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ORIGINAL ARTICLE

Sleep-disordered breathing in Australian children with Prader-Willi syndrome following initiation of growth hormone therapy

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Aim: In children with Prader-Willi syndrome (PWS), growth hormone (GH) improves height and body composition; however, may be associated with worsening sleep-disordered breathing (SDB). Some studies have reported less SDB after GH initiation, but follow-up with polysomnography is still advised in most clinical guidelines.

Methods: This retrospective, multicentre study, included children with PWS treated with GH at seven PWS treatment centres in Australia over the last 18 years. A paired analysis comparing polysomnographic measures of central and obstructive SDB in the same child, before and after GH initiation was performed with Wilcoxon signed-rank test. The proportion of children who developed moderate/severe obstructive sleep apnoea (OSA) was calculated with their binomial confidence intervals.

Results: We included 112 patients with available paired data. The median age at start of GH was 1.9 years (range 0.1–13.5 years). Median obstructive apnoea hypopnoea index (AHI) at baseline was 0.43/h (range 0–32.9); 35% had an obstructive AHI above 1.0/h. Follow-up polysomnography within 2 years after the start of GH was available in 94 children who did not receive OSA treatment. After GH initiation, there was no change in central AHI. The median obstructive AHI did not increase significantly ($P = 0.13$), but 12 children (13%, $CI_{95\%}$ 7–21%) developed moderate/severe OSA, with clinical management implications.

Conclusions: Our findings of a worsening of OSA severity in 13% of children with PWS support current advice to perform polysomnography after GH initiation. Early identification of worsening OSA may prevent severe sequelae in a subgroup of children.

Key words: central sleep apnoea; growth hormone; obstructive sleep apnoea; polysomnography; Prader-Willi syndrome; sleep-disordered breathing.

What is already known on this topic

1 Growth hormone improves height and body composition in children with Prader-Willi syndrome but has been linked with worsening sleep-disordered breathing.
2 Previous studies were unable to show significant worsening of obstructive sleep apnoea after initiation of growth hormone using polysomnography, although severe worsening of

What this paper adds

1 In line with previous studies, we found an increase in moderate/severe obstructive sleep apnoea in a subgroup of patients after initiation of growth hormone.
2 This led to changes in clinical management in 13% of our study population.

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obstructive events in a small subgroup was mentioned in several studies.
3 There is much debate over the usefulness of standard follow-up with polysomnography after growth hormone initiation in children with Prader-Willi syndrome, which is currently still advised in national and international clinical guidelines.
3 Our results offer support for the current advice to perform follow-up polysomnography in children with Prader-Willi syndrome after growth hormone is initiated.

Prader-Willi syndrome (PWS) is a rare multisystem disorder affecting approximately 1 in 15 000 live births[1] arising from the lack of gene expression from the paternally inherited 15q11-q13 region on chromosome 15. The cardinal features of PWS are muscular hypotonia, hypogonadism, psychomotor delay, short stature and hyperphagia that can lead to severe obesity after the age of 2–4 years.[1] Life expectancy in previously published cohorts is shortened such that 13–20% are deceased by 35 years.[2] Recent improvement in survival is attributed to earlier diagnosis and therapeutic intervention, particularly delaying or preventing the onset of obesity.[3] Respiratory and sleep disorders including hypoventilation, decreased pulmonary function, obstructive and central sleep apnoea and reduced response to hypoxia and hypercapnia are more common in children with PWS than in the general population.[4] Respiratory-related causes have been identified as the most common cause of death in children with PWS and may contribute to the increased risk of sudden death in patients with PWS.[5]

Growth hormone (GH) treatment in PWS results in a significant increase in height, improvement in body composition, reduced incidence of type 2 diabetes mellitus and enhanced mental and motor development.[6,7] In Australia, these benefits have led to approval of subsidised GH treatment in all children with PWS under the Commonwealth Pharmaceutical Benefits Scheme since 2009. A major concern of GH treatment in children with PWS, however, has been the potential association with sudden unexpected death.[8] It has been postulated that this is due to worsening of obstructive sleep apnoea (OSA) as a result of GH therapy.[9] Indeed, the growth of lymphoid tissue and/or pharyngeal wall thickening has been observed in patients with endogenous production of excess GH.[10] The association between GH therapy and sudden death remains controversial as sudden death in PWS has been described well before the introduction of GH.[11] Others have reported an apparent association, noting in one study that death and noted this most often occurred during the first 9 months following the initiation of GH.[12]

The higher prevalence of both obstructive and central sleep disturbed breathing in children with PWS compared to the general paediatric population is well documented[13–15]; however, the effect of GH treatment on sleep-disordered breathing in PWS remains controversial. Three previous studies reported no significant increase in obstructive events, although they all noted worsening in a small subgroup of patients.[13–15] A more recent study by Berini *et al.* reported significant worsening of obstructive events after GH initiation, but this effect was outweighed by the improvement in central breathing events, causing an overall improvement in total apnoea hypopnoea index (AHI) after GH.[16] Most, but not all authors have advised a cautious approach with standard screening using polysomnography (PSG) in the follow-up 6 months after the initiation of GH therapy.[13–15,17]

Current guidelines advise sleep studies before initiation and within 6 months after start of GH therapy in all children with PWS.[18] The Australian GH programme requires evaluation via PSG for airway obstruction within 12 months prior to the initiation of GH treatment and re-evaluation via PSG within the first 32 weeks of treatment for continuation. In New Zealand, a PSG or oximetry study is required prior to the initiation of GH therapy and 6–12 weeks after starting treatment in children under 2 years. Continuation is allowed if no adverse events attributable to GH are noted, without the explicit requirement for a repeat PSG.

The regulatory requirement to perform repeated sleep studies, in combination with the existence of a national PWS collaboration in Australia, has created an ideal opportunity to systematically analyse and evaluate the utility of repeated sleep studies in a large group of Australian children with PWS on GH therapy. Previous analysis of these showed a prevalence of OSA of 44% at baseline[19]; however, the course of sleep disturbed breathing after the initiation of GH has not been evaluated to date. This study sets out to analyse the short-term relationships between the initiation of GH therapy in young children with PWS and central and obstructive sleep-disordered breathing using repeated PSG.

Methods

Study design

This study was a retrospective observational study and patients were selected based on recorded administration of GH and availability of a baseline and follow-up PSG. If more than one PSG was performed before the initiation of GH, then only the last one performed closest to the date of GH initiation was considered and defined as the baseline PSG. Data were collected from seven specialised Australian PWS treatment clinics to describe clinical and PSG findings before and after the initiation of GH therapy, the first PSG for each child being performed between September 2001 and November 2017. A clinician-report questionnaire was administered using the Research Electronic Data Capture tool with each clinician being provided with a unique link for each of their patients who were eligible for this study. Specifically, data were provided to describe the child's age, sex and genetic mutation group, other sleep-related diagnoses and treatments such as tonsillectomy and supplemental oxygen, and the date that GH therapy commenced. PSG was carried out in an attended in-laboratory setting in all cases and scoring was performed in accordance with standard scoring rules for children.[20]

Table 1 Description of children at baseline PSG ($n = 112$)

			N (%)
Clinical centre, State		Sydney Children's Hospital, New South Wales	34 (30.4)
		Westmead Children's Hospital, New South Wales	24 (21.4)
		Queensland Children's Hospital, Queensland	21 (18.8)
		Perth Children's Hospital, Western Australia	15 (13.4)
		John Hunter Children's Hospital, New South Wales	10 (8.9)
		Women's and Children's Hospital, South Australia	4 (3.6)
		Monash Children's Hospital, Victoria	4 (3.6)
Gender		Male	62 (55.4)
		Female	50 (44.6)
Mutation group		Paternal deletion	43 (38.4)
		Uniparental maternal disomy	36 (32.1)
		Imprinting disorder	3 (2.7)
		Unknown/other	30 (26.8)
Adenoidectomy and/or tonsillectomy prior to baseline PSG			16 (14.3)
Respiratory support (oxygen or CPAP) during baseline study			13 (11.6)
		Median (range)	
Age at start of GH (year)		1.9 (0.1–13.5)	
Sleep-disordered breathing at baseline	Total AHI	2.9 (0–52.6)	
	Obstructive AHI	0.43 (0–32.9)	
	Central AHI	1.44 (0–50.0)	
	OSA severity	Normal	73 (65.2)
		Mild OSA	36 (32.1)
		Moderate OSA	0 (0)
		Severe OSA	3 (2.7)
	CSA	Absent	89 (79.5)
		Present	23 (20.5)

AHI, apnoea hypopnoea index; CSA, central sleep apnoea; GH, growth hormone; OSA, obstructive sleep apnoea; PSG, polysomnography.

Obstructive and central AHIs were derived from pre- and post-GH PSG and clinical data at the time of PSG were noted including the child's weight and whether there was need for respiratory support. Additionally, the obstructive AHI was categorised as normal (≤1/h), mild (1 < 5/h), moderate (5 < 10/h) and severe (≥10/h). The central AHI was categorised as normal (<5/h) or abnormal (≥5/h). We included children who commenced GH therapy between January 2002 and March 2018.

Statistical analyses

Continuous variables describing obstructive and central sleep-disturbed breathing before and after commencing GH therapy were compared with the Wilcoxon signed-rank test. We used non-parametric methods on account of clear departures from normality in the changes over time in the index scores. Categorised levels of obstructive and central AHI (normal/mild vs. moderate/severe) before and after commencing GH therapy were compared. Binomial confidence intervals for the proportion of children who developed moderate/severe OSA or central sleep apnoea (CSA) were calculated using the exact method of Clopper-Pearson. SPSS (V25) was used for all statistical analyses.

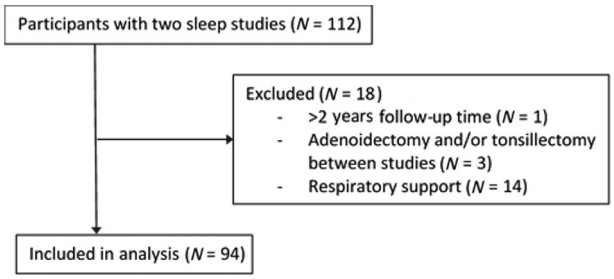

Fig. 1 Flowchart study participants.

Results

Participants

Obstructive and central AHI before and after commencing GH therapy was available for 112 children (50 female; median (range) age 1.9 (0–13.5) years), provided by seven clinics across five states in Australia. Genetic data showed that 32% had uniparental maternal disomy and 38% had a paternal deletion. GH was initiated in these patients between the years 2002 and 2018. Sixteen children had an adenoidectomy and/or tonsillectomy prior to the baseline sleep

Table 2 Polysomnography data in children included in paired analysis ($n = 94$)

	PSG prior to commencing GH Median (range)	PSG after commencing GH Median (range)	*P* value
Age at PSG (years)	1.5 (0.1–13.2)	2.2 (0.4–13.9)	n/a
Time between 1st PSG and start of GH (months)	3.4 (0.1–26.9)	-	n/a
Time between start of GH and follow-up PSG (months)	-	2.8 (0.6–23.6)	n/a
Weight *Z*-score†	−0.9 (−4.2 to 3.0)	−0.5 (−3.6 to 3.1)	0.17
Obstructive AHI	0.40 (0–4.9)	0.50 (0–51.7)	0.13
Categories of OSA, *N* (%)			
Normal	64 (86)	61 (65)	
Mild OSA	30 (32)	21 (22)	
Moderate OSA	0 (0)	8 (9)	
Severe OSA	0 (0)	4 (4)	
Central AHI	1.4 (0–36.0)	1.5 (0–32.2)	0.20
Categories of CSA, *N* (%)			
Absent	76 (81)	80 (85)	
Present	18 (19)	14 (15)	

Of the $n = 94$ children included in the comparative analysis, 11 children (12%) underwent adenoidectomy and/or tonsillectomy prior to baseline polysomnography. †For analysis including weight *Z*-scores, $N = 85$ due to missing data in nine children. AHI, apnoea hypopnoea index; CSA, central sleep apnoea; GH, growth hormone; OSA, obstructive sleep apnoea; PSG, polysomnography.

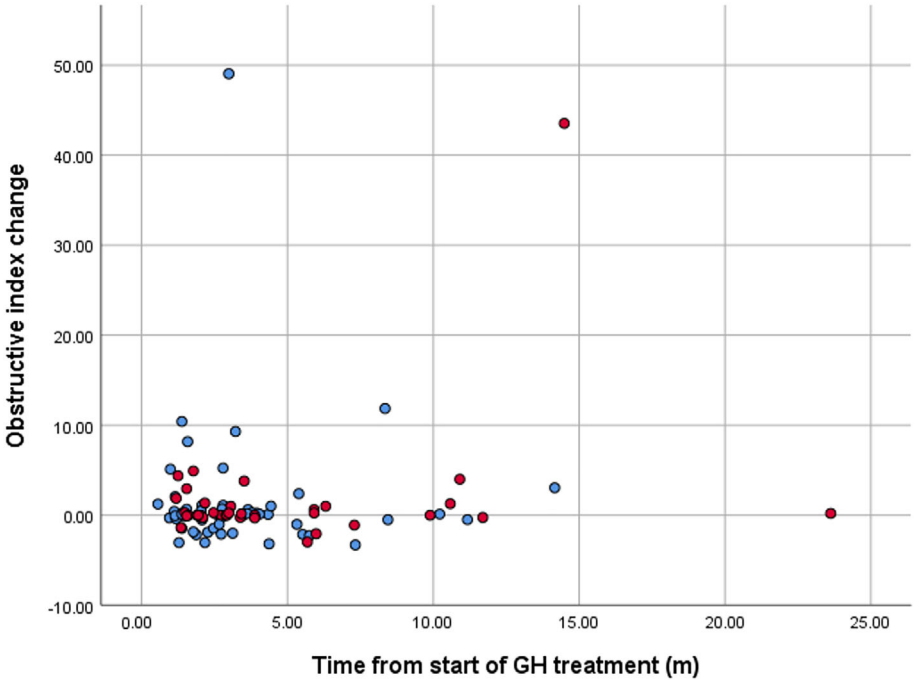

Fig. 2 Change in obstructive AHI between paired sleep studies for children younger and older than 3 years, by the time from start of GH treatment to 2nd sleep study in months. Age groups: (●) Under 3 years and (●) over 3 years.

study (Table 1). The post-GH therapy PSG was conducted within 3 months in 54 (57.4%) of children, after three to 6 months in 26 (27.7%), after 6–9 months in 5 (5.3%), after 9–12 months in 6 (6.4%) and between 12 and 24 months after the initial PSG in 3 (3.2%) children. In total, 18 children were excluded from the comparative analysis (Fig. 1), the most common reason being that they were on some form of respiratory support, either at the time of baseline ($N = 13$) or only at follow-up PSG ($N = 1$). Because respiratory support, even supplemental oxygen, can have a profound effect on the scoring of both obstructive and central events, this was deemed reason for exclusion from the comparative analysis. The three children who were diagnosed with severe OSA

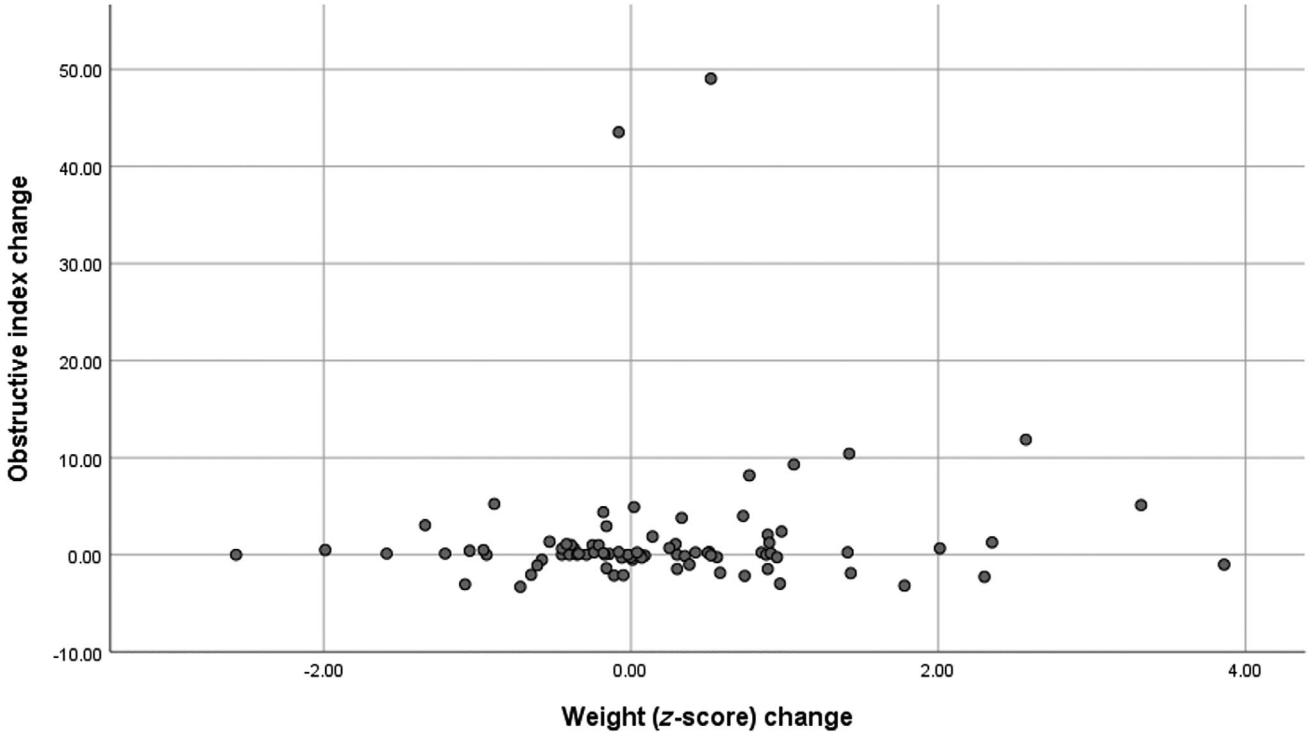

Fig. 3 Change in obstructive AHI by the change in weight *Z*-score between the two sleep studies.

based on the baseline PSG all received some form of OSA treatment between baseline study and GH initiation and were therefore excluded from the comparative analysis for this reason. In the comparative analysis, the remaining 94 children are included.

Obstructive sleep apnoea

In 94 children, the median (range) obstructive AHI was not significantly different between the two studies (0.4/h (0–4.9) prior to commencement of GH and 0.5/h (0–51.7) after GH ($P = 0.13$)). Twelve children (13%; $CI_{95\%}$ 7–21%) changed category from normal/mild OSA to moderate/severe OSA (Table 2). Changes in the obstructive AHI were similar for children younger and older than 3 years and across different inter-testing intervals. However, there were some large changes over a short interval for the younger children (Fig. 2).

Eleven of the 94 children included in the comparative analysis underwent adenoidectomy and/or tonsillectomy prior to the baseline PSG. Restricting analysis to the 83 children who had not undergone previous surgery also did not show significant change in the median obstructive AHI before (0.3/h) and after GH initiation (0.5/h) ($P = 0.14$). Ten of these 83 children developed moderate/severe OSA (12%; $CI_{95\%}$ 6–21%). In the small subgroup of 11 children with ENT surgery prior to the baseline PSG, 2 children (18%) still changed from normal/mild to moderate/severe OSA, in both cases the surgery previously performed was adenotonsillectomy.

The median (range) *Z*-score for weight was −0.9 (−4.2 to +3.0) before GH, which increased to −0.5 (−3.6 to +3.1) after GH therapy ($P = 0.17$) (Table 2). Changes in obstructive AHI were not associated with changes in weight *Z*-score (Fig. 3). Also at follow-up, the absolute body mass index (BMI) score was not significantly associated with the probability of having moderate to severe OSA ($P = 0.27$, log binomial regression).

Central sleep apnoea

For 94 children, the median (range) central AHI did not change after commencement of GH (from 1.4/h (0–36.0) to 1.5/h (0–32.2), $P = 0.20$). Eighteen children (19%) had central sleep apnoea before commencing GH and 14 children (15%) had central sleep apnoea after GH (Table 2). Changes in the central AHI were similar for children younger and older than 3 years at time of GH initiation (Fig. 4).

Discussion

In this Australian multicentre retrospective analysis of children with PWS using PSG before and after introduction of GH therapy, we found that the median obstructive AHI for the group did not increase significantly after the initiation of GH. However, 13% ($CI_{95\%}$ 7–21%) of children with no or mild OSA at baseline developed moderate/severe OSA after the initiation of GH. Development of moderate–severe OSA could not be explained by changes in body weight and appeared to be more pronounced in the children under 3 years of age. In this cohort, we found no evidence of a change in central sleep apnoea after GH initiation.

There is ongoing controversy in the literature about the possible effects of GH on OSA. Several observational studies with

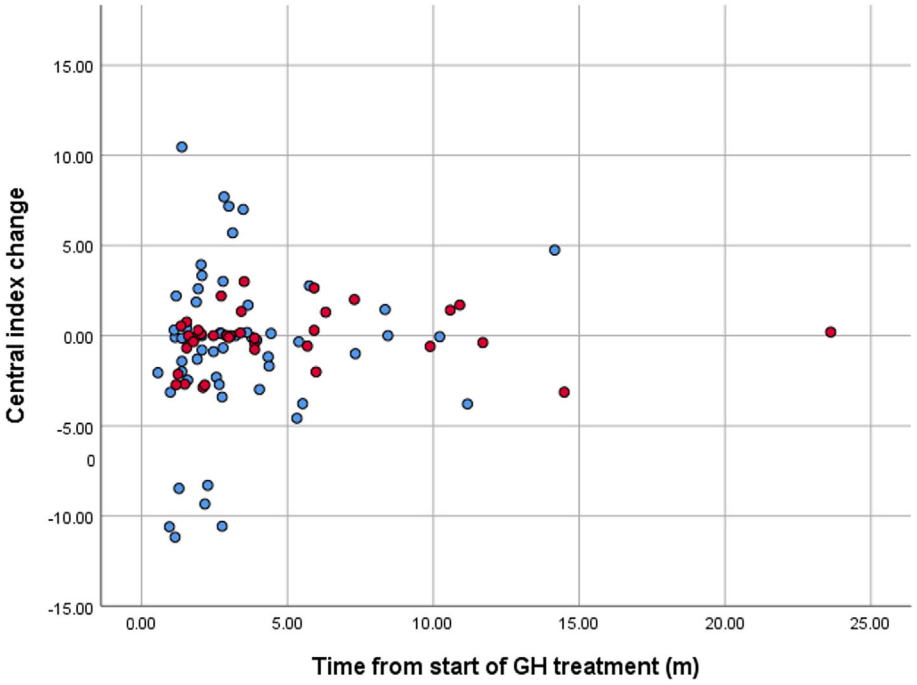

Fig. 4 Change in central AHI between sleep studies for children younger and older than 3 years, by the time from start of GH treatment to 2nd sleep study in months. Age groups: (●) Under 3 years and (●) over 3 years.

smaller sample sizes did not report significant worsening of sleep-disordered breathing 6 weeks to 6 months after the initiation of GH.[13–16,21,22] The largest previous study ($n = 50$) reported an overall improvement in the respiratory disturbance index but, in line with our findings, the separate analysis of central and obstructive events revealed a significant increase in the proportion of children with an obstructive AHI >1/h from 6% at baseline to 22% 1.5 months after GH initiation.[16] Three other studies with sample sizes ranging from 15 to 30 reported no significant effect on the average frequency of obstructive events but reported a subset of children ($n = 2$ in each study) who had a sudden worsening of the obstructive AHI after GH initiation, prompting cessation of GH.[13,15,22] It is possible that the lack of significant difference in obstructive AHI was a reflection of low power due to the small sample size. Most authors have reasoned that the risk of severe OSA developing in even a small subset of children justifies standard follow-up with PSG after GH initiation,[13,15] and clinical consensus guidelines have also chosen this approach.[18] Others however have stressed the absence of a consistent significant association between GH and OSA, suggesting that standard polysomnographic follow-up may not be indicated.[17] Our study in combination with results by Berini *et al.*[16] confirm that there is indeed an increase in obstructive events after introduction of GH in a significant subset of children, in our study leading to the development of moderate to severe OSA in 13% of children with PWS.

A recent randomised placebo controlled cross-over trial in 27 young adults with PWS on long-term GH therapy found no effect on the frequency of polysomnographic proven central or obstructive apnoeas with GH versus placebo.[23] However, these findings cannot be generalised to our much younger population in whom GH is initiated for the first time. An important limitation in all previous studies of pre-school to school-aged children, including the current study, is the lack of a control group. This makes it impossible to attribute changes in the course of sleep-disordered breathing to GH therapy. The increase in obstructive events after GH might be explained by natural history as adenoid and tonsillar growth is maximal below the age of 5 years. Our data suggest that the increase in obstructive events was more pronounced in the group that started GH under the age of 3 years (median age 1.2 years). However, the increase in obstructive AHI appears to occur within the first months after the initiation of GH, and not to worsen with longer periods of follow-up (Fig. 2), as one would expect if the increase in obstructive events was based solely on natural history.

Previous studies have focussed mainly on the increased risk of obstructive breathing events after GH, based on the hypothesis of that higher IGF-1 levels could induce tonsillar and adenoid tissue hyperplasia or retropharyngeal fluid accumulation, increasing the likelihood of upper airway collapse. In contrast, other authors have postulated that GH initiation could contribute to a decrease in obstructive events, potentially by improvements in muscle strength,[24] improved CO_2 responsiveness[25] or improved body composition and lower BMI.[14] For this last hypothesis, our data show little evidence, given there was no relation between changes in BMI and changes in obstructive AHI.

We found no significant associations between GH initiation and central sleep-disordered breathing in children with PWS. Several previous studies have suggested an improvement of sleep-disordered breathing after GH initiation due mainly to a reduction in central events.[13,16,22] A potential positive effect of GH on central breathing drive may be explained by an improved ventilatory sensitivity to both carbon dioxide and oxygen in response to elevated IGF-1.[25] Other studies however did not find a significant association between GH and central breathing events,[14,15,21,23] in line with our findings. Discrepancies could be

explained by differences in the age of investigated children, as the strongest effects on central sleep-disordered breathing have previously been reported in the children under the age of 1 year.[22] Up to eight central apnoeas per hour could be considered physiologic in infancy, with a natural reduction in frequency continuing up to the second year of life.[26] In children with PWS, an increased prevalence of central sleep apnoea has been reported both under the age of 2 years (43%), and later in childhood (5%).[27] Logically, the power to detect a significant decrease in central AHI will be higher during the peak incidence in infancy, when the potential for improvement is highest. However, it is quite likely that at least part of the previously reported beneficial effects after GH initiation is based on the favourable natural course of central breathing events with age.

A key strength of the current study is the large sample size recruited from multiple institutions across Australia where baseline and follow-up PSG is routinely performed as a prerequisite for publicly funded GH. As such, we were able to exclude children who received treatment for sleep-disordered breathing to avoid confounding our analysis in relation to GH initiation. It should be noted however, that this may have led to exclusion of cases with a relatively high propensity to develop sleep-disordered breathing.

Several limitations of this study need to be considered. As noted, our study lacks a control group in whom no GH was given. Therefore, changes in the course of sleep disturbed breathing may reflect natural history rather than an effect of GH treatment. Determining the separate effect of increasing age and GH on the development of OSA would require a randomised controlled trial with age matched patients, and such a trial is unlikely to be undertaken given the established benefits of GH therapy in PWS. Previous randomised controlled trials in pre-schoolers did not show development of moderate–severe OSA in the control arm over 6–12 months of follow-up in children with mild OSA at baseline and so the change demonstrated in our study would be unlikely based on natural history alone.[28] Secondly, in this retrospective study, the timing of the follow-up PSG after the initiation of GH was variable, ranging from 2 weeks up to 23 months. Thirdly, sleep study scoring was done in multiple sleep laboratories, spread out over a period of 20 years. Although scoring rules may have changed over this period, the effect of this is minimised by comparison of PSG before and after GH initiation using studies from the same facility with a median timespan of 6 months in between. All collaborating Australian sleep centres followed the current American Academy of Sleep Medicine scoring manual throughout the study period.[20] Fourthly, although we aimed to include all PWS patients treated with GH during the study period, patient selection was dependent on the availability of repeated PSG. The strict requirement for these studies in order to qualify for GH treatment reimbursement increases the likelihood that most eligible patients were included. However, selection may have occurred if PSG was performed in outside the major public hospitals included in our study group. We find it unlikely that this selection would have resulted in any systematic selection bias relevant to our findings. Finally, we did not find any cases of sudden death in our study population, but it should be clearly noted that patient selection was based on the availability of baseline and follow-up PSG, and not designed to screen for exceedingly rare events.

What are the implications of our findings? There is little debate about the efficacy of GH in children with PWS, particularly the long-term benefits on linear growth and BMI.[7] The relationship between GH initiation and sleep-disturbed breathing, however, remains strongly debated. To our knowledge, this is the largest study to date investigating the course of sleep-related breathing disorders in relation to GH initiation in children with PWS. Our study provides evidence that a significant subset of children develops moderate/severe OSA, particularly in the first months after the initiation of GH. Although causality cannot be inferred, our data offer support for the standard screening for development of OSA within the first 6 months after GH initiation, as is currently standard practice in Australia.

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Ethical approval

This study was approved by the Human Research Ethics Committees at the Child and Adolescent Health Services (1739EP) and Children's Health Queensland (HREC/17/QRCH/201) as the lead state for the other sites in New South Wales, Victoria and South Australia. Governance was confirmed at all sites.

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You are my Sunshine by Tarlia McGlashan (age 10) from Operation Art 2021