

Gender Bias in Children Receiving Growth Hormone Treatment

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Background: About twice as many boys than girls are treated with GH. Ascertainment bias is a possible explanation.

Hypotheses: For ascertainment bias, the gender least frequently treated should be relatively shorter, and in an unbiased population sample, equal numbers of boys and girls should be eligible for GH treatment.

Subjects and Setting: In 2007 a total of 1485 Australian children received GH (OZGROW database). Heights were also obtained from two recent unbiased surveys consisting of 3596 and 4794 Australian children.

Methods: Numbers of boys and girls treated with GH were determined for each treatment indication. Height *sd* scores (SDS) at first presentation for GH-treated boys and girls were assessed. Frequency of boys and girls from two unbiased populations with height SDS less than -2.326 were recorded.

Outcomes: Outcomes included gender frequencies and height SDSs. Hypotheses were formed before interrogation of preexisting databases.

Results: More boys than girls received GH ($P = 3.68 \times 10^{-20}$). By indication: biochemical GH deficiency ($P = 0.001$), cranial irradiation ($P = 0.002$), slow growing ($P = 2.09 \times 10^{-16}$), and chronic renal failure ($P = 0.061$). Approximately equal numbers of girls and boys were treated for hypoglycemia ($P = 0.543$). Slow-growing girls were relatively shorter than boys for ages spanning 4.50–8.49 yr ($P = 3.80 \times 10^{-4}$), but boys were relatively shorter in the 6.00- to 17.99-month age group ($P = 0.011$). Biochemical boys were relatively shorter than girls ($P = 0.023$). In the two unbiased surveys, boys outnumbered girls 11 to six and 16 to eight for height SDS less than -2.326 .

Conclusions: There is a gender bias in this GH-treated population. Ascertainment bias does not appear to be the major cause. (*J Clin Endocrinol Metab* 95: 1191–1198, 2010)

About twice as many boys than girls are treated with GH for conditions that result in short stature. This difference is consistently seen across many different countries and health systems (1–12). The reasons behind the gender bias in GH treatment have not been rigorously

investigated. Anecdotally it has been claimed that the more likely explanation is that boys are more frequently referred to growth clinics because it is socially more acceptable for girls to be short than boys (3, 4, 13). This conclusion was supported by a 1996 survey of U.S. pedi-

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Abbreviations: ANCNPA, Australian National Children's Nutrition and Physical Activity; CDC, Centers for Disease Control and Prevention; HKQ, Healthy Kids Queensland; IGFBP, IGF binding protein; LMS, generalized mean (M), generalized coefficient of variation (S), and power in the Box-Cox transformation (L); PBS, pharmaceutical benefit scheme; SDS, *sd* score.

atric endocrinologists. Given a number of identical hypothetical clinical scenarios, boys were 1.3 times more likely to be recommended for GH treatment than girls (14). Two studies, by August *et al.* (2) and Grimberg *et al.* (5), suggested that an ascertainment bias was likely to be occurring in their referred populations. This conclusion was based on the observation that girls were significantly shorter on average, in terms of height SD scores (SDS), than boys on referral, at least for some diagnostic categories. Recently Grimberg *et al.* (13) surveyed their prereferral, pediatric primary care practices and detected a lesser degree of gender bias than in the referred population thus supporting the ascertainment bias theory.

In addition, a retrospective study by Grimberg *et al.* (9) of data from the Pfizer International Growth Study came to the same conclusion. However, ascertainment bias is unlikely to be the whole explanation for the observed gender differences, even in the populations noted above. First, in these studies the significance of the difference in median height SDS (Mann-Whitney *U* test) between boys and girls was marginal [*e.g.* from Grimberg *et al.* (5), $P = 0.02$] in comparison with the *P* values obtained for frequency differences (χ^2 test) between genders ($P = 2.5 \times 10^{-7}$). It can easily be shown, by Monte-Carlo simulation, that if a shift in the threshold for ascertainment is the sole cause for the gender-frequency disparity that the *P* values should be essentially equivalent, with the Mann-Whitney *U* test *P* value usually being smaller. Second, when August *et al.* (2) used diagnostic categories of idiopathic, organic, and other, only the idiopathic category presented a significant SDS difference, whereas all categories comprised significantly more boys than girls. Lee *et al.* (10) investigated all new patients (526) to be evaluated for short stature at the Michigan Medical Center from 2001 to 2003 and found no evidence of ascertainment bias. Although boys constituted 63.9% of this group, which did not include Turner syndrome girls, they found no significant differences between boys and girls in height SDS or height deficit. Finally, two studies have been conducted in which heights were measured in a random sample of school-age children. Lindsay *et al.* (6) conducted serial measurements of more than 79,000 children aged 5–11 yr from randomly selected Utah schools to assess height and growth velocity. Similarly, Bao *et al.* (1) measured the heights of more than 100,000 6- to 15-yr-old school children in Beijing. Again, in both studies, boys were significantly overrepresented with respect to clinically short stature despite there being no referral bias possible in these studies.

Here we report a gender bias in favor of boys with respect to GH treatment in Australia. Using the methods advocated by the various authors mentioned above, we specifically investigated ascertainment bias as a possible cause in the Australian population.

Subjects and Methods

Subjects

OZGROW

All children receiving GH as part of the Commonwealth Government's Pharmaceutical Benefit Scheme (PBS) in Australia are recorded and their treatment monitored. Basic demographic and clinical information is collected on each patient at each visit and recorded in a national database (OZGROW). In all cases, informed consent is obtained from the patient's parent/guardian for these data to be used for research into, and evaluation of, GH use under the PBS program. Information is deidentified to maintain confidentiality whereas each patient is allocated an OZGROW database number. In this study patients who were currently recorded as receiving GH (as of December 3, 2007) were selected and had made at least one visit to a growth clinic in 2007. A total of 1485 children fulfilled these criteria and were included in the study. To receive GH, children were first referred to specialist pediatric growth clinics from general practitioners or pediatricians. These children were identified as having clinically short stature (less than the first centile) or slow growth (less than the 25th centile) or were diagnosed with a condition, *e.g.* renal failure, that may be treated with GH.

Healthy Kids Queensland (HKQ)

As part of the HKQ Survey 2006 (15), the height of participating children, 1737 boys and 1859 girls, was recorded. The children were 5–17 yr of age and enrolled in yr 1, 5, or 10 in government and nongovernment Queensland schools. Techniques were used to ensure that sampling was random within the target population. This survey should thus be free of any ascertainment bias in terms of the numbers of boys and girls observed to be below the first centile for height according to the Centers for Disease Control and Prevention (CDC) growth curves, *i.e.* the height criterion for eligibility to receive GH treatment.

2007 Australian National Children's Nutrition and Physical Activity (ANCNPA) survey

This survey included children aged 2–16 yr from all states and territories of Australia (16). Heights were measured for 2415 boys and 2379 girls. An initial target quota of 1000 children (50% boys and 50% girls) for each age group (2.00–3.99, 4.00–8.99, 9.00–13.99, and 14.00–16.99 yr) was set. This was supplemented in South Australia to allow more detailed estimates for that state, increasing the final survey sample by at least 400 approximately equally divided across the age groups. Households with children aged 2–16 yr were randomly selected using random digit dialing from all Australian states and territories in metropolitan, rural, and remote areas. The number of children included from each state was proportional to the population of children in that state (16). Thus, again, the ANCNPA survey should be free of any ascertainment bias in terms of the numbers of boys and girls observed to fall below the first centile for height. These data were accessed with permission from the Australian Social Sciences Data Archive (<http://assda.anu.edu.au/>).

Height measurements

For children in the OZGROW database, height and age was recorded at each visit to a growth center. Height was measured by experienced clinical nurses or pediatricians using standard

auxological methods. Heights were measured as part of the HKQ survey 2006 and the 2007 ANCNPA survey as described (15, 16). Height measurements were converted to SDS values according to sex and age at measurement using the generalized mean (M), generalized coefficient of variation (S), and power in the Box-Cox transformation (L) (LMS) procedure and the U.S. growth charts of the CDC (17).

Indications for subsidized GH treatment

To receive GH on the PBS, patients must satisfy one of the eligibility criteria or indications. These can be summarized as: 1) short stature and slow growth (slow growing), in which height less than the first centile [CDC growth charts (17)] with growth velocity less than the 25th centile for skeletal age and sex (18); 2) biochemical GH deficiency, in which short stature with peak serum GH concentration of 10 mU/liter or less in response to two stimulation tests or one test and other evidence of GH deficiency; 3) intracranial lesion or cranial irradiation, in which short stature, even if above the first centile for height is combined with GH deficiency and a low growth velocity; 4) hypoglycemia secondary to GH deficiency, and usually these patients are infants with a structural midline defect and multiple pituitary insufficiency; 5) Turner syndrome, in which height at or below the 95th centile on Turner-specific chart (19); and 6) chronic renal insufficiency, in which a glomerular filtration rate less than 30 ml/min per 1.73 m² body surface area with height less than the 25th centile (17) and growth velocity less than the 25th centile for bone age (18). For details of these eligibility criteria, see the Guidelines for the Availability of Human Growth Hormone as a pharmaceutical benefit (20).

Analyses and statistical procedures

Frequency differences between girls and boys were assessed by goodness-of-fit χ^2 analyses in which it was assumed the proportions of boys and girls under the age of 17 yr in Australia in 2007 were 0.51277 and 0.48723, respectively, based on Australian Bureau of Statistics estimates (21). It was hypothesized that if there is ascertainment bias in favor of boys being prescribed GH for short stature, the boys will, on average, be less severely affected by short stature on first presentation than similarly presented girls. This was the hypothesis used by August *et al.* (2) and Grimberg *et al.* (5) in making a conclusion of ascertainment bias in their studies. Differences between girls and boys in average height SDS at first visit to a growth center were assessed by *t* tests and Mann-Whitney *U* tests. Similar comparisons were made between boys and girls with respect to target heights and height deficit. Target heights are the predicted height SDS of an individual given parental height SDSs and were calculated as described by Hermanussen and Cole (22). The height deficit is the target height SDS minus the observed height SDS. Because some distributions were close to normality and others deviated significantly from normality, both parametric and nonparametric tests were performed for all comparisons but only valid results reported if significant. Distributions were tested for normality using the D'Agostino-Pearson omnibus test. Statistical tests were performed using Microsoft Excel (Richmond, CA) or SPSS 15.0 for Windows (Chicago, IL).

Unbiased samples of children's height SDSs were obtained from the HKQ and the 2007 ANCNPA surveys. Heights were converted to SDS values according to sex and age at measurement using the LMS procedure and the CDC growth charts (23). The number of children of each sex whose height fell below the first CDC centile (SDS < -2.326) was then calculated.

TABLE 1. Numbers of girls and boys receiving GH in 2007.

	Girls	Boys	P value
Total	674	811	0.009
Total not including Turner syndrome	453	811	3.68×10^{-20}
Indications			
Biochemical	98	157	0.001
Cranial irradiation	26	56	0.002
Chronic renal failure	19	34	0.061
Hypoglycemia	26	23	0.543
Slow growing	284	541	2.09×10^{-16}
Turner syndrome	221		

Results

Gender frequencies

Table 1 shows the difference in frequency of boys and girls receiving GH treatment in 2007. The total numbers, and total with Turner syndrome individuals removed, are given as well as the frequencies observed for each indication. Differences in frequency were tested using a χ^2 goodness of fit test as mentioned previously. Boys are seen to outnumber girls for all indications (biochemical 61.6%, cranial irradiation 68.3%, chronic renal failure 64.2%, and slow growing 65.6%, with the exception of hypoglycemia 46.9%). In total, boys constituted 54.6% of the clinical population, which is similar to the 55% reported from the Kabi International Growth Study database for Europe, Australia, and New Zealand (9).

Height SDS

The mean and median height SDS at the first visit to a growth center was calculated for boys and girls as shown in Table 2. These were calculated for total girls and total boys and for each gender within each indication. Means and medians were compared using two-sample *t* tests and Mann-Whitney *U* tests with *P* values as shown in Table 2. Significant departure from normality is represented by a D'Agostino-Pearson test with a *P* < 0.05. From Table 2 it is evident that for most indications, there is no significant difference in mean or median height SDS between boys and girls. However, a significant difference is seen between the height SDSs of total boys and girls. This significance disappears, however, when the largest single gender-specific condition, Turner syndrome, is removed. Turner's girls have a significantly greater median height SDS on first presentation than both total boys (*P* = 4.31×10^{-8}) and girls other than Turner's (*P* = 0.006). For the indications of biochemical and cranial irradiation, boys are significantly shorter (have a smaller median height SDS) than girls on first presentation (see Table 2).

TABLE 2. Mean and median height SDSs of boys and girls

	Girls			Boys			P value	
	Mean	Median	n	Mean	Median	n	TT ^a	MWU ^b
Total	-2.290	-2.390	673 ^c	-2.611	-2.590	811 ^c		7.09×10^{-5}
Total - Turner	-2.362	-2.522	452 ^c					0.073
Indication								
Biochemical	-1.600	-1.480	98	-2.092	-2.075	157	0.023	0.027
C. Irrad.	-0.549	-0.434	26	-1.557	-1.329	56 ^c		0.004
CRF	-1.971	-1.809	19	-2.361	-2.159	34 ^c		0.481
Hypoglyc.	-1.901	0.219	25	-1.000	-0.469	23	0.493	0.657
Slow grow.	-2.857	-2.886	284 ^c	-2.960	-2.779	541 ^c		0.863
Turner	-2.145	-2.125	221					4.31×10^{-8}

Comparison shown is with boys. Comparison with girls-Turner; MWU, $P = 0.006$. MWU, Mann-Whitney U test; n, number of individuals; C. irradi., cranial irradiation; CRF, chronic renal failure; Hypoglyc., hypoglycemia; Slow grow., slow growing; Turner, Turner syndrome.

^a P value for t test (TT); ^b P value for Mann-Whitney U test; ^c distribution is significantly different from normal as $P < 0.05$ for the D'Agostino-Pearson test for normality.

Where the D'Agostino-Pearson test identified a significant departure from normality, this was, in all cases, due mainly to kurtosis rather than skewness.

Target heights and height deficit

Target height and height deficit means and medians were calculated as described for height SDS (Supplemental Tables 1 and 2, published as supplemental data on The Endocrine Society's Journals Online web site at <http://jcem.endojournals.org>). No significant differences were observed except for that between total boys and total girls for target height. This, again, was due to the Turner's girls target heights being significantly greater than those of other girls ($P = 1.10 \times 10^{-4}$) and boys ($P = 2.44 \times 10^{-6}$).

Number of children below the first centile for height in unbiased samples

Analysis of heights of children from the HKQ survey revealed that 11 of 1737 boys and six of 1859 girls ($P = 0.175$) were below the first CDC centile for height. Sim-

ilarly, from the ANCNPA survey, 16 of 2415 boys and eight of 2379 girls ($P = 0.110$) were found to be below the first CDC centile for height.

Age at first presentation

From Table 3, it is evident that of children prescribed GH, girls are significantly younger ($P = 2.25 \times 10^{-5}$) at first presentation than boys. In particular, girls show a significantly earlier first presentation for the Biochemical indication ($P = 2.49 \times 10^{-4}$). The nature of these age differences can be appreciated from Figs. 1 and 2 that depict frequency polygons for age at first presentation for the biochemical and slow growing indications. For biochemical (Fig. 1), both genders peak at 6 months with the frequency of girls presented dropping sharply to 3.5 yr in which the frequency essentially stabilizes. Boys, however, show a less precipitous decline to 3.5 yr and then a definite peak at 4.5–5.5 yr followed by another at 11.5–12.5 yr. In both biochemical and slow growing, boys continue to be presented at later ages than girls as would be expected.

TABLE 3. Mean and median ages in months at first presentation

	Girls			Boys			P value	
	Mean	Median	n	Mean	Median	n	TT ^a	MWU ^b
Total	54.788	46.044	673 ^c	65.100	57.041	815 ^c		2.25×10^{-5}
Total - Turner	54.890	46.882	453 ^c					1.65×10^{-4}
Indication								
Biochemical	34.830	15.600	98 ^c	58.580	48.033	157 ^c		2.49×10^{-4}
C. irradi.	90.393	94.504	26	102.325	100.208	56	0.174	0.223
CRF	32.617	32.617	19	56.728	57.008	34	0.0389	0.075
Hypoglyc.	4.292	0.888	24 ^c	6.528	1.0192	23 ^c		0.744
Slow grow.	64.936	60.921	285 ^c	66.573	58.044	545 ^c		0.668
Turner	54.577	44.679	221 ^c					0.004

Comparison shown is with boys. Comparison with girls-Turner; MWU, $P = 0.003$. MWU, Mann-Whitney U test; n, number of individuals; C. irradi., cranial irradiation; CRF, chronic renal failure; Hypoglyc., hypoglycemia; Slow grow., slow growing; Turner, Turner syndrome.

^a P value for t test (TT); ^b P value for Mann-Whitney U test; ^c distribution is significantly different from normal as $P < 0.05$ for the D'Agostino-Pearson test for normality.

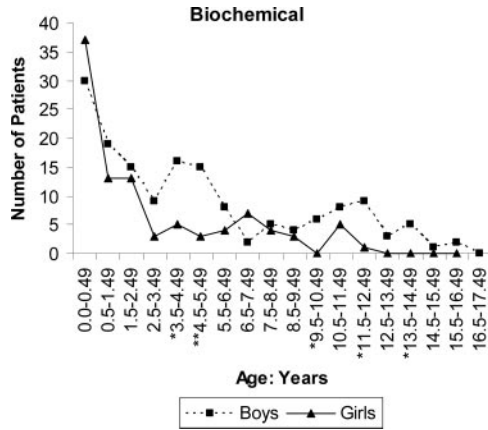


FIG. 1. Age at first presentation for boys and girls categorized by indication as biochemical. *, Frequency difference: 0.01 less than $P < 0.05$; **, frequency difference: $P < 0.01$.

Significant differences in frequency between boys and girls are indicated in Figs. 1 and 2.

Height SDS, target height, and height deficit in relation to age at first presentation

For the most common indications of biochemical and slow growing, it is possible to perform analyses within each age group of ages at first presentation (Figs. 3 and 4). Whereas it was observed that, overall, boys from the biochemical indication had a significantly smaller median height SDS than girls, a significant difference was seen in only one age group, 10.5–11.49 yr ($P = 0.028$). Conversely, for the slow growing indication, no overall difference was detected between the height SDSs of boys and girls. However, girls had smaller median height SDSs than boys for four contiguous age groups spanning 4.5–8.49 yr ($P = 3.80 \times 10^{-4}$). Offsetting this, boys were significantly shorter (smaller median height SDS) in the 0.5- to 1.49-yr age group ($P = 0.011$). No significant ($P < 0.05$) differences were seen in other age groups. The observed differ-

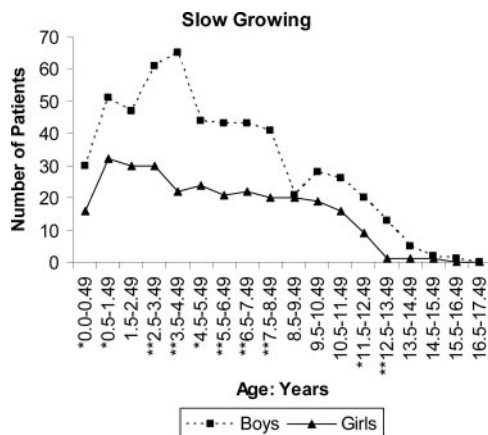


FIG. 2. Age at first presentation for boys and girls categorized by indication as slow growing. *, Frequency difference: 0.01 less than $P < 0.05$; **, frequency difference: $P < 0.01$.

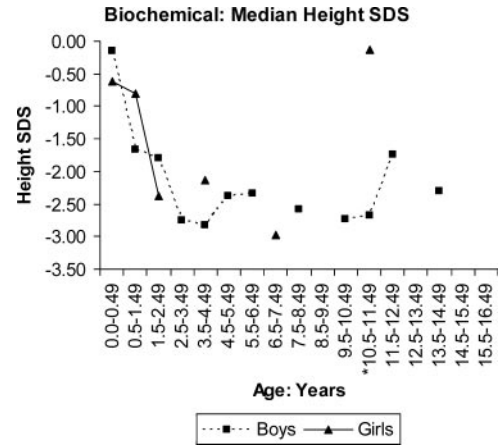


FIG. 3. Median height SDS for age at first presentation for boys and girls categorized by indication as biochemical. Medians shown for age groups with five or more observations. *, Median difference: 0.01 less than $P < 0.05$.

ences in height SDS over the 0.5- to 1.49-yr period and the 4.5- to 8.49-yr period were not repeated with respect to either target height or height deficit.

Discussion

We have shown that a gender bias exists in the 2007 cohort of children receiving GH on the PBS in Australia. This gender bias was seen across most indications (the diagnostic category for government subsidy) with the exception of hypoglycemia. The distribution of presentations in relation to age (Figs. 1 and 2) differs according to the indication on which GH was prescribed. When the indication is a biochemical deficiency of GH defined as a peak GH less than 10 mU/liter in response to provocative testing, there are increased numbers of boys first presenting at 4.5–5.5 yr and again at around 12.5 yr. As would be expected, from 13.5 yr no girls presented, whereas boys pre-

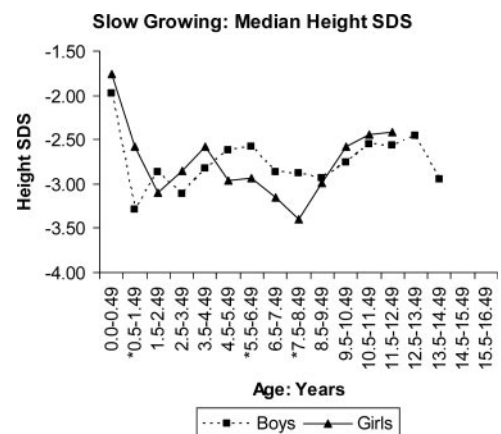


FIG. 4. Median height SDS for age at first presentation for boys and girls categorized by indication as slow growing. Medians shown for age groups with five or more observations. *, Median difference: 0.01 less than $P < 0.05$.

sented until 16.5 yr. With regard to the slow growing indication, the profile for boys and girls is similar but boys outnumber girls at all ages. Again, there is a relative peak of boys around 3.5–4.5 yr. These results are similar to those reported by Lee *et al.* (10), who looked at age at presentation for all children presented to the University of Michigan Medical Center for evaluation of poor growth or short stature irrespective of diagnosis or actual height. A similar spike was seen at 4–6 yr for boys as we observed for our biochemical (4.5–5.5 yr) and slow growing (3.5–4.5 yr) indications. However, Lee *et al.* (10) also reported an even more substantial peak of presentations of boys from 12 to 14 yr of age. We noted a smaller peak at a similar age (11.5–12.5 yr) in our biochemical boys. This difference may reflect the more inclusive nature of the cohort of Lee *et al.* (10) in which many boys may present with constitutional delay at this age but would not be determined eligible for GH in our OZGROW cohort.

It has been argued that ascertainment bias is the cause of the gender bias under discussion and that this can be detected by observation of those girls that are ascertained being significantly shorter, as determined by height SDS, than similarly ascertained boys (2, 5). From the results of this work, we would suggest that ascertainment bias may play a part but is in no way the full explanation for the gender bias seen. We found no evidence of ascertainment bias in favor of boys for the indications of biochemical, cranial irradiation, chronic renal failure, or hypoglycemia. In fact, we found boys to be significantly shorter, in terms of height SDS, than girls at presentation for biochemical and cranial irradiation. However, when the height SDS data were analyzed with respect to age at first presentation, it was observed that, for the slow growing indication, girls were shorter (smaller height SDS) in the age groups spanning 4.50–8.49 yr. In Australia, children begin school at around 5 yr of age, and it is possible that this, affording an easier comparison of heights with peers, leads to an impetus for parents to seek advice in regard to a short child. If this occurs more for boys than girls, ascertainment bias will occur. The fact that no significant difference was seen with respect to height deficit in this period could suggest that a comparison with peers is indeed occurring. However, there was no increase in boys presented, either absolute or in relation to girls, in this period, which might have been expected if the suggested scenario was true.

Ascertainment bias does not account, however, for the major peak in slow growing boys (and largest differential between boys and girls) presented between 2.50 and 4.49 yr immediately before this period. This period also coincides with the peak in presentations of boys prescribed GH under the biochemical indication. The second age bracket when boys presenting with the biochemical indication

outnumber girls, 11.5–12.49 yr, coincides with the onset of puberty. Delayed puberty may be a contributing factor because it is often considered to be more common in boys (24), although recently this view has been challenged (25). Unless provocative testing is carried out under sex-steroid priming, the peak GH level may be less than 10 mU/liter and the child could thus, erroneously, be classified as having GH deficiency. In addition, medications used in the treatment of attention deficit hyperactivity disorder, an increasingly treated condition that is more common in boys (26), can slow growth and delay puberty (27).

Height deficit has also been used to identify potential ascertainment bias (5). We found no significant differences between boys and girls with respect to height deficit or target heights in our population. Thus, again, on this evidence, ascertainment bias is unlikely to be the major cause of the observed gender bias.

This conclusion was also supported by observations of the numbers of boys and girls found to be below the first CDC centile for height in unbiased samples of Australian children constituting the HKQ and ANCNPA surveys. In both cases approximately twice as many boys than girls were seen to fall below the first CDC centile for height. This is the situation that would be expected in the general population if ascertainment bias played no role in generating the gender bias in our GH-treated cohort. These results were also in agreement with those seen in other unbiased population samples that were assessed for clinically defined shortness and/or GH deficiency (1, 6, 7, 11). An exception to these general observations is reported in a recent study by Grimberg *et al.* (13).

There are a number of possible explanations for the observed gender bias. First, there is ascertainment bias, as has been discussed. Second is a statistical anomaly due to the secular trend in height. Current height SDS distributions are different from those defined historically by the CDC. If the changes occurring over time are different between girls and boys, this may account for the frequency differences seen. Third, the requirement to interpret measures such as growth or GH levels may, in itself, be important. Certainly when congenital GH deficiency is severe enough to cause a set of clear, definitive clinical signs, as in Hypoglycemia, the number of boys and girls is essentially the same. Fourth, there is an effect related to a difference in the nature and timing of puberty or other prepubertal hormonal differences between boys and girls. We noted a peak of GH-deficient boys around puberty, whereas others reported a peak of referrals for short stature around puberty (10, 13) in which boys outnumber girls (10). Constitutional delay of growth and puberty has already been mentioned as a possible factor (24, 28). A differential effect between boys and girls in the secular

trend for height at the time of puberty, developmental tempo, is also possible (29–31). However, the largest differential in boys to girls referred for short stature or GH deficiency in this study occurred in the 4- to 5-yr age group. At this age sex steroids are at negligible concentrations in both boys and girls (32).

Before puberty, however, there are noted differences in serum levels of GH binding protein (GHBP) between boys (lower) and girls (higher), probably associated with body fat differences (33). Similarly, serum IGF-I and IGFBP-3 concentrations, and the IGF-I to IGFBP-3 ratio are higher in prepubertal girls than boys (34). An *IGF-1* mutation has been found to be associated with gender-specific differences in height (35), and IGF-I concentration is associated with trunk and leg growth in prepubertal boys but only trunk growth in girls (36). Fifth, a predisposition to the effects of GH deficiency or secretion abnormalities in boys due to their growth being more affected for a given GH deficit than girls. Growth response to GH is determined by not only concentration but also the frequency of pulsatile release of GH (37–40). As such it is difficult to correlate measures of endogenous GH with growth impairment. However, a differential sensitivity to GH between sexes is suggested from responses to GH treatment. In adults and pubertal girls, estrogen attenuates GH stimulation of IGF-I such that women require higher doses (41, 42), and in pubertal boys the IGF-I response to GH treatment is significantly greater than in pubertal girls (41). However, prepubertally there is also evidence of a differential response to GH treatment. A study by Cohen *et al.* (43) showed a linear response (growth and IGF-I concentration) to increasing doses of GH (0.175, 0.35, and 0.7 mg/kg·wk) for boys, whereas girls reached a plateau by the middle dose. Sixth is a predisposition in boys to factors resulting in poor growth. Deal *et al.* (44) noted a skewed sex ratio in children with hypothalamus/pituitary abnormalities detected by magnetic resonance imaging and suggested boys could be genetically more susceptible. And finally is a result of a difference in sensitivity to the pulsatile nature of GH release between boys and girls. At puberty, a marked difference is seen in pulsatility between genders (40). Before puberty the pulsatile nature of GH release does not appear to be significantly different between boys and girls (40), although it has been shown that the rhythmicity of pulses is significantly correlated with height in prepubertal boys with constitutional short stature (45).

We report a gender bias in favor of boys for all indications of GH treatment in Australia with the exception of hypoglycemia. Ascertainment bias does not appear to be the major cause of this gender bias, although it may contribute around the time of commencement of schooling.

Other factors that may differentially modulate the tempo of growth and development need to be considered.

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Disclosure Summary: I.P.H., M.H., and P.S.W.D. have nothing to disclose. C.S.C. is current chair and A.C. has served on the OZGROW committee advising APEG.

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