Chapter 3. Results

Search Results

The results of the primary and supplemental Medline search strategies are shown in Appendix Tables 1 and 2 (Appendix 1). Including studies found from other sources, a total of 13,537 English language citations were reviewed. Screening of the abstracts and titles identified 825 articles potentially useful to address the three questions formulated by the Evidence-based Practice Center (EPC) staff, pediatric experts, and representatives of the Social Security Administration (SSA). These studies were retrieved for review. Detailed examination of these articles identified 31 studies that met inclusion criteria for Question 1, 31 studies for Question 2, and 53 studies for Question 3. Detailed data extraction was performed on these 115 studies. The results of the detailed data extraction are presented in the evidence tables.

Evidence Found Regarding Key Questions

Question 1. Is short stature (height less than the 5th percentile) as a result of a medically determinable impairment associated with severe functional limitations, according to, but not limited to, SSA's definition of disability?

See Evidence Table 1.

We reviewed 31 papers that provided information on functional abilities among children with short stature due to medically determinable impairments. As described in Evidence Table 1, a number of these papers provided analyses from the same samples of children. One study reported on different outcomes in two separate papers. Therefore, 24 papers from 23 studies are summarized here. Few studies explicitly examined functional impairment, per se. Data are reported on the association of short stature with academic achievement, intelligence, visual-motor skills, psychomotor development, and teacher-graded behavior. Detailed information on all 31 papers is reported in Evidence Table 1.

Association of Short Stature with Academic Achievement

Table 1. Mean Academic Achievement Scores of Children with Short Stature due to Medical Impairment

Author Year	Sample N (Controls)	Mean Height, SDS	Test	Mean Academic Achievement Score				Bias [a]	Quality [b]
				Math	Reading	Compre-hension	Spelling		
Isolated Short Stature or Constitutional Growth Delay									
Downie 1997	106 (119)	< –2	BAS	**40** [44]	**44** [48]				●
Wilson 1986	~350 (~6,400)	< –1.6	WRAT	**~92** [c]					◉
Stathis 1999	113 (3,178)	< –2	PPVT-R			**92** [97]		>IQ	○
Siegel 1994	90 (90)	–2.8	WRAT	96 **22% <80** [d]	102		98	>IQ	○
Kranzler 2000	34 (29) [e]	–1.7	KTEA	**105** [121]	**106** [115]	107 [114] Total [f]	104 [101]	>IQ	○
Kranzler 2000	27 (29) [g]	–2.7	KTEA	**107** [121]	**104** [115]	106 [114] Total [f]	105 [101]	>IQ	○
Gordon 1984	24 (23)	< –1.6	PIAT	103	102	102		Matched	○
Isolated Growth Hormone or Multiple Hormone Deficiency									
Siegel 1986	42	< –2	WRAT	**85**	96			>IQ	◉
Abbott 1982	11	ND	WRAT	83	88		85	No stat	◉
Siegel 1994	87 (90)	–2.7	WRAT	99	103		98	>IQ	○
Isolated Short Stature or Growth Hormone Deficiency									
Siegel 1998	25 (25)	–3.1	WRAT	102	105		99		●
Turner Syndrome									
Siegel 1998	22 (25)	–3.3	WRAT	90	98		95		●
Ross 1997	20 w/GH [h]	ND	WRAT		100			No stat	◉
Ross 1997	20 w/o GH [i]	ND	WRAT		97			No stat	◉
Russell-Silver Syndrome									
Lai 1994	25	–2.2	Neale [j]	Delay 7 mo	Delay 15 mo			No stat	○

Mean scores in bold were significantly different than normal population; results not in bold not significantly different, except as noted in bias column.
Mean score for normal population for each test is 100, unless otherwise noted in brackets

BAS = British Ability Scales; KTEA = Kaufman Test of Educational Achievement; Neale = Neale analysis of reading ability, British edition; PIAT = Peabody Individual Achievement Test; PPVT-R = Peabody Picture Vocabulary Test-Revised; WRAT = Wide Range Achievement Test

a Studies noted with ">IQ" excluded subjects with low intelligence quotient or known mental impairment excluded.
Studies noted with "No stat" did not perform statistical analysis comparing IQ of subjects to normal controls.
Study noted with "Matched" used controls that were matched for IQ among other factors.
b See Methods, Summary Tables, Study Quality.
c Significant correlation between height and reading and arithmetic subtests of WRAT. WRAT score reported graphically.
d Significantly more children with ISS had an arithmetic score less than 80 than controls (7%).
e Non-referred subjects, shortest 10% at school.
f Control children had math and reading scores of 121 and 115, respectively
g Referred to endocrinology clinic for short stature.
h Subjects with Turner syndrome, treated with growth hormone
i Subjects with Turner syndrome, not treated with growth hormone
j Neale assessment of reading ability measured reading competence. No data clearly provided on how arithmetic competence was measured.

Eleven studies evaluated academic achievement in approximately 996 children with short stature as a result of a medically determinable impairment (Table 1). Six studies evaluated children with isolated short stature (ISS) or constitutional growth delay (CGD); three evaluated children with isolated growth hormone deficiency (GHD) or multiple hormone deficiency (MHD); one evaluated children with either ISS or GHD; two evaluated children with Turner syndrome; and one evaluated children with Russell-Silver syndrome.

Isolated Short Stature / Constitutional Growth Delay

Six studies evaluated academic achievement in approximately 744 children with ISS or CGD. Academic achievement was measured with a variety of tests, including the Wide Ranging Achievement Test (WRAT), the Peabody Picture Vocabulary Test – Revised (PPVT-R), the British Ability Scales (BAS), the Kaufman Test of Educational Achievement (KTEA), and Peabody Individual Achievement Test (PIAT). The scores of the children with short stature were all compared to controls. All studies analyzed prospective data. Two were longitudinal, four were cross-sectional. One study was of good quality, one was of fair quality, and four were rated poor quality because they excluded children with low intelligence quotients (IQ) for analyses of cognitive function or analyzed cognitive function despite matching subjects and controls by IQ.

In four prospective, longitudinal papers (Downie, Mulligan, McCaughey, et al., 1996; Downie, Mulligan, Stratford, et al., 1997; Voss, Bailey, Mulligan, et al., 1991; Voss and Mulligan, 1994) children with ISS were tested repeatedly at different ages. In the final analysis (Downie, Mulligan, Stratford, et al., 1997) 106 13 year old children with ISS had significantly lower reading and mathematics attainment scores on BAS than the same aged controls. The scores remained significantly lower than for controls after adjusting for social class. However the absolute difference in scores were within 1 standard deviation (SD) of the average control subjects' scores.

Wilson, Duncan, Dornbusch, et al. (1986) reported on a prospective, longitudinal study of 6,768 adolescents, aged 12 to 17 years old, who were in Cycle III of the National Health Examination Survey from 1966-1970. Approximately 350 of these children had height below the 5th percentile. There was a small but significant correlation between standardized height and WRAT score. Mean WRAT score for different height percentile groups of children rose consistently with height. Similar results were found for the same children when they were 6 to 11 years old.

Stathis, O'Callaghan, Williams, et al. (1999), in a prospective, cross-sectional analysis of 113 4 to 6 year old children with height less than the 3rd percentile, found that receptive vocabulary, measured with PPVT-R, was significantly lower among both boys and girls than among children of normal height. However, the absolute differences in scores were within 1 SD of the mean for normal children. The value of this study is limited, though, since 14 children with PPVT-R scores less than 50, with cerebral palsy, or with other neurological disorders were excluded from the analysis.

In a prospective, cross-sectional study, Siegel, Clopper, Stoppani, et al. (1994) evaluated WRAT-R in 90 children with ISS with a mean age of 11 years old. There were no significant differences between mean reading, spelling, and math scores in the children with ISS and the normal controls. However, significantly more ISS children (22 percent) had a skill deficit in mathematics (score less than 80) compared to both GHD children (10 percent) and normal

children (7 percent). The value of this study is limited, though, since children with "known mental impairments" were excluded.

Kranzler, Rosenbloom, Proctor, et al. (2000) evaluated two groups of 6 to 12 year old children with ISS in a prospective, cross-sectional study. One group consisted of 34 children who were identified in local public schools as being in the shortest 10 percent of the class ("non-referred"). The second group consisted of 27 children with ISS who had been referred to pediatric endocrinology because of short stature. Among both groups, children with ISS scored significantly lower than normal height controls on both mathematics and reading KTEA. For both groups, spelling and composite achievement scores were similar to controls. However, mean scores for all groups of children were above standardized norms. The value of this study is limited, though, since children with IQ less than 75 were excluded.

Gordon, Post, Crouthamel, et al. (1984) evaluated 24 6 to 12 year old children with height less than the 5th percentile due to CGD in a prospective, cross-sectional study. The children had normal scores on math, reading recognition, and comprehension PIAT. These scores were not significantly different from controls; however the controls were matched for Full Scale IQ.

Growth Hormone Deficiency / Multiple Hormone Deficiency

Three studies evaluated academic achievement in children with GHD and multiple hormone deficiency (MHD). A total of 140 children were evaluated by WRAT. The test results were either compared to controls or population norms. Two of the studies (Siegel, Clopper, Stoppani, et al., 1994; Siegel and Hopwood, 1986) excluded subjects with low IQ or known mental impairment. All were prospective; one was longitudinal, two were cross-sectional. Two were rated as fair quality; one poor.

Siegel and Hopwood (1986) evaluated 42 children with short stature due to hypopituitarism (28 with isolated GHD and 14 with MHD) and a mean age of 12 years. Academic achievement was evaluated by WRAT and was compared to population norms in a prospective, cross-sectional study. A significant decrease in math scores was found in the hypopituitary children but no difference in reading scores. The children with hypopituitarism had WRAT scores within 1 SD of the mean. Of note, the study excluded one child with hypopituitarism because severe mental retardation prevented using some of the tests.

Eleven children, aged 4 to 18 years old, with short stature due to GHD and/or other pituitary hormone deficiency were evaluated in a longitudinal, prospective study by Abbott, Rotnem, Genel, et al. (1982). Their academic achievement tests (WRAT) were less than the mean but within 1 SD of the mean (except for WRAT arithmetic scores, which were within 1.5 SD of the mean) when compared to population norms.

Siegel, Clopper, Stoppani, et al. (1994) evaluated 87 children with height less than the 3rd percentile either due to GHD and mean age of 11 years. The children were compared to average stature control children matched for age, sex and socioeconomic status in a prospective, cross-sectional study. Academic achievement in the children with short stature tested by the WRAT-R test was not significantly different from the results of the controls. However, children with known mental impairment were excluded from this study.

Combined Isolated Short Stature and Growth Hormone Deficiency

One study evaluated academic achievement with WRAT in 25 girls with a mean age of 10 years who had either ISS or short stature due to GHD. In a longitudinal, prospective study, Siegel, Clopper, and Stabler (1998) compared the girls with ISS/GHD to a group of girls with short stature due to Turner syndrome and a control group of girls with average stature. The girls with short stature had similar academic achievement testing, measured by WRAT, compared to control girls of average stature and girls with Turner syndrome. These results were from the baseline study for an evaluation of the effects of growth hormone on girls with short stature. The study was of good quality.

Turner Syndrome

Two studies evaluated academic achievement (WRAT) in 62 girls with short stature secondary to Turner syndrome. The test results were compared to population norms or to controls. Both were longitudinal, prospective studies. One was of good quality; one of fair quality.

Siegel, Clopper, and Stabler (1998) tested 22 girls with Turner syndrome with a mean age of 10 years for academic achievement (WRAT). Test scores for the girls with Turner syndrome were not significantly different from control girls of average stature. This was a longitudinal, prospective study.

In a prospective study that was part of a double-blind randomized controlled trial of growth hormone for the treatment of Turner syndrome, Ross, Feuillan, Kushner, et al. (1997) evaluated 40 girls with a mean age of 9 years. The study found that girls with Turner syndrome had WRAT scores that were at or just below the population average, whether they received growth hormone or a placebo.

Russell-Silver Syndrome

One study evaluated academic achievement in 25 children with Russell-Silver syndrome. Lai, Skuse, Stanhope, et al. (1994) tested children aged 6 to 12 years old with the clinical diagnosis of Russell-Silver syndrome with the Neale analysis of reading and an undefined test of arithmetic competence in a prospective, cross-sectional study. The children with Russell-Silver syndrome were found to have substantial delays in both reading and arithmetic competence. Because of the poor reporting and the lack of statistical analysis, the study was graded poor quality.

Short Stature and Academic Achievement

Six studies examined academic achievement among children with ISS or CGD. Four found that the short children had significantly lower scores on various tests of academic achievement than normal height children. Two studies found that, overall, short children had similar scores as normal controls. Among all the studies, short children scored either above population norms or within 1 SD of normal scores. One study found that short children were significantly more likely to have a skill deficit (in mathematics) than normal height children even though mean scores

were similar. Three of the studies excluded children with low IQ and a fourth matched short children with normal children with similar IQs.

Three studies examined academic achievement among children with GHD or MHD. One found that short children had significantly lower mathematics test scores than normal height controls. All three found that test scores among short children were within 1.5 SD of population means. One study excluded one child with severe mental retardation; another excluded children with low IQs.

A single study examined academic achievement among children with either ISS or GHD. These children scored at or above population means.

Two studies examined academic achievement among children with Turner syndrome. One study found no significant difference between girls with Turner syndrome and controls. Both studies found that girls with Turner syndrome scored within 1 SD of population norms.

One study examined academic achievement among children with Russell-Silver syndrome. These children were found to have substantial delays in both reading and arithmetic competence.

Association of Short Stature with Intelligence

Table 2. Mean Intelligence Quotients of Children with Short Stature due to Medical Impairment

Author Year	Sample N (Controls)	Mean Height, SDS	Mean IQ Full	Mean IQ Verbal	Mean IQ Performance	Bias [a]	Quality [b]
Isolated Short Stature or Constitutional Growth Delay							
Downie 1997	106 (119)	<–2	**103** [d]				●
Wilson 1986	~350 (~1800)	< –1.6	**~93** [c]				◐
Rovet 1985	25	< -2	101	98	102	No stat	◐
Siegel 1994	90 (90)	–2.8	107 **18%<90** [e]			>IQ	○
Kranzler 2000	34 (29) [f]	–1.7	105	104	105 Matrices	>IQ	○
Kranzler 2000	27 (29) [g]	–2.7	103	**101** [h]	106 Matrices	>IQ	○
Gordon 1984	24 (23)	< –1.6	108	107	108	Matched	○
Holmes 1985	21	<–2		104		No stat	○
McCauley 1987	16	–4.5		100	108	>IQ No stat	○
Isolated Growth Hormone or Multiple Hormone Deficiency							
Siegel 1986	42	< -2		**94**	**94**	>IQ	◐
Frisch 1990	23	–2.5	**115**	104	**114**		◐
Meyer-Bahlburg 1978	13 w/GHD	–3.7	101			No stat	◐
Abbott 1982	11	ND	88	89	89	No stat	◐
Meyer-Bahlburg 1978	9 w/MHD	–4.0	102			No stat	◐
Siegel 1994	87 (90)	–2.7	110 **9%<90** [e]			>IQ	○
Holmes 1985	17	< –2		97			○

(continued)

Table 2. cont.

Author Year	Sample N (Controls)	Mean Height, SDS	Mean IQ Full	Verbal	Performance	Bias [a]	Quality [b]
Combined Isolated Short Stature, Constitutional Growth Delay, and Growth Hormone Deficiency							
Siegel 1998	25 (25)	–3.1	105				●
Steinhausen 1976	32	–3.7	103	102	103	No stat	◉
Pollitt 1964	13	–6.9	103	103	102		◉
Young-Hyman 1986	27	< –2	110			>IQ	○
Turner Syndrome							
Siegel 1998	22 (25)	–3.3	102				●
Ross 1997	20 w/ GH [i]	ND	98	104	92	No stat	◉
Ross 1997	20 w/o GH [j]	ND	99	102	96	No stat	◉
Robinson 1983	9 (17)	ND	**87**	93	**83**		◉
McCauley 1987	17	–5.0		95	91	>IQ No stat	○
Holmes 1985	9	< –2		103		No stat	○
Russell-Silver Syndrome							
Lai 1994	25	–2.2	**86**	**89**	**84**		◉
Tanner 1975	11	–2.6	103			No stat	○
Angehrn 1979	9 [k]	–4.4	91			No stat	○
Combined Isolated Short Stature and Russell-Silver Syndrome							
Skuse 1996	22 (21)	–2.5	**96**	95	**97**	>IQ	○

Mean IQ results in bold were significantly different than normal population; results not in bold not significantly different, except as noted.
w/ GHD = Children with growth hormone deficiency; w/MHD = Children with multiple hormone deficiency

a Studies noted with ">IQ" excluded subjects with low IQ or known mental impairment excluded.
Studies noted with "No stat" did not perform statistical analysis comparing IQ of subjects to normal controls.
Study noted with "Matched " used controls that were matched for IQ among other factors.
b See Methods, Summary Tables, Study Quality.
c Significant correlation between height and IQ. IQ value reported graphically.
d Controls had mean IQ of 109
e Significantly more children with ISS and with GHD had IQ < 90 than controls (3%).
f Non-referred subjects, shortest 10% at school.
g Referred to endocrinology clinic for short stature.
h Controls had mean verbal IQ of 110
i Subjects with Turner syndrome, treated with growth hormone
j Subjects with Turner syndrome, not treated with growth hormone
k 5 additional children who were not tested were "probably of normal intelligence." No data on 6 other children in study.

Twenty-one studies evaluated IQ in approximately 1,156 children with short stature as a result of a medically determinable impairment (Table 2). Eight studies evaluated children with ISS or CGD; six evaluated children with GHD or MHD; four evaluated children with either ISS, GHD or GHD; five evaluated children with Turner syndrome; three evaluated children with Russell-Silver syndrome; and one evaluated children with either ISS or Russell-Silver syndrome.

Isolated Short Stature / Constitutional Growth Delay

Eight studies evaluated intelligence in children with ISS or CGD with approximately 693 subjects. Tests included Wechsler Intelligence Scale for Children (WISC), British Ability Scales (BAS), Kaufman-Brief Intelligence Test (K-BIT), and Slosson Intelligence Test (SIT). Test results were either compared to controls or to population norms. All studies analyzed prospective data. Three were longitudinal; five were cross-sectional. One study was of good quality; two were of fair quality; and five were of poor quality, primarily because of excluding subjects with low IQ or known mental impairment.

In four prospective, longitudinal papers (Downie, Mulligan, McCaughey, et al., 1996; Downie, Mulligan, Stratford, et al., 1997; Voss, Bailey, Mulligan, et al., 1991; Voss and Mulligan, 1994) children with ISS were tested repeatedly at different ages. In the final analysis (Downie, Mulligan, Stratford, et al., 1997) 106 13 year old children with ISS had IQ measured with BAS. Children with short stature had significantly lower IQ than normal height controls, even after adjusting for socioeconomic status. However, mean IQ among study subjects was greater than 100.

Wilson, Duncan, Dornbusch, et al. (1986) reported on a prospective, longitudinal study of 6,768 adolescents, aged 12 to 17 years old, who were in Cycle III of the National Health Examination Survey from 1966-1970. Approximately 350 of these children had height below the 5th percentile. These children had significantly lower IQ scores, measured by WISC, than the general population mean. IQ was significantly correlated with height for all children. However, average WISC scores for short children were within 1 SD of the mean. Similar results were found for the same children when they were 6 to 11 years old.

Rovet, Netley, and MacLeod (1986) evaluated 25 boys with a mean age of 14 years who had ISS in a prospective, cross-sectional study. Verbal, performance and full-scale IQs, measured by WISC, were similar to the population average.

In a prospective, cross-sectional study Siegel, Clopper, Stoppani, et al. (1994) evaluated intelligence with SIT in 90 children with ISS and a mean age of 11 years old. There were no significant differences between mean IQ in the children with ISS and the normal controls. However, significantly more ISS children (18 percent) had an IQ less than 90 than normal children (3 percent). The value of this study is limited, though, since children with "known mental impairments" were excluded.

Kranzler, Rosenbloom, Proctor, et al. (2000) evaluated two groups of 6 to 12 year old children with ISS in a prospective, cross-sectional study. One group consisted of 34 children who were identified in local public schools as being in the shortest 10 percent of the class ("non-referred"). The second group consisted of 27 children with ISS who had been referred to pediatric endocrinology because of short stature. Among both groups, children with ISS had similar composite and matrices IQ measured by K-BIT as normal height controls. Non-referred short children had similar verbal IQ as controls, while referred short children had significantly lower IQ than controls. However, the mean verbal IQs for all groups of children were above 100. The value of this study is limited, though, since children with IQ less than 75 were excluded.

Gordon, Post, Crouthamel, et al. (1984) evaluated 24 6 to 12 year old children with height less than the 5th percentile due to CGD in a prospective, cross-sectional study. The children had above normal scores on full, verbal, and performance IQ by WISC. These scores were not significantly different from controls; however the controls were matched for Full Scale IQ.

Holmes, Karlsson, and Thompson (1985) evaluated 21 children with short stature due to CGD who were age 12 years at the start of a prospective longitudinal study. The verbal IQs, measured by WISC, of these children were slightly above the population mean. No statistical analysis was performed and the study suffered from incomplete reporting.

In a prospective, cross-sectional study, McCauley, Kay, Ito, et al. (1987) evaluated 16 girls with ISS and a mean age of 13 years. These girls had scored at or above the population mean for both verbal and performance IQ measured by WISC. However, children with IQ less than 79 were excluded.

Growth Hormone Deficiency / Multiple Hormone Deficiency

Six studies evaluated intelligence in children with short stature due to GHD or MHD with a total of 202 subjects. The tests used included the WISC and SIT. Test results for children with short stature due to GHD/MHD were either compared to average stature controls or to population norms. All of the studies were prospective. Two were longitudinal; four were cross-sectional. No study was of good quality; four were of fair quality; and two were of poor quality.

Siegel and Hopwood (1986) evaluated 42 children with short stature due to hypopituitarism (28 with isolated GHD and 14 with MHD) and a mean age of 12 years. IQ was evaluated by WISC and was compared to population norms in a prospective, cross-sectional study. Their verbal and performance IQs were significantly less than the population average, but within 1 SD of the population average. Of note, the study excluded one child with hypopituitarism because severe mental retardation prevented using some of the tests.

Frisch, Hausler, Lindenbauer, et al. (1990) evaluated 23 children aged 7 to 16 years old with isolated GHD or MHD who were evaluated by IQ testing with the German language version of WISC in a prospective, cross-sectional study. The children scored statistically higher on full score and performance IQ tests than the population at large. Verbal IQ scores were similar to controls. No correlation was found between standardized height and IQ score.

In a prospective, cross-sectional study, 13 children with short stature due to isolated GHD and nine children with MHD were evaluated by Meyer-Bahlburg, Feinman, MacGillivray, et al. (1978) by IQ testing (WISC). The children ranged in age from about 4 to 18 years old. Both groups of children had normal full score IQs.

Eleven children, aged 4 to 18 years old, with short stature due to GHD and/or other pituitary hormone deficiency were evaluated in a longitudinal, prospective study by Abbott, Rotnem, Genel, et al. (1982). The children had verbal, performance and full-scale IQs that were less then the general population mean but within 1 SD of the mean. No statistical analysis was reported. The study found that overall IQ scores were more related to socioeconomic level and specific physical dysfunction, such as eye defects, than to hypopituitarism.

In a prospective, cross-sectional study Siegel, Clopper, Stoppani, et al. (1994) evaluated intelligence with SIT in 87 children with GHD and a mean age of 11 years old. There were no significant differences between mean IQ in the children with GHD and the normal controls. However, significantly more GHD children (9 percent) had an IQ less than 90 than normal children (3 percent). The value of this study is limited, though, since children with “known mental impairments” were excluded.

Holmes, Karlsson, and Thompson (1985) evaluated 17 children with short stature due to GHD who were age 12 years at the start of the study in a prospective longitudinal study. The

verbal IQs, measured by WISC, of these children were slightly below the population mean. No statistical analysis was performed and the study suffered from incomplete reporting.

Combined Isolated Short Stature, Constitutional Growth Delay, and Growth Hormone Deficiency

Four studies evaluated intelligence with WISC or SIT in 97 subjects with ISS, CGD and GHD. The test results were compared to controls of average stature or to population norms. One study excluded subjects with low IQ or known mental impairment. All of the studies were prospective. One was longitudinal; three were cross-sectional. One study was of good quality; two were of fair quality; and one was of poor quality.

Siegel, Clopper, and Stabler (1998) evaluated IQ with SIT in 25 girls with a mean age of 10 years who had either ISS or short stature due to GHD. This longitudinal, prospective study, compared the girls with ISS/GHD to a group of girls with short stature due to Turner syndrome and a control group of girls with average stature. These results were from the baseline study for an evaluation of the effects of growth hormone on girls with short stature. No significant difference was found in the IQ of girls with GHD/ISS compared to control girls of average stature.

Steinhausen and Stahnke (1976) reported IQ testing (WISC) in 32 children ranging from 9 to 17 years old with height less than the 3rd percentile due to either hypopituitarism or familial reasons and compared these children to age-matched children of "normal" height. Performance, verbal and full-scale IQ testing scores were similar among these children and controls. This was a prospective, cross-sectional study.

Intelligence testing was performed in 13 children aged 3 to 16 years with short stature due to GHD, CGD, or Turner syndrome by Pollitt and Money (1964) in a prospective, cross-sectional study. Average full-scale, verbal and performance IQ scores (measured by WISC) were normal. Results were all slightly above the population mean (verbal 103, performance 101, full-scale 102). The 2 children who were tested with the Stanford-Binet, revised had IQs (48), which were slightly below the population norm. The study did not find a significant difference in intelligence in children with short stature.

Young-Hyman (1986) evaluated 27 children with ISS, GHD or CGD and a mean age of 12 years in a prospective, cross-sectional study. The full-scale IQs (WISC) were on average above the normal range. However, no statistical analysis was performed and the study excluded children with mental disability or learning problems.

Turner Syndrome

Five studies evaluated intelligence in girls with short stature secondary to Turner syndrome with a total of 97 subjects. Tests used included WISC and SIT. The test results were compared either to controls or to population norms. One study excluded subjects with low IQ or known mental impairment. All studies were prospective. Three were longitudinal; two were cross-sectional. One study was of good quality; two were of fair quality; and two were of poor quality.

Siegel, Clopper, and Stabler (1998) evaluated IQ with SIT in 22 girls with a mean age of 10 years who had Turner syndrome. This longitudinal, prospective study, compared these girls to girls with ISS/GHD and to a control group of girls with average stature. These results were from the baseline study for an evaluation of the effects of growth hormone on girls with short stature.

The girls with Turner syndrome had IQ scores that were slightly above the population mean, but slightly less than the scores for the control girls of average height (108).

In a prospective study that was part of a double-blind randomized controlled trial of growth hormone for the treatment of Turner syndrome, Ross, Feuillan, Kushner, et al. (1997) evaluated 40 girls with a mean age of 9 years. The study found that girls with Turner syndrome had IQ scores (measured by WISC) that were similar to the population norm, whether they received growth hormone or a placebo.

Robinson, Bender, Borelli, et al. (1983), in a small prospective, cross-sectional study, evaluated nine girls with Turner syndrome who ranged from 7 to 15 years old. Measured by WISC, the average full-scale and verbal IQs of these girls were significantly below normal, although still within 1 SD of normal mean. The mean verbal IQ was not significantly lower than normal.

McCauley, Kay, Ito, et al. (1987) tested IQ in 17 3 to 16 year old girls with short stature due to Turner syndrome. The girls had somewhat low verbal and performance IQs (measured by WISC) that were within 1 SD of the mean. No statistical analyses were performed in this prospective, cross-sectional study. Children with IQ less than 79 were excluded from the study.

Holmes, Karlsson, and Thompson (1985) evaluated 9 children with Turner syndrome who were age 12 years at the start of a prospective longitudinal study. The verbal IQs, measured by WISC, of these children were slightly above the population mean. No statistical analysis was performed and the study suffered from incomplete reporting.

Russell-Silver Syndrome

Three studies evaluated intelligence in children with short stature due to Russell-Silver syndrome with 45 total subjects. The test scores were compared to population norms. Two were prospective; one was retrospective. Two were longitudinal; one was cross-sectional. One study was of fair quality; two were of poor quality.

Lai, Skuse, Stanhope, et al. (1994) evaluated IQ with WISC in 25 children with Russell-Silver syndrome in a prospective, cross-sectional study. The children were 6 to 12 years old and had significantly lower full-scale, verbal, and performance IQs than the general population norm. However, the scores were within 1 SD of the general population mean. The full-scale IQ range was 46-130 with 8 children (32 percent) having IQs less than 70.

A longitudinal, retrospective study by Tanner, Lejarraga, and Cameron (1975) evaluated 39 children with Russell-Silver syndrome aged 1½ to 10 years old in an attempt to understand the natural history of this condition. IQ testing was only available for 11 of the children and the specific test used was not reported . The mean full-scale IQ was slightly above the population mean of 100.

A longitudinal, prospective study by Angehrn, Zachmann, and Prader (1979) evaluated growth and development in 20 children with Russell-Silver syndrome and a mean age of 4 years old. IQs (specific test not reported) were reported for only nine of the children. Six of them had IQs in the normal range (mean of 102) and 3 had IQs less than 86 (85, 83 and 38).

Combined Isolated Short Stature and Russell-Silver Syndrome

One study evaluated intelligence via WISC in 22 children with either ISS or Russell-Silver syndrome. The test scores were compared to the average stature control group. Skuse and

Gilmour (1997) evaluated seven children with Russell-Silver syndrome and 15 with ISS in a prospective, cross-sectional study. The children with short stature had significantly lower average full-scale and performance IQ scores and lower verbal IQ than control children who had mean IQ scores from 105 to 108. However, the mean scores of the short children were within 1 SD of the population mean. The study was graded to be of poor quality because it excluded children with IQ less than 72.

Short Stature and Intelligence

Eight studies evaluated intelligence among children with ISS or CGD. Three studies found that short children had significantly lower IQs than normal controls. All studies found that, overall, short children had IQs that were either above or within 1 SD of population norms. One study found that short children were significantly more likely to have some intelligence deficit (IQ less than 90) even though mean scores were similar. Four studies excluded children with low IQ and one study matched short children with normal height children with similar IQs.

Seven studies evaluated intelligence among children with GHD or MHD. Two studies found that short children had significantly lower IQs than normal controls. All studies found that, overall, short children had IQs that were either above or within 1 SD of population norms. One study found that short children were significantly more likely to have some intelligence deficit (IQ less than 90) even though mean scores were similar. One study excluded one child with severe mental retardation; one excluded children with low IQs.

Four studies evaluated intelligence among children with either ISS, CGD or GHD. None found that short children had significantly lower IQs than normal controls. All found that, overall, short children had IQs that were above population norms. One study excluded children with low IQs.

Five studies evaluated intelligence among girls with Turner syndrome. One small study found that girls with Turner syndrome had significantly lower IQs than normal height controls and that their IQs were, on average, about 1.5 SD below population norms. The remaining studies found that girls with Turner syndrome had IQs that were within 1 SD of population norms. Ones study excluded girls with low IQ.

Three studies evaluated children with Russell-Silver syndrome and one with either Russell-Silver syndrome or ISS. Two studies found that the short children had significantly lower IQs than normal height controls. One excluded children with low IQs. All studies found that children with Russell-Silver syndrome, overall, had IQs within 1.5 SD of population norms.

Association of Short Stature with Visual-Motor Skills

Table 3. Association of Height to Visual-Motor Skills Among Children with Short Stature due to Medical Impairment

Author, Year	Sample N (Controls)	Mean Height	Measure	Results	Quality [a]
Isolated Short Stature					
Abbott 1982	11	81-132 cm	Bender Visual Motor Beery Visual Motor Integration	**– 2 y 1 mo** [b] **–3 y 8 mo** [b]	●
Young-Hyman 1986	27	ND	Bender Visual Motor	**– 2 y 6 mo** [b]	○
Growth Hormone or Multiple Hormone Deficiency					
Siegel 1986	42	< -2 SDS	Bender Visual Motor Score < 16th percentile & ≥ 4 brain injury indicators	26%	●

Results in bold were significantly different than normal population.

a See Methods, Summary Tables, Study Quality.
b Discrepancy between chronological age and age equivalence, in years and months.

Three studies evaluated 81 patients with ISS, GHD or MHD for visual-motor skills with either the Developmental Test of Visual-Motor Integration or the Bender Visual-Motor Gestalt Test (Table 3). The testing used estimates a child's level of perceptual-motor integration as evaluated by their ability to copy a series of designs. All were prospective. One was longitudinal; two were cross-sectional. Two were of fair quality; one was of poor quality.

Isolated Short Stature

Eleven children, aged 4 to 18 years old, with short stature due to GHD and/or other pituitary hormone deficiency had Bender Visual Motor Gestalt testing done by Abbott, Rotnem, Genel, et al. (1982) in a longitudinal, prospective study. Visual integration skills were significantly delayed in these children compared to population norms.

Young-Hyman (1986) evaluated 27 children with short stature who had presented to an endocrine clinic in a prospective, cross-sectional study. Perceptual motor skills as assessed by the Bender visual-motor skills were significantly delayed. The tested children had skills rated at 9.2 y compared to their chronological age of 11.8 years. Reporting of the analysis was poor.

Growth Hormone Deficiency / Multiple Hormone deficiency

Siegel and Hopwood (1986) evaluated Bender visual-motor integration testing in 42 children who were 6 to 16 years old and had short stature due to hypopituitarism. Significant visual-motor integration deficits occurred in one-quarter of the children. This was a prospective, cross-sectional study. Reporting of the analysis was poor.

Short Stature and Visual-Motor Skills

Three studies evaluated visual-motor skills in children with either ISS, GHD, or MHD. All three found that short children were significantly more likely to a reduction in visual-motor skills. The degree of functional deficit or disability in visual-motor skills was not reported.

Association of short stature with psychomotor development

Table 4. Association of Height to Psychomotor Development Among Children with Short Stature due to Medical Impairment

Author Year	Sample N (Controls)	Mean Height, SDS	Measure	Association	Quality [a]
Russell-Silver Syndrome					
Angehrn 1979	14	–4.4	DDST	>90th %ile in >50% subjects	○

DDST = Denver developmental screening test

a See Methods, Summary Tables, Study Quality.

One poor quality study evaluated 14 children with short stature due to Russell-Silver syndrome for psychomotor development by the Denver Developmental Screening Test (Table 4). Angehrn, Zachmann, and Prader (1979) conducted a prospective, longitudinal study of children with Russell-Silver syndrome. In these children, more than half of the developmental landmarks evaluated by the Denver Developmental Screening Test were met at or after the age when 90% of average children had met that landmark.

Short Stature and Psychomotor Development

One study evaluated psychomotor development among children with Russell-Silver syndrome. This study found that these children tended to be delayed in meeting their early developmental landmarks.

Association of Short Stature with Behavior

Table 5. Association of Height to Teacher-Graded Behavior Problems Among Children with Short Stature due to Medical Impairment

Author Year	Sample N (Controls)	Mean Height, SDS	Test	Total (Control)	Internalizing (Control)	Externalizing (Control)	School (Control)	Quality [a]
Isolated Short Stature								
Voss 1991 [b]	140 (140)		RBQ	29% >9 (21%) Disturbance	**16%** >3 (8%) Hyperactivity			
Voss 1994 [b]	132 (132)	< –2.0	RBQ	6.2 (5.1)	1.2 (1.0) Conduct	1.2 (1.2) Emotion	1.7 (1.1) Activity	●
Downie 1997 [b]	98 (115)		N&S			**17 (14)** Locus of control		
Gordon 1984	24 (23)	–1.7	CBCL	31 (28)				◉
Kranzler 2000	34 (29) [c]	–1.7	BASC		51 (50)	47 (48)	47 (46)	○
Kranzler 2000	27 (29) [d]	–2.7	BASC		50 (50)	51 (48)	50 (46)	○
Growth Hormone Deficient or Constitutional Growth Delay								
Steinhausen 1976	32 (32)	–2.0	HANES		13 (16) Neuroticism	11 (12) Extraversion		◉
Isolated Short Stature or Russell-Silver Syndrome								
Skuse 1994	17 (15)	–2.5	CBCL	**49** (42)	NS [e]	NS [e]		○

Bold = significantly different from control

BASC = Behavior Assessment System for Children; CBCL = Child Behavior Checklist; HANES = Hamburg Neuroticism Extraversion Scale; RBQ = Rutter's Behavior Questionnaire ; N&S = Nowicki and Strickland Locus of control scale; NS = Non-significant

a See Methods, Summary Tables, Study Quality.
b Voss 1991, Voss 1994, and Downie 1997 included same overall sample of subjects.
c Non-referred subjects, shortest 10% at school.
d Referred to endocrinology clinic for short stature.
e Exact data not reported.

Five studies evaluated behavior in children with short stature by a variety of tests (Table 5). Included tests were Child Behavior Checklist (CBCL), Hamburg Neuroticism Extraversion Scale (HANES), Rutter's Behavior Questionnaire (RBQ), Nowicki and Strickland Locus of Control Scale (N&S), and Behavior Assessment System for Children (BASC). Only results of teacher-graded tests are evaluated. A total of 274 children were evaluated and compared to controls. All the studies were prospective. One was longitudinal; four were cross-sectional. One set of studies was of good quality; two studies were of fair quality; two studies were of poor quality.

Isolated Short Stature

In three prospective, longitudinal papers (Downie, Mulligan, Stratford, et al., 1997; Voss, Bailey, Mulligan, et al., 1991; Voss and Mulligan, 1994) children with ISS were tested repeatedly at different ages. In the first study (Voss, Bailey, Mulligan, et al., 1991) of 140 short children between 7 and 9 years old, 29 percent were found to have a behavior disturbance (defined as total RBQ score greater than 9), which was somewhat higher than among control children (21 percent); the difference was not significant. In these same children, hyperactivity

(defined as activity sub-scale score of greater than 3) occurred in significantly more short children than controls (16 percent versus 8 percent). As reported in Voss and Mulligan (1994) for a subset of 132 of the children with short stature, mean behavior scale scores for short children were non-significantly higher than for control children for total behavior, conduct, emotion, and activity, after controlling for socio-economic status. In Downie, Mulligan, Stratford, et al. (1997) 98 of the children were evaluated at age 13 years with N&S. Locus of control score was significantly higher among the children with short stature.

Gordon, Post, Crouthamel, et al. (1984) evaluated 24 children aged 6 to 12 years old with CGD in a prospective, cross-sectional study. Behavior was assessed with CBCL. There was no significant difference in behavior between short stature children and controls.

Kranzler, Rosenbloom, Proctor, et al. (2000) evaluated two groups of 6 to 12 year old children with ISS in a prospective, cross-sectional study. One group consisted of 34 children who were identified in local public schools as being in the shortest 10 percent of the class ("non-referred"). The second group consisted of 27 children with ISS who had been referred to pediatric endocrinology because of short stature. Behavioral functioning was assessed with BASC. Both the referred and non-referred children had behavior functioning scores that were similar to controls.

Growth Hormone Deficient or Constitutional Growth Delay

Steinhausen and Stahnke (1976) evaluated 32 children ranging from 9 to 17 years old with height less than the 3rd percentile due to either hypopituitarism or familial reasons and compared these children to age-matched children of "normal" height. Extraversion and neuroticism were measured with HANES. The children with short stature had similar scores as controls. This was a prospective, cross-sectional study.

Isolated Short Stature or Russell-Silver Syndrome

Skuse and Gilmour (1997) evaluated 22 children aged 6 to 12 years with Russell-Silver syndrome or ISS in a prospective, cross-sectional study. Among a subset of 17 short children, they had statistically higher total behavior scores, but similar internalizing and externalizing scores compared to controls. However, this was only a preliminary analysis of available data on a subset of the total sample. Reporting of the results was also incomplete.

Short Stature and Behavior

Three studies evaluated teacher-graded behavior among children with ISS. One study found that short children scored significantly worse in terms of locus of control and that significantly more short children were likely to have hyperactivity than normal height controls. Other tests of behavior were found to be similar among short and normal height children. No study described any functional limitations or disabilities based on behavior.

One study evaluated behavior among children with either GHD or CGD and found that neuroticism and extraversion scores were similar among short children and normal height controls. One study evaluated children with either ISS or Russell-Silver syndrome and found that short children had significantly more total behavior problems than normal height controls. Neither study described any functional limitations or disabilities based on behavior.

Question 2. What is the evidence that short stature (height < 5th percentile) due to a skeletal dysplasia is disabling according to, but not limited to, SSA's definition of disability? If so, are children disabled by virtue of their size or other features of their conditions?

See Evidence Table 2.

We reviewed 31 papers that provided information on functional abilities among children with short stature due to skeletal dysplasias. As described in Evidence Table 2, a number of these papers probably provided analyses from the same samples of children. Two studies reported on different outcomes in two sets of two separate papers. One set of five papers probably included data from overlapping groups of the same overall sample of children. Therefore, 31 papers from 25 study groups are summarized here. Few studies explicitly examined functional impairment, per se. Data are reported on the association of short stature with academic achievement, intelligence, psychomotor development (visual-motor skills, motor development, and motor development patterns), neuromuscular function, ambulation and mobility, limb range of motion, spinal curvature, hearing loss, respiratory dysfunction (sleep apnea and pulmonary function), and psychological outcomes. Detailed information on all 31 papers is reported in Evidence Table 2.

Association of Short Stature Due to Skeletal Dysplasia with Academic Achievement

Table 6. Academic Achievement Score of Children with Short Stature Due to Skeletal dysplasia

Author Year	Sample N (Controls)	Test	Mean Academic Achievement Score				Bias [a]	Quality [b]
			Math	Reading	Compre-hension	Spelling		
Achondroplasia								
Brinkman, 1993	30 (30) [c]	CAS	**49** [55]	**46** [54] [d]	51 [55] [e]	**48** [56] [f]		○
Thompson, 1999	12-15 (17) [g]	WRAT	89 [96]	80 [95] [h]		88 [97]	>IQ	○
Osteogenesis Imperfecta								
Alston, 1983	40 (40)	Multi [i]	104 [105] [j]	100 [102]		102 [104]		●

Mean scores in bold were significantly different than normal population; results not in bold not significantly different, except as noted in bias column.
Mean score for normal population for each test is 100, unless otherwise noted in brackets

CAS = Cognitive abilities score, WRAT = Wide range achievement test

a Studies noted with ">IQ" excluded subjects with low IQ or known mental impairment excluded.
Studies noted with "No stat" did not perform statistical analysis comparing IQ of subjects to normal controls
b See Methods, Summary Tables, Study Quality.
c 30 normal height controls. Also had 30 sibling controls and 30 short stature controls.
d Verbal
e Reasoning
f Total
g 17 normally developing controls. Also had 19 premature arrested hydrocephalus controls.
h Sentence writing
i Raven's Progressive Matrices, Primary Reading Test, Wide Span Reading Test, Gapadol Reading Test, Graded Word Spelling Test
j Non-verbal Intelligence

Three studies evaluated academic achievement in 84 children with skeletal dysplasia (See Table 6). Two studies evaluated children with achondroplasia; one evaluated children with osteogenesis imperfecta.

Achondroplasia

Two studies evaluated academic achievement in approximately 43 children with achondroplasia. Academic achievement was measured with either the Cognitive Abilities Score or WRAT. The scores of the children with skeletal dysplasia were compared to controls. Both were prospective cross-sectional studies. Both were of fair quality.

Brinkmann, Schlitt, Zorowka, et al. (1993) performed cognitive testing, including verbal comprehension, arithmetic thinking, and reasoning, on children with achondroplasia. In a prospective, cross-sectional study, 30 subjects with a mean age of 9 years old were compared with 30 of their own siblings, 30 children with short stature not due to skeletal dysplasia. Controls were matched for age, sex, and socioeconomic status. The children with achondroplasia were found to have testing within the normal range, although they did score significantly lower than all three control groups.

Thompson, Hecht, Bohan, et al. (1999) prospectively examined children with a mean age of 7 years old with achondroplasia with WRAT-R, comparing them with normally developing controls in a cross-sectional study. In order to separate out the effect of the common neuroanatomic defect, hydrocephalus, from the effect of the dwarfing condition itself, they were also compared with 19 children born prematurely with low birthweight who had arrested, unshunted hydrocephalus. All results were age-corrected. The different sub-test results of the WRAT-R were reported for between 12 and 15 children with achondroplasia. In general, achondroplasia children had average cognitive abilities within 1 SD of population norms. The three groups had statistically similar in academic achievement. However, the small sample size minimized the possibility of finding statistically significant differences and children with low IQs were excluded.

Osteogenesis Imperfecta

One study evaluated academic achievement in children with osteogenesis imperfecta. The study was a prospective cross-sectional analysis of good quality. Alston (1979) evaluated 40 children ranging from 5 to 16 years old for nonverbal intellectual ability including reading and spelling. The controls were chosen from the same class or neighborhood as subjects, and were matched for age, sex, and social class. Children with osteogenesis imperfecta had normal scores that were not significantly different than controls.

Skeletal Dysplasia and Academic Achievement

Three studies examined academic achievement among children with achondroplasia or osteogenesis imperfecta. One found that children with achondroplasia had significantly lower scores on academic achievement tests than normal height children. However, among all the studies, children with skeletal dysplasias scored either above population norms or within 1 SD of normal scores. One of the studies excluded children with low IQ.

Association of Short Stature Due to Skeletal Dysplasia with Intelligence

Table 7. Intelligence Quotient of Children with Short Stature Due to Skeletal Dysplasia

Author, Year	Sample N (Controls)	Test	Mean IQ Full	Mean IQ Verbal	Mean IQ Performance	Bias [a]	Quality [b]
Achondroplasia							
Rogers, 1979	19 [c]	WISC	96	95	100	No stat	●
	15 [d]	BSID/SB	97				
Thompson, 1999	16	WISC		94	101	>IQ No stat	●
Hecht, 1991	13	BSID	97			No stat	○
Osteogenesis Imperfecta							
Reite, 1972	12	WISC	107			No stat	○
Skeletal Dysplasia							
Rogers, 1979	22 [e]	WISC	104	104	103	No stat	●
	12 [f]	BSID/SB	100				
Shurka, 1976	7	WISC	102	103	99	No stat	○

Mean scores in bold were significantly different than normal population; results not in bold not significantly different, except as noted in bias column.
Mean score for normal population for each test is 100, unless otherwise noted in brackets

IQ = Intelligence quotient, BSID = Bayley Scales of Infant Development, SB = Stanford-Binet Intelligence Scale; WISC = Wechsler Intelligence Scale for Children

a Studies noted with ">IQ" excluded subjects with low IQ or known mental impairment excluded.
Studies noted with "No stat" did not perform statistical analysis comparing IQ of subjects to normal controls
b See Methods, Summary Tables, Study Quality.
c School age children
d Preschool age children
e School age children with skeletal dysplasias other than achondroplasia
f Preschool age children with skeletal dysplasias other than achondroplasia

Five studies tested IQ in 116 children with skeletal dysplasia (See Table 7). Three studies evaluated children with achondroplasia; one evaluated children with osteogenesis imperfecta; and two evaluated children with a variety of skeletal dysplasias.

Achondroplasia

Three studies evaluated intelligence in 63 children with achondroplasia. IQs were measured with either Wechsler Intelligence Scale for Children, Bayley Scales of Infant Development, or the Stanford-Binet Intelligence Scale. The scores of the children with skeletal dysplasia were compared to population norms. All were prospective cross-sectional studies. Two were of fair quality; one was of poor quality.

In a prospective cross-sectional study by Rogers, Perry, and Rosenberg (1979), 34 children aged from 6 months to 15 years with achondroplasia were studied with intelligence testing. The mean IQ scores for both the pre-school and school age children were within the normal range.

Thompson, Hecht, Bohan, et al. (1999) prospectively examined 16 children with a mean age of 7 years old with achondroplasia with intelligence testing in a cross-sectional study. Achondroplasia children had average cognitive abilities within 1 SD of population norms. Of note, though, children with low IQ were excluded from analysis.

In a paper by Hecht, Thompson, Weir, et al. (1991), 13 infants with achondroplasia were evaluated for intelligence in a prospective cross-sectional study. The children with achondroplasia had a mean mental developmental index within the normal range. However, a wide range of scores was obtained. Their results were correlated with ventricular size, degree of cortical atrophy, and neurological and respiratory complications. Three of the infants were also found to have abnormal polysomnograms showing obstructive apnea or hypoxemia. There was a significant correlation between an abnormal polysomnogram and a low test score. They concluded that the mental performance in the children with achondroplasia was average, and that the respiratory complications, not the achondroplasia itself, may contribute to decreased intellectual potential.

Osteogenesis Imperfecta

One study evaluated intelligence in children with osteogenesis imperfecta. The study was prospective, cross-sectional and of poor quality. Reite, Davis, Solomons, et al. (1972) evaluated 12 6 to 17 year old children with severe osteogenesis imperfecta. The children's mean IQ was somewhat above normal.

Skeletal Dysplasias

Two studies evaluated intelligence in children with a variety of skeletal dysplasias. Both were prospective cross-sectional studies. One was of fair quality; one was of poor quality.

In a prospective cross-sectional study by Rogers, Perry, and Rosenberg (1979), 34 children aged from 6 months to 15 years with skeletal dysplasias other than achondroplasia were studied with intelligence testing. The mean IQ scores for both the pre-school and school age children were within the normal range.

In a small prospective cross-sectional study, Shurka and Laron (1976) measured IQ in 7 children with skeletal dysplasia and a mean age of 14 years old. The children had mean IQs that were within the normal range.

Skeletal Dysplasia and Intelligence

Five studies evaluated intelligence among children with achondroplasia, osteogenesis imperfecta and other skeletal dysplasias. The studies found no evidence of significantly impaired intelligence in the children. The mean IQs were all within 1 SD of population norms. None of the studies performed statistical analyses or reported comparisons with control groups. One study excluded children with low IQ from evaluation.

Association of Short Stature Due to Skeletal Dysplasia with Psychomotor Development

Table 8. Visual Motor Skills in Children with Short Stature Due to Skeletal Dysplasia

Author, Year	Sample N (Controls)	Population	Measure	Results	Quality [a]
Achondroplasia					
Thompson, 1999	13 (12)	All	Beery Visual Motor Integration	**82** [92]	●
			Judgment of Line Orientation	**85** [100]	
	12 (17)		Fine Motor Skills (various tests)	No significant difference	
Hecht, 1991	13	Infants	Psychomotor Development Index	63 (62% < 50) [b]	○

Results in bold were significantly different than control; results not in bold were not statistically analyzed.
Results in brackets are those of normal controls.

a See Methods, Summary Tables, Study Quality.
b Population norm = 100

Table 9. Motor Development in Children with Short Stature Due to Skeletal Dysplasia

Author, Year	Sample N (Controls)	Population	Months to Milestone, Mean			Quality [a]
			Sit Alone	Stand Alone	Walk Alone	
Achondroplasia						
Brinkmann, 1993	30 (90)	All	12 [7] [b]	14 [10] [b]	18 [12] [b]	●
Fowler, 1997 [c]	21-37	All	**12**	**19** [d]	**18** [d]	○

Results in bold were significantly different than population means. Those not in bold were not statistically different than controls.
Results in brackets are those of normal controls.
a See Methods, Summary Tables, Study Quality.
b Results presented for normal controls (n=30). Results for sibling and other short controls were similar.
c Probable overlap of subjects with those in Pauli, Horton, Glinski, et al. (1995) in Table 10.
d Walking alone appears to have occurred earlier than standing alone due to "statistical aberration" due to different subjects' parents responding to questionnaire.

Table 10. Motor Development Patterns in Children with Short Stature Due to Skeletal Dysplasia

Author, Year	Sample N (Controls)	Population	Patterns of Development (%)					Quality [a]
			Abnormal Arrested	Delayed Arrested	Normal Arrested	Delayed	Normal	
Achondroplasia								
Pauli, 1995 [b]	52	All	10% had "disproportionate developmental delays"					○
Osteogenesis Imperfecta								
Daly, 1996	31	Congenita B	19	19	29	29	3	●
	15	Tarda A	0	27	7	20	47	
	4	Tarda B	0	0	0	0	100	
	15	Type I	0	0	7	27	67	
	29	Type III	21	34	28	17	0	
	7	Type IV	0	14	14	43	29	

a See Methods, Summary Tables, Study Quality.
b Probable overlap of subjects with those in Fowler, Glinski, Reiser, et al. (1997) in Table 9.

Six studies investigated psychomotor development in up to 196 children with skeletal dysplasia (Tables 8-10). Five considered children with achondroplasia, and one evaluated children with osteogenesis imperfecta.

Achondroplasia

Five studies evaluated psychomotor development in children with achondroplasia. All were prospective. One was longitudinal; four were cross-sectional. Two were of fair quality; three were of poor quality.

Thompson, Hecht, Bohan, et al. (1999) prospectively examined 13 children with achondroplasia who had a mean age of 7 years old with neuropsychological testing, comparing them with normal controls in a cross-sectional study (See Table 8). All results were age-corrected. Achondroplasia subjects performed significantly less well in visual-motor integration skills than controls. Fine motor skills were not significantly different between groups, but children in the achondroplasia performed below average. Small sample size may have prevented statistical significance for some of these comparisons.

In a prospective cross-sectional study by Hecht, Thompson, Weir, et al. (1991), 13 infants with achondroplasia underwent psychometric testing using the Bayley Scales of Infant Development as part of a comprehensive neurological assessment (See Table 8). The mean Psychomotor Development Index component score was more than 2 SD below normal and almost two-thirds of subjects had scores below 50. However, psychomotor testing was not predictive of cognitive function in these children.

In Brinkmann, Schlitt, Zorowka, et al. (1993), a prospective, cross-sectional study, 30 children with achondroplasia who had a mean age of 9 years old, were compared with 30 of their own siblings, 30 children with different skeletal dysplasias, and 30 children with short stature not due to skeletal dysplasia (See Table 9). Controls were matched for age, sex, and socioeconomic status. According to parental reports, the average age of sitting unassisted, standing alone, and walking alone were all delayed when compared to controls. However, statistical analyses were not presented.

In a paper primarily intended to describe prospective observations of aberrant, but probably adaptive, pre-walking movements in children with achondroplasia, Fowler, Glinski, Reiser, et al. (1997) presented a cross-section of gross motor and fine motor developmental milestones for their patients, aged 1 to 60 months old (See Table 9). Although 93 subjects were included, only some children had results reported for any given item, ranging from 6 to 38 children per item. Subjects evaluated in this study appear to overlap with subjects included in report by Pauli, Horton, Glinski, et al. (1995), below. The Standard Denver Developmental Screening Test and Denver II Test, which rely on parent recollection and report, were used. All parameters for both gross motor and fine motor function were delayed when compared with published percentiles for average children. Specifically, the median ages at which 37, 21, and 24 children, respectively, were able to sit, stand, and walk unsupported were all significantly older than normal. These authors concluded that these delays are aberrant but not maladaptive, and different but not defective, representing adaptation because of biophysical abnormalities. However, their conclusions are hypotheses, not based on results presented in this paper.

Pauli, Horton, Glinski, et al. (1995) reported on 52 infants and young children with achondroplasia in a prospective longitudinal study (See Table 10). The subjects reported in this

paper appear to overlap with the patients examined in Fowler, Glinski, Reiser, et al. (1997), described above. By history, 10 percent had disproportionate developmental delay. Many had other neurological abnormalities by history or by exam discussed elsewhere in this report.

Osteogenesis Imperfecta

One study evaluated psychomotor development in children with osteogenesis imperfecta. The study was prospective cross-sectional in design, and was of fair quality. Daly, Wisbeach, Sanpera, Jr., et al. (1996) compared the ability of two commonly used classifications of osteogenesis imperfecta to predict motor development of the child (See Table 10). By questionnaire, 51 children with osteogenesis imperfecta who had a mean age of 7 years old, were evaluated for pattern of development. Children were classified into categories described by Shapiro based on radiographic appearance of bones and history of fractures (Congenita A, Congenita B, Tarda A, and Tarda B) and into categories described by Sillence (I, III, and IV). Five patterns of development were described: abnormal/arrested, delayed/arrested, normal/arrested, delayed, and normal. Overall, approximately half the children had normal or only slightly delayed motor development. Only one child with osteogenesis imperfecta Congenita had normal development and became a walker. Only half the children with osteogenesis imperfecta Tarda A had normal development; the others were delayed and/or arrested. All four with osteogenesis imperfecta Tarda B had normal development. All children with Type I disease had either normal or slightly delayed development. None of those with osteogenesis imperfecta Type III had normal development. Of those with Type IV, approximately three-quarters had delayed and/or arrested development.

Skeletal Dysplasia and Psychomotor Development

Among the reviewed studies, substantial proportions of children with achondroplasia were found to have delayed and/or abnormal gross, fine, or visual motor development. The one study of children with osteogenesis imperfecta similarly found abnormal patterns of development in the more severely affected patients. All studies are small and used different testing instruments, making comparisons among studies difficult. Two studies (Fowler, Glinski, Reiser, et al., 1997; Pauli, Horton, Glinski, et al., 1995) reported on similar outcomes in samples of children that probably overlapped.

Association of Short Stature Due to Skeletal Dysplasia with Neuromuscular Function

Table 11. Neuromuscular Findings in Children with Skeletal Dysplasia

Author Year	Population	Sample N (Controls)	Outcome	Result	Quality [a]
Achondroplasia					
Thompson, 1999	All	13 (13)	Gross Motor Arm Coordination score	**73** [93] [b]	◐
			Gross Motor Leg Coordination score	**79** [104] [b]	
Pauli, 1995	All	52	Weakness by history	14%	○
		52	Sensory abnormality by history	4%	
		52	"Abnormality" by history	42%	
		52	Asymmetry by history	21%	
		52	Seizures by history	8%	
		44	Decreased limb tone by exam	70%	
		40	Abnormal arm strength by exam	32%	
		40	Abnormal leg strength by exam	50%	
		39	Decreased truncal tone by exam	70%	
Ruiz-Garcia, 1997	All	39	Weakness by exam	31% (26%) [c]	○
			Sensory deficit by exam	10% (5%) [c]	
			Hypotonia by exam	59% (49%) [c]	
			Quadriparesis by exam	15% (13%) [c]	
			Compressive neural syndrome	31%	
Reid, 1988	All	26	Paresis	42%	○
Osteogenesis Imperfecta					
Engelbert, 2001	Type I	17	Arm strength score (0=None, 5=Normal)	4.5	◐
	Type III	11		3.5	
	Type IV	12		4.5	
	Type I	17	Leg strength score (0=None, 5=Normal)	4.8	
	Type III	11		3.6	
	Type IV	12		3.8	
Morquio Disease					
Skeletal Dysplasia Group, 1989	All	15	"Known neurological complications"	33%	○

a See Methods, Summary Tables, Study Quality.
b Significantly lower than controls
c Reported results differ in table and text (in parentheses).

Six studies evaluated neuromuscular function in 185 children with skeletal dysplasia (Table 11). Four studies evaluated children with achondroplasia; one evaluated children with osteogenesis imperfecta; and one evaluated children with Morquio disease. Each study used different methods to measure neuromuscular function.

Achondroplasia

Four studies evaluated neuromuscular function in children with achondroplasia. All were prospective. Two were longitudinal; two were cross-sectional. One was of fair quality; three were of poor quality.

Thompson, Hecht, Bohan, et al. (1999) prospectively examined 13 children with achondroplasia who had a mean age of 7 years old for gross motor coordination, comparing them with normal controls in a cross-sectional study. All results were age-corrected. Sample size for gross motor skills were reduced because some children were unable to complete the testing due to fatigue or time constraints. Achondroplasia subjects performed significantly less well in gross motor arm and leg coordination skills than control children.

Pauli, Horton, Glinski, et al. (1995) reported on 52 infants and young children with achondroplasia in a prospective longitudinal study. By history and neurological examination, neurological abnormalities referable to the upper cervical cord were found to be common. Seizures occurred in a small percentage of subjects.

Ruiz-Garcia, Tovar-Baudin, Castillo-Ruiz, et al. (1997) prospectively evaluated 39 children with achondroplasia who had a mean age of 4 years old in a cross-sectional study. Children who had had prior neurosurgery were excluded. Each had comprehensive neurological examination including history, physical examination, and CT imaging. The reported results for findings on neurological examination differed in the text from the summary table. Both sets of results are presented in Table 11. Hypotonia, weakness, and even quadriparesis were common. Furthermore, nearly a third had compressive neural syndromes confirmed by neurological examination, neurophysiological and neuroimaging studies. Sensory deficits were also found.

Reid, Pyeritz, Kopits, et al. (1988) conducted a prospective longitudinal evaluation of 26 children less than 7 years old with achondroplasia. Of note, about three-quarters of the subjects were referred to the study because they were symptomatic. By neurological exam, 42 percent had varying forms of paresis, some of these children were asymptomatic. For some, this was the clue to the presence of cervicomedullary compression, in that the children were otherwise asymptomatic. The findings in this study may not be applicable to all children with achondroplasia because the subjects were highly selected.

Osteogenesis Imperfecta

One study evaluated neuromuscular function in children with osteogenesis imperfecta. The study was of fair quality. Engelbert, Gulmans, Uiterwaal, et al. (2001), in a prospective, cross-sectional study, measured muscle strength in 40 children with osteogenesis imperfecta who had a mean age of 12 years old. Muscle strength of upper and lower extremity muscle groups was measured using standardized criteria using a six point scale. All subjects had some degree of weakness. In children with osteogenesis imperfecta Type I, muscle strength was almost comparable to the healthy population. In children with osteogenesis imperfecta Type III, muscle strength was severely decreased in both upper and lower extremities. In those with osteogenesis imperfecta Type IV, muscle strength was also decreased, particularly in the lower extremities. Of note, the level of ambulation and functional skills regarding mobility correlated highly with muscle strength.

Morquio Disease

One study evaluated neuromuscular function in children with Morquio disease. The study was of poor quality. In a retrospective cross-sectional review of cervical spine anomalies in all patients on the register of the Skeletal Dysplasia Group (1989), 15 children, between ages 1 and 15 years old, had Morquio disease. All had either hypoplasia or absence of the odontoid. Of

these children, 1/3 had known neurological complications related to the odontoid abnormalities. The descriptions of the neurological complications were not reported.

Skeletal Dysplasia and Neuromuscular Function

Four papers that reviewed neuromuscular function in children with achondroplasia all found abnormalities. The three that measured strength found substantial weakness and hypotonia. Asymmetry, sensory deficits, poor coordination, and even seizures were found in frequencies higher than either controls or than expected in the healthy population. All highlighted the significant risk of often occult cervical cord compression in these young children. The one paper that evaluated osteogenesis imperfecta also found significant weakness in children who are moderately to severely affected. The one paper that reviewed other skeletal dysplasias found cervical cord complications in children with the mucopolysaccharidosis Morquio disease.

Association of Short Stature Due to Skeletal Dysplasia with Ambulation and Mobility

Table 12. Ambulation/Mobility of Children with Short Stature due to Skeletal Dysplasia

Author Year	Sample N	Population	Ambulation Ability (%)									Quality [a]
			Without Assistance				Assistance Needed				Wheelchair	
			C	N	H	Th	C	N	H	Th		
Osteogenesis Imperfecta												
Engelbert, 2000 [b]	41	Type I	59	10	12	0	5	0	7	7	0 [e]	●
	11	Type III	0	0	0	0	0	9	27	19	45 [e]	
	18	Type IV	28	0	0	0	11	6	11	22	22 [e]	
Daly, 1996	31	Congenita B	13				0				87	◐
	15	Tarda A	60				13				27	
	15	Type I	93				7				0	
	29	Type III	3				0				97	
	7	Type IV	29				14				57	
Engelbert, 1999 [b]	19	Type I	53[c]	26[c]	16[c]	5 [c]	[c]	[c]	[c]	[c]	0 [d]	◐
	13	Type III	0	0	31[c]	8 [c]	0	0	[c]	[c]	61 [d]	
	10	Type IV	10[c]	10[c]	10[c]	40[c]	[c]	[c]	[c]	[c]	30 [d]	
Alston, 1983	40	All									38	◐
Engelbert, 2001 [b]	17	Type I	50[f]									○
	11	Type III								50[f]		
	12	Type IV	50[f]									
Norimatsu, 1982	8	Congenita	0				62				38	○
	14	Tarda	0				86				14	

			Result [g]	Scale	
Engelbert, 1997 [b]	16 [h]	Type I [h]	Mobility = 31 Self-care = 39	PEDI: Median of healthy children ≤ 7.5 y = 50	◐
	8 [h]	Type III [h]	Mobility = 5 Self-care = 31		
	6 [h]	Type IV [h]	Mobility = 10 Self-care = 37		
	16 [i]	Type I [i]	Mobility = 100 Self-care = 100	PEDI: Normal healthy children > 7.5 y = 100	
	6 [i]	Type III i	Mobility = 70		

			Self-care = 41		
	9 [i]	Type IV [i]	Mobility = 93 Self-care = 62		
Bleck, 1981	12	Severe Congenita	Ambulation = 0.7	0 = None 4 = Community walker	○
			Mobility = 3.0	0 = None 4 = Travel beyond community	
			Indep = 2.6	0 = None 4 = Normal activity	
			ADL = 2.5	0 = None possible 4 = Normal ADL	
	12	Tarda	Ambulation = 2.8	0 = None 4 = Community walker	
			Mobility = 3.8	0 = None 4 = Travel beyond community	
			Indep = 3.4	0 = None 4 = Normal activity	
			ADL = 3.7	0 = None possible 4 = Normal ADL	

C = Community walker, N = Neighborhood walker, H = Home walker, Th = Therapy/exercise walker
PEDI = Pediatric Evaluation of Disability Inventory; Indep = Independence, ADL = Activities of daily living

a See Methods, Summary Tables, Study Quality.
b Likely overlap in subjects among studies by Engelbert
c No distinction made between those who require assistance and those who can walk independently
d Bottom shufflers, Sit unsupported only, Sit supported only.
e Non-walkers
f Average child fell into reported category
g Engelbert, 1997: Median scores. Bleck, 1981: Mean scores.
h Children aged ≤ 7.5 years
i Children aged > 7.5 years

Eight papers evaluated ambulation and/or mobility of up to 345 children with short stature due to skeletal dysplasia (Table 12). All evaluated patients with osteogenesis imperfecta.

Osteogenesis Imperfecta

Among eight studies, six reported the frequency of different ambulatory abilities. Two studies scored subjects on scales to estimate ambulation and mobility abilities. Four papers by the same authors are likely to have substantial overlap in subjects. Seven were prospective; one was retrospective. Three were longitudinal; five were cross-sectional. One study was of good quality; five were of fair quality; and two were of poor quality.

Engelbert and co-authors reported on ambulation ability on children with osteogenesis imperfecta in four papers with separate, but probably overlapping groups of children. The largest (Engelbert, Uiterwaal, Gulmans, et al., 2000) evaluated 70 children with either Type I, III, or IV osteogenesis imperfecta who had a mean age of 11 years old. Questionnaires were sent to parents of children with “definite” osteogenesis imperfecta in this prospective cross-sectional study. The study attempted to identify predictors of walking ability in the children. They categorized mobility using a nine-level classification of walking ranging from electric wheelchair bound to independent community walking without cane or crutches. By parent report, most children with Type I disease were community walkers without aides. All children were walkers, but a substantial percentage of children were restricted in their walking ability or required assistance for walking. Of children with Type III disease, almost half were wheelchair bound and all walkers required assistance. Of children with Type IV disease, about a quarter were community walkers without aids, half required assistance with walking, and about a quarter were non-walkers. Using univariate analysis, they found that rolling over by age 8 months, sitting without support by 9 months, and getting to sitting or standing position without support by 12 months

were all correlated with improved chances of walking. Multivariate analysis, however, showed that the most important predictor is the type of osteogenesis imperfecta, or severity of illness. Developmental milestones added little predictive value. The presence of intermedullary rods and dentinogenesis imperfecta were better indicators than development of worse prognosis for most types.

Daly, Wisbeach, Sanpera, Jr., et al. (1996) aimed to compare the ability of the two popularly used classifications of osteogenesis imperfecta to predict walking and general motor development of the child. Questionnaires were mailed to families of children with osteogenesis imperfecta in a prospective cross-sectional study. Questionnaires were returned for 51 children with a mean age of 7 years old. The children were classified into categories described by Shapiro based on radiographic appearance of bones and history of fractures (Congenita A, Congenita B, Tarda A, and Tarda B) and into categories described by Sillence (I, III, and IV). They correlated the classifications with ultimate progression to walking, either aided or independent. Not all categories had sufficient numbers of children for analysis. Substantial percentages of children with either Congenita B or Tarda A osteogenesis imperfecta, or with Type III or IV disease were either wheelchair bound or required assistance with walking. Only one child with Type I disease required assistance with walking. In addition they found that of those children who could sit by 10 months, 76 percent became walkers. Of those who could not independently sit by 10 months, only 18 percent ultimately walked. They concluded that the Sillence classification, the Shapiro classification and the ability to sit independently by 10 months were all predictors of ultimate ability to walk in children with osteogenesis imperfecta. .

In a second report by Engelbert, Beemer, van der, et al. (1999), 42 children with a mean age of 7 years who had osteogenesis imperfecta were followed in a prospective, longitudinal study. Children who had had intramedullary fixation surgery within 6 months or who had any other disability or impairment were excluded. Level of ambulation was measured. At follow-up, half the children with Type I disease were community walkers. All attained at least some degree of walking. Of children with Type III disease, about 40 percent were household or exercise (therapy only) walkers. The rest of the children were wheelchair bound. Of children with Type IV disease, only 10 percent were community walkers. Most children had some walking limitation or required a wheelchair. For all groups of children, it was not clear how many of the children could walk unassisted. Of note, little progression in walking ability occurred over time, particularly in the more severely affected.

In a prospective, cross- sectional study by Alston (1979), 40 children with osteogenesis imperfecta who ranged in age from 5 to 16 years old were evaluated. Type of mobility was examined in an attempt to correlate these with the subject's type of school. Approximately one-third of the children were wheelchair bound. The ambulatory level of the walking children was not reported and the type and severity of osteogenesis imperfecta were not defined for these subjects.

The third study by Engelbert, Gulmans, Uiterwaal, et al. (2001) was a prospective, cross-sectional study of 40 children with osteogenesis imperfecta who had a mean age of 12 years old. The study reported limited data on ambulation ability. Children were categorized by a nine-level classification of walking ability. The mean scores for children with each type of disease were reported. Type I patients had median level of 9 or independent walking. Type III patients had a median level of 2 or capable of at most therapy walking with the aid of crutches or canes. Type IV patients had a median level of 5 or capable of household walking without the use of crutches or canes.

Norimatsu, Mayuzumi, and Takahashi (1982) published a retrospective longitudinal case series of 22 children with osteogenesis imperfecta who were followed for up to 20 years and were between 4 and 22 years at final examination. Walking ability were reported in these patients. Three of the eight children with osteogenesis imperfecta congenita were wheelchair bound; the remainder walked with assistance. Among children with osteogenesis imperfecta tarda, two of 14 were wheelchair bound; the remainder walked with assistance. The low rate of successful walking may have been related to a high prevalence of scoliosis in this sample of children.

In the fourth study by Engelbert, Custers, van der Net, et al. (1997), 61 children with osteogenesis imperfecta were evaluated in a prospective cross-sectional study. Children under age 7.5 years were evaluated separately from those who were between ages 7.5 and 18 years old. Mobility and self-care were evaluated by questionnaires administered to either the parents or children. Younger and older children with Type I osteogenesis imperfecta scored within 2 SD of the test's normal median for mobility. All younger and older children with Type III disease and most with Type IV disease had mobility scores considerably below 2 SD from the median. Younger children with all types of disease and older children with Types I and IV disease scored within 2 SD of the test's normal median for self-care. Only older children with Type III disease were likely to have self-care scores below 2 SD from the normal median.

A study by Bleck (1981) evaluated 24 children with varying degrees of severity of osteogenesis imperfecta who had a mean age of 13 years old at the end of the study. In this prospective longitudinal study children were managed with surgery as needed and orthotics aiming for early weight bearing in order to minimize osteoporosis thereby preventing refracture and deformity. Ambulation and mobility were measured using 5-point scales ranging from no function to no limitation. Those children with the most severe disease (osteogenesis imperfecta congenita) had limitations in activities of daily living, mobility efficiency, and independence and severe limitation in ambulation even after aggressive orthotic management. Those with the mild to moderate osteogenesis imperfecta tarda also had mild limitations in mobility and activities of daily living and moderate limitations in independence and ambulation. Despite the limitations, all 12 with osteogenesis imperfecta tarda attained complete independence in daily living, mobility and ambulation.

Skeletal Dysplasia and Ambulation/Mobility

The eight papers that evaluated mobility and ambulation in children with skeletal dysplasia all included only children with osteogenesis imperfecta. All found significant impairment in ambulation, with greater impairment, as expected, in the patients with more severe disease. Children with the less severe types of osteogenesis imperfecta (tarda, Type I, and Type IV) were more likely to attain some walking capability, but still with a significant amount of assistance. Few children with congenita or Type III disease had any walking ability without assistance. Orthopedic abnormalities such as scoliosis, decreased range of motion, decreased muscle strength and fracture were found to contribute to limitations of ambulation. Although all the studies are relatively small, they are reasonably sized given the rarity of the disorder. Information regarding ambulation and mobility in children with short stature due to other skeletal dysplasias was not found.

Association of Short Stature Due to Skeletal Dysplasia with Limb Range of Motion

Table 13. Limb Range of Motion in Children with Skeletal Dysplasia

Author Year	Joint	Scale	Sample N (Controls)	Category	Measure (Range)	Quality [a]
Achondroplasia						
Bailey, 1971	Elbow	Angle from full extension	41	0-2 years 3-12 years 13-20 years	11° (5°-25°) 19° (10°-40°) 24° (0°-40°)	○
Osteogenesis Imperfecta						
Engelbert, 2001	Arm	0 = Normal 4 = Maximally decreased	17	Type I	0.5	●
			11	Type III	1.8	
			12	Type IV	1.3	
	Leg		17	Type I	0	
			11	Type III	3.3	
			12	Type IV	1.7	

a See Methods, Summary Tables, Study Quality.

Two studies evaluated limb range of motion in children with short stature due to skeletal dysplasia (Table 13). One study evaluated children with achondroplasia. The other evaluated children with osteogenesis imperfecta.

Achondroplasia

One poor quality study evaluated joint range of motion in children with achondroplasia. In a small descriptive paper, Bailey (1971) retrospectively looked at a cross-section of 41 children with achondroplasia, describing upper limb bony abnormalities. The entire study included subjects up to 72 years old. Data are reported for infants to 20 year olds. Nine upper limb abnormalities evaluated. Only two were found frequently in the sample. Almost all children had lack of full elbow extension (93 percent) and some had limited elbow supination (34 percent). Other abnormalities were found infrequently. Degree of elbow flexion deformity worsened with age. Although these orthopedic abnormalities were found, functional limitations were not evaluated. However, “none of the patients volunteered disability from this problem.”

Osteogenesis Imperfecta

One fair quality study evaluated joint range of motion in children with osteogenesis imperfecta. Engelbert, Gulmans, Uiterwaal, et al. (2001), in a prospective, cross-sectional study, measured motor function, including joint range of motion (ROM) in 40 children with osteogenesis imperfecta who had a mean age of 12 years old. Using standard goniometry, the total ROM in the upper and lower extremities were measured. Measurements were evaluated using the Joint Alignment and Motion Scale, where a score of 0 is normal ROM and a score of 4 is maximally decreased ROM. Subjects with Type I disease all had normal or nearly normal ROM in both arms and legs. Subjects with Type III disease had somewhat limited ROM in upper extremities and substantially limited ROM in lower extremities. Subjects with Type IV disease

had somewhat limited ROM in upper and lower extremities. Of note, level of ambulation strongly correlated with joint ROM.

Skeletal Dysplasia and Joint Range of Motion

Two studies demonstrate upper and lower ROM abnormalities in children with achondroplasia and with various types of osteogenesis imperfecta. ROM limitation correlated with functional disability in children with osteogenesis imperfecta but not with achondroplasia.

Association of Short Stature Due to Skeletal Dysplasia with Spinal Curvature

Table 14. Spinal Curvature in Children with Skeletal Dysplasia

Author Year	Sample N (Controls)	Population	Scoliosis Cobb Angle	Scoliosis % of Subjects	Kyphosis Cobb Angle	Kyphosis % of Subjects	Quality [a]
Osteogenesis Imperfecta							
Benson, 1978	103	All	10°-19°	19			●
			20°-49°	14			
			≥ 50°	22			
Engelbert, 1998	17	Type I	> 10°	12	< 10° or > 40°	12	●
	16	Type III	> 10°	63	< 10° or > 40°	75	
	14	Type IV	> 10°	71	< 10° or > 40°	29	
Norimatsu, 1982	8	Congenita	5°-29°	13			○
			30°-50°	0			
			> 50°	87			
	14	Tarda	5°-29°	62			
			30°-50°	15			
			> 50°	23			
Diastrophic Dysplasia							
Poussa, 1991	38	All	> 15°	29			●

a See Methods, Summary Tables, Study Quality.

Four papers assess spinal deformities in 209 children with short stature due to skeletal dysplasia (Table 14). Three studied children with osteogenesis imperfecta; one studied children with diastrophic dysplasia.

Osteogenesis Imperfecta

Three studies evaluated spinal curvature in children with osteogenesis imperfecta. One was prospective studies; two were retrospective. Two were longitudinal; one was cross-sectional. Two studies were of fair quality; one was of poor quality.

Benson, Donaldson, and Millar (1978) evaluated children with osteogenesis imperfecta aged 1 month to 16 years in a retrospective longitudinal study. Scoliosis was measured by roentgenographic measurement in 103 children. Different forms of osteogenesis imperfecta were not analyzed separately. Scoliosis of at least 10 degrees was found in 55 percent of the children. Of note, progression of curvature was common. Younger children had less curvature and older

children had more. Furthermore, in patients for whom more than one radiograph was available, progression was almost always noted.

Engelbert, Gerver, Breslau-Siderius, et al. (1998) reported a prospective cross-sectional study of 47 children with a mean age of 7 years who had osteogenesis imperfecta and were examined for the presence of spinal deformities. Scoliosis was defined as spinal curvature of greater than 10 degrees. Pathologic kyphosis was defined as curvature of less than 10 degrees or more than 40 degrees. Scoliosis was highly prevalent among children with Types III and IV disease and less prevalent in children with Type I disease. Kyphosis was highly prevalent in children with Type III disease; those with Types I and IV disease were less likely to have kyphosis. Of note, no significant association was found between age and presence of scoliosis or pathological kyphosis. Children with scoliosis were twice as likely to also have pathological kyphosis.

Norimatsu, Mayuzumi, and Takahashi (1982) published a retrospective longitudinal study of 22 children with osteogenesis imperfecta followed over the course of 20 years. Evaluation of the scoliosis was performed by Cobb's method on radiographic examinations. All children had some degree of scoliosis (at least 5 degrees). Most children with osteogenesis congenita had severe scoliosis, while most children with osteogenesis tarda had mild scoliosis. Progression of scoliosis was found with age, and rapid progression occurred once curvature exceeded 50 degrees. However, the data for these findings were not reported. Of note, multiple subjects reported were closely related.

Diastrophic Dysplasia

One study evaluated spinal scoliosis in children with diastrophic dysplasia. The study was prospective longitudinal in design and of fair quality. Poussa, Merikanto, Ryoppy, et al. (1991) evaluated 38 children with diastrophic dysplasia, 20 years old or younger. Scoliosis was measured using Cobb's method, and was defined as curvature greater than 15 degrees. Among the whole group, almost a third had scoliosis. Progression of scoliosis was suggested because older subgroups had a higher incidence of scoliosis than younger groups. The mean magnitude of curvature of those with scoliosis was 39 degrees.

Skeletal Dysplasia and Spinal Curvature

Among the four studies reviewed, a high prevalence of scoliosis was found in children with both osteogenesis imperfecta and diastrophic dysplasia. One study also found high prevalence of pathologic kyphosis. None of the papers used control groups for comparison. Although two groups followed their patient longitudinally, progression of spinal deformity was only implied from comparing age groups, as paired measurements were not presented for the majority of subjects. All groups likely represent a selected, perhaps more severe, population of patients followed by academic medical centers.

Association of Short Stature Due to Skeletal Dysplasia with Hearing Loss

Table 15. Hearing Loss in Children with Short Stature Due to Skeletal Dysplasia

Author Year	Sample N (Controls)	Population	Definition	Results	Quality [a]
Achondroplasia				**% of Subjects**	
Brinkmann, 1993	27 (28, 27) [b]	All	Parental Report	63 (18, 19) [c]	●
Ruiz-Garcia, 1997	32	All	Abnormal BAER [d]	50%	○
Osteogenesis Imperfecta				**% of Subjects**	
Kuurila, 2000	45	All	Pure Tone < 20 dB Conductive < 15 dB	7	●
Cox, 1982	15	All	Pure Tone: < 30 dB at < 1000 Hz < 25 dB at > 2000 Hz	33	○
Stewart, 1987	13	All	Pure Tone < 30 dB Conductive < 15 dB	15	○
Skeletal Dysplasia				**Score**	
Apasajalo, 1998	19 (239)	Achondroplasia	Hearing HRQOL	95 [e]	●
		Diastrophic Dysplasia	Hearing HRQOL	93 [e]	
		Cartilage-hair Hypoplasia	Hearing HRQOL	85 [e]	

BAER = Brainstem auditory evoked responses; HRQOL = Health Related Quality of Life

a See Methods, Summary Tables, Study Quality.
b Short controls and normal controls, respectively
c Subgroup of all 13 children with osteogenesis imperfecta
d Abnormal defined as deviation from population normals by at least 3 SD.
e Score (where 100 is normal)

Six studies tested hearing in 151 children with skeletal dysplasia (Table 15). Two studies evaluated children with achondroplasia; three evaluated children with osteogenesis imperfecta; and one evaluated children with a variety of skeletal dysplasias.

Achondroplasia

Two prospective cross-sectional studies evaluated hearing loss in children with achondroplasia. One study was of fair quality; one was of poor quality.

Brinkmann, Schlitt, Zorowka, et al. (1993) evaluated 27 children with achondroplasia with a mean age of 9 years old in a prospective cross-sectional study. The children were compared with 28 children with short stature not due to skeletal dysplasia and 27 normal controls. Controls were matched for age, sex, and socioeconomic status. Hearing deficits were present in 63% of children with achondroplasia as reported by their parents, compared to 18% of short stature controls and 19% of normal controls. Statistical significance of this comparison was not reported. Hearing testing was performed in only some of these patients. Of those reported to have hearing deficits, many had middle ear disease, tympanotstomy tubes, and speech and language delay and difficulty.

Ruiz-Garcia, Tovar-Baudin, Castillo-Ruiz, et al. (1997) prospectively evaluated children with achondroplasia who had a mean age of 4 years old in a cross-sectional study. Children who had prior neurosurgery were excluded. In 32 children hearing was assessed with brainstem auditory

evoked response (BAER) testing. Half of the subjects had abnormal BAER studies revealing hearing loss. It was reported that the children had middle ear lesions due to repetitive ear infections.

Osteogenesis Imperfecta

Three studies evaluated hearing deficits in children with osteogenesis imperfecta. All were prospective cross-sectional studies. One was of fair quality; two were of poor quality.

Kuurila, Grenman, Johansson, et al. (2000) evaluated 45 children with mild to severe osteogenesis imperfecta for hearing loss in a prospective, cross-sectional study. The children had a mean age of 10 years old. All subjects underwent audiometry. Only three of the 45 (7 percent) children were found to have hearing loss. Only two of the children, both with conductive hearing loss, were thought to have hearing loss related to osteogenesis imperfecta. One child had sensorineural deafness in the first year of life thought due to another etiology.

In Cox and Simmons (1982), a prospective, cross-sectional study, 15 children with a mean age of 9 years old with osteogenesis imperfecta had objective audiological evaluation. The children were all from five families. Five of the fifteen children (33 percent) had some degree of hearing loss using a standard definition. All five were characterized as mild conductive loss.

Stewart and O'Reilly (1989) reported on 13 children between 10 and 19 years old with osteogenesis imperfecta. Hearing was tested with audiometry. A prospective cross-sectional examination found that two of the children (15 percent) had hearing loss. One of these two had pure sensorineural hearing loss, which is not considered to be the typical hearing loss of osteogenesis imperfecta, but no other explanation could be found. Of the 11 with no hearing loss, three had abnormal tympanometry possibly suggestive of early conductive hearing loss.

Skeletal Dysplasias

One prospective cross-sectional study evaluated hearing deficits in children with a variety of skeletal dysplasias. The study was of fair quality. Apajasalo, Sintonen, Rautonen, et al. (1998) evaluated 19 adolescent patients (aged 12 to 15 years old) with either achondroplasia, diastrophic dysplasia, or cartilage-hair dysplasia. Hearing function was self-reported on a measure of Health Related Quality of Life, a validated questionnaire tool. They were compared with a large control group of age-matched area students who also completed the questionnaire. There was no difference children with skeletal dysplasias and controls in their self-report of the hearing dimension. No actual hearing testing was performed.

Skeletal Dysplasia and Hearing Loss

Six studies evaluated hearing loss in children with skeletal dysplasia. Only four performed objective hearing testing. One relied on parental reporting and one was a study of health related quality of life. A large proportion of children with achondroplasia were reported to have hearing problems, either by parental report or by BAER testing. The papers that reported on hearing testing in young patients with osteogenesis imperfeca all reported a sizable proportion with hearing loss, although the prevalence varied due to selection and small sample sizes. One study concluded that hearing quality of life was not different among children with a variety of skeletal dysplasias as normal controls.

Association of Short Stature Due to Skeletal Dysplasia with Respiratory Dysfunction

Sleep Apnea

Table 16. Sleep Apnea in Children with Short Stature Due to Skeletal Dysplasia

Author Year	Sample N (Controls)	Population	% with Sleep Apnea			Quality [a]
			Central Hypopnea	Central Apnea	Obstructive Apnea	
Achondroplasia						
Waters, 1993	20 [b]	All		75		◐
Pauli, 1995	35	All	40	66	23	○
Reid, 1988	26	All			35	○
Hecht, 1991	13	All	7 [c]		15	○

a See Methods, Summary Tables, Study Quality.
b 15 children; 5 adults
c Hypoxemia and respiratory acidosis

Four studies evaluated sleep abnormalities in 94 children with short stature due to skeletal dysplasia. All evaluated patients with achondroplasia and reported the percentage of children with either hypopnea or apnea during sleep. All were prospective. Two were longitudinal; two were cross-sectional. One study was of fair quality; and three were of poor quality.

Achondroplasia

Waters, Everett, Sillence, et al. (1993) performed overnight sleep studies on 20 patients with achondroplasia to measure and characterize the types of apnea and other respiratory abnormalities in a prospective cross-sectional study. Fifteen of the subjects were aged 1 to 14 years old; five were between 20 to 31 years old. All subjects had at least snoring, implying at least some degree of airway obstruction during sleep. Three-quarters had abnormal frequency of apnea. Of the 15 subjects with apnea, 12 had periodic breathing (called “cyclic apnea” in this paper) and 9 had obstructive apnea. Because the sleep apnea seen in achondroplasia is thought to be due to constriction of the brainstem because of abnormal shape and size of the skull base, they also performed a test of brainstem dysfunction, somatasensory evoked potentials (SEP) in 19. More than half the subjects had normal studies; abnormal results in were found in 42 percent. Abnormal SEP did not correlate with sleep abnormalities, and could not be used to predict the sleep respiratory abnormalities.

Pauli, Horton, Glinski, et al. (1995) evaluated 35 infants and young children with achondroplasia in a prospective longitudinal study. The children were followed for clinical problems attributable to cervicomedullary junction compression. Overnight polysomnography revealed frequent central apnea, central hypopnea, and/or obstructive apnea.

Reid, Pyeritz, Kopits, et al. (1988) conducted a prospective longitudinal evaluation of 26 children under 7 years old with achondroplasia. Three-quarters of the children had been referred to the clinic for various undefined symptoms. History, physical examination, and respiratory evaluation including arterial blood gases, electrocardiogram, echocardiogram, chest radiograph,

and multi-channel polysomnography were performed. By history 22 subjects (85 percent) had respiratory abnormality in the preceding 6 months, including pneumonia, loud snoring, cyanotic spells, or apnea. On testing, 85 percent of the subjects had respiratory abnormalities, such as hypoxemia, hypercapnea, pulmonary infiltrates, abnormal right systolic time intervals on echocardiography, right ventricular hypertrophy on electrocardiogram, and apnea. One-third of subjects had obstructive apnea. An unreported number of those with obstructive apnea also had central apnea. The subjects evaluated were highly selected patients, in that most were referred for respiratory and/or neurological symptoms, and the others were followed in a tertiary center.

In a prospective, cross-sectional study, Hecht, Thompson, Weir, et al. (1991) evaluated 13 infants with achondroplasia. Four of the subjects had a history consistent with respiratory dysfunction, including one with tachypnea, two with obstructive apnea, and one with daytime apnea. Three of the infants were also found to have abnormal polysomnograms showing obstructive apnea or hypoxemia with respiratory acidosis. The subjects were a small, selected group, in that five of them were referred for symptoms of the complications they were studying.

Skeletal Dysplasia and Sleep Apnea

Of the four papers evaluating sleep and respiratory dysfunction in children with achondroplasia, all found a high incidence of abnormality, including central hypopnea, central apnea, and obstructive apnea. All four papers, however, reported on small groups; two of which were highly selected samples.

Pulmonary Function

Table 17. Pulmonary Function in Children with Short Stature Due to Skeletal Dysplasia

Author Year	Sample N (Controls)	Population	Pulmonary Function % Predicted or mm Hg					Quality [a]
			FVC	RV	FEV_1 / FVC	P O_2	P CO_2	
Achondroplasia								
Stokes, 1988	24	All	**72%** [b]					O
Osteogenesis Imperfecta								
Falvo, 1973	10	All	85 [c]	119 [c]	99	88	35	O

FVC = Forced vital capacity; FEV_1/FVC = Forced expiratory volume in 1 second divided by forced vital capacity; P O_2 = Oxygen partial pressure; P CO_2 = Carbon dioxide partial pressure; RV = Residual volume

a See Methods, Summary Tables, Study Quality.
b Significantly lower than population norms
c Reduction of FVC and increase in RV were found only in subjects with kyphoscoliosis

Two studies measured pulmonary function in children with skeletal dysplasias (Table 17). One study evaluated children with achondroplasia. The other evaluated children with osteogenesis imperfecta.

Achondroplasia

One study of fair quality evaluated pulmonary function in children with achondroplasia. Using a prospective, cross-sectional cohort design, Stokes, Pyeritz, Wise, et al. (1988) systematically measured pulmonary function tests in 24 children under age 18 years old with achondroplasia. Mean forced vital capacity for the group of children was significantly lower than predicted values for children with comparable sitting height. Although only a small number of children were included, the sample evaluated was relatively unselected, and probably is broadly representative of the average child with achondroplasia.

Osteogenesis Imperfecta

One study of fair quality evaluated pulmonary function in children with osteogenesis imperfecta. Falvo, Klain, Krauss, et al. (1973) performed pulmonary function testing on 10 children between ages 4 and 19 years old with osteogenesis imperfecta of varying severity. While it was implied that the data were collected prospectively for a cross-section of patients, the study methodology is unclear. Results were compared with population norms. Vital capacity and residual volume were abnormal only in the four subjects who also had kyphoscoliosis. No patient had severe hypoxemia or hypercapnea. Other parameters of pulmonary function were within normal limits. The number of subjects is small, and no statistical comparisons were reported.

Skeletal Dysplasia and Pulmonary Function

One study found abnormal pulmonary function in a small group of children with achondroplasia. A second study found no significant abnormality in a smaller group of children with osteogenesis imperfecta.

Association of Short Stature Due to Skeletal Dysplasia with Psychological Outcomes

Table 18. Psychological Outcomes in Children with Skeletal Dysplasia

Author, Year	Sample N (Controls)	Population	Measure	Results [a]	Quality [b]
Skeletal Dysplasia					
Hunter, 1998	55 (37)	Not defined	BDI score (mean)	6.5 [6.4]	O
			Moderate to severe depression (%)	7% [11%]	
			SSTAI score- State (mean)	27.6 [27.9]	
			SSTAI score- Trait (mean)	32.5 [31.7]	

BDI = Beck Depression Inventory; SSTAI = Spielberger State-Trait Anxiety Inventory Score

a Results of normal controls are in brackets.
b See Methods, Summary Tables, Study Quality.

Only one paper was found that adequately studied the association of short stature due to skeletal dysplasia with psychological outcomes (Table 18). It was a prospective cross-sectional study that was of fair quality. Hunter (1998) evaluated 55 children aged less than 15 years old with the diagnosis of primary skeletal dysplasia. Levels of depression and anxiety were assessed using the Beck Depression Inventory, childhood version, and the Spielberger State-Trait Anxiety Inventory, respectively. Average scores on the Beck inventory and percentage of children with moderate or severe depression were similar for children with skeletal dysplasia as their sibling controls. Likewise, Spielberger inventory scores for both state (current level of anxiety) and trait (proneness toward developing anxiety) were similar for children with skeletal dysplasia and controls. In fact, the trait anxiety scores for children were below (implying less anxiety) general population norms.

The single study of depression and anxiety among children with skeletal dysplasias found no evidence for increased rates of depression or anxiety.

Question 3. What is the evidence that a sustained decrease in linear growth velocity can be used as a marker of severity of an underlying disease? Is such a process likely to be disabling?

See Evidence Table 3.

We reviewed 53 articles that evaluated whether a sustained decrease in linear growth velocity can be used as a marker of the severity of 12 medical conditions and whether such a process is likely to be disabling. One study separately evaluated children with both asthma and congenital heart disease. The evidence from four conditions - congenital heart disease, Crohn's disease, juvenile rheumatoid arthritis, and human immunodeficiency virus (HIV) infection - appear to indicate that a sustained decrease in linear growth velocity can be used as a marker of the severity of these underlying conditions. Evidence is less clear for asthma, diabetes, ß-thalassemia, chronic kidney failure, and atopic dermatitis. There was only one study each for cerebral palsy, sickle cell anemia and congenital adrenal hyperplasia, so it is difficult to draw conclusions for these conditions. None of the studies addressed the question of whether the process of having a decreasing linear growth velocity was likely to be disabling. Detailed information on all 31 papers is reported in Evidence Table 3.

Association of Severity of Asthma with Decreased Growth Velocity

Table 19. Height Association with Severity of Asthma

Author Year	General-izability [a]	Sample N	Population	Disease Severity	Height [b,c]	Height Velocity [b,c]	Quality [a]
Neville 1996	🧍🧍🧍	699	Asthmatic children	Low potency medications	⇔		●
				High dose inhaled steroids	⬆		
Martin 1981	🧍🧍🧍	315 [d]	Age 10 y	Mild - Severe	⇔		●
				Very severe	⬆		
			Age 14 y	Mild - Severe	⇔		
				Very severe	⬆		
			Age 21 y	Mild - Very severe	⇔		
McNicol 1970	🧍🧍🧍	226	Asthmatic children	Frequency of asthma episodes	⇔		●
Rona 1980	🧍🧍🧍	102	Asthmatic children	Frequency of asthma episodes	⬆ unadjusted ⬆ adjusted [e]	⇧ unadjusted ⇧ adjusted [e]	●
Hauspie 1979	🧍🧍	500	Asthmatic boys	Class II-IV (Osváth)	⬆		●
		607		CARA vs asthma vs asthma w/eczema	⬆		
				Steroid requirements	⬆		
Sant'Anna 1996	🧍🧍	514	Asthmatic children	Mild - Severe	⇧		●
Spock 1965	🧍🧍	200	Asthmatic children	Poor - Excellent		⇧	●
Ferguson 1982	🧍	36	Short asthmatic children	Mild-Severe	⇔		●
Cernelc 1975	🧍🧍	337	Asthmatic children	Pulmonary function	⇔		○
Klein 1991	🧍🧍	176	Non-steroid-dependent asthmatic	Mild-Moderate	⇔		○
Balfour-Lynn 1986	🧍🧍	66	Asthmatic children	Medications required	⇔ initial height ⇔ adult height	⇔	○

CARA = Chronic aspecific respiratory affection

a See Methods…

b Univariate analysis, unless noted otherwise.
c ⇧ Non-significant trend toward more severe asthma associated with growth retardation (or no statistical analysis)
⬆ More severe asthma significantly associated with growth retardation
⇔ No association between asthma severity and growth retardation.
d Same children at different ages.
e Adjusted for parental height, socioeconomic status, and number of siblings.

Eleven studies evaluated the association between severity of asthma and height or height velocity in 3,778 children (Table 19). Only three of the studies measured height velocity; 10 studies measured only the association of severity of disease with height. Each study used its own definitions of severity of disease classifications. Five used various scales to directly measure severity, two measured frequency of asthma episodes, two graded severity based on medication requirements, one measured pulmonary function, and one used a disease severity scale in one group of children and both disease subtypes and steroid requirements in a second group of children. Seven studies were prospective; four were retrospective. Six studies were longitudinal; five were cross-sectional. No study was of good quality; nine were of fair quality, and two were of poor quality.

In a secondary analysis of a prospective longitudinal cohort of 2,915 children with asthma, Neville, McCowan, Thomas, et al. (1996) evaluated height measurements in 699 children aged 3 to 13 years old. Children were grouped based on their medication requirements over the previous year. Only children who required high dose inhaled steroids had a mild decrease in height in comparison to the general local population. Children who required less intense therapy were of equivalent height in comparison to the general local population. Height velocity was not measured.

Martin, Landau, and Phelan (1981) reported on a prospective longitudinal cohort study of 315 children with asthma who were examined at 10, 14 and 21 years of age. Disease severity was based on the frequency and recency of wheezing episodes. Height percentile was compared to that of 62 non-asthmatic children evaluated at the same ages. Children with very severe asthma were significantly more likely to have height less than tenth percentile than non-asthmatic children at 10 and 14 years old, but by 21 years of age, there was no significant difference in the prevalence of height less than tenth percentile between groups. Height velocity was not measured.

Mcnicol, Williams, and Gillam (1970) reported on a prospective longitudinal cohort study of 226 children with asthma and 94 controls at age 10 years. Asthmatic children were grouped as mild, moderate and severe based on number of episodes of asthma by age 10 years and symptoms within 12 months of examination. Children with asthma were evaluated for height and compared to non-asthmatic controls. There was no significant difference in height found between the control group and any group of asthmatic children regardless of degree of severity of asthma. Height velocity was not measured.

In a retrospective cross-sectional study of 102 5 to 11 year old children attending primary school in the United Kingdom, Rona and du (1980) reported on children identified with asthma based on parental report. Severity of disease was graded by number of asthma episodes a year. Height velocity, measured as centimeters gained in the previous 12 months, was lower for both boys and girls with more frequent asthma (3 or more asthma episodes per year) than for children with less frequent asthma, who also had lower height velocity than non-asthmatic controls. However, the difference in height velocities were not statistically significant in unadjusted

models or models that adjusted for parental height, social class, and number of siblings. In both unadjusted and adjusted models, children with frequent asthma were significantly shorter (mean of –0.4 SDS) than controls. Children with less frequent asthma were of similar height as controls.

In a retrospective cross-sectional study, Hauspie, Gyenis, Alexander, et al. (1979) reported on two different samples of 3 to 16 year old boys with asthma (500 Hungarian boys in institutional setting and 607 Belgian boys who were a sub-sample of a longitudinal growth study). Among the Hungarian boys, severity of disease was based on Osvath (1976). Belgian boys were categorized as having either chronic aspecific respiratory affection, asthma alone, or asthma with eczema; steroid requirements were also measured. The study found similar results for both groups. Height was retarded in subjects with more severe disease and longer duration of corticotherapy. It is unclear if those with more severe disease had more steroid use. Height velocity was not measured.

Sant'Anna, Sole, and Naspitz (1996) reported a retrospective cross-sectional case series of 514 6 month to 16 year old children with various degrees of asthma. Children were measured upon admission to an asthma/allergy clinic. Asthma severity was based on the International Consensus Report on Diagnosis and Treatment of Asthma (International consensus report on diagnosis and treatment of asthma, 1992). Heights were compared to National Standards for age (National Center for Health Statistics standard) and the number of children with heights less than third percentile were noted. No significant increase in short stature was noted for the asthmatics in this study. Moreover, age, asthma severity, and steroid use had no statistically significant effect on heights of these asthmatic children. Height velocity was not measured.

Spock (1965) reported on a retrospective longitudinal cohort study of 200 children with asthma (initial age 4-12 years old) who had growth parameters followed for at least 4 years. Asthma severity was graded poor to excellent, although the scale was not defined. Height velocity was approximately normal in all groups of children. Children with excellent clinical status had height velocity 9 percent above normal values established by the Child Research Council of the University of Colorado. Children with good clinical status had height velocity 7 percent above normal, those with fair clinical status had height velocity 2 percent above normal, and those with poor clinical status had height velocity 3 percent below normal. These differences were not statistically different. The study also found that appropriate asthma therapy did not result in a growth spurt, but that steroid therapy dosage and duration was associated with retarded growth in asthmatic children.

Ferguson, Murray, and Tze (1982) evaluated 36 3 to 17 year old asthmatic children with short stature (height less than third percentile) in a prospective longitudinal study. Disease severity was based on wheezing frequency and duration, therapy requirements and duration. No significant association was found between height and severity of asthma. Height velocity was not measured.

Cernelc and Cernelc (1974) reported on a prospective cross-sectional study of 337 asthmatic children. The children’s ages were not reported. Asthma severity was based on normal versus abnormal pulmonary function tests. No significant difference in height was found between the two groups of children. Height velocity was not measured.

In a prospective cross-sectional study Klein, Dungy, and Galant (1991) evaluated 176 2 to 15 year old children with non-steroid dependent asthma. Asthma severity was based on hospitalization and medication requirements over the previous year. No significant difference was found between the height and asthma severity. Height velocity was not measured.

Balfour-Lynn (1986) reported on a prospective longitudinal study of 66 2 to 12 year old children who were followed for height from entrance into a pediatric asthma clinic until they reached adult heights. Disease severity was based on medication requirements. No significant difference was found "growth retardation," although this term was not defined. The proportion of children with height less than the tenth percentile was similar in all groups; no child had height below the third percentile. All children "grew along expected centile lines without appreciable deviation… until age 10 years, regardless of treatment required."

Among the 11 reviewed studies, the evidence of the association between asthma severity and children's heights were mixed. Four studies found a significant association between the severity of asthma and height; one found a non-significant trend toward an association; and five found no association between asthma severity and height. No study found an association between mild asthma and growth retardation. The three studies that examined the association of asthma severity and height velocity did not find a statistically significant association between the two, although two studies found a possible trend toward slower height velocity with more severe asthma.

Poorly defined samples, limited data and analysis, missing data and varying definitions of disease severity limited these studies. Asthma severity was commonly defined by medication requirements, including steroid treatment. The underlying question of how growth is affected by severity of asthma is not clearly answered by these studies in part due to lack of consistency in defining asthma severity between the studies as well as differences in the treatment of asthma in the studies.

Association of Severity of Congenital Heart Disease with Decreased Growth Velocity

Table 20. Growth Retardation Association with Severity of Congenital Heart Disease

Author Year	General-izability [a]	Sample N	Population	Disease Severity	Height [b,c]	Height Velocity [b,c]	Quality [a]
Levy 1977	🚹🚺	777	Ventricular septal defect	Severity based on pressure and resistance	⬆		⭘
Strangway 1976	🚹🚺	181	Congenital heart disease, Age 0-2 y	Cyanosis		⬆	⭘
				Cardiac enlargement		⇔	
				Congestive heart failure		⇧	
		387	Congenital heart disease, Age 2-11 y	Cyanosis		⇔	
				Cardiac enlargement		⇔	
				Congestive heart failure		⇧	
Baum 1980	🚹🚺	26	Congenital heart disease	Congestive heart failure	⬆		⭘

Author Year	General-izability [a]	Sample N	Population	Disease Severity	Height [b,c]	Height Velocity [b,c]	Quality [a]
Feldt 1969	🚹🚹	73	Aortic or pulmonary stenosis	Valvular gradient > 50 mm Hg	⇧		○
		83	Tetralogy of Fallot	Various including hemoglobin	⇔		
		155	Ventricular septal defect	Pulmonary vascular pressure	⇔		
Cernelc 1975	🚹🚹	22	Congenital heart disease	Cyanosis	⬆		○
White 1970	🚹	80	Congenital heart disease	Cyanosis	⬆		○

a See Methods…
b Univariate analysis, unless noted otherwise.
c ⇧ Non-significant trend toward more severe cardiac disease associated with growth retardation (or no statistical analysis)
⬆ More severe cardiac disease significantly associated with growth retardation
⇔ No association between cardiac disease severity and growth retardation.

Six studies evaluated the association between severity of congenital heart diseases and height or height velocity in 1,784 children (Table 20). Only one study measured height velocity; the other five measured only the association of severity of disease with height. Each study used its own definitions of disease classifications. Multiple different heart defects were examined. Five studies were prospective; one was retrospective. Three studies were longitudinal; three were cross-sectional. No study was of good quality; three were of fair quality; and three were of poor quality.

Levy, Rosenthal, Miettinen, et al. (1978) evaluated 777 children with ventricular septal defect (VSD) with a mean age of 4 years old in a retrospective longitudinal study. Subjects were evaluated for growth and hemodynamic severity based on pulmonary artery pressure and systemic resistance ratio. The study found that children with VSD had subnormal height, regardless of the severity of the defect and that the more severe the hemodynamic disturbance, the shorter the children. Height velocity was not evaluated.

Strangway, Fowler, Cunningham, et al. (1976) evaluated two groups of children with a variety of congenital heart defects in a prospective longitudinal study. The study evaluated 181 infants to age 2 years and 387 children between 2 and 11 years old. Children with additional major congenital lesions or who had undergone corrective cardiac surgery were excluded. The children were classified by the presence of cyanosis, cardiac enlargement, and congestive heart failure. Overall, short stature was uncommon and growth rates were close to normal for both infants and children. Among cyanotic infants, height velocities were significantly delayed compared to those infants without cyanosis. Cyanosis was not associated with height velocity in older children. Cardiac enlargement and congestive heart failure were not significantly associated with height velocity in either infants or children.

In a prospective cross-sectional study Baum, Beck, Kodama, et al. (1980) evaluated 26 children with a variety of acyanotic congenital heart diseases and a mean age of 4 years. Disease

severity was based on congestive heart failure (CHF), although this was not defined. The study found that children with acyanotic congenital heart disease with CHF had a significant reduction in height (by 5 to 9 cm) in comparison to children without CHF. Furthermore, half the children with CHF had height less than the fifth percentile, while none of the children without CHF did. Height velocity was not analyzed.

Feldt, Strickler, and Weidman (1969) reported on 311 children of all ages with a variety of congenital heart diseases in a prospective longitudinal study. For children with aortic or pulmonary stenosis, disease severity was based on valvular gradient. For children with tetralogy of Fallot, disease severity was based on cyanosis, hematocrit level, magnitude of shunt, and history of hypoxemia. For children with VSD, disease severity was based on pulmonary vascular pressure. Growth failure was based on both height and weight being more than 2 SD below the mean. Among the 73 children with valvular stenoses, those with pressure gradients above 50 mm Hg were more likely to have "severe growth failure." Among the 83 children with tetralogy of Fallot, growth failure was not associated with any of the measures of defect severity. Among the 155 children wit VSD, growth failure was not associated with pulmonary vascular pressure. However, no statistical analyses were explicitly reported. Height velocity was not analyzed.

Cernelc and Cernelc (1974) evaluated 22 children with congenital heart disease in a prospective cross-sectional study. The age of the children and the types of heart defects among the children were not reported. Disease severity was based on the presence of cyanosis. The study found that children with cyanotic congenital heart disease were significantly shorter than the general population while those without cyanosis were not significantly different in height than the general population. Height velocity was not analyzed.

White, Jr., Jordan, Fischer, et al. (1971) evaluated 80 12 to 18 year old children with a variety of congenital heart diseases in a prospective cross-sectional study. Children who had undergone total corrective surgery for tetralogy of Fallot were excluded. Disease severity was based on the presence of cyanosis. Of the children with cyanosis, 19 percent had height less than the second percentile compared to only 2 percent of the children without cyanosis. However, no statistical analysis was performed. Height velocity was not analyzed.

Among the reviewed studies, there was general agreement that those children with more severe congenital heart disease were more likely to have growth retardation. One study, however, found no association between height and severity of either tetralogy of Fallot or VSD. Only one study evaluated height velocity and found that reduced height velocity was associated with cyanosis in infants; however, the association was not found in older children. They also found a trend toward reduced height velocity being associated with the presence of CHF. Many studies were limited by incomplete data and statistical analysis and some studies were limited because they excluded children with the most severe congenital heart defects.

Association of Severity of Insulin Dependent Diabetes Mellitus with Decreased Growth Velocity

Table 21. Growth Retardation Association with Control / Severity of Insulin Dependent Diabetes Mellitus

Author Year	General-izability [a]	Sample N	Population	Disease Severity	Height [b,c]	Height Velocity [b,c]	Quality [a]
Wise 1992	🧍🧍🧍	122	Type I DM	Hgb A_{1c}		⬆	●
Soliman 1996	🧍🧍🧍	45	Type I DM	Hgb A_{1c} > 10%		⬆	●
Court 1982	🧍🧍🧍	111	Diabetes	Glucosuria	⬆	⬆	◉
Izumi 1995	🧍🧍🧍	107	Type I DM	Hgb A_{1c}	⇔		◉
Salardi 1987	🧍🧍🧍	79	Type I DM	Hgb A_{1c}	⇔	⇔	◉
Pitukchee-wanont 1995	🧍🧍	82	Type I DM	Hgb A_{1c}	⇔ unadjusted ⇔ adjusted [d]	⇔	◉
Arreola 1991	🧍🧍🧍	~198	Type I DM	Hgb A_{1c}		⬆	○
Rosenbloom 1982	🧍🧍	142	Type I DM	Limited joint mobility	⬆		○
Jivani 1973	🧍🧍	104	Diabetes	Poor or Good	⇔	⇔	○
Herber 1988	🧍🧍	67	Type I DM	Hgb A_{1c}		⇔	○
Vanelli 1992	🧍	42	Type I DM pubertal girls	Insulin requirement		⬆	○

DM = Diabetes mellitus; Hgb A_{1c} = Glycosylated hemoglobin
a See Methods…
b Univariate analysis, unless noted otherwise.
c ⬆ More severe diabetes significantly associated with growth retardation
⇔ No association between diabetes severity and growth retardation.
d Multivariate analysis adjusting for age of diabetes onset and initial height

Eleven studies evaluated the association between severity of diabetes mellitus and height or height velocity in 1,099 children (Table 21). Nine of the studies clearly include only children with Type I diabetes; the remaining two only imply that they are evaluating insulin dependent diabetes. No study explicitly evaluates children with Type II diabetes. All but two of the studies measured height velocity. Six studies measured the association of severity of disease with height. Various definitions of severity of disease were used. Seven used glycosylated hemoglobin (i.e., hemoglobin A_{1c}, Hgb A_{1c}) levels to determine disease severity. The remaining studies use either glucosuria, limited joint mobility, insulin requirements, or a scale based on a variety of signs and symptoms. Five studies were prospective; six were retrospective. Ten studies were longitudinal; one was cross-sectional. Two studies were of good quality; four were of fair quality, and five were of poor quality.

Wise, Kolb, and Sauder (1992) evaluated 122 children with Type I diabetes in a prospective longitudinal study over a 5-year period. No data were reported on the age of the children. Height velocity and glycemic control, using Hgb A_{1c} levels, were assessed. A significant linear relationship was seen between Hgb A_{1c} and growth velocity. The most severe growth retardation

occurred when Hgb A_{1c} levels were greater than 16 percent. These children had average height velocity 0.07 SDS below the mean. In contrast, Hgb A_{1c} levels less than 8 percent were associated with growth acceleration; average height velocity was 0.10 SDS above the mean. The level of Hgb A_{1c} at which growth suppression occurred was dependent on pubertal status. Children who were prepubertal or in the early stages of puberty were most vulnerable to growth suppression. For these children growth suppression was seen with Hgb A_{1c} greater than 8 percent.

In a prospective longitudinal study Soliman, Ahmed, and Asfour (1996) evaluated 45 children aged 2 to 12 years with Type I diabetes who had height velocity and glycemic control evaluated. Good glycemic control was defined as Hgb A_{1c} less than 10 percent. Children with good glycemic control had significant higher growth velocity (mean +0.75 SDS) than those with poor glycemic control (mean –1.6 SDS).

Court, Parkin, Roberts, et al. (1982) evaluated 121 diabetic children with a mean age of 13 years in a retrospective cross-sectional study. The study implied only that the subjects all had Type I diabetes. Diabetic control was measured by urinary glucose score or by 24-hour urinary glucose excretion. Children whose diabetes was under poor control had average height (–0.96 SDS) that was significantly lower than those under good control (–0.22 SDS). Likewise, average height velocity was significantly lower for children under poor control (–1.22 SDS) than those under good control (–0.61 SDS).

Izumi, Hoshi, Kuno, et al. (1995) evaluated 107 Type I diabetic children with a mean age of 14 years old in a retrospective longitudinal study. Severity of diabetes was based on Hgb A_{1c} levels and were graded mild (less than 10 percent), moderate (10 to 12 percent) and severe (more than 12 percent). The study found no height and diabetic control. Height velocity was not evaluated.

Salardi, Tonioli, Tassoni, et al. (1987) evaluated 79 children ranging in age from 1 to 15 years with Type I diabetes in a prospective longitudinal study. Diabetics control was measured by Hgb A_{1c} levels. Height and height velocity were not associated with diabetic control.

In a retrospective longitudinal cohort study Pitukcheewanont, Alemzadeh, Jacobs, et al. (1995) evaluated 82 children with Type I diabetes with a mean age of 11 years old over a 6-year period. Glycemic control was determined with Hgb A_{1c} levels. There was no association between mean Hgb A_{1c} and height in univariate or multivariate analyses. There was also no association between Hgb A_{1c} and height velocity at any Tanner stage in univariate analysis.

Arreola, Junco, Partida-Hernandez, et al. (1991) reported on a retrospective longitudinal cohort study of about 198 children with Type I diabetes. The children's medical records were examined yearly for five years. They were between 1 and 16 years old in the first year evaluated. The exact number of children included varied from year to year. Diabetic control was based on Hgb A_{1c} levels. Children with poor control (Hgb A_{1c} greater than 11 percent) had significantly lower height velocity (approximately 0.54 cm/month) compared to those with good control (approximately 0.22 cm/month). Overall, there was a significant correlation between Hgb A_{1c} level and height velocity.

Rosenbloom, Silverstein, Lezotte, et al. (1982) performed a prospective longitudinal cohort study of 142 pre-pubertal children with diabetes who had had diabetes for at least 3 years. The study used joint mobility as an indication of severity of microvascular disease. Diabetic children with mild, moderate or severe limitations of joint mobility were significantly more likely to be below the 25th percentile for height than those without limited joint mobility. However, the correlation between Hgb A_{1c} and joint mobility was poor. There were no data on height velocity

Jivani and Rayner (1973) evaluated 104 diabetic children aged between 9 months and 13 years old in a retrospective longitudinal study. Diabetes control was measured good, fair or poor based on ketonuria, glycosuria, serum glucose, and hypoglycemic reactions. Data on subjects with "fair" control were not reported. Height and height velocity were not associated with severity of diabetes.

Herber and Dunsmore (1988) evaluated 67 children with Type I diabetes who had an initial mean age of 11 years and were followed over 3 years in a retrospective longitudinal study. Disease severity was based on Hgb A_{1c} levels. The study found no association between change in height and Hgb A_{1c}. Height velocity was also similar to the general population. The range of diabetes severity was somewhat limited in that, in general, the study population was in good control.

Vanelli, de Fanti, Adinolfi, et al. (1992) evaluated 42 girls with Type I diabetes who became diabetic at the onset of puberty in a prospective longitudinal study. Diabetes severity was insulin requirements. It is likely that the children were stratified into high and low insulin requirement groups *post hoc*. The children treated with greater amounts of insulin had lower mean Hgb A_{1c} (9 percent) and significantly higher mean peak height velocity (8.5 cm per year) than those treated with less insulin (Hgb A_{1c} 10 percent; peak height velocity 6.9 cm per year).

Among the reviewed studies, there were mixed results correlating severity of diabetes with height and height velocity. Five studies demonstrated a positive relationship between poor diabetes control/increased severity of disease and decreased growth velocity; four studies found no association. Two studies found an association between markers of severity of diabetes and height; three found no association. Several studies associated growth deceleration with peripubertal onset of illness. Some studies were limited because they did not use a well-defined, objective measure like Hgb A_{1c} to assess severity/control. Some studies were limited by unclear statistical analysis, lack of specific data included or summary results.

Association of Severity of b-Thalassemia with Decreased Growth Velocity

Table 22. Growth Retardation Association with Hemoglobin Level / Severity of b-Thalassemia

Author Year	General-izability [a]	Sample N	Population	Disease Severity	Height [b,c]	Height Velocity [b,c]	Quality [a]
Kattamis 1970	🧍🧍🧍	74	β-thalassaemia	Hemoglobin	⬆		○
Madeddu 1978	🧍🧍🧍	50	β-thalassaemia	Hemoglobin	⇔		○
Constantoulakis 1975	🧍🧍	171	β-thalassaemia	β-thalassemia severity index	⇧ [d]		○
				Hemoglobin	⇧ [d]		
				Total blood transfusion	⇔ [d]		

a See Methods…
b Univariate analysis, unless noted otherwise.
c ⇧ Non-significant trend toward more severe β-thalassemia associated with growth retardation (or no statistical analysis)
⬆ More severe β-thalassemia significantly associated with growth retardation
⇔ No association between β-thalassemia severity and growth retardation.
d Linear regression model adjusting for age and other variables listed.

Three studies evaluated the association between severity of β-thalassemia and height in 295 children (Table 22). None of the studies measured height velocity. All the studies used hemoglobin levels to grade severity of disease. One study also used a severity index and blood transfusion requirements to grade disease severity. Two were prospective cross-sectional studies; one was a retrospective longitudinal study. All studies were of poor quality.

In a prospective cross-sectional study, Kattamis, Touliatos, Haidas, et al. (1970) evaluated 74 children aged 1 to 11 years old with homozygous β-thalassemia. Subjects height percentiles were compared in reference to the severity of their anemia. Severity of anemia was determined by pre-transfusion hemoglobin (Hgb) concentration. Children were transfused either when Hgb was at levels greater than 8 mg/dL, between 6 and 8 mg/dL, or below than 6 mg/dL. Children with higher pre-transfusion Hgb were significantly taller (mean height of 56th percentile) than children with moderate Hgb levels (22nd percentile) and lower Hgb (7th percentile). However, the study may have confounded disease severity with treatment options. The children in the moderate anemia group were not followed as regularly and were either of low socioeconomic status or had to travel long distances for transfusion. The children in the severe anemia group mostly were allowed to have their Hgb levels fall below 5 mg/dL before transfusion. Height velocity was not evaluated.

Madeddu, Dore, Marongiu, et al. (1978) evaluated 50 children with homozygous β-thalassemia ages 2 to 13 years old in a prospective cross-sectional study. Severity of disease was based on pre-transfusion Hgb levels. Children with height less than the 3rd percentile had somewhat lower mean Hgb (6.6 g/dL) than taller children (approximately 7.1 g/dL). There was no significant association between Hgb level and height. Height velocity was not evaluated.

In a retrospective longitudinal, Constantoulakis, Panagopoulos, and Augoustaki (1975) evaluated 171 patients aged 7 months to 28 years with homozygous β-thalassemia. A variety of measures were used to determine disease severity. These measures were included in a multiple regression analysis to determine the association between height and the measures. A “severity of disease index” was created that was based on the amount of blood transfused in the previous two years. The regression also included total blood transfused since birth, mean Hgb level of the previous two to four years, and age. Of note is that none of the variables included in the model are independent of other included variables. In the model there was a trend toward lower height percentiles being associated with low Hgb levels and severity of disease index; however, neither was statistically significant in a linear regression controlling for age. Total blood transfused since birth was not associated with height. Height velocity was not evaluated.

Among the three reviewed studies, the evidence of the association between β-thalassemia severity and children’s heights was inconclusive. One study found a significant association between pre-transfusion Hgb and height. However, the study may have confounded underlying severity of disease with treatment choices. Another study may have found some evidence of an association between disease severity and height, but the value of their finding is limited by the poor regression technique used. The third study found no association, although a trend may have been indicated.

Association of Severity of Inflammatory Bowel Disease with Decreased Growth Velocity

Table 23. Growth Retardation Association with Severity of Inflammatory Bowel Disease

Author Year	General-izability [a]	Sample N	Population	Disease Severity	Height [b,c]	Height Velocity [b,c]	Quality [a]
Saha 1998	🧍🧍🧍	29	UC	Disease severity	⇧	⬆	⭘
		18	Crohn's		⇧	⬆	
Griffiths 1993	🧍🧍	100	Crohn's	Frequency / Chronicity	⇔	⬆ [d]	⭘
				Disease location	⇔	⇔	
Farmer 1979	🧍🧍	513	Crohn's	Disease location	⇔		○

UC = Ulcerative colitis

a See Methods…
b Univariate analysis, unless noted otherwise.
c ⇧ Non-significant trend toward more severe inflammatory bowel disease associated with growth retardation (or no statistical analysis)
⬆ More severe inflammatory bowel disease significantly associated with growth retardation
⇔ No association between inflammatory bowel disease severity and growth retardation.
d Linear regression adjusting for corticosteroid use.

Three studies evaluated the association between severity of inflammatory bowel disease and height in 660 children (Table 23). Two of the studies measured height velocity. The studies used various measures to grade severity of disease, including disease location. All were retrospective longitudinal studies. Two studies were of fair quality; one was of poor quality.

Saha, Ruuska, Laippala, et al. (1998) evaluated 47 prepubertal children with a mean age of 7 years old who had either ulcerative colitis or Crohn's disease in a retrospective longitudinal study. The children were followed for the first four years after diagnosis or until they reached age 12 years old. Mean height and height velocity standard deviation scores were calculated at diagnosis and yearly after that. Disease severity was scored based on number of relapses, hospitalizations, surgeries and medications. For both children with ulcerative colitis and Crohn's disease, disease severity was significantly associated with height velocity. Children with more severe disease were the shortest, but the difference in height among children with different disease severity was not statistically significant. Of note, no statistical difference in HVSDS in children receiving or not receiving Prednisone was found.

In a retrospective longitudinal study, Griffiths, Nguyen, Smith, et al. (1993) evaluated 100 prepubertal children with a mean age of 11 years old at initial diagnosis of Crohn's disease who had been followed for at least two years. The study evaluated the relationship between growth velocity, defined as growth in cm/year, and severity of the Crohn's disease, determined by gastrointestinal symptom frequency and chronicity, and disease location. The study found that the severity of gastrointestinal symptoms was the major factor influencing linear growth during the first two years after diagnosis. Height velocity decreased with increasing symptoms. No difference in mean linear growth velocities were found among patients stratified by anatomical localization of disease. Longer term follow-up found that those children who reached maturity by

the end of the study achieved their expected height, regardless of disease severity or location. Of note, duration of corticosteroid administration was not a significant predictor of height velocity.

Farmer and Michener (1979) performed a retrospective longitudinal case series study of 513 patients younger than 20 years old who had Crohn's disease. The mean duration of follow-up was almost 8 years. Growth retardation was defined as height less than third percentile on the growth curve for any given age. Short stature occurred at similar frequencies among children diagnosed with Crohn's disease no matter what the pattern of disease: ileocolic (7 percent), colon (8 percent) and small intestine (6 percent). The study did not report whether those with short stature had different complication rates than taller children. Height velocity was not explicitly measured.

All three studies evaluating the relationship between growth retardation and the severity of inflammatory bowel disease included children with Crohn's disease. One study also included children with ulcerative colitis. Severity of inflammatory bowel disease was found to correlate with loss of height velocity in two studies. Crohn's disease location, however, did not correlate with either height or height velocity in two studies. There were no data presented to suggest that the process of growth failure is likely to be disabling.

Association of Severity of Juvenile Rheumatoid Arthritis with Decreased Growth Velocity

Table 24. Growth Retardation Association with Subtypes / Severity of Juvenile Rheumatoid Arthritis

Author Year	General-izability [a]	Sample N	Population	Disease Severity	Height [b,c]	Height Velocity [b,c]	Quality [a]
Bernstein 1977	🧍🧍🧍	31	JRA	Systemic vs Other		⬆	⭘
Polito 1997	🧍🧍	58	JRA	Systemic / Polyarticular vs Pauciarticular		⇧	⭘
	🧍	37	Systemic or Polyarticular	Number of affected joints		⇔	
				Total disease flares		⬆	
				Functional class		⬆	
Saha 1999	🧍🧍	64	JRA	Polyarticular vs Systemic / Pauciarticular	⬆ [d,e]	⬆ [d,e] for 1st year	○
				Severity Score	⬆ [d,f]	⬆ [d,f] for 1st year	

JRA = Juvenile rheumatoid arthritis

a See Methods…
b Univariate analysis, unless noted otherwise.
c ⇧ Non-significant trend toward more severe juvenile rheumatoid arthritis associated with growth retardation (or no statistical analysis)
⬆ More severe juvenile rheumatoid arthritis significantly associated with growth retardation
⇔ No association between juvenile rheumatoid arthritis severity and growth retardation.
d Statistical significance not explicitly reported. Implied significance.
e Adjusted for sex and duration of disease (implied).
f Adjusted for glucocorticoid use and duration of disease (implied).

Three studies evaluated the association between severity of juvenile rheumatoid arthritis (JRA) and height in 153 children (Table 24). All of the studies measured height velocity. The studies categorized patients by disease type. Two studies also used various measures to grade severity of disease. All were retrospective longitudinal studies. Two studies were of fair quality; one was of poor quality.

Bernstein, Stobie, Singsen, et al. (1977) performed a retrospective longitudinal cohort study of 31 children with JRA. At initial evaluation, the children were between 1 and 11 years old and were followed for a mean of 6.6 years. Children with JRA were classified into systemic, polyarticular, and pauciarticular groups according to the mode of onset of their disease. Children with systemic JRA (more severe disease) had significantly lower mean change in height in comparison to children with polyarticular and pauciarticular JRA.

In a retrospective longitudinal study of 58 children with JRA who had a mean age of 6 years old at initial evaluation, Polito, Strano, Olivieri, et al. (1997) evaluated subjects for at least 1 year. The study evaluated height velocity compared to a population standard and measured disease severity based on disease type in all subjects. In children with systemic or polyarticular disease, height velocity was also evaluated based on number of affected joints, the total duration of disease flares, and an undefined functional class. Children with more severe JRA (systemic or polyarticular) were significantly more likely to have a decreased growth velocity when followed over time in comparison to children with less severe JRA (pauciarticular). Among those with either systemic or polyarticular disease, decreased height velocity significantly correlated with duration of flares and with functional class, but not with the number of joints affected. Furthermore, the study concluded that decreased growth velocity was likely secondary to the JRA separate from steroid medication use. Of note, though, since steroid use was an exclusion criteria, those most seriously affected were likely excluded.

Saha, Verronen, Laippala, et al. (1999) conducted a retrospective longitudinal study of 64 prepubertal children diagnosed with juvenile chronic arthritis who were followed from the time of diagnosis for 2 years or until they reached age 12. At initial evaluation, the children had a mean age of 4 years old. Children with the most severe disease were excluded. Disease severity was based on type of disease (pauciarticular, polyarticular, and systemic) and by a severity score based on medication requirements. The paper implied that associations with height and height velocity were adjusted in multivariate analyses. The study found that both height and height velocity were significantly decreased with increased severity of disease type or severity in the first year after diagnosis. However, height severity normalized after this.

All studies indicated an association between decreased growth velocity and increased severity of JRA. One of the studies, however, found that height velocity normalized after the first year of treatment. Two studies excluded children with the most severe disease There were no data reported to address the question of whether decreased growth velocity is in itself disabling.

Association of Severity of Chronic Kidney Disease with Decreased Growth Velocity

Table 25. Growth Retardation Association with Severity of Chronic Kidney Disease

Author Year	General-izability [a]	Sample N	Population	Disease Severity	Height [b,c]	Height Velocity [b,c]	Quality [a]
Schaefer 1996 [d]	🧍🧍🧍	321	CKD	GFR		⬆	◉
				GFR < 25	⬆	⬆	
Karlberg 1996 [d]	🧍🧍	47	CKD, aged 9 mo-2 y	GFR		⇔ [e]	◉
		14	Infants with CKD			⇔ [e]	
Konrad 1995 [d]	🧍	24	ARPKD girls	GFR < 60	⬆		◉
		34	ARPKD boys	GFR < 60	⇔		
Norman 2000	🧍🧍🧍	60	CKD	GFR categories	⬆		◉
Rizzoni 1984	🧍🧍🧍	47	CKD	GFR	⇔	⇔	◉
Tsau 1989	🧍🧍	52	Nephrotic syndrome	Relapsing vs non-relapsing disease		⬆	◉
Schärer 1999	🧍🧍	33	Prepubertal nephrotics	No CKI [f]		⇔	◉
				CKI [f]		⇔	
				ESRD [f]		⬆	
	🧍	16	Steroid resistant nephrotics	Serum albumin / protein		⬆	
Ismaili 2001	🧍🧍	11	Infants with CKD	GFR < 15 at 6 months		⬆	◉
Claris-Appiani 1989	🧍🧍	17	Predialysis CKD	Creatinine clearance	⬆	⇔ [g]	○
Tejani 1983	🧍	24	Focal segmental sclerosis	Steroid resistant vs sensitive	⬆		○

ARPKD = autosomal recessive polycystic kidney disease, CKD = chronic kidney disease, GFR = glomerular filtration rate.

a See Methods…
b Univariate analysis, unless noted otherwise.
c ⇧ Non-significant trend toward more severe juvenile rheumatoid arthritis associated with growth retardation (or no statistical analysis)
⬆ More severe juvenile rheumatoid arthritis significantly associated with growth retardation
⇔ No association between juvenile rheumatoid arthritis severity and growth retardation.
d Karlberg, Schaefer, Hennicke, et al. (1996), Schaefer, Wingen, Hennicke, et al. (1996) and Konrad, Zerres, Wuhl, et al. (1995) used subjects from same dataset.
e Multivariate analysis. No data on other variables in model.
f No CKI = Reached final height without kidney function deterioration (chronic kidney insufficiency).
CKI = Reached final height with serum creatinine > 1.2 mg/dL after age 13.6 years.
ESRD = Developed end stage renal disease before reaching final height.
g Adjusted for multiple variables including bone age, blood urea nitrogen, nutrition, and parathyroid hormone.

Ten studies evaluated the association between severity of chronic kidney disease (CKD) and height in up to 684 children (Table 25). Seven of the studies measured height velocity; six measured height. Most studies based disease severity on kidney function, although other measures were used. Six studies were prospective; four were retrospective. Eight studies were longitudinal; two were cross-sectional. Eight studies were of fair quality; two were of poor quality.

Three papers reported separate analyses on different sets of subjects from the same overall sample of patients (Karlberg, Schaefer, Hennicke, et al., 1996; Konrad, Zerres, Wuhl, et al., 1995; Schaefer, Wingen, Hennicke, et al., 1996). The largest, by Schaefer, Wingen, Hennicke, et al. (1996) reported on a prospective longitudinal study of 321 children with CKD followed to age 10 years old. Disease severity was based on a measure of kidney function, glomerular filtration rate (GFR). For children in most age groups evaluated, those with lower GFR had lower height velocities. Among children of all ages, those with GFR less than 25 mL/min had significantly lower heights and height velocities compared to children with greater kidney function.

In a subset of children reported in Schaefer, Wingen, Hennicke, et al. (1996), 61 children diagnosed with CKD prior to age 6 months and who were younger than 2 years old were evaluated by Karlberg, Schaefer, Hennicke, et al. (1996) in a prospective longitudinal analysis. In a multivariate analysis, kidney function, measured by GFR, was not associated with height velocity in either infants or young children.

In another subset of patients, Konrad, Zerres, Wuhl, et al. (1995) reported a prospective longitudinal study of 58 prepubertal children with autosomal recessive polycystic kidney disease (ARPKD) who were older than 1 year at initial evaluation. Severity of CKD was measured by GFR. Girls with ARPKD who had GFR less than 60 mL/min/1.73 m^2 were significantly shorter than girls with greater kidney function. However, in boys, height was not associated with kidney function. Height velocity was not analyzed.

Norman, Coleman, Macdonald, et al. (2000) performed a prospective cross-sectional study of 60 children with CKD aged 2 to 17 years old. Severity of CKD was defined as mild (GFR 50-75 mL/min/1.73 m^2), moderate (GFR 25-50 mL/min/1.73 m^2) and severe (GFR less than 25 mL/min/1.73 m^2). The study found that those with more severe CKD (moderate and severe) were more likely to be significantly shorter than children with only mild CKD. Height velocity was not analyzed.

Rizzoni, Basso, and Setari (1984), in a retrospective longitudinal study, evaluated 47 children with CKD, from neonate to age 15 years old. CKD severity was measured with GFR. No relationship between GFR and growth velocity or height was found.

Tsau, Chen, and Lee (1989) performed a retrospective longitudinal analysis of 52 children with nephrotic syndrome, with a mean age of 5 years old. The children were categorized into two groups based on clinical course. Those with frequent relapsing, steroid-dependent and steroid-resistant disease were classified as having a less favorable clinical course. Those with occasional relapsing disease or who had not had relapses were classified as having a more favorable course. Growth data were obtained and analyzed up to the age of 15 years old. The study found that children with more severe nephrotic disease had significantly decreased yearly growth velocity in comparison to children with more mild nephrotic syndrome. However, further analysis concluded that the duration of steroid administered per year was found to be the major determinant of growth suppression in nephrotic children.

Scharer, Essigmann, and Schaefer (1999) performed a prospective cross-sectional study of 33 prepubertal children with nephrotic syndrome, who had a mean age of 4 years old. Children were

followed for a minimum of 1.2 years. Children were classified by the degree of deterioration of their kidney function during follow-up. Nephrotic children with no or with moderate deterioration of kidney function did not experience reduction of height velocity compared to population norms. Those children who went on to develop end-stage renal disease had significant reduction of height velocity compared to population norms. In a subgroup of 16 children who had steroid resistant nephrotic syndrome, disease severity was determined by serum total protein and albumin levels. Height velocity correlated significantly with total protein and albumin levels, such that those with more severe nephrotic syndrome had lower height velocity.

Ismaili, Schurmans, Wissing, et al. (2001) performed a retrospective longitudinal study of 11 infants with kidney dysplasia and CKD. The authors analyzed kidney function and growth from birth to 4 years of age. Disease severity was based on GFR at 6 months of age, using 15 mL/min as a threshold for severity. Infants with more severe CKD at 6 months had a significantly more severe delay in height compared to those children with less severe CKD.

Claris-Appiani, Bianchi, Bini, et al. (1989) performed a prospective longitudinal cohort study of 17 children with CKD who were aged 1 to 9 years old and were followed for 1 year. Severity of CKD was measured using creatinine clearance. Children with more severe CKD were significantly shorter. However, growth velocity did not correlate with creatinine clearance in multivariate analysis controlling for a variety of factors.

Tejani, Nicastri, Sen, et al. (1983) performed a retrospective longitudinal evaluation of 24 children with nephrotic syndrome and focal segmental glomerular sclerosis (FSGS). The children were between 3 and 19 years old at follow-up. The children were classified based on whether their disease was steroid resistant or steroid sensitive. Sixty-nine percent of children with steroid resistant FSGS had short stature, compared to 12% of children with steroid sensitive disease. The growth retardation was less common in steroid sensitive FSGS despite increased exposure to steroids in these children.

Among the reviewed studies, the majority found a positive relationship between increased severity of CKD and either decreased growth velocity or short stature. However, these findings were not universal. Single studies of sub-populations, such as children with ARPKD and very young children found conflicting evidence. Two studies commented on the use of steroids and how they related to growth. In one study of children with nephrotic syndrome, steroid use was associated with growth retardation. However, the second study, of children with focal segmental sclerosis, found that children whose disease was amenable to steroid use, and therefore received steroids, grew faster than children with steroid resistant disease. Some studies were limited by using a severity marker that was not GFR or by small sample sizes or limited data reporting. No data were available to assess if a decreased height velocity is in itself disabling

Association of Severity of Human Immunodeficiency Virus Infection with Decreased Growth Velocity

Table 26. Growth Retardation Association with Severity of Human Immunodeficiency Virus

Author Year	General-izability [a]	Sample N	Population	Disease Severity	Height [b,c]	Height Velocity [b,c]	Quality [a]
Brettler 1990	🚹🚹	36	Hemophiliac boys with HIV	Progression to AIDS or ARC		⬆ [d]	●
Matarazzo 1994	🚹🚹	24	Perinatal HIV	Clinical deterioration	⇧	⇧	○

HIV = human immunodeficiency virus; AIDS = acquired immunodeficiency syndrome; ARC = AIDS related complex
a See Methods…
b Univariate analysis, unless noted otherwise.
c ⇧ Non-significant trend toward more severe HIV disease associated with growth retardation (or no statistical analysis)
⬆ More severe HIV disease significantly associated with growth retardation
⇔ No association between HIV disease severity and growth retardation.
d Multivariate analysis. Included CD4 count and p24 antigenemia and possibly other variables not reported.

Two studies evaluated the association between severity of HIV infection and height in 60 children (Table 26). Both studies measured height velocity; one also measured height. Various measures of disease severity were used. One study used both prospective and retrospective data; the other was prospective. Both studies were longitudinal. One study was of fair quality; one was of poor quality.

Brettler, Forsberg, Bolivar, et al. (1990) evaluated 36 boys with hemophilia A and HIV in a longitudinal study. Data were collected both retrospectively and prospectively. The boys had a median age of 8 years old and were younger than 12.5 years old. Growth failure was defined as a decrease in at least 15 percentile points in height or weight for age for two consecutive years. In a multivariate analysis that controlled for CD4 count and p24 antigenemia, growth failure was found to be the strongest prognostic variable for the progression to acquired immunodeficiency syndrome (AIDS) or AIDS-related complex (ARC). The authors conclude that "growth abnormalities in HIV-infected children without symptoms should be considered as an early sign of progression toward symptomatic disease."

Matarazzo, Palomba, Lala, et al. (1994) performed a prospective longitudinal cohort study of 24 children who were perinatally infected with HIV who were evaluated for 24 months. Disease severity was based on clinical deterioration; although this was not defined. At both 1 and 2 year follow-up, children who had clinical deterioration were substantially shorter and had substantially lower height velocity than children with stable clinical condition. At follow-up, most children with a stable clinical condition maintained normal growth whereas those with growth reduction showed progression in the severity of the disease. However, statistical analysis was not performed.

Both studies that evaluated growth retardation in children with HIV found that linear growth retardation is a marker for progression to active disease in HIV positive children and that linear growth deceleration may precede the onset of symptoms of active disease. These studies were limited by incomplete reporting of data and poorly defined methods, predictors and outcomes. Despite the limitations, the studies seem to indicate that a sustained decrease in linear growth

velocity is a marker for progression from seropositive status to active disease. No data were included that assess whether a decreased linear growth velocity is in itself likely to be disabling.

Association of Severity of Atopic Dermatitis with Decreased Growth Velocity

Table 27. Growth Retardation Association with Severity of Atopic Dermatitis / Eczema

Author Year	General-izability [a]	Sample N	Population	Disease Severity	Height [b,c]	Height Velocity [b,c]	Quality [a]
Massarano 1993	🧍🧍🧍	68	Eczema	% BSA affected	⬆ [d]		●
				>50% vs <50% BSA affected	⬆		
Patel 1988	🧍🧍🧍	80	Atopic dermatitis	>50% vs <50% BSA affected	⇔	⇔	○
				Asthma vs no asthma	⇔	⇔	

BSA = body surface area

a See Methods…
b Univariate analysis, unless noted otherwise.
c ⬆ More severe atopic dermatitis or eczema significantly associated with growth retardation
⇔ No association between atopic dermatitis or eczema severity and growth retardation.
d In multivariate analysis controlling for parental height, diet, duration of eczema, treatment and asthma.

Two studies evaluated the association between severity of eczema or atopic dermatitis and height in 148 children (Table 27). One study measured both height and height velocity; the other measured only height. Both studies used percentage of total skin affected; one study also considered the presence of asthma. Both studies were prospective. One study was longitudinal; one was cross-sectional. One study was of good quality; one was of poor quality.

Massarano, Hollis, Devlin, et al. (1993) performed a prospective cross-sectional analysis of 68 children age 2 to 12 years old with atopic eczema. Disease severity was based on percentage of skin affected by eczema. All children had been treated with topical steroids; however those with more than 50% skin involvement were treated with more potent steroids. Both groups had similar asthma and asthma treatment scores. In a multivariate analysis, height was significantly associated with percent of skin affected by eczema. Furthermore, the mean height of those children with more than 50% skin involvement was significantly less those with less skin involvement. Children on systemic steroids were included in the study. There were no data on height velocity.

Patel, Clayton, Addison, et al. (1998) performed a prospective longitudinal study of 80 prepubertal children with atopic dermatitis. The children had a mean age of 5 years old at initial evaluation and were followed over a 2-year period. In one analysis, height severity was based on percentage of skin involvement. Neither height velocity nor height differed between patients

with less than 50% skin involvement and those with at least 50% skin involvement. In a secondary analysis, affected children with and without asthma had similar heights and height velocities. Of note, there were also no differences in height or height velocities between children treated with mild potency topical glucocorticoids and those treated with moderate potency ones. Children with systemic steroids were excluded from the study.

The two studies of growth in children with atopic dermatitis reported conflicting results. One study, which included children on systemic steroids, found a positive association between increased severity and decreased height. The other study, which excluded children on systemic steroids, found no association between increased severity and decreased height or height velocity. These studies do not clearly provide evidence that a sustained decrease in linear growth velocity is a marker for the severity of the underlying disease. Further prospective longitudinal studies that evaluate the severity of the dermatitis and the contribution of systemic and topical steroid use and coexisting conditions like asthma are needed to determine whether growth failure is related to severity of illness or to medication treatment or co-morbid medical illness. No data were provided that look at whether the process of a decreasing linear growth velocity is in itself disabling.

Association of Severity of Other Diseases with Decreased Growth Velocity

Table 28. Growth Retardation Association with Severity of Miscellaneous Chronic Diseases

Author Year	General-izability [a]	Sample N	Population	Disease Severity	Height [b,c]	Height Velocity [b,c]	Quality [a]
Samson-Fang 1998	🧍🧍	81	Cerebral palsy	Cognitive impairment		⬆	●
		72		Non-ambulatory		⬆	
		80		Type of disease		⇔	
Evliyaoglu 1996	🧍🧍	24	Sickle cell anemia	Severe vs Mild	⬆		◉
Rasat 1995	🧍🧍	9	Congenital adrenal hyperplasia	Number of escapes from suppression	⇔		○

a See Methods…
b Univariate analysis, unless noted otherwise.
c ⇧ Non-significant trend toward more severe chronic disease associated with growth retardation (or no statistical analysis)
⬆ More severe chronic disease significantly associated with growth retardation
⇔ No association between chronic disease severity and growth retardation.

The relationship between growth and the severity of three chronic diseases – cerebral palsy, sickle cell anemia, and congenital adrenal hyperplasia – were evaluated in one paper each.

The association of growth and severity of cerebral palsy was evaluated by Samson-Fang and Stevenson (1998) in a retrospective cross-sectional study of good quality. The study included 81 children with cerebral palsy younger than 10 years old. Severity of disease was evaluated in three ways: presence of a cognitive impairment, ambulation ability, and type of cerebral palsy (spastic

disease, extra-pyramidal disease, and mixed disease). Cognitive impairment and non-ambulatory status were independently associated with a lower height velocity. Height velocity, however, was not associated with disease type.

The association of growth and severity of sickle cell anemia was evaluated by Evliyaoglu, Kilinc, and Sargin (1996) in a prospective cross-sectional study of fair quality. The study included 24 children with homozygous SS sickle cell anemia with a mean age of 9 years old. Sickle cell patients were classified into two groups: a mild clinical course group who did not require blood transfusions and had no sickle crises; and a severe clinical course group who needed blood transfusions beginning early in life and had suffered from frequent sickle crises. The children with severe sickle cell anemia were significantly shorter than those with mild courses. Height velocity was not analyzed.

The association of growth and severity of congenital adrenal hyperplasia was evaluated by Rasat, Espiner, and Abbott (1995) in a retrospective longitudinal study of poor quality. The study analyzed 9 children with congenital adrenal hyperplasia who had a mean age at initial evaluation of 15 years old and were followed for a median of 14 years. All subjects had been treated with glucocorticoids. Disease severity was expressed as the frequency of biochemical escapes from adrenal suppression. There was no association between final height and number of suppression escapes. Height velocity was not evaluated.

In one study, height velocity was found to be associated with severity of impairments due to cerebral palsy, but not with type of disease. Height was associated with severity of course of sickle cell anemia in a single study. In a small study, no association was found between final height and severity of congenital adrenal hyperplasia. Further studies disease are needed to confirm these results and to more clearly evaluate height velocity and severity of disease. No data were presented to answer the question about whether the process of having a decreasing linear growth velocity is in itself disabling in children with any of these diseases.