 *	17.3	17	Mild	None	White British
10	135.1 131 *	39.9	21.9	Moderate	None	White British
11	126.4 128 *	27.3	16.7	Mild	None	White British
12	134.3 136.5 *	44.6	23.9	Mild	None	White British

*Arm span measurement

OI disease severity definitions:

Mild - Normal/near normal growth velocity and height, no intrinsic bone deformity, ambulant; Moderate - Decreased growth velocity and height, anterior femoral and tibial bowing, ambulant; Severe - Severely decreased growth velocity and height, progressive deformity of long bones and spine, wheelchair dependent [26].

Table 2 Spirometry data. FEV_1 = Forced expiratory volume in 1 s; fvc = forced vital capacity

Spirometry Measurement (*n* = 10)	Median 25th; 75th Centiles
FEV_1 (litres)	1.62 (1.16, 1.83)
FEV_1 (z score)	−0.35 (−2.05, 0.61)
FVC (litres)	2.02 (1.39, 2.18)
FVC (z score)	−0.15 (−1.15, 0.76)
FEV_1/FVC	0.87 (0.81, 0.93)
FEV_1/FVC (z score)	−0.28 (−1.37, 0.17)

was 0.65/hr (0.4–1.35). Three participants were classified as having mild SDB; one with moderate SDB and one with severe SDB based on AHI findings alongside seven participants with AHI values within the normal range. The participant with severe SDB also demonstrated an elevated 3% oxygen desaturation index (ODI_3) based on oximetry from PSG. In addition, this participant had a minimum oxygen saturation (SpO_2) value of 63%. Three participants demonstrated a sleep efficiency < 85% on their PSG, suggesting poor sleep quality.

Questionnaires and scales

The results for the PedsQL (generic and fatigue modules), OIQoL, Paediatric daytime sleepiness scale and Pittsburgh sleep quality index are shown in Tables 4, 5, 6 and 7.

Clinical findings

When abnormalities were identified on polysomnography or spirometry, appropriate onwards referrals or therapies were offered where clinically appropriate.

Four out of the twelve participants were referred onto the paediatric sleep service due to clinically relevant findings. One participant had significant obstructive sleep apnoea with an AHI of 38/hr and was subsequently started on continuous positive airway pressure (CPAP) therapy, with clinical resolution of abnormalities noted on subsequent home oximetry on CPAP. Three participants demonstrated elevated leg movement indices on PSG with periodic limb movement indices (PLMI) in the clinically significant range of PLMI > 4/hr (4.8; 7.1; 9.6/hr respectively). Although PLM index was not an a priori outcome measure of this pilot study, it is measured clinically and, as such, these data are reported here. These three participants were seen in the sleep clinic. Two participants also had clinical features of restless leg syndrome and periodic limb movements of sleep and so were followed up by the clinical sleep service and were prescribed clonidine. These two participants also had poor sleep quality with sleep efficiencies < 85%. Sleep efficiency is defined as the percentage of sleep within the time in bed trying to sleep. In addition, one participant had ongoing non-physiological sleep support from the sleep service team to help reduce a prolonged sleep onset

Table 3 Polysomnography data. N1 = stage 1 sleep; N2 = stage 2 sleep; N3 = stage 3 sleep; REM sleep = rapid eye movement sleep; OAHI = obstructive apnoea/hypopnoea index; AHI = apnoea/hypopnoea index; SpO_2 = oxygen saturation level (ODI_3); CO_2 = carbon dioxide level; kPa = kilopascal

Polysomnography	Median (25th/75th centiles or *n*%)
Sleep onset latency (mins)	22.3 (7.4,38.6)
Total sleep time (mins)	453.8 (425.5,467)
Sleep efficiency (%)	88.3 (83.5,93.5)
Arousal frequency (per hour slept)	6.1 (5.4,6.7)
N1 sleep stage (%)	5.4 (3.3,7.8)
N2 sleep stage (%)	50.4 (45,52.5)
N3 sleep stage (%)	27.2 (23.9,29.3)
REM sleep stage (%)	17 (15.3,19.7)
Central apnoea frequency	5 (2.5,10.5)
Central apnoea index (per hour slept)	0.65 (0.4,1.35)
Obstructive apnoea frequency	0 (0,0)
Obstructive apnoea index (per hour slept)	0 (0,0)
Hypopnoea frequency	2 (1,3)
Hypopnoea (per hour slept)	0.35 (0.1,0.45)
Mixed apnoea frequency	0 (0,1)
Mixed apnoea index (per hour slept)	0 (0,0.15)
Overall OAHI (per hour slept)	0.4 (0.3,0.55)
Overall AHI (per hour slept)	1.3 (0.7,2.2)
Snore (%)	0.05 (0,0.8)
Minimum SpO_2 (%)	91 (90,94)
> 3% SpO_2 dip rate (per hour slept) ODI_3	2.1 (1.4,5.1)
SpO_2 average baseline (%)	97 (97,98)
Average CO_2 (kPa)	6.4 (5.8,6.6)
Max CO_2 (kPa)	6.9 (6.7,7.2)

Table 4 PedsQL generic and fatigue modules

PedsQL generic module (0-100)	Median (25th/75th centiles)	PedsQL fatigue module (0-100)	Median (25th/75th centiles)
Patient physical	43.8 (34.4,56.3)	Patient general	62.5 (41.7,79.2)
Patient psycho-social	60 (43.3,73.3)	Patient sleep	58.3 (33.3,65)
Patient total	56.5 (37,67.4)	Patient cognitive	75 (58.3,75)
		Patient total	56.5 (37,67.4)
Parent physical	32.8 (25,57.8)	Parent general	47.9 (41.1,60.4)
Parent psycho-social	60 (45,68.7)	Parent sleep	50 (35.4,68.7)
Parent total	48.9 (36.9,64.2)	Parent cognitive	62.5 (45.8,72.9)
		Parent total	48.9 (36.9)

latency. This latency is defined as the time taken to fall asleep when attempting to sleep.

The three participants with abnormal spirometry results presented with different types of abnormality. The first was the only participant who had performed spirometry previously. Their results demonstrated severe restrictive airways disease. The participant had severe OI related scoliosis, which had necessitated a posterior T3-L4 instrumented scoliosis correction in 2017. The results for the second participant showed reversible airways obstruction (with 17% reversibility post 400mcg Salbutamol via Metered Dose Inhaler and spacer). This participant was very physically active and did not complain of any respiratory symptoms. Their General Practitioner (GP) and the OI Team were informed of the spirometry results so that they could be taken into consideration should they present in the future with symptoms such as wheeze, cough or breathlessness. The third participant's results showed obstructive airways disease without evidence of significant reversibility. This participant has a history of prematurity and was ventilated at birth. A letter was written to the GP informing them of the study results and suggesting that starting on inhalers may be beneficial. They were also offered the option to refer to the Respiratory team (at Sheffield or another local Respiratory centre). It is not known whether the abnormal findings for participants 2 and 3 were related to their OI or if they were incidental.

Table 5 OIQoL data

OI QoL (0-100)	Median (25th/75th centiles)
Safe & careful	37.5 (23,50)
Fatigue	46 (17,54)
Reduced function	60 (30,100)
Pain	60 (40,85)
Fear	73 (46,81)
Life skills	59 (44,64.5)
Total (%)	53.5 (40,60)

Table 6 Paediatric daytime sleepiness scale

Paediatric daytime sleepiness scale (0–4)	Median (25th/75th centiles)
Fall asleep or drowsy in class	2 (1,3)
Fall asleep or drowsy doing homework	2 (1,3)
Daytime alertness	1.5 (0.5,2)
Tired/grumpy	2 (1,3)
Trouble getting out of bed in the morning	2 (1,3.5)
Falling back to sleep after being awakened	2 (0.5,3.5)
Need someone to wake you in the morning	2.5 (1,4)
Need more sleep	2 (1.5,4)
Total (0–32)	16 (10,21)

Table 7 Pittsburgh sleep quality index

Pittsburgh sleep quality index (0–3)	Median (25th/75th centiles)
Subjective sleep quality	1 (1,2)
Sleep latency	2 (1.5,3)
Sleep duration	0 (0,0)
Habitual sleep	0 (0,1)
Sleep disturbance	1 (1,2)
Use of sleeping medication	0 (0,0)
Daytime dysfunction	1 (1,2)
Global PSQ score (0–21)	7 (5.5,7.5)

Discussion

The purpose of this pilot study was to evaluate the feasibility of a clinical trial investigating sleep and breathing related complications in children with osteogenesis imperfecta.

Recruitment strategy, rate and retention

The recruitment rate was much slower than anticipated. There were three main factors that contributed to this:

1) Availability of a sleep study bed on the sleep unit. The sleep unit during the time of the research had very long waiting lists and clinical bookings had filled up potential research slots, making availability on the sleep unit difficult, alongside the requirement for the child to be free of fractures. Since covid-19 and the associated rise in respiratory infections, clinical bookings for the sleep unit are only booked two weeks in advance and so for a future research study, coordinating research slots on the sleep unit should be more efficient.
2) A change in treatment regime. When this study was designed, families attending for bisphosphonate infusion were required to stay overnight in the hospital. Having a sleep study on the night of a hospital stay was therefore an option. In fact, using the sleep unit bed would also ease bed pressures and likely reduced infusion cancellations. During the study, there was a change in clinical practice resulting in children receiving Zoledronate infusion in one day and no longer requiring an overnight stay. Undertaking the overnight sleep study was therefore an extra burden to families in terms of extended time off work and school.
3) Another important factor was parents or children being put off taking part by the look of the sleep study equipment. The retention rate however was 100%, where all the children who enrolled completed the study. This may be partly due to the short duration of participation but also reflects the acceptability of the investigational techniques including the sleep study equipment which we could now feedback to families considering a future research trial involving a sleep study.

This pilot study has shown that improving the recruitment rate is paramount for future work. Further examination of possible feasibility issues would help shape any future multicentre study. For example, considerations including power calculations to determine sample size; ways of improving recruitment rate and how many centres would be required for an adequate sample size.

Suitability and characteristics of chosen outcome measures

It was noted that three participants had slightly elevated PLMI values for leg jerks during sleep. The PLMI was not a planned outcome measure. However, the data has been included post hoc and should be considered an outcome measure worth utilising in a future larger study in this population, along with investigating potential causes of elevated PLMs in the paediatric OI population.

Acceptability of investigational techniques

Two families chose not to take part in the study due to concerns about the sleep study equipment, and in particular the chest bands. The study however was successfully completed by children with a range of severities of OI without any adverse events and all children that took part in the study coped well with the equipment. We did not, however, ask families to formally rate the acceptability of the investigational techniques and this is another consideration for future work.

Data collection and management

Data collection tools were found to be fit for purpose. This is partly attributed to having been developed in conjunction with the study statistician which meant that data was categorised and recorded in a manner that was easy to input and then handle once data collection was completed. The value of cross-checking data entry was demonstrated as a number of inaccuracies, that were attributed to human error, were identified and corrected prior to analysis.

All the PSGs were scored by the same experienced sleep physiologist. This was manageable as the study numbers were small and avoided any issues with inter rater reliability. For the study to be carried out on a larger scale, more than one scorer would be required, and plans put in place to ensure that problems with inter rater reliability do not occur. Scorers should be blind to participant symptoms and whether participants have OI or are matched controls. A subset of PSG records should be blindly rescored to measure inter and intra rater reliability in a larger scale multicentre study.

Clinical discussion

Generic HRQoL measured using PedsQL demonstrated lower values than those children and young people without chronic disease. Only one participant scored above the population norm for total score (80.9) and physical health score (84.6). Two participants scored above the population norm for psychosocial health (78.4) [27]. In agreement with our findings, Pinquart [28] also reported large declines in HRQoL in children with osteogenesis imperfecta compared to their healthy peers, particularly in the areas of physical health, social functioning and

school functioning. Our data also agrees with that of Pinquart [28] who described lower parental reports for psychosocial health than their child.

Generic QoL measures don't always accurately capture the complete experience in different chronic diseases, and therefore the use of a disease specific measure is relevant. Median OIQoL values for being safe and careful (29.2), reduced function (62.5), pain (79.2) and fear (79.2) were reported during questionnaire development [15]. Our cohort had similar values for reduced function (60.0) and fear (73.0), the value for being safe and careful (37,5) was higher in our cohort, however pain (60.0) was lower. This may have been due to our small pilot sample size or a lower proportion of children with severe OI. It remains important to include both generic and disease specific HRQoL questionnaires within a larger study to enable both comparison to other diseases and ensure high content validity. Future assessment of pain using a visual analogue scale should differentiate between chronic and acute pain.

The median PDSS score in the current sample was 16/32. This value is in agreement with previously reported summary scores of 16.6 by Drake et al. [16] and 15.74 by Perez-Chada et al. [29]. As yet there are no reference values for the PDSS, however in the study by Perez-Chada on 2,884 10–15-year-olds, the 75th centile scores were 20 [29]. Three participants in the current study had PDSS summary scores > 20. These three participants were incidentally those who had onward referral to the clinical sleep service for periodic limb movement disorder or obstructive sleep apnoea; and required subsequent treatment. Previous work has used the PDSS in 7-year-olds and above [17, 29]. Our sample covers a wider age range and detected a high score in the 9 year old with severe sleep apnoea. The data for the PSQI demonstrated that 9/12 participants had a global score > 5 (clinical cut off), suggesting that this small sample reported problems with their sleep quality and fragmentation. These findings suggest that the PDSS and PSQI should be included in the larger scale study as potential measures of subjective daytime sleepiness and sleep quality, respectively along with the fact that more paediatric age data is required.

Only one of the OI participants had routinely undertaken spirometry before, but technically acceptable tests were achieved by all ten patients that attempted spirometry and had successful recordings. Almost a third of these participants presented with significantly abnormal spirometry results. Whilst the likelihood is of one of these findings being directly related to OI (restrictive picture with scoliosis), it is not known whether the abnormal findings for the other two participants were related to their OI, potentially through the mechanism of collagen abnormality, or if they were incidental. LoMauro et al. [5] postulates however that the restriction in lung function is not due to the scoliosis itself but rather to the rib cage deformity and resultant change in breathing mechanics. This is also supported by the work of Sanchis-Gimeno et al. [30]. Both studies were carried out largely with adults although the LoMauro study [5] did include some children over the age of 9. A larger study population would be needed to enable the prevalence of lung function abnormalities to be compared with those of a non-OI population and to understand whether there is a relationship between severity of OI and altered lung function. The relatively high prevalence of lung function abnormalities identified in this study however suggests that spirometry should be considered as part of at least an annual clinical review assessment with the possibility of repeating the test more frequently if abnormalities are identified. It is also likely that respiratory problems (whether caused by OI or not) are under recognised in children and young people with OI. There are a number of factors that may contribute to this situation as many don't get the opportunity to physically exert themselves as much as their non-OI peers due to either being non-ambulant or not being encouraged to participate in strenuous exercise/activity due to the increased risk of fracture. Obesity and high body mass index (BMI) is also noted to link to sleep disorder [31], although BMI was calculated in this cohort, no individuals were deemed obese. Assessing growth in individuals with moderate and severe OI can be complicated. There are currently no growth charts specifically for OI, standard growth charts will overestimate weight/height and subsequently BMI in individuals with short stature [32].

Three of the twelve participants required ongoing treatments due to sleep disorders that were identified as a result of this pilot study. This represents a quarter of all participants and therefore indicates that further sleep disorder screening and clinical questioning is required during clinical consultations with the metabolic bone team with regards to sleep and breathing.

The one participant with severe SDB that required CPAP therapy, also demonstrated an elevated ODI_3 index on oximetry. However, the oximetry channel alone would not have been able to determine whether the oxygen desaturations were caused by obstructive or central apnoeas. Future research in this area still requires PSG at this stage to determine the aetiology of SDB abnormalities that might be identified on oximetry alone. Once more evidence is gathered around the prevalence of SDB in OI, then ideally simpler technologies to determine SDB can be used more effectively. In addition, a range of a priori AHI cut offs for SDB classifications should be explored further in future work.

Leotard et al. [12] retrospectively reviewed PSGs from 14 paediatric OI patients who were referred to a sleep service with suspected SDB. These authors found high

levels of SDB in their small sample: 11/14 were classified as having SDB using the same clinical cut offs that the current paper used with seven having mild SDB; two with moderate SDB and two with severe SDB. Taken in the context of their whole OI population, OSA was reported with a prevalence of 6.4% however, only those patients with suspected SDB underwent a sleep study. Both Leotard et al. and the current study have demonstrated in very small samples that SDB occurs in patients with OI at a higher level than the expected prevalence values for OSA in a normal population (1–5%) even when using a more conservative SDB cut off of an AHI > 5 to represent SDB potentially requiring treatment [31], however it should be noted that the samples sizes were very limited. It was also noted in the current study that 8/12 of the study participants showed a pCO2 value > 6.7 kPa at some point during sleep. It would be useful in future studies to investigate the % sleep time with a pCO2 value > 6.7 kPa. This parameter was not recorded in the current study, however AASM guidelines suggest that if > 25% of the sleep time has a pCO2 > 6.7 kPa then this is suggestive of hypoventilation [23].

Clinical implications

In the immediate term, clinicians should be aware that children with OI can experience sleep and breathing related problems, should incorporate appropriate questions into routine consultations, and investigate accordingly. If sleep and breathing issues are identified, then onward referral to sleep and respiratory specialists should occur. As a result of this pilot study, children with OI and their families who attend SCH for intervention or review, are offered healthy sleep advice in the form of an information sheet. Strategies are discussed with families and advice is individualised to the child and their family circumstance.

In the short term, the outcomes from this study will facilitate the planning and implementation of the multicentre study needed to improve the care of children with OI. This will enable us to proactively identify children with sleep and breathing related problems and allow us to minimise the negative effects of these problems. In the long term, it will enable us to develop a screening tool for the early identification of sleep and breathing related complications in children with OI.

Limitations and recommendations for future work

This is a pilot study and has inherent study limitations. As with many research projects, families are self-selected. Two participants responded to a call for a patient and public involvement and engagement (PPIE) session on OI and sleep to help with the planning of this project. In discussion during the PPIE session, the participants were shown to have excessive daytime sleepiness and were falling asleep in school. This led to the two participants being referred to the clinical sleep service. A further participant was referred due to symptoms of snoring and sleep disturbance. These three participants were included in the analysis and so could have biased the findings. Families are also more likely to participate in the study if they perceive sleep to be a problem which further increases the potential bias. The sample size was also small so no firm clinical conclusions should be drawn.

The main findings of the pilot study are that the investigations carried out were well tolerated and so can be used in a larger scale study which would hypothesise that SDB is more prevalent in the OI population. Undergoing a detailed investigation such as polysomnography is likely to affect sleep. The addition of an age and sex matched control group would help determine whether any differences in outcomes are OI related or not. It is well documented that sleep variables vary with age and any studies in children are going to have the added variability of different population norms for sleep parameters for different age groups [33]. Age matching controls or comparisons with existing normative data in a larger scale study would assist with this weakness. Capturing further relevant clinical background information could also be useful in a future trial. This would include scoliosis, previous spinal surgery, chest wall deformities and obesity as all could influence the outcome measures of SDB and FVC, allowing associative relationships to be explored.

This pilot study also highlighted some concerns with regard to spirometry. It is accepted that good spirometry technique requires practice, whereas the majority of patients in this study, and in current OI clinical practice, have not performed spirometry before. Some spirometry results in the current study were noted to have poor technique at times. Experienced personnel carried out the tests in this study so were able to recognise this and coach to improve technique. In addition, spirometry uses a forced manoeuvre which may be imposing at first for a child with OI and concerning for the parent. Further studies should have specialist facilities and experienced staff, both for PSG and to perform lung function tests that produce reliable data in children naive or with little prior experience of these tests. Raising the lower age limit to 5 years for study inclusion may also improve spirometry technique in future work and avoid missing data points.

Challenges were also highlighted with the comparison of spirometry values with reference equations. Reference values are reliant on an accurate height measurement, but it is well known that height in children and young people is affected by OI. This study measured both arm span and standing height (where possible) and the greater of the two measurements was used in an attempt to address this. It would also be possible to use ulna length

[34] or segmental measures [35] in future studies, but this also has its limitations as long bone deformity can be present in children and young people with OI. Reference equations have however progressed over time making comparison of lung function in OI with other studies difficult where different reference equations have been used. LoMauro et al. [5] used two different reference Eqs. [36, 37] and got vastly different percent predicted measurements with the first showing essentially normal values and the second showing significantly reduced values. This study used the more recently developed reference values by Quanjer et al. [38], however Tam et al. [39] demonstrated that, particularly in those with more severe OI types, pulmonary involvement may still be underestimated. Further strategies to reduce this disparity will be needed in future studies measuring lung function in children and young people with OI.

Conclusion

We have demonstrated that it is feasible to carry out a study investigating sleep and breathing problems safely in children with all severities of OI. Children with OI have reduced HRQoL compared to their healthy peers, and parental reports for both HRQoL and fatigue are lower than their child's report. Focus needs to be on how to improve recruitment rates into such studies.

Abnormal test results were recorded both for PSG and spirometry and a case-controlled multicentre trial is required to understand if there is a relationship between these and OI or whether these reflect the prevalence in a normal population.

Abbreviations

AASM	American Academy of Sleep Medicine
AHI	Apnoea/hypopnoea Index
CI	Confidence Interval
CO_2	Carbon Dioxide
CPAP	Continuous Positive Airway Pressure
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GP	General Practitioner
OAHI	Obstructive apnoea / hypopnoea index
ODI_3	Oxygen desaturation index (3%)
OI	Osteogenesis Imperfecta
OIQoL	Osteogenesis imperfecta specific quality of life questionnaire
OSA	Obstructive sleep apnoea
PedsQL	Pediatric Quality of Life Inventory
PDSS	Pediatric Daytime Sleepiness Scale
PLMI	Periodic Limb Movement Index
PPIE	Patient and public involvement and engagement
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
REM	Rapid eye movement
SCH	Sheffield Children's Hospital
SDB	Sleep disordered breathing
SpO_2	Oxygen saturation
VAS	Visual analogue scale

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12891-025-09208-4.

Supplementary Material 1.

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Authors' contributions

CLH, RNK & NB conceived and designed the study. CLH, RNK and NB analysed and interpreted the data. CLH, RNK and NB drafted the paper. All authors contributed to critical revisions and editing of the final manuscript and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Data availability

All data generated or analysed during this study are included in this published article [and its supplementary information files – additional file 1].

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and received approval from the National Research Ethics Committee (London – Queen Square Research Ethics Committee on 28th April 2017; Reference Number: 17/LO/0733). Parents provided written informed consent on behalf of their child (as legal representatives), and wherever possible informed written assent was also obtained from the child.

Consent for publication

Not applicable.

Competing interests

Claire Hill developed the OIQoL questionnaire, a disease specific quality of life questionnaire for children with Osteogenesis Imperfecta. The University of Sheffield hold the IP rights to the questionnaire.

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