Effects of 8 years of growth hormone treatment on scoliosis in children with Prader–Willi syndrome

Lionne N Grootjen[1,2,4], Joost P H J Rutges[3], Layla Damen[1,2,4], Stephany H Donze[1,2,4], Alicia F Juriaans[1,2,4], Gerthe F Kerkhof[2] and Anita C S Hokken-Koelega[1,2,4]

[1]Dutch Reference Center for Prader-Willi Syndrome, Rotterdam, The Netherlands, [2]Department of Pediatrics, Subdivision of Endocrinology, Erasmus University Medical Center-Sophia Children's Hospital, Rotterdam, The Netherlands, [3]Department of Orthopaedic Surgery, Erasmus University Medical Center, Rotterdam, The Netherlands, and [4]Dutch Growth Research Foundation, Rotterdam, The Netherlands

Correspondence should be addressed to L N Grootjen
Email
l.grootjen@kindengroei.nl

Abstract

Objective: Scoliosis is frequently seen in children with Prader–Willi syndrome (PWS). There is still concern that growth hormone (GH) treatment might increase the risk of onset or progression of scoliosis. Short-term data suggested no adverse effects of GH on scoliosis, but long-term effects of GH treatment on development of scoliosis in PWS are unknown. This study investigated the effects of 8 years of GH treatment on scoliosis in children with PWS.
Design: Open-label, prospective cohort study in 103 children with PWS receiving GH for 8 years was analyzed. Prevalence and severity of scoliosis were compared to a group of 23 age-matched GH-untreated children with PWS.
Methods: Spine X-rays and DEXA-scans were performed, and Cobb angel was measured by two independent observers.
Results: After 8 years of GH treatment, at median age of 10.8 years, prevalence of scoliosis was 77.7%. No difference in prevalence or severity of scoliosis was found between GH-treated and age-matched untreated children with PWS (P = 0.409 and P = 0.709, respectively). Height SDS and trunkLBM were significantly higher in GH-treated children. Higher bone mineral density of the lumbar spine was found in children without scoliosis after 8 years of GH. Bone mineral apparent density of lumbar spine ($BMAD_{LS}$) SDS was associated with lower Cobb angle (r = –0.270, P = 0.008).
Conclusions: Eight years of GH treatment has no adverse effects on the prevalence and severity of scoliosis in children with PWS until 11 years of age. As $BMAD_{LS}$ SDS is inversely associated with Cobb angle, it is pivotal to optimize the BMD status in children with PWS.

European Journal of Endocrinology
(2021) **185**, 47–55

European Journal of Endocrinology

Introduction

Prader–Willi syndrome (PWS) is a rare syndrome caused by the lack of expression of the paternally derived chromosome 15q11-q13, caused by a paternal deletion, maternal uniparental disomy (mUPD), and in rare cases by an imprinting center defect (ICD) or paternal chromosomal translocation (1, 2). Clinical findings characterizing PWS are developmental delay, muscular hypotonia, behavioral problems, hyperphagia with obesity and short stature (2, 3, 4, 5). Hypothalamic dysfunction may be responsible for many features of PWS (6, 7).

Scoliosis is frequently seen in children and adults with PWS. The reported prevalence of scoliosis in children with PWS varies between 32.1 and 86% (8, 9, 10, 11, 12). In comparison, the prevalence of scoliosis in the general Dutch adolescent population is 2.7% (13). Children with PWS can exhibit two types of scoliotic curves. Long C-curve scoliosis (LCS) is mostly seen in very young children with PWS, due to the underlying hypotonia. Later in childhood, the curve may convert to an S-shaped scoliosis, defined as idiopathic scoliosis (IS) (14).

https://eje.bioscientifica.com
https://doi.org/10.1530/EJE-21-0211

Published by Bioscientifica Ltd.

Scoliosis and scoliosis treatment have a significant impact on the quality of life of children with PWS. Physical therapy plays an important role in the prevention and treatment of scoliosis. Hypotonia, as seen in children with PWS, has been associated with the development of scoliosis and creating more muscle mass may prevent the development and progression of scoliosis. Treatment options of scoliosis are brace treatment or surgery (15).

Growth hormone (GH) treatment is registered for children with PWS since 2000. It improves body composition, psychomotor development and cognition in children with PWS (16, 17, 18, 19, 20). Because GH induces catch-up growth in height, there have been concerns about development of scoliosis or worsening of existing scoliosis. However, our previous randomized controlled study of 2 years of GH treatment in children with PWS showed no significant difference between GH-treated children and -untreated controls with regard to the onset of scoliosis, curve progression and start of scoliosis treatment (14). Other studies found similar findings (21, 22, 23). GH increases lean body mass, which may counteract the adverse effects of accelerated growth on scoliosis.

Although previous studies were reassuring for short-term effects of GH treatment on scoliosis, long-term effects of GH on scoliosis are still unknown. The aim of this study was to investigate the long-term effects of GH on the prevalence and severity of scoliosis in children with PWS. Secondary objectives were to assess if the age at the start of GH treatment and the amount of lean body mass or bone mineral density are correlated with the development of scoliosis. We hypothesized that the prevalence of scoliosis in children with PWS after 8 years of GH treatment would be similar to the prevalence in non-GH-treated children with PWS.

Methods

Patients

All participants were diagnosed with PWS, confirmed by methylation pattern analysis of the PWS region, and participated in the Dutch PWS cohort study (24, 25). All children were studied from the start of their GH treatment and all started GH before the 1st of July 2011. At the start of GH, all children were prepubertal, defined as a Tanner breast stage < 2 for girls and testicular volume < 4 mL for boys (26). Those who reached adult height within less than 8 years after GH start were excluded from the present study, as the GH dosage was lowered after attainment of adult height. The control group consisted of age-matched children with PWS, selected from a larger historical control group, and who had not started their GH treatment yet. Most controls were from the untreated arm of the randomized controlled trial we previously performed (14, 24) and some were from the pre-GH treatment era.

Design

This is a prospective study investigating the long-term effects of GH treatment in children with PWS. All children in the GH-group were treated with 1.0 mg GH/m^2 (~0.035 mg/kg) once daily for 8 consecutive years. During each visit, the GH dose was adjusted to the body surface area. The median (IQR) GH dose after 8 years of GH treatment was 0.97 mg/m^2/day (0.66; 1.00).

All children visited the Dutch PWS Reference Center in Rotterdam and received multidisciplinary care from the PWS team, including regular follow-up by an orthopedic surgeon. The study protocol was approved by the Medical Ethics Committee of the Erasmus University Medical Center. Written informed consent was obtained from parents and children older than 12 years. Assent was obtained from children younger than 12 years.

Radiographics

Standardized X-rays of the spine were taken before the start of the GH treatment and every year thereafter. For the GH-treated children, X-rays before the start of GH and at 8 years thereafter were used for analysis. For the control-group, the X-ray prior to the start of GH treatment was used. X-rays were taken in supine position in young children who were too hypotonic to stand. Most X-rays were taken at the Erasmus University Medical Center. Some X-rays were performed in other medical centers in The Netherlands, but these were sent to Erasmus Medical Center, where they were assessed. In ten children, the 8-year X-ray was not available, in those cases the X-ray closest in time to the 8 years was used (max. 1 year below or 2 years above the 8-year X-ray).

To diagnose scoliosis, the Cobb angle was measured on a posterior-anterior or anterior-posterior x-ray of the complete spine. The Cobb angle is the angle between the most tilted upper and the most tilted lower vertebra contained in the curve and is measured between the cranial endplate of the upper vertebra and caudal endplate of

the lower vertebra (27). Normally, there is no measurable deviation. Scoliosis is defined as a spinal curve with a Cobb angle more than 10°. Cobb angles were measured by two independent trained observers. The interobserver variation was minimal (mean (SD) difference −0.07° (2.5), intraclass coefficient (ICC)=0.995, $P < 0.001$). In addition to these measurements, an orthopedic surgeon, specialized in spine disorders (JR), measured Cobb angles in a random sample (ICC=0.983, $P < 0.001$).

Anthropometrics

Standing height was measured with a Harpenden Stadiometer and supine length with a Harpenden Infantometer (Holtain Ltd., Crosswell, UK). Weight was measured on a calibrated scale (Servo Balance KA-20-150S; Servo Berkel Prior, Katwijk, the Netherlands). Height, weight and BMI SDSwere calculated with Growth Analyser RCT 4.1 (www.growthanalyser.org), based on Dutch reference values (28, 29).

Dual energy x-ray absorptiometry

Dual energy x-ray absorptiometry (DXA) (Lunar Prodigy type; GE healthcare, Chalfont St. Giles, UK) was annually performed in all children to measure the lean body mass (LBM), fat percentage, bone mineral density of the lumbar spine (BMD_{LS}) and bone mineral density of the total body (BMD_{TB} SDS). The DXA-machine was calibrated daily. To analyze the effects of GH on relative muscle mass, a ratio of trunkLBM vs body surface area (BSA) ratio (trunkLBM:BSA) was used, as previously described (8). FM% SDS was calculated according to age- and sex-matched Dutch reference values (30). As the BMD_{LS} is underestimated by the areal presentation, we corrected for bone size by calculating the bone mineral apparent density of the lumbar spine ($BMAD_{LS}$) (31). BMD_{TB} SDS and $BMAD_{LS}$ SDS were calculated to age-matched and sex-matched reference values of the Dutch population (32).

Assay

Fasting blood samples were collected for assessment of serum IGF-1 levels. All blood samples were measured in the Biochemical and Endocrine laboratories of the Erasmus University Medical Center, Rotterdam. Because serum IGF-1 levels are age- and sex-dependent, values were transformed to SDS values, based on Dutch population (33).

Statistics

Statistical analysis was performed with SPSS 24.0 (SPSS Inc.). As not all data were normally distributed, non-parametric tests were used and data are expressed as median (interquartile range (IQR)). Mann–Withney *U* tests were used for differences between the GH-treated- and the untreated group, regarding height SDS, change in height SDS, weight SDS, age, Cobb angle, IGF-1 SDS and TrunkLBM:BSA ratio. Chi square tests were used to analyze differences in gender, genetic subtype, pubertal stage, and treatment for scoliosis. Mann–Withney *U* tests and chi square tests were used to compare the group with and without scoliosis after 8 years of GH treatment. Spearman's Rho was used to analyze correlations between Cobb angle and the age of start of GH, serum IGF-1 SDS, sex, genotype, trunkLBM:BSA, $BMAD_{LS}$ SDS and BMD_{TS} SDS of the GH-treated group. Change in height was defined as the difference in height SDS between the start of GH and at 8 years of the GH treatment. As the C-curve is not seen later in childhood, idiopathic scoliosis was used for analysis. Severe scoliosis was set at a Cobb angle > 25°. All children with brace treatment or surgery for their scoliosis were included in the group with Cobb angle > 25°. Pubertal stage was defined as prepubertal (testes volume < 4mL and tanner breast stage < 2), early pubertal (testes volume 4–10 mL and tanner breast stage 2–3) or late pubertal (testes volume > 10 mL and tanner breast stage ≥ 4) (26). Level of significance was set at a *P*-value of 0.05.

Results

Clinical characteristics

In this study, 137 children started the GH treatment before the 1st of July 2011. Of these children, 34 were excluded from analyses: 4 were lost to follow-up and 30 reached adult height within the 8 years after the start of GH. In total, 103 children completed at least 8 years of continuous GH treatment and were eligible for the evaluation of 8 years of GH. The GH-untreated group consisted of 23 age-matched children with PWS, prior to the start of GH.

Table 1 shows the clinical characteristics of the GH-treated and untreated group. Of the 103 GH-treated children, 53 were males and 50 females. In the untreated group, 10 were males and 13 females. At the start of GH treatment, the median (IQR) age was 2.8 (1.3; 5.9) years, median (IQR) trunkLBM:BSA 7.2 (6.8; 7.7) and median (IQR) Cobb angle 10.3° (7.1; 13.0).

Table 1 Baseline characteristics. Data are expressed as median (IQR) or *n* (%).

	GH treatment group	GH-untreated children	*P*-value
Gender			0.489
Male	53	10	
Female	50	13	
Genetic subtype			0.653
Deletion	51 (49.5%)	9 (39.1%)	
mUPD	42 (40.8%)	9 (39.1%)	
ICD	5 (4.9%)	3 (8.7%)	
At start of GH treatment			
Age (years)	2.8 (1.3; 5.9)	NA	
Height SDS	−2.1 (−2.9; −1.4)	NA	
Weight for height SDS	0.3 (−0.9; 1.5)	NA	
BMI SDS	0.4 (−0.9; 1.4)	NA	
TrunkLBM:BSA	7.2 (6.8; 7.7)	NA	
Cobb angle (°)	10.3 (7.1; 13.0)	NA	

GH, growth hormone; ICD, imprinting center defect; mUPD, maternal uniparental disomy; NA, not available; trunkLBM:BSA, trunk lean body mass/body surface area.

Effect of 8 years of GH treatment on scoliosis in children with PWS

Table 2 shows scoliosis measurements, anthropometrics, and body composition in children with PWS after 8 years of GH compared to age-matched untreated children with PWS. Median (IQR) age of the GH-treated children after 8 years of GH and the untreated children was similar, being 10.81 (9.27; 13.76) vs 11.4 (9.7; 13.35) years (P= 0.912), respectively. The GH-treated children were significantly taller compared to untreated children (P< 0.001). After 8 years of GH, 49 children (47.6%) were still prepubertal, compared to 18 children (78.3%) in the untreated group (P =0.020). Serum IGF-1 SDS was significantly higher in GH-treated children (P= 0.023). Median (IQR) BMD_{TB} SDS, $BMAD_{LS}$ SDS and fat mass % SDS were not different between the groups. Median (IQR) trunkLBM:BSA ratio was higher in GH-treated children than in GH-untreated children (8.83 (8.13, 9.66) and 8.16 (7.40; 8.62) (P= 0.001), respectively).

Median (IQR) Cobb angle in the GH-treated group was 18.0° (10.5; 30.0) and 15.0° (7.5; 32.0) in the GH-untreated group (P= 0.232). The prevalence of scoliosis was not different between groups, being 77.7% in the GH-treated group and 69.6% in the untreated group (P= 0.409). The prevalence of more severe scoliosis (Cobb angle > 25°) and scoliosis treatment was also similar between the groups.

Scoliosis compared to no scoliosis after 8 years of GH treatment

Table 3 presents data of children who had developed scoliosis after 8 years of GH treatment compared to those who did not. Median (IQR) age at the start of GH did not differ between groups, being 2.96 years (1.32; 6.12) in the

Table 2 Results after 8 years of GH-treatment compared to age-matched untreated controls. Data are expressed as median (IQR) or *n* (%). Both the surgical and the brace group consisted of six individual patients.

	After 8 years of GH (*n* = 103)	GH-untreated children (*n* = 23)	*P*-value
Age (years)	10.81 (9.27; 13.76)	11.42 (9.7; 13.35)	0.912
Pubertal stage			0.020
Prepubertal/girls	49 (47.6%)/18	18 (78.3%)/9	
Early puberal/girls	42 (40.8%)/23	5 (21.7%)/4	
Late pubertal/girls	12 (11.7%)/9	0 (0.0%)	
Height SDS	0.17 (−0.87; 0.94)	−2.60 (−3.46; −1.93)	<0.001
BMD_{TB} SDS	−0.42 (−1.25; 0.58)	−0.74 (−1.35; 0.15)	0.490
BMD_{LS} SDS	0.39 (−0.53; 1.28)	−0.94 (−1.32; −0.07)	0.001
$BMAD_{LS}$ SDS	0.32 (−0.34; 1.14)	0.12 (−0.67; 1.50)	0.768
BMI SDS	1.19 (0.17; 1.85)	1.41 (0.62; 2.17)	0.284
Fat% SDS	1.93 (1.43; 2.38)	1.75 (1.26; 2.17)	0.245
TrunkLBM:BSA	8.83 (8.13; 9.66)	8.16 (7.40; 8.62)	0.001
Serum IGF-1 SDS at X-ray	2.12 (1.72; 2.53)	−2.41 (-2.97; 1.68)	0.023
Cobb angle (°)	18.0 (10.5; 30.0)	15.0 (7.5; 32.0)	0.232
Scoliose (%)	80 (77.7%)	16 (69.6%)	0.409
10–24.9°	49 (61.3%)	9 (56.3%)	0.709
>25°	31 (38.8)	7 (43.8)	0.709
Brace (%)	6 (5.8%)	2 (8.7%)	0.637
Surgery (%)	6 (5.8%)	2 (8.7%)	0.637

$BMAD_L$ bone mineral apparent density of the lumbar spine; BMDTB, bone mineral density of the total body; GH, growth hormone; trunkLBM:BSA: trunk lean body mass/body surface area.

Table 3 Scoliosis compared to no scoliosis after 8 years of GH treatment. Data are expressed as median (IQR) or *n* (%).

	Scoliosis (*n* = 80)	**No scoliosis** (*n* = 23)	***P*-value**
Age start GH	2.96 (1.32; 6.12)	2.51 (1.55; 4.56)	0.638
Genotype			0.316
Deletion	42 (52.5%)	9 (39.1%)	
mUPD	29 (36.3%)	13 (56.5%)	
ICD	4 (5.0%)	1 (4.3%)	
Sex (M)	40 (50%)	11 (55%)	0.581
Height SDS	−0.02 (−0.88; 0.69)	0.78 (−0.84; 1.67)	0.051
Change in height SDS	2.07 (1.53; 2.82)	2.32 (1.94; 2.85)	0.118
Pubertal stage			0.513
Prepubertal	40 (50%)	9 (39.1%)	
Early pubertal	32 (40%)	10 (43.5%)	
Late pubertal	8 (10%)	4 (17.4%)	
BMD_{TB} SDS	−0.56 (−1.40; 0.37)	0.14 (−1.01; 1.13)	0.036
BMD_{LS} SDS	0.31 (−0.85; 1.11)	0.88 (−0.01; 1.78)	0.013
$BMAD_{LS}$ SDS	0.28 (−0.56; 1.00)	0.63 (0.16; 1.53)	0.054
BMI SDS	1.15 (0.16; 1.82)	1.61 (0.48; 1.89)	0.343
Fat% SDS	1.88 (1.34; 2.33)	2.16 (1.52; 2.48)	0.141
TrunkLBM:BSA	8.94 (8.11; 9.80)	8.72 (8.30; 9.59)	0.713
Serum IGF-1 SDS at 8 years	2.13 (1.73; 2.53)	2.08 (1.45; 2.54)	0.692
Average serum IGF-1 SDS during 8 years	2.39 (1.90; 2.79)	2.33 (1.85; 2.87)	0.984
Serum 25 (OH) vit D* (nmol/L)	63 (50; 88)	67 (43; 73)	0.758

*Normal range 50–120 nmol/L.
BMAD, bone mineral apparent density; BMD, bone mineral density; GH, growth hormone; trunkLBM:BSA, trunk lean body mass/body surface area.

group with scoliosis after 8 years of GH and 2.51 years (1.55; 4.56) in the group without scoliosis after 8 years of GH. No difference in sex, genotype or pubertal stage was found between the groups. Median (IQR) height in the group with scoliosis was −0.02 SDS (−0.88; 0.69) and in the group without scoliosis 0.78 SDS (−0.84; 1.67) (P= 0.051). Change in height SDS did not differ between the groups. Median (IQR) BMD_{TB} SDS was lower in children who developed scoliosis compared to those without scoliosis (−0.56 (−1.40; 0.37) vs 0.14 (−1.01; 1.13), respectively (P= 0.036)). Median $BMAD_{LS}$ SDS tended to be lower in children with scoliosis (P= 0.054). Average serum IGF-1 SDS during 8 years of GH treatment, serum IGF-1 SDS at 8 years, vitamin D level, trunkLBM:BSA ratio, BMI SDS, and fat% SDS were not different between GH-treated children with or without scoliosis.

Influence of clinical characteristics on scoliosis in children after 8 years of GH treatment

Twelve children (11.6%) of the GH-treated group were treated with bracing therapy or surgery for their scoliosis. Gender or genotype did not significantly differ between the children who needed scoliosis treatment vs those who did not (data not shown).

Serum IGF-1 SDS after 8 years of treatment and the average serum IGF-1 SDS during 8 years of treatment were not were not associated with Cobb angle after 8 years of GH treatment, neither was there an association with the age at the start of GH (P> 0.79). No difference in Cobb angle was found for sex, genotype, or pubertal stage (data not shown). No correlation was found between height SDS and trunkLBM:BSA and Cobb angle (data not shown). BMD_{TB} SDS was not associated with Cobb angle (r = −0.186, P= 0.066). $BMAD_{LS}$ SDS was inversely associated with Cobb angle after 8 years of GH (r = −0.270, P= 0.008).

Discussion

This is the first long-term study investigating the prevalence and severity of scoliosis in 103 children with PWS after 8 years of continuous GH treatment. The results demonstrate no difference in the prevalence of scoliosis between GH-treated children vs age-matched GH-untreated children with PWS at 11 years of age. We also found that GH-treated children do not have more severe scoliosis, as the median Cobb angle between GH-treated and untreated children was similar. Our data show that 8 years of GH treatment has no adverse effects on the prevalence and severity of scoliosis in children with PWS. Our findings do also show that $BMAD_{LS}$ SDS is inversely associated with Cobb angle, indicating that it is

important to optimize BMD status in children with PWS. Furthermore, GH-treated children had a taller stature and higher trunkLBM:BSA ratio, which is in line with previous studies showing that the GH treatment improves height and lean body mass in children with PWS (24, 34, 35).

Prevalence of scoliosis and median Cobb angle were similar in GH-treated children and in age-matched GH-untreated children. Prevalence of a more severe scoliosis (>25°) tended to be lower in the GH-treated group and GH-treated children were less likely to need surgery or brace therapy than the control group (both 5.8% vs 8.7%, respectively), albeit not significantly. These long-term results are in line with our previous study, a randomized controlled trial investigating the effects of 2-year GH on onset and progression of scoliosis in PWS. During that 2-year study, height velocity and IGF-1 SDS were not associated with curve progression (14). A retrospective study showed similar findings (36). However, these studies were investigating the effects of short-term GH treatment on scoliosis in PWS, while we know that it takes several years to develop scoliosis and that the prevalence of scoliosis increases with age (8). Our present findings show that also on the long-term, GH treatment does not affect the prevalence or severity of scoliosis in children with PWS.

Age at the start of GH treatment was not associated with Cobb angle after 8 years of GH. A survey from the PWSA found that for every month delay in starting GH, the risk of needing scoliosis surgery increased by 0.7% (15). Our data do not support this finding. An explanation of this difference could be the fact that children who receive GH are likely to also receive multidisciplinary care from a younger age than children who do not receive GH, including physical therapy, which is also beneficial against the development of scoliosis. In addition, almost all children in our GH-treated group started GH at a young age, which might explain why we were not able to find an age correlation. Due to the positive effects of GH treatment (16, 17, 18, 19, 20) and our present findings, we strongly advice to start GH treatment at a young age.

Lower $BMAD_{LS}$ SDS was associated with higher Cobb angle after 8 years of GH, and there was a trend toward an association between lower BMD_{TB} SDS and higher Cobb angle. A lower BMD was not the result of vitamin D deficiency, as all vitamin D levels were within the normal range. After 8 years of GH, BMD_{TB} SDS was lower in children with scoliosis compared to those without and $BMAD_{LS}$ SDS tended to be lower in children with scoliosis. Nakamura *et al*. did not find a difference in mean BMD between PWS patients with scoliosis and without scoliosis (36), but in the general population, a low BMD is associated with adolescent idiopathic scoliosis (AIS) (37). Our study shows the importance of BMD status in relation to scoliosis in children with PWS and we, therefore, advise to optimize BMD status in children and adolescents with PWS.

After 8 years of GH, we found no difference in height SDS between children who developed scoliosis and those without scoliosis (−0.02 and 0.78 SDS, respectively). This finding does not support the current hypothesis that catch-up growth after the start of GH increases the risk of developing scoliosis in children with PWS. It contrasts with findings in AIS, where growth acceleration during puberty has a major influence on the spinal curvature (38, 39). Our data suggest that hypotonia is a main cause of scoliosis in children with PWS and not the catch-up growth after the start of GH treatment. GH-treated children were taller and had higher trunkLBM:BSA ratio, suggesting that higher lean body mass of the trunk may counteract the effect of the GH-induced accelerated growth on the development of scoliosis in children with PWS.

Children treated with GH for 8 years had a higher pubertal stage than untreated age-matched controls, but a similar prevalence and severity of scoliosis. As the prevalence of scoliosis increases with pubertal stage in untreated children with PWS (8), we had expected to find a higher prevalence of scoliosis in the GH-treated children. Their more advanced pubertal stage might also explain the comparable fat mass% SDS, since the GH-untreated children were almost all still prepubertal. These results convincingly show that 8 years of GH treatment do not increase the prevalence and severity of scoliosis in children with PWS.

Our data showed no difference in prevalence and severity of scoliosis between boys and girls. In the general population, AIS is more frequent in girls (40). A greater risk for developing scoliosis was also reported for girls with PWS (22). In contrast, others showed that male PWS patients were more at risk of needing treatment for scoliosis (9). According to the PWSA survey, girls were more prone to develop scoliosis, but the scoliotic curve progression between sexes was equal (15). In our present study, in 103 children with PWS, sex did neither affect the prevalence of scoliosis nor the severity of scoliosis.

There was no significant difference in genetic subtype between the groups with and without scoliosis after 8 years of GH treatment, and Cobb angle was not associated with the genetic subtype. The PWSA survey among caregivers

of persons with PWS reported that patients with mUPD appeared to have an increased risk of developing scoliosis, with similar progression of the scoliotic curve between genetic subtypes (15). Our findings are in line with other studies reporting that genetic causes underlying PWS do not influence the frequency and severity of scoliosis (10, 11, 12).

Because all Dutch children with PWS are nowadays treated with GH from a young age, we could only include a small number of untreated children in the age-matched control group. An RCT would have been the first-choice design to investigate the long-term effects of GH on scoliosis in children in PWS, but it would nowadays be unethical to withhold children with PWS from GH treatment for 8 years. The PWS control group was prior to start of GH treatment and could, therefore, act as an age-matched untreated control group. At time of inclusion in this study, all patients visited our reference center. Physical therapy has for many years played a key role in our care for children with PWS, particularly for the prevention and treatment of scoliosis in PWS. The fact that the BMI SDS in the GH-treated and the control group is comparable supports our assumption that the groups are comparable and that selection bias is very unlikely.

In our Dutch PWS cohort, GH treatment was started at young age. Our GH-treated group is, therefore, still young after 8 years of GH treatment. Surgery for scoliosis in PWS occurs mostly at an older age (41). It might be that the prevalence of surgery or brace therapy in our study is an underestimation due to the relatively young age. Further longer-term studies on the effects of GH treatment on scoliosis development and progression in PWS are needed.

In conclusion, this is the first study investigating the effects of 8 years of GH treatment on the prevalence and severity of scoliosis in children with PWS until the age of 11 years. We found no adverse effects on the prevalence and severity of scoliosis in children with PWS. Based on these findings, scoliosis should neither be considered as a contraindication to start GH treatment nor as a reason to discontinue GH or to lower the GH dose in children with PWS who develop scoliosis. Because of the high prevalence of scoliosis in PWS, it is recommended to perform X-rays and physical examination on regular basis. Extra attention for BMD status of children with PWS is pivotal, as $BMAD_{LS}$ SDS is inversely associated with Cobb angle. Multidisciplinary care and start of GH treatment at a very young age will further optimize the treatment of children with PWS.

Declaration of interest
Investigator-initiated study for which AHK received an independent research grant from Pfizer.

Funding
This study was an investigator-initiated study, supported by an independent research grant from Pfizer. Pfizer was not involved in the conception or design of the study, nor in the collection, analysis or interpretation of data, writing the manuscript, or decision to submit the manuscript for publication.

Acknowledgements
The authors express their gratitude to all children and their parents for their enthusiastic participation in this study, to M van Eekelen and M Mondeel for their help and to all collaborating pediatric-endocrinologists, pediatricians, and other health care providers.

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Received 23 February 2021
Revised version received 5 April 2021
Accepted 21 April 2021