Growth Hormone plus Childhood Low-Dose Estrogen in Turner's Syndrome

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Present by R5 郭恬妮

Introduction

- *Turner's syndrome :*
  - partial or complete X-chromosome monosomy,
  - 1 in 2000 live female births
  - short stature, ovarian dysgenesis, and neurocognitive problems.
- The marked short stature (an average, untreated adult height 20 cm below that of the population) can be ameliorated by treatment with recombinant human growth hormone.
- But data from randomized, double-blind, placebo-controlled studies have been lacking.

- Ovarian failure: presents important treatment challenges because of uncertainty about the appropriate timing, route, formulation, and dosage for estrogen-replacement therapy.
- common clinical practice : postpone estrogen-replacement therapy until the mid-teens because estrogen reduces adult height by accelerating epiphyseal fusion.
- lower, more physiologic estrogen replacement during childhood might increase adult height and have other potential benefits.
- To test this hypothesis, we conducted a placebo-controlled trial to assess the effects on adult height of
  - growth hormone treatment alone
  - in combination with childhood ultra-low-dose estrogen, followed by pubertal estrogen-replacement therapy.

Methods

(Patients)

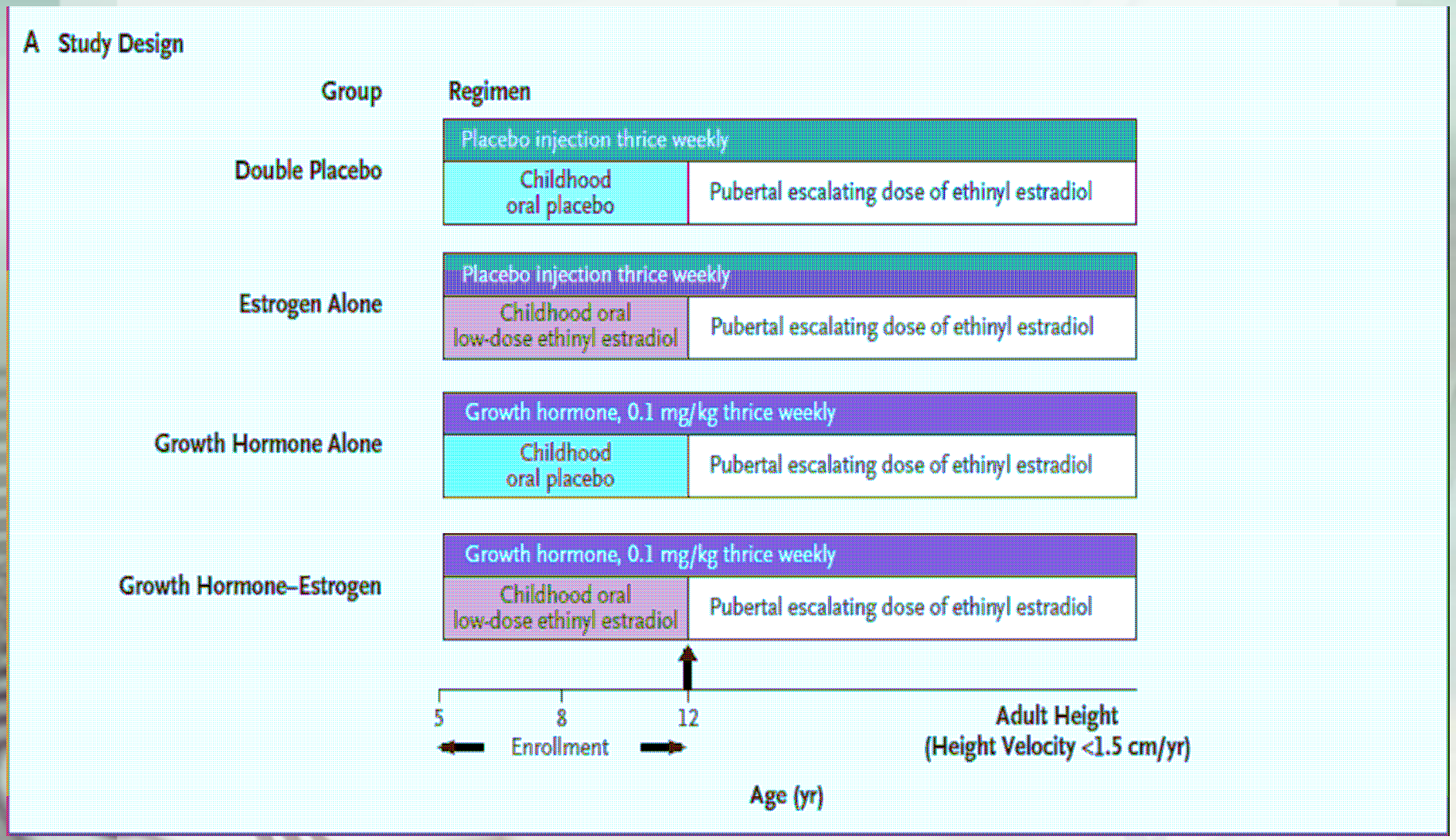
- recruited from referring physicians and pediatric endocrine clinics to the National Institutes of Health (NIH) and Thomas Jefferson University.
- Criteria for study entry:
  - a karyotype diagnosis of Turner's syndrome
  - age of 5.0 ~ 12.9 years, bone age of ≦12 years,
  - breast development at Tanner stage 1 to 2,
  - height ≦ the 10th percentile of the general population (measurements within 6 months before study)
  - adequate thyroid hormone–replacement therapy for at least 3 months in patients with hypothyroidism
  - no recent or concurrent treatment that might influence growth.

(Study Design)

- between 1987 and 2003 (enrollment closed in November 1996) → After FDA approval of growth hormone treatment for Turner's syndrome (in December 1996.

(Treatments and Procedures)

- An oral liquid medication (either placebo or estrogen [ethinyl estradiol]) QD and a subcutaneously injected medication (either placebo or growth hormone) three times/wks
- randomly assigned to one of four treatment groups:
  - placebo injection plus childhood oral placebo
  - placebo injection plus childhood oral low-dose estrogen
  - Growth hormone injection plus childhood oral placebo
  - Growth hormone injection plus childhood oral low-dose estrogen (Fig. 1).


A Study Design
Group
Regimen
Double Placebo
Placebo injection thrice weekly
Childhood oral placebo
Pubertal escalating dose of ethinyl estradiol
Estrogen Alone
Placebo injection thrice weekly
Childhood oral low-dose ethinyl estradiol
Pubertal escalating dose of ethinyl estradiol
Growth Hormone Alone
Growth hormone, 0.1 mg/kg thrice weekly
Childhood oral placebo
Pubertal escalating dose of ethinyl estradiol
Growth Hormone–Estrogen
Growth hormone, 0.1 mg/kg thrice weekly
Childhood oral low-dose ethinyl estradiol
Pubertal escalating dose of ethinyl estradiol
5
8
12
Enrollment
Adult Height
(Height Velocity <1.5 cm/yr)
Age (yr)

- From the time of the first study visit after the 12th birthday, all patients were to receive pubertal estrogen-replacement therapy according to an escalating dosage regimen:
  - 100 ng/kg/day →>12.0 and < 14.0 y/o
  - 200 ng /kg/day → >14.0 and < 15.0 y/o
  - 400 ng /kg/day → >15.0 and < 16.0 y/o
  - 800 ng /kg/day → >16 y/o

- Cyclic therapy with ethinyl estradiol and progestin (with the addition of medroxyprogesterone acetate for 10 days per month or by changing to an oral contraceptive containing 30 μg of ethinyl estradiol) was introduced after estradiol-induced menarche

- Patients were assessed at 6-month intervals until their annualized height velocity was less than 1.5 cm per year, which indicated that they had reached the protocol-specified adult height
- An additional height measurement was obtained approximately 1 year after study completion or after height velocity was less than 1.5 cm per year for patients who withdrew from the study before protocol completion.

(Efficacy and Safety Outcome Measures)

- The following evaluations were performed every 6 months: height (by stadiometer), weight, Tanner stage, and bone age
- The primary outcome measure was adult height, defined as the last height measured once the height velocity was less than 1.5 cm per year.
- Height and midparental (target) height standard-deviation scores were based on data from the Centers for Disease Control and Prevention.
- Safety was evaluated at each visit by means of physical examination, laboratory testing, and assessment for adverse events

(Statistical Analysis)

- We hypothesized that the adult height would be significantly higher for patients treated with growth hormone than for those given placebo injections.
- The efficacy analyses focused on two prospectively defined populations:
  - the adult-height population included all patients with a height measurement available after height velocity was less than 1.5 cm per year
  - the modified intention-to treat population comprised all patients whose height had been measured 120 days or more after randomization, irrespective of treatment duration.

Results
(Study Participants)

- 149 girls (5.0~12.5 y/o)
- Adult-height data were available for 91 patients (61%):
  - 84 met adult-height criteria while in the study
  - 7 withdrew from the study
- Apart from modest differences in chronologic age and bone age, the baseline characteristics were similar among the four study groups (Table 1).
- Karyotype distribution overall was 45,X, 73%; 45,X/46,XXiq, 8%; 45,X/46,XX, 5%; other, 14% (P = 0.63 among groups).

B **Randomization and Analysis Populations**

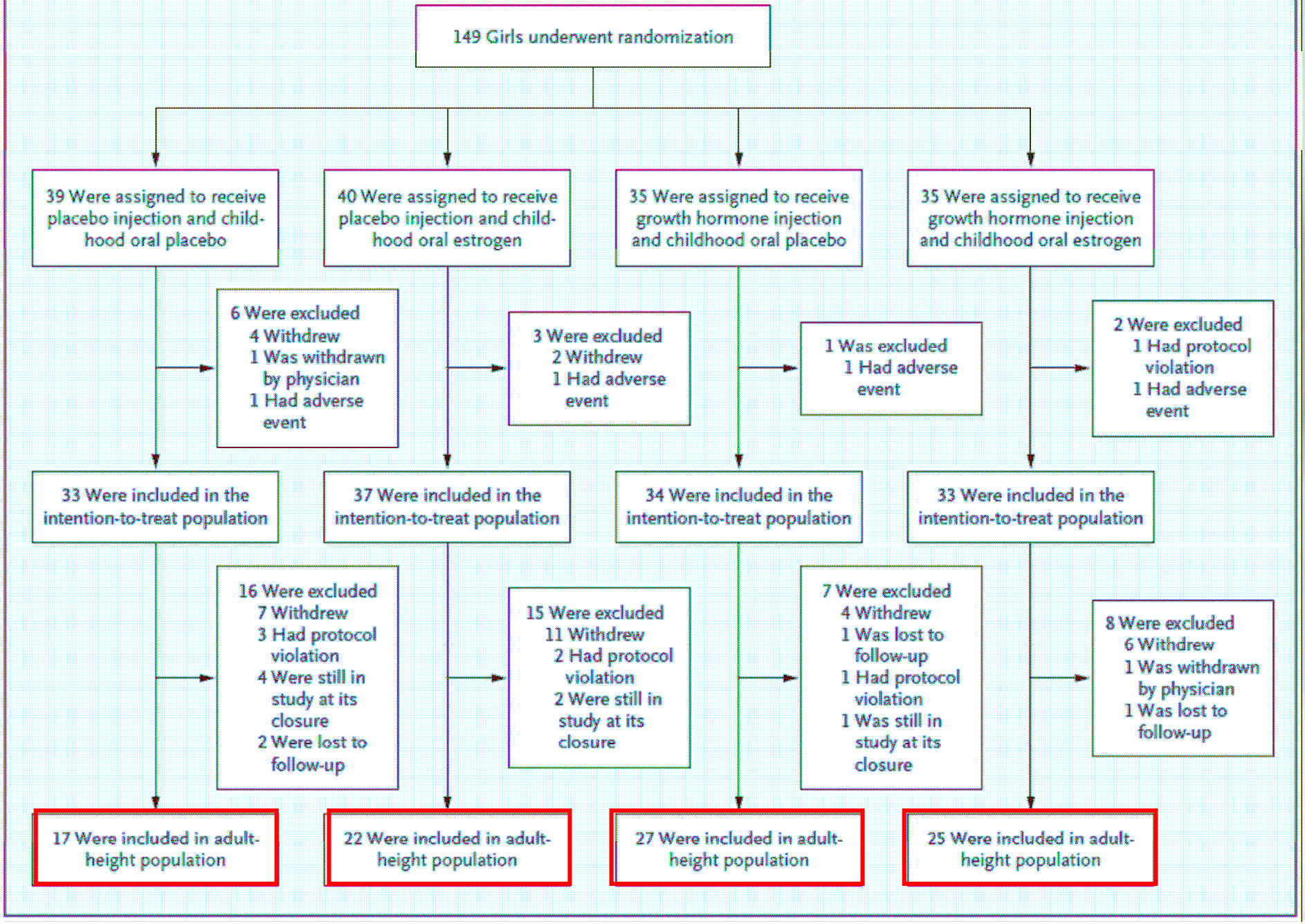


Table 1. Baseline and End-Point Characteristics of the Intention-to-Treat and Adult-Height Populations.*

Characteristic	Intention-to-Treat Population (N=121)					Adult-Height Population (N=91)				
	Double-Placebo Group (N=33)	Estrogen-Alone Group (N=37)	GH-Alone Group (N=34)	GH–Estrogen Group (N=33)	P Value	Double-Placebo Group (N=17)	Estrogen-Alone Group (N=22)	GH-Alone Group (N=27)	GH–Estrogen Group (N=25)	P Value
Baseline										
Chronologic age (yr)	7.5±2.3	8.5±2.7	8.2±2.6	9.3±2.5	0.041	8.2±2.6	9.5±2.4	8.4±2.7	9.6±2.6	0.14
Bone age (yr)	6.0±2.3	7.0±2.8	7.2±2.8	7.9±2.4	0.043	6.7±2.5	8.0±2.4	7.4±2.8	8.2±2.2	0.25
Bone-age delay (yr)	1.5±1.1	1.5±1.0	1.1±1.2	1.3±1.3	0.55	1.5±1.4	1.5±1.1	0.9±1.1	1.4±1.1	0.20
Height (cm)	109.7±12.2	112.1±13.6	112.5±13.2	117.3±11.3	0.10	113.5±13.1	117.0±11.9	114.0±13.3	119.1±11.1	0.39
Height SDS	−2.59±0.96	−3.01±0.74	−2.69±0.91	−2.71±0.81	0.18	−2.50±0.98	−2.96±0.72	−2.50±0.91	−2.66±0.82	0.25
Target height SDS	0.29±0.94	0.08±0.82	0.07±0.92	0.18±0.93	0.73	0.23±0.91	0.15±0.92	0.23±0.92	0.35±0.91	0.89
Weight (kg)	21.5±7.8	23.5±10.5	24.5±10.6	26.8±10.9	0.19	23.7±9.1	25.0±8.9	26.0±11.3	28.2±11.9	0.55
Weight SDS	−1.41±1.58	−1.75±1.32	−1.12±1.25	−1.20±1.24	0.21	−1.29±1.27	−1.82±1.21	−0.90±1.22	−1.16±1.30	0.09
Body-mass index†	17.4±4.0	17.8±4.2	18.6±4.3	18.8±4.7	0.49	17.6±3.0	18.3±4.3	19.1±4.6	19.3±5.3	0.60
End point										
Chronologic age (yr)	15.2±2.9	14.9±3.7	16.2±2.4	16.5±2.4	0.07	16.8±1.0	17.0±1.3	16.8±0.9	17.3±1.0	0.33
Bone age (yr)	13.8±3.4	13.7±3.6	14.9±2.8	15.1±2.6	0.15	15.9±1.0	15.7±1.3	15.6±1.3	15.9±1.0	0.72
Treatment duration (yr)	7.3±2.8	5.9±2.9	6.5±3.4	6.4±2.5	0.28	8.2±2.8	6.8±1.9	7.4±2.8	6.8±2.1	0.23
Height (cm)	138.1±12.3	134.4±14.0	144.8±11.2	146.8±11.3	<0.001	144.6±5.5	140.8±5.0	147.9±7.2	149.3±6.6	<0.001
Height SDS	−3.08±0.95	−3.40±0.74	−2.45±1.13	−2.18±1.00	<0.001	−2.81±0.85	−3.39±0.74	−2.29±1.10	−2.10±1.02	<0.001
Height SDS at 18 yr of age‡	−2.94±0.12	−2.97±0.10	−2.37±0.11	−2.00±0.10	<0.001	NA	NA	NA	NA	NA
Change in height SDS from baseline§	−0.41±0.10	−0.41±0.10	0.22±0.10	0.49±0.10	<0.001	−0.23±0.15	−0.42±0.13	0.26±0.12	0.58±0.12	<0.001
Weight (kg)¶	45.8±14.3	43.3±14.1	51.1±18.6	53.6±18.8	0.040	51.8±11.9	48.3±8.6	57.1±15.3	55.4±16.3	0.13
Weight SDS¶	−0.92±1.66	−1.14±1.47	−0.38±1.44	−0.36±1.40	0.07	−0.71±1.51	−1.06±1.52	−0.01±1.29	−0.32±1.27	0.058
Body-mass index¶	23.5±5.1	23.4±5.2	24.7±6.6	24.8±7.2	0.69	24.8±5.0	24.5±3.8	26.3±6.3	24.8±6.9	0.66

(Effect of Growth Hormone Treatment on the Standard-Deviation Score for Height)

Adult-Height Population

- The primary efficacy ANCOVA showed that the patients treated with growth hormone had greater adult height than did those who received placebo injections ($P<0.001$).
- This difference resulted from the overall decline in height standard-deviation score of 0.39 for the placebo-injection groups and the gain of 0.39 for the growth hormone–treated groups (Fig. 3A).

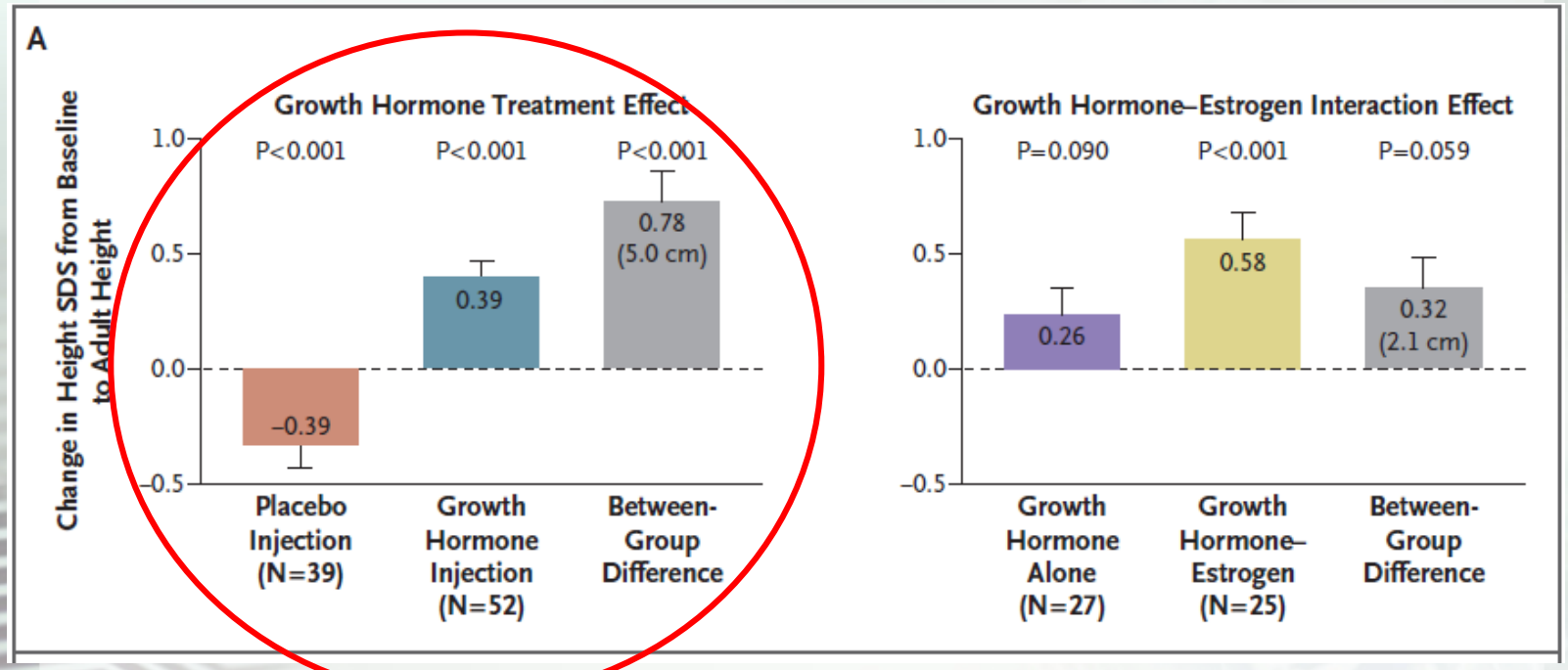
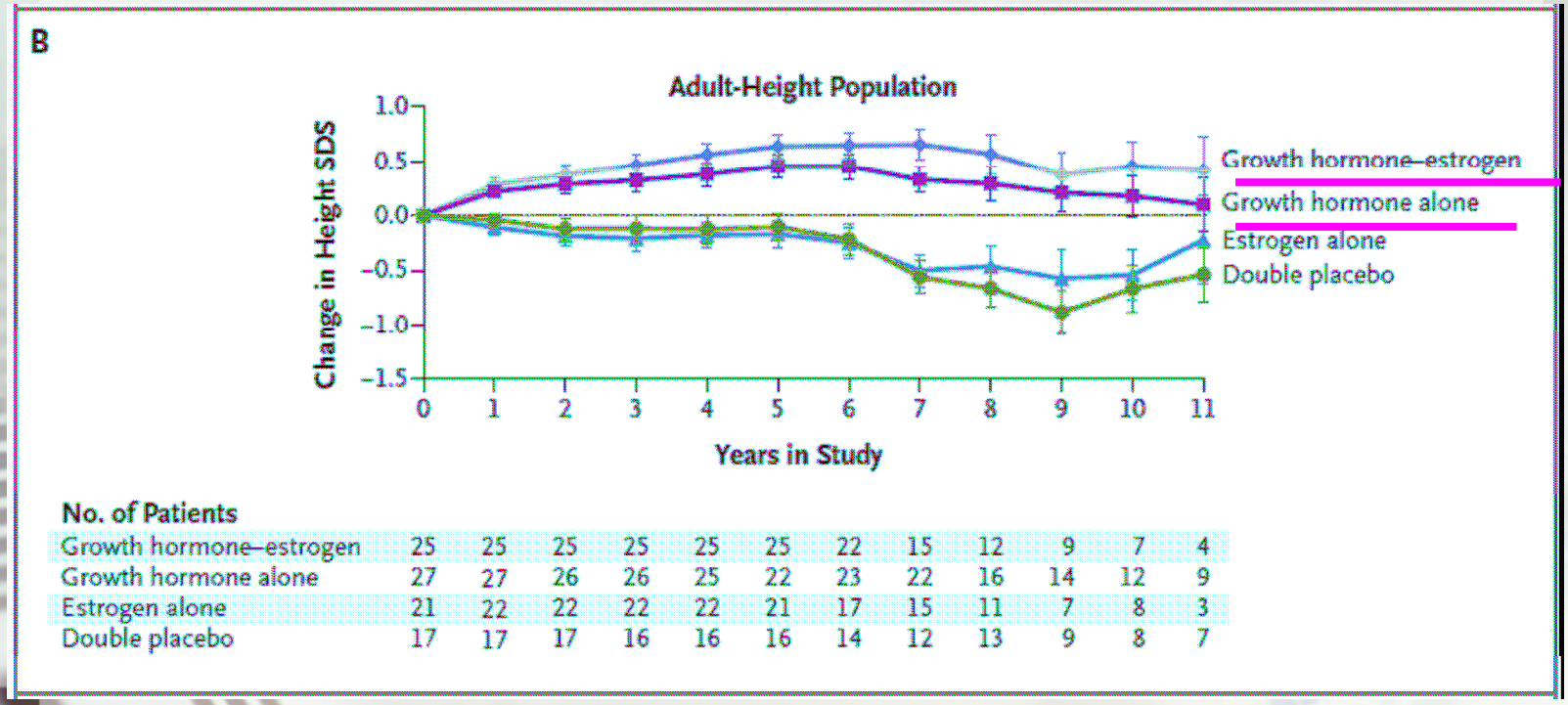

A
Change in Height SDS from Baseline to Adult Height
Growth Hormone Treatment Effect
P<0.001
P<0.001
P<0.001
1.0
0.5
0.0
−0.5
−0.39
0.39
0.78
(5.0 cm)
Placebo Injection (N=39)
Growth Hormone Injection (N=52)
Between-Group Difference
Growth Hormone–Estrogen Interaction Effect
P=0.090
P<0.001
P=0.059
0.26
0.58
0.32
(2.1 cm)
Growth Hormone Alone (N=27)
Growth Hormone–Estrogen (N=25)
Between-Group Difference

Table 1. Baseline and End-Point Characteristics of the Intention-to-Treat and Adult-Height Populations.*

Characteristic	Intention-to-Treat Population (N=137)					Adult-Height Population (N=91)				
	Double-Placebo Group (N=33)	Estrogen-Alone Group (N=37)	GH-Alone Group (N=34)	GH–Estrogen Group (N=33)	P Value	Double-Placebo Group (N=17)	Estrogen-Alone Group (N=22)	GH-Alone Group (N=27)	GH–Estrogen Group (N=25)	P Value
Baseline										
Chronologic age (yr)	7.5±2.3	8.5±2.7	8.2±2.6	9.3±2.5	0.041	8.2±2.6	9.5±2.4	8.4±2.7	9.6±2.6	0.14
Bone age (yr)	6.0±2.3	7.0±2.8	7.1±2.8	7.9±2.4	0.043	6.7±2.5	8.0±2.4	7.4±2.8	8.2±2.2	0.25
Bone-age delay (yr)	1.5±1.3	1.5±1.0	1.1±1.2	1.3±1.3	0.55	1.5±1.4	1.5±1.1	0.9±1.1	1.4±1.1	0.20
Height (cm)	109.7±12.2	112.1±13.6	112.5±13.2	117.3±11.3	0.10	113.5±13.1	117.0±11.9	114.0±13.3	119.1±11.1	0.39
Height SDS	−2.59±0.95	−3.01±0.74	−2.65±0.91	−2.71±0.81	0.18	−2.50±0.98	−2.96±0.72	−2.50±0.91	−2.66±0.82	0.25
Target height SDS	0.29±0.94	0.08±0.82	0.07±0.92	0.18±0.93	0.73	0.23±0.91	0.15±0.92	0.23±0.92	0.35±0.91	0.89
Weight (kg)	21.5±7.8	23.5±10.5	24.5±10.6	26.8±10.9	0.19	23.7±9.1	25.0±8.9	26.0±11.3	28.2±11.9	0.55
Weight SDS	−1.41±1.38	−1.75±1.32	−1.12±1.25	−1.20±1.24	0.21	−1.29±1.27	−1.82±1.21	−0.90±1.22	−1.16±1.30	0.09
Body-mass index†	17.4±4.0	17.8±4.2	18.6±4.3	18.8±4.7	0.49	17.6±3.0	18.3±4.3	19.1±4.6	19.3±5.3	0.60
End point										
Chronologic age (yr)	15.2±2.9	14.9±3.7	16.2±2.4	16.5±2.4	0.07	16.8±1.0	17.0±1.3	16.8±0.9	17.3±1.0	0.33
Bone age (yr)	13.8±3.4	13.7±3.6	14.9±2.8	15.1±2.6	0.15	15.9±1.0	15.7±1.3	15.6±1.3	15.9±1.0	0.72
Treatment duration (yr)	7.3±2.8	5.9±2.9	6.5±3.4	6.4±2.5	0.28	8.2±2.8	6.8±1.9	7.4±2.8	6.8±2.1	0.23
Height (cm)	138.1±12.3	134.4±14.0	144.8±11.2	146.8±11.3	<0.001	144.6±5.5	140.8±5.0	147.9±7.2	149.3±6.6	<0.001
Height SDS	−3.08±0.95	−3.40±0.74	−2.45±1.13	−2.18±1.00	<0.001	−2.81±0.85	−3.39±0.74	−2.29±1.10	−2.10±1.02	<0.001
Height SDS at 18 yr of age‡	−2.94±0.12	−2.97±0.10	−2.37±0.11	−2.00±0.10	<0.001	NA	NA	NA	NA	NA
Change in height SDS from baseline§	−0.41±0.10	−0.41±0.10	0.22±0.10	0.49±0.10	<0.001	−0.23±0.15	−0.42±0.13	0.26±0.12	0.58±0.12	<0.001
Weight (kg)¶	45.8±14.3	43.3±14.1	51.1±18.6	53.6±18.8	0.040	51.8±11.9	48.3±8.6	57.1±15.3	55.4±16.3	0.13
Weight SDS¶	−0.92±1.66	−1.14±1.47	−0.38±1.44	−0.36±1.40	0.07	−0.71±1.51	−1.06±1.52	−0.01±1.29	−0.32±1.27	0.058
Body-mass index¶	23.5±5.1	23.4±5.2	24.7±6.6	24.8±7.2	0.69	24.8±5.0	24.5±3.8	26.3±6.3	24.8±6.9	0.66

- The treatment effect accrued gradually, as shown by the progressive increases in the standard-deviation score for height in the growth hormone–treated groups versus the progressive declines in the corresponding placebo groups (Fig. 3B).



No. of Patients												
Growth hormone–estrogen	25	25	25	25	25	25	22	15	12	9	7	4
Growth hormone alone	27	27	26	26	25	22	23	22	16	14	12	9
Estrogen alone	21	22	22	22	22	21	17	15	11	7	8	3
Double placebo	17	17	17	16	16	16	14	12	13	9	8	7

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Bone age (yr)	6.0±2.3	7.0±2.8	7.[illegible]±2.8	7.9±2.4	0.043	6.7±2.5	8.0±2.4	7.4±2.8	8.2±2.2	0.25
Bone-age delay (yr)	1.5±1.1	1.5±1.0	1.[illegible]±1.2	1.3±1.3	0.55	1.5±1.4	1.5±1.1	0.9±1.1	1.4±1.1	0.20
Height (cm)	109.7±12.2	112.1±13.6	112.[illegible]±13.2	117.3±11.3	0.10	113.5±13.1	117.0±11.9	114.0±13.3	119.1±11.1	0.39
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Weight SDS	−1.41±1.58	−1.75±1.32	−1.1[illegible]±1.25	−1.20±1.24	0.21	−1.29±1.27	−1.82±1.21	−0.90±1.22	−1.16±1.30	0.09
Body-mass index†	17.4±4.0	17.8±4.2	18.[illegible]±4.3	18.8±4.7	0.49	17.6±3.0	18.3±4.3	19.1±4.6	19.3±5.3	0.60
End point										
Chronologic age (yr)	15.2±2.9	14.9±3.7	16.2±2.4	16.5±2.4	0.07	16.8±1.0	17.0±1.3	16.8±0.9	17.3±1.0	0.33
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Treatment duration (yr)	7.3±2.8	5.9±2.9	6.5±3.4	6.4±2.5	0.28	8.2±2.8	6.8±1.9	7.4±2.8	6.8±2.1	0.23
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Height SDS at 18 yr of age‡	−2.94±0.12	−2.97±0.10	−2.37±0.11	−2.00±0.10	<0.001	NA	NA	NA	NA	NA
Change in height SDS from baseline§	−0.41±0.10	−0.41±0.10	0.22±0.10	0.49±0.10	<0.001	−0.23±0.15	−0.42±0.13	0.26±0.12	0.58±0.12	<0.001
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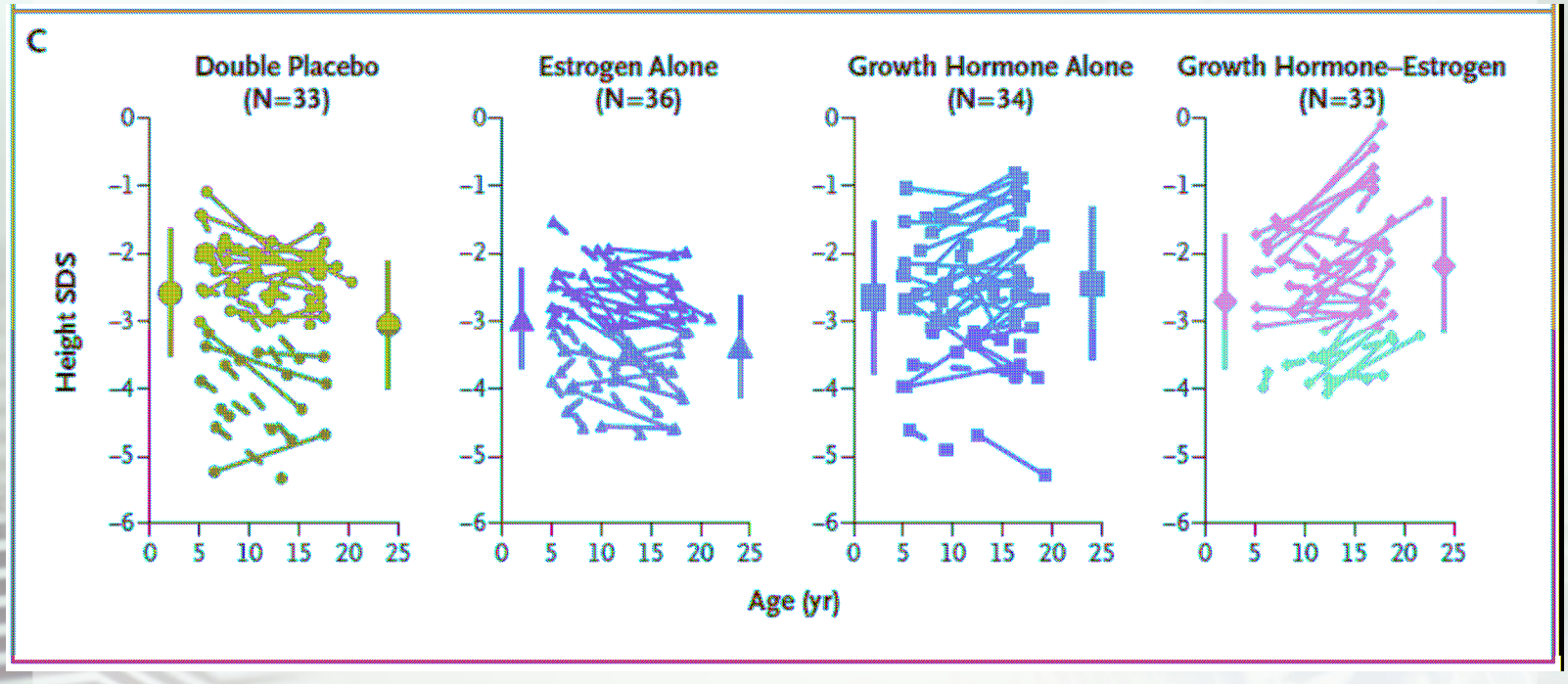
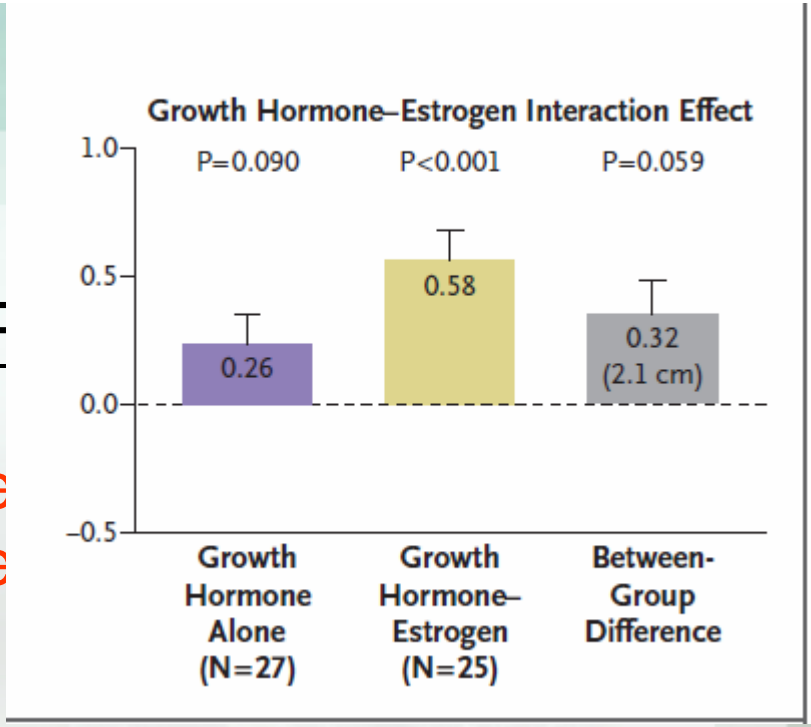
- Furthermore, repeated-measures analysis revealed a similar effect of growth hormone treatment, both on an annual basis and overall (an increase of 0.78±0.10 in the standard-deviation score [5.0 cm], P<0.001).
- Gains in height were observed for 15% of the double-placebo group, 32% of the estrogen-alone group, 65% of the growth hormone–alone group, and 79% of the growth hormone–estrogen group (P<0.001 for differences among groups) (Fig. 3C).
- Adult height was within the normal range (greater than –2 SD) for 27 of the 67 growth hormone–treated patients (40%) versus 3 of the 70 placebo-treated patients (4%) (P<0.001, by Fisher's exact test).

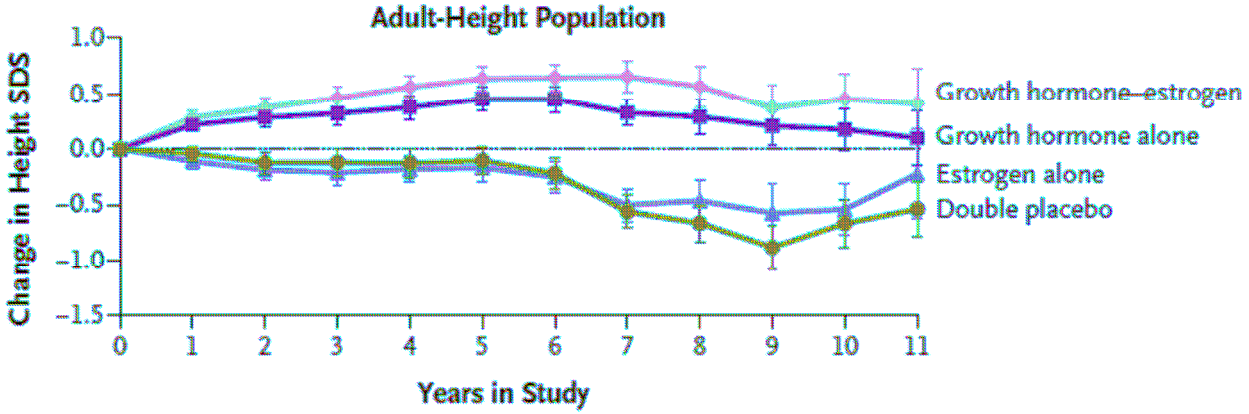

C
Double Placebo
(N=33)
Estrogen Alone
(N=36)
Growth Hormone Alone
(N=34)
Growth Hormone–Estrogen
(N=33)
Height SDS
0
−1
−2
−3
−4
−5
−6
0
5
10
15
20
25
Age (yr)

(Combined Effects of
and childhood eth
Adult-Height F

- The height gain was greate
  estrogen group than for the
  group (Fig. 3A)



B



No. of Patients												
Growth hormone–estrogen	25	25	25	25	25	25	22	15	12	9	7	4
Growth hormone alone	27	27	26	26	25	22	23	22	16	14	12	9
Estrogen alone	21	22	22	22	22	21	17	15	11	7	8	3
Double placebo	17	17	17	16	16	16	14	12	13	9	8	7

(Adverse Events)

- No deaths occurred during the study.
- Adverse events occurring during treatment were reported in all the patients (Table 2)
- Gynecologic disorders, pain, otitis media, scoliosis, and thyroid disorders were commonly reported adverse events.
- A slipped capital femoral epiphysis occurred in one patient, and the fasting blood glucose level was reported to be elevated in one patient, both of whom were in the growth hormone–estrogen group.
- Overall, there were no new or unexpected safety findings with respect to growth hormone or estrogen treatment in this study.

Table 2. Relevant Adverse Events That Occurred during Treatment among All Randomly Assigned Patients.*

Event	Double-Placebo Group (N = 39)	Estrogen-Alone Group (N = 40)	GH-Alone Group (N = 35)	GH–Estrogen Group (N = 35)	Total (N = 149)	P Value†	
						GH vs. Placebo Injection	Estrogen vs. Oral Placebo
	percent of patients						
Any event	100	100	100	100	100	1.00	1.00
Gynecologic disorders‡	43.6	60.0	54.3	60.0	54.4	0.62	0.20
Pain (no precipitant reported)	33.3	52.5	37.1	54.3	44.3	0.87	0.03
Otitis media	43.6	45.0	42.9	42.9	43.6	0.87	1.00
Scoliosis	30.8	40.0	48.6	40.0	39.6	0.27	1.00
Thyroid disorders	35.9	35.0	37.1	34.3	35.6	1.00	0.87
Edema	33.2	22.5	20.0	28.6	26.2	0.71	0.85
Lipid abnormalities	33.3	25.0	14.3	11.4	21.5	0.02	0.43
Nevi	25.6	17.5	14.3	28.6	21.5	1.00	0.84
Cardiac disorders	25.6	25.0	20.0	11.4	20.8	0.16	0.55
Lymphoid enlargement	15.4	12.5	17.1	5.7	12.8	0.81	0.23
Hearing disturbance	15.4	17.5	8.6	5.7	12.1	0.13	1.00
Bone disorders	15.4	10.0	2.9	5.7	8.7	0.09	0.78
Neoplasia§	5.1	12.5	8.6	2.9	7.4	0.54	1.00
Elevated blood glucose	0.0	0.0	0.0	2.9	0.7	0.47	1.00
Slipped growth plate	0.0	0.0	0.0	2.9	0.7	0.47	1.00

Discussion

- This randomized trial provides objective evidence concerning the efficacy and safety of growth hormone treatment initiated in mid-childhood for short stature associated with Turner's syndrome.
- As compared with placebo, growth hormone treatment given at a dose of 0.1 mg per kilogram three times per week increased adult height by approximately 5.0 cm over an average period of 7.2 years.

- There are probably multiple reasons for the somewhat smaller gain in height in our study than in some previous studies.
- the growth hormone regimen in our study, which was designed in the mid-1980s, may be considered suboptimal by current standards.
- We used a dose of 0.3 mg/kg/week, which is 20% lower than the currently approved dose for children with Turner's syndrome (0.375 mg/kg/week), and the thrice-weekly injection schedule in our study is less effective than daily administration.

- Our results showed a trend toward a synergistic growth benefit from childhood low-dose estrogen combined with growth hormone, as indicated by the greater height gain in the growth hormone–estrogen group than in the group given growth hormone alone.
- the synergy might be due to a local increase in responsiveness to IGF-1 or growth hormone mediated by ultra-low estradiol concentration acting directly at the skeletal growth plate.

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- Although estrogen replacement during mid childhood (prepuberty) may seem counterintuitive, this approach has a physiological rationale: the normal mid-childhood ovary is not entirely quiescent — plasma estradiol concentrations in healthy prepubertal girls, albeit low, are up to eight times as high as those in prepubertal boys.
- Furthermore, low-dose estrogen administration in childhood has beneficial effects on cognition and self-image in patients with Turner's syndrome
- Nonverbal processing speed, motor performance, and verbal and nonverbal memory were significantly better in estrogen-treated girls 5.0 to 12.0 years of age than in placebo recipients of the same age

- In addition to the timing, the dosage, type, and route of estrogen administration appear to influence its tissue-specific effects.
- We previously reported differential effects of varying doses of estrogen with respect to linear growth, vaginal maturation, and IGF-1 production.
- In the present study, we used an ultra-low-dose estrogen regimen.
- However, because our study was designed more than 20 years ago, the estrogen regimen has some limitations as a guide to current therapy.

- The protocol-specified dosages were excessive for most girls, with dose reductions required to minimize premature pubertal development and undue skeletal maturation.
- Finally, some girls with Turner's syndrome do not require estrogen supplementation because spontaneous pubertal development may occur (breast development observed in 13% of girls who received oral placebo during the childhood phase of this study)

- In conclusion, this placebo-controlled trial shows that growth hormone treatment initiated at an average age of 9 years increases adult height in girls with Turner's syndrome.
- Furthermore, the modest growth benefit observed with the combination of ultra-low-dose childhood estrogen replacement and growth hormone suggests that the practice of delaying estrogen therapy should be reconsidered.

- A regimen combining carefully individualized childhood estrogen replacement with growth hormone in girls with Turner's syndrome has the potential not only to optimize adult height but also to provide the neurocognitive and behavioral benefits of early estrogen administration.

Thanks for your attention!