Criteria for Determining Disability in Infants and Children: Short Stature

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 6010 Executive Blvd., Suite 300, Rockville, MD 20852.

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Structured Abstract

Objectives. The evidence report provides a systematic review of the scientific evidence to answer three questions of whether short stature in a child 1) due to a medically determinable cause or 2) due to skeletal dysplasia may be associated with disability, and 3) whether decreasing growth velocity in a child with a chronic disease may serve as an indicator of severity of the disease.

Search Strategy. Systematic searches were performed for relevant articles in MEDLINE® from 1966 through February 2001, with updates through October 2001. Additional studies were identified from other databases, reference lists of review and primary articles, and from domain experts.

Selection Criteria. Eligibility criteria for study inclusion included: primary articles reporting original data on at least 10 children; in studies of children with short stature, data on association between height and functional ability or limitation; in studies of children with chronic diseases, association between a measure of severity of disease and either height or height velocity. Studies could be cross-sectional or longitudinal, prospective or retrospective, comparative or not.

Main Results. A total of 13,537 English language citations were reviewed. Of these, 825 articles were reviewed for inclusion. For Question 1, 31 studies met inclusion criteria; for Question 2, 31 studies; and for Question 3, 53 studies. Detailed data extraction was performed on these 115 studies.

Based on the reviewed articles, no severe functional limitations were found in children with short stature due to isolated short stature, growth hormone deficiency, multiple hormone deficiency, Turner syndrome, or Russell-Silver syndrome. The studies reviewed focused on intelligence, academic achievement, behavior, visual-motor perception, and psychomotor development. In each of these categories, children with short stature either had testing that was not significantly different from the controls or from the population mean, or if the testing were significantly poorer, it was generally within 1 standard deviation (SD) of the population mean.

Based on the articles reviewed, children with skeletal dysplasias were not at increased risk of having severe impairments in intelligence, academic achievement, or psychological outcome. There was an increased risk for delay in achievement of motor skills in children with achondroplasia and osteogenesis imperfecta, and decreased ambulation, range of motion and mobility in children with more severe forms of osteogenesis imperfecta. The results for hearing impairment, respiratory dysfunction and spinal curvature appear to indicate an increased risk for impairment in these three areas, but the studies were limited in the number of children evaluated and how the samples were selected.

The evidence from four conditions (congenital heart disease, juvenile rheumatoid arthritis, Crohn's disease 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, atopic dermatitis, diabetes, ß-thalassemia, and chronic kidney disease. There was only one study each for sickle cell disease, congenital adrenal hyperplasia and cerebral palsy so it is difficult to draw conclusions for these conditions. No study addressed whether the process of having a decreasing height velocity was likely to be disabling.

Conclusions. No severe functional limitations were found in children with short stature due to growth hormone deficiency, multi-hormone deficiency, Turner syndrome, Russell-Silver syndrome or isolated short stature. These children generally scored within 1 SD of the population mean. Children with skeletal dysplasias were not at increased risk of having severe impairments in intelligence, academic achievement, or psychological outcome. Sustained decrease in linear growth velocity has been shown to be associated with the severity of congenital heart disease, juvenile rheumatoid arthritis, Crohn's disease, and HIV.

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Summary

Overview

The Social Security Administration (SSA) requested that the Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Center (EPC) program, provide a systematic review of the scientific evidence about whether short stature in a child due to a medically determinable cause may be associated with disability, whether skeletal dysplasias in a child may be considered a disability, and whether decreasing growth velocity in a child with a chronic disease may serve as an indicator of severity of the disease. The population of interest includes children age 17 years or younger, both male and female, of all racial, ethnic, and socioeconomic groupings.

The evidence report was prepared to assist SSA in updating its *Listing of Impairments* and revising its disability policy, as may be appropriate.

Causes of Short Stature in Children

There are multiple causes of short stature. The most common causes are familial short stature (FSS) and constitutional growth delay (CGD). FSS occurs when a child has height below the third percentile due to a genetic tendency to short stature in his or her family. Children with FSS typically reach adult height consistent with their family background. CGD occurs when a child is shorter than would be expected by her or his genetic background and no determinable medical cause of the short stature can be found. Often children with CGD experience a delayed onset of pubertal development and usually obtain normal or near normal adult height. Neither FSS nor CGD is

considered to be due to medically determinable causes in most cases. Since it can be difficult to differentiate between these two conditions, the term isolated short stature (ISS), is often used interchangeably for both FSS and CGD.

Medically determinable causes of short stature include abnormalities in the growth hormone axis such as decreased growth hormone production and diminished response to growth hormone. Other endocrine abnormalities such as hypothyroidism and Cushing disease may lead to short stature and a variety of genetic disorders including chromosomal, metabolic, and single gene disorders can also result in short stature.

Skeletal dysplasias are genetic disorders that result in abnormal formation of part or all of the skeleton. Not all skeletal dysplasia will result in short stature. The skeletal dysplasias most likely to lead to short stature are those that involve formation and growth of the long bones and/or the spine.

The presence of a chronic disease in a child has long been known to be a risk factor for decreased growth to a varying degree. However, the underlying cause of the decreased growth has not been determined in all chronic diseases.

Reporting the Evidence

The following key questions were refined by the EPC Evidence Review Team and technical experts from those posed by the SSA.

Question 1. Is short stature (height < 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?

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?

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?

Methodology

Definition of Short Stature

A range of definitions of short stature among children exists. In general, short stature has been defined as a height less than the 3rd percentile. This corresponds to a value of 1.9 standard deviations below the mean height (which is commonly rounded up to 2.0). However, many studies use a variety of definitions including height less than the 5th and 10th percentiles (corresponding to 1.65 and 1.3 standard deviations below the mean, respectively). The total number of children who have short stature due to either a medically determinable cause or a skeletal dysplasia as opposed to FSS has not been reported. However, by definition, approximately 2.2 million American children have short stature (US Census, 2001).

Literature Search

Systematic searches were performed for full journal articles of original data. The primary search for the literature review consisted of a MEDLINE® search from 1966 through February 2001, with updates through October 2001. Supplemental searches were also performed in ERIC, PsycInfo, Healthstar and EMBASE. Additional studies were identified from reference lists of review and primary articles, and from domain experts.

Development of the search strategies was an iterative process that included input from domain experts. Keywords from known relevant studies were used to refine and focus the final search strategies used.

Study Selection

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 report questions. A set of minimum inclusion criteria were used in this initial screening: primary articles reporting original data on at least 10 children that provided primary or secondary evaluation of growth failure and had a primary or secondary outcome of a potential functional limitation. Studies could be cross-sectional or longitudinal, prospective or retrospective, comparative or not.

Summarizing the Literature

A total of 825 studies were retrieved for careful evaluation. 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.

Findings

Question 1. Is short stature (height < 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?

We reviewed 31 papers that provided information on functional abilities among children with short stature due to medically determinable impairments. 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.

Fifteen of the 23 studies were prospective cross-sectional studies; seven were prospective longitudinal studies; and one was a retrospective longitudinal study. Two were of good quality, eleven were of fair quality, and nine were of poor quality. One study was of fair quality in its analysis of intelligence, but of poor quality in its analysis of academic achievement.

Based on the reviewed articles, no severe functional limitations were found in children with short stature due to growth hormone deficiency, multi-hormone deficiency, Turner syndrome, Russell-Silver syndrome, or isolated short stature. These specific causes of short stature were chosen because they allowed us to isolate the effect of short stature and thus enable us to determine if there was an increased risk for disability related problems just due to short stature. The articles focused on intelligence, academic achievement, behavior, visual-motor perception, and psychomotor development. In each of these categories, children with short stature either had testing that was not significantly different from the controls or from the population mean, or if the testing were significantly poorer it was still for the most part within one standard deviation (SD) of the population mean.

Association of short stature with academic achievement. Eleven studies evaluated academic achievement in approximately 996 children with short stature as a result of a medically determinable impairment. Five of the studies found that children with short stature had academic achievement scores at or above the population norm. The other six studies found scores below the population norm but the great majority was still within one SD of the mean. These results imply that children with short stature do not have enough difficulties with academic achievement to qualify as a disability. A major limitation in five of the studies was the exclusion of children with a low intelligence quotient (IQ).

Association of short stature with intelligence. Twenty-one studies evaluated IQ in approximately 1,156 children with short stature as a result of a medically determinable impairment. Fifteen studies found short stature children to have IQs at or above the population mean, while the remaining studies reported IQs for the most part less then one SD below the mean. Three of the studies that found IQs at or above the mean excluded children with low IQs. The studies were limited by the IQ exclusion and also by an absence of a control population in many of the studies. Future studies are required to better delineate this question.

Association of short stature with visual-motor skills. Only three studies involving 81 patients could be found that evaluated visual-motor perception in children with short stature. All three found significantly lower visual-motor skills in the evaluated children. These studies, however, were limited by their reporting of the data. Furthermore, it is not clear how a decrease in visual-motor skill can be correlated with the SSA definition of disability. Future studies are needed to evaluate disabilities caused by functional limitations in visual-motor skills.

Association of short stature with psychomotor development. One poor quality study evaluated 14 children with short stature due to Russell-Silver syndrome for psychomotor development by the Denver Developmental Screening Test. These children were found to have delays in meeting their developmental landmarks. However, the value of this finding in relation to disability is questionable since the children did eventually meet their developmental landmarks (e.g., walking). Future studies are needed to determine the significance of these findings.

Association of short stature with behavior. Teacher-based evaluation of behavior in children with short stature was reported in five studies involving 274 children. In general, behavior in the children with short stature was not significantly different from the controls. Exceptions to this were increased hyperactivity reported in one study, increased locus of control in another study, and general increased behavior problems in a third study. It is difficult to extrapolate behavior in general from these studies since they tended to use different tests, and the test results do not always overlap. In addition, sub-group results were not given for each study. Furthermore, the value of behavioral impairments for determining a child's level of disability is questionable. Further studies are needed that evaluate large groups of non-selected short stature children, use the same behavior-based test, compare results to matched controls, and determine likelihood of disability.

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?

There were 31 papers from 25 study groups that provided information on functional abilities among children with short stature due to skeletal dysplasia. Of the studies, 22 were prospective cross-sectional studies; 5 were prospective longitudinal studies; 2 were retrospective longitudinal; and 2 were retrospective cross-sectional. One was of good quality, 16 were of fair quality, and 12 were of poor quality. One study was of good quality in its analysis of academic achievement, but of fair quality in its analysis of ambulation and mobility. One study was of fair quality in its analysis of neuromuscular function and range of motion, but of poor quality in its analysis of ambulation and mobility.

Based on the articles reviewed, children with skeletal dysplasias were not at increased risk of having severe impairments in intelligence, academic achievement, or psychological outcome. There was an increased risk for delay in achievement of motor skills in children with achondroplasia and osteogenesis imperfecta, and decreased ambulation, range of motion, and mobility in children with more severe forms of osteogenesis imperfecta. The results for hearing impairment, respiratory dysfunction, and spinal curvature appear to indicate an increased risk for impairment in these three areas, but the studies were limited in the number of children evaluated and how the samples were selected, thus making it difficult to arrive at a definitive conclusion in these areas.

Association with academic achievement. Three studies examined academic achievement among 84 children with achondroplasia or osteogenesis imperfecta. In two studies, achondroplasia patients scored lower than control groups, yet remained in the normal range. Further studies on this issue are needed to evaluate a larger population of children with achondroplasia, osteogenesis imperfecta, and other types of skeletal dysplasias.

Association with intelligence. Five studies with 116 children evaluated intelligence in children with achondroplasia, osteogenesis imperfecta, and other skeletal dysplasias. No evidence of significantly impaired intelligence was found in any of the skeletal dysplasias by intelligence testing with all scores either above the population norm or within 0.5 SD of the norm. These studies were generally small for the comparisons made. Further studies on this issue are needed to evaluate a larger population with skeletal dysplasias clearly defined by up-to-date standards.

Association with psychomotor development. Six studies involving a total of 196 children found generally delayed achievement of psychomotor abilities or development in children with achondroplasia and osteogenesis imperfecta. Each group evaluated was small, used different testing instruments, and had varying ages of subjects. Furthermore, none was followed longitudinally. Clinically useful conclusions about ultimate motor function in children with skeletal dysplasias cannot be made from these studies. Larger, longitudinal studies are needed that test psychomotor functional abilities.

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Association with neuromuscular function. From review of the available literature, children with short stature due to various skeletal dysplasias appear to be at risk for neuromuscular abnormalities. Six studies with 185 children evaluated neuromuscular function in children with skeletal dysplasias. The four studies that looked solely at children with achondroplasia found varied abnormalities. The three that measured strength found substantial weakness and hypotonia. Asymmetry, sensory deficits, poor coordination, and seizures were found in frequencies higher than controls or than are expected in the healthy population. All studies highlighted the significant risk of often occult cervical cord compression in these young children. The one paper that evaluated osteogenesis imperfecta found substantial muscle weakness in children who are moderately to severely affected by their disease. The one paper that reviewed other skeletal dysplasias found cervical cord complications in children with Morquio disease. Further studies of children with skeletal dysplasias, especially achondroplasia, are needed to better delineate the extent of neuromuscular impairment.

Association with ambulation and mobility. Of the eight papers considering ambulation and mobility in children (N=345) with short stature due to skeletal dysplasia, all considered children with osteogenesis imperfecta. All found significant impairment in ambulation, with greater impairment, as expected, in patients with more severe disease. Children with the less severe types of osteogenesis imperfecta (tarda, Type I, Type IV) were more likely to attain some walking capability, although a substantial proportion of these children did require assistance. Orthopedic abnormalities such as scoliosis, decreased range of motion, decreased muscle strength, and fracture contribute to limitations of ambulation. All of the studies were of small size; although given the rarity of osteogenesis imperfecta, the studies were of reasonable size. Definitions of levels of ambulation were consistent and fairly objective. Studies of ambulation and mobility disabilities are necessary for children with skeletal dysplasias other than osteogenesis imperfecta.

Association with limb range of motion. Two studies evaluated upper and lower range of motion (ROM) abnormalities in children with various types of osteogenesis imperfecta (N=40) and with achondroplasia (N=41). Decreased ROM was found in children with osteogenesis imperfecta, but no such correlation was seen in children with achondroplasia. Decreased lower extremity ROM may impact on ability to independently ambulate. Decreased upper extremity ROM may limit an individual's independence by reducing his or her ability to engage in self-care. Further studies are necessary to better delineate the connection between limb ROM and various skeletal dysplasias.

Association with spinal curvature. Four papers assessed spinal deformities in 209 children with short stature due to skeletal dysplasia. Three studied children with osteogenesis imperfecta, and one studied children with diastrophic dysplasia. A high prevalence of scoliosis was found in children with both conditions. One study also found a high prevalence of pathologic kyphosis. All studies, however, likely represent a selected, perhaps more severe, population of patients followed by academic medical centers. Thus to find prevalence in the general population of individuals with skeletal dysplasias, it will be necessary to evaluate scoliosis and kyphosis in a group of unselected individuals with skeletal dysplasias.

Association with hearing loss. Of the six studies that reported on hearing loss in 151 children with skeletal dysplasia, only three performed objective hearing testing. All papers that reported actual hearing testing in young osteogenesis imperfecta patients reported a sizable proportion with hearing loss, although the prevalence varied due to selection and cohort size differences. Subjective reports of hearing problems in achondroplasia patients were common. However, one study found no difference in self-reported hearing function between children with a mix of skeletal dysplasias, including achondroplasia, and control children. The available literature supports that children with at least some skeletal dysplasias, specifically achondroplasia and osteogenesis imperfecta, are at risk for hearing problems. Further studies with a larger, unselected population of children with skeletal dysplasia are needed to better define the extent, severity, and type of hearing loss.

Association of short stature with respiratory dysfunction. Of the four papers evaluating sleep and respiratory dysfunction in 94 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 numbers of children. Two of the groups contained patients referred for their respiratory or neurologic symptoms, and therefore may not represent the general achondroplasia population. Further studies that look at larger groups of non-selected achondroplasia patients are needed to define the prevalence of apnea in this population.

Little information on pulmonary function in children with skeletal dysplasia was found. One group found abnormal pulmonary function in a small group of children with achondroplasia, and one found no significant abnormality in a smaller group of children with osteogenesis imperfecta. More data are required before meaningful conclusions can be drawn.

Association of short stature with psychological outcomes. Only one paper adequately studied the association of short stature due to skeletal dysplasia with psychological outcomes. The study found no evidence for increased rates of depression or anxiety in children with skeletal dysplasia. Further studies that evaluate psychological problems such as depression and anxiety are needed to validate these results.

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?

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—appears 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, β-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.

Association of severity of asthma. Eleven studies evaluated the association between severity of asthma and height or height velocity in 3,778 children. Overall, the studies did not find a consistent result. Six of the studies found no association between severity of asthma and growth retardation. No study found an association between mild asthma and growth retardation.

Studies were limited by poorly defined samples, limited data and analysis, missing data and, frequently, by the fact that severity of disease was measured by steroid treatment. These studies do not clearly provide evidence that a sustained decrease in linear growth velocity can be used as a marker of severity of asthma or whether a decrease in growth velocity is likely to be disabling. Future well-designed studies are needed.

Congenital heart disease. Six studies evaluated the association between severity of congenital heart diseases and height or height velocity in 1,784 children. Many studies were limited by incomplete data and statistical analysis and some studies were limited because they excluded children with the most severe congenital cardiac defects. Given the limitations, the results do suggest that height and height velocity retardation is seen in children with severe congenital heart defects and may be a marker for more severe disease. Whether the decrease in height or height velocity in itself is disabling is not answered.

Insulin-dependent diabetes mellitus. Eleven studies involving 1,099 children evaluated the relationship between growth retardation and control or severity of insulin-dependent diabetes mellitus. Overall, the studies showed mixed results with five studies demonstrating a positive relationship between poor diabetes control or increased severity of disease and decreased growth velocity. Several studies associated growth deceleration with peripubertal onset of illness. Some studies were limited because they did not use a well-defined, objective measure, such as glycohemoglobin (Hgb A1c), to assess severity or control. Some studies were limited by unclear statistical analysis, lack of specific data included, or summary results. These studies did not find clear evidence that a sustained decrease in linear growth velocity can be used as a marker of severity of diabetes or whether a

decrease in linear growth velocity is in itself disabling. Further prospective, longitudinal studies of the linear growth of children with diabetes mellitus, using objective measures of control like Hgb A1c, are needed to clarify whether a decrease in linear growth velocity may be a marker for severity of disease.

β-Thalassemia. There were three studies involving 295 children that evaluated the relationship between growth retardation and severity of anemia in β-thalassemia. One study showed a relationship between increased severity of anemia and reduced height, and one study showed a trend toward increased severity of disease and decreased growth. The studies were limited by incomplete data reporting and by inconsistent definitions of severity. These studies do not show clear evidence that a sustained decrease in linear growth velocity can be used as a marker of the severity of the disease. Prospective longitudinal cohort studies with clear definitions of severity (i.e., hemoglobin levels) and measurements of height velocity may answer the question.

Inflammatory bowel disease. There were three studies involving 660 children that evaluated the relationship between growth retardation and the severity of inflammatory bowel disease. Two studies included only children with Crohn's disease. The other two studies included children with both Crohn's disease and ulcerative colitis. Disease severity was associated with height velocity among children with both Crohn's disease and ulcerative colitis; however, height was not significantly associated with disease severity in any study. There are no data presented to suggest that the process of growth failure is likely to be disabling. Further prospective longitudinal studies that include larger numbers of patients who have ulcerative colitis and Crohn's disease, and that compare both with population standards and with each other, may clarify whether growth retardation is a marker associated with severity of all inflammatory bowel diseases, or is related to one in particular.

Juvenile rheumatoid arthritis. Three studies involving 153 children evaluated the relationship between growth retardation and the subtypes or severity of juvenile rheumatoid arthritis. All studies indicated an association between decreased growth velocity and increased severity of the disease. One study noted that height velocity normalized after the first year of treatment. The studies were limited in two cases by excluding children with the most severe disease, by incomplete statistical analyses in one, and by poorly defined outcomes in another. With these caveats, the studies suggest that a decrease in linear growth velocity is associated with more severe disease and may serve as a marker of severity of the underlying disease. There are no data reported addressing the question of whether decreased growth velocity is in itself disabling. Future well-designed studies with broad inclusion criteria are needed to clarify the issue.

Chronic kidney disease. Ten studies involving 684 children evaluated the relationship between growth retardation and severity of chronic kidney disease. Eight of the studies

found a positive relationship between increased severity of kidney failure and decreased height or height velocity. Single studies of sub-populations of children with autosomal recessive polycystic kidney disease (ARPKD) and very young children with chronic kidney disease found no association of disease severity with height velocity. There was conflicting evidence about the role of steroid use in causing growth retardation. Some studies were limited by using a severity marker other than glomerular filtration rate, by small sample sizes, or by incomplete data reporting. Overall, the studies suggest that a decrease in linear growth velocity is associated with the severity of the underlying disease but this finding was not universal. No data were available to assess if a decreased height velocity is in itself disabling. Additional prospective, longitudinal studies that evaluate whether a decrease in linear growth velocity can be used as a marker of severity of underlying kidney disease are needed.

Human immunodeficiency virus infection. There were two studies evaluating the relationship between growth retardation and progression to disease in 60 HIV-positive children. Both studies found that linear growth retardation is a marker for progression to active disease in HIV-positive children and linear growth deceleration may precede the onset of symptoms of active disease. These studies were limited by incomplete data reporting and poorly defined methods, predictors, and outcomes. Despite the limitations, the studies do 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. Larger, prospective, longitudinal studies of the relationship between decreasing linear growth velocity and progression of disease could confirm the usefulness of decreased linear growth velocity as a marker for increasing severity of disease.

Atopic dermatitis. Two studies involving 148 children evaluated the relationship between growth retardation and severity of atopic dermatitis. The studies reported conflicting results with one study reporting a positive association between increased severity and decreased height and the other study showing no association between increased severity and decreased height or height velocity. In the first study the more severely affected group had higher steroid use and some used systemic steroids. In the second study, those using systemic glucocorticoids were excluded from analysis. This study was also limited by a failure to report complete results and a failure to report statistical analyses. 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. No data were provided that look at whether the process of a decreasing linear growth velocity is in itself disabling. Further prospective longitudinal studies are needed to clarify whether

growth velocity is affected by the severity of atopic dermatitis, or whether the apparent effect is related to steroid treatment.

Cerebral palsy. There was only one study with 81 subjects that looked at the relationship between growth retardation and cerebral palsy. The study did not find a significant association between the type of cerebral palsy and decreased growth velocity but cognitive impairment, and non-ambulatory status were associated with decreased growth velocity. This suggests that those more severely affected by both motor and non-motor neurological deficits have decreased growth velocity. This study was limited by the exclusion criteria, which likely excluded the most severely affected children. No data were presented to answer the question about whether the process of having a decreasing linear growth velocity is in itself disabling. Further prospective longitudinal studies of children with varying severity of cerebral palsy are needed to confirm whether a decreasing linear growth velocity is a marker for the severity of the underlying disorder.

Sickle cell disease. There was only one study with 24 subjects that evaluated the association of growth retardation with the severity of sickle cell disease. That study found a positive association between severe sickle cell disease (measured by need for transfusions and the number of crises) and decreased height percentile compared to controls. The study was small and did not explicitly compare less severe sickle cell disease to more severe disease. The study also did not look at height velocity as a predictor of more severe disease. Further prospective longitudinal studies that compare larger numbers of patients with mild, moderate, and severe sickle cell disease are needed to determine if a decreasing linear growth velocity can serve as a marker for the severity of the underlying disease.

Congenital adrenal hyperplasia. There was only one study with 9 subjects that looked at the relationship between growth retardation and congenital adrenal hyperplasia. It did not find an association between number of escapes (more severe disease) and decreased growth velocity. The study was limited by its small size and by its reporting of results in graphic form only. There is not clear evidence that a decreasing linear growth velocity can be used as a marker for the underlying severity of congenital adrenal hyperplasia. No data were presented that look at whether the process of a decreasing linear growth velocity is in itself disabling. Further prospective longitudinal studies of larger numbers of patients with congenital adrenal hyperplasia are needed to answer the question of whether decreasing linear growth velocity can be used as a marker for severity of the underlying disease.

Limitations

There were several limitations encountered in evaluating Questions 1 and 2. Very few studies looked specifically at disability as defined by SSA. Most studies in fact were looking at functional ability such as IQ or academic achievement. Such

areas are focused on in the published literature because they allow for acquisition of data that can be compared to published norms. Results from such studies have to be extrapolated to determine if the children evaluated meet the SSA definition of disability. For example, one SSA criterion of disability includes acquiring and using information. Reduced IQ in a child may lead to limitations in acquiring or using information, but there is not a linear relationship between decreased IQ and reduced ability to acquire and use information. Even those studies that evaluated functional impairment, such as those that evaluated inability or limitation of walking, do not necessarily correlate directly with SSA's definitions of disability.

One limitation to evaluating Question 3 relates to difficulties in trying to correlate the severity of disease with decreasing growth velocity. Frequently a report that details height in a specific disorder does not directly correlate this with severity of disease. Also the way in which severity of disease was reported may vary between reports discussing the same disease. The same problem was seen with reporting of growth data, which is given in a variety of different formats (e.g., one-time height, growth velocity, and standard deviation from the mean). This makes it more difficult to determine the overall validity of the results.

Future Research

Further research is needed to better define the relationships both between short stature and disability and between growth velocity and severity of chronic disease. Research on disability should focus on functional deficits rather than functional ability. Studies that examine physical limitations directly related to short stature are needed. Further prospective longitudinal studies of growth velocity in chronic disease are needed. Studies are needed of children of various ages,

including puberty. Studies need to clearly define severity of disease and avoid confounding severity with treatment options.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for AHRQ by Tufts-New England Medical Center Evidence-based Practice Center under Contract No. 290-97-0019. It is expected to be available in spring 2003. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 73, *Criteria for Determining Disability in Infants and Children: Short Stature.* Internet users will be able to access the report online through AHRQ's Web site at www.ahrq.gov.

Chapter 1. Introduction

The Social Security Administration (SSA) of the Department of Health and Human Services requested that the Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Center (EPC) program, provide the scientific basis for SSA to determine disability claims for children with short stature, with skeletal dysplasias, and with chronic disease in which decreasing growth velocity may be a component. This evidence report is prepared to assist SSA in updating its *Listing of Impairments* and revising its disability policy, as may be appropriate.

This report summarizes the scientific evidence about whether short stature in a child due to a medically determinable cause may be associated with disability, whether skeletal dysplasias in a child may be considered a disability, and whether decreasing growth velocity in a child with a chronic disease may serve as an indicator of severity of the disease. The population of interest includes children age 17 years or younger, both male and female, of all racial, ethnic and socioeconomic groupings.

Scope of the Problem

A range of definitions of short stature among children exists. In general, short stature has been defined as a height less than the 3rd percentile (Plotnick, 1990). This corresponds to a value of 1.9 standard deviations below the mean height (which is commonly rounded up to 2.0). However, many studies use a variety of definitions including height less than the 5th and 10th percentiles (corresponding to 1.65 and 1.3 standard deviations below the mean, respectively). The total number of children who have short stature due to either a medically determinable cause or a skeletal dysplasia as opposed to familial short stature has not been reported. However, by definition, approximately 2.2 million American children have short stature (US Census, 2001).

Causes of short stature in children

There are multiple causes of short stature. The most common causes are familial short stature (FSS) and constitutional growth delay (CGD). FSS occurs when a child has height below the third percentile due to a genetic tendency to short stature in his or her family (Mahoney, 1987). Children with FSS typically reach adult height consistent with their family background. CGD occurs when a child is shorter than would be expected by her or his genetic background and no determinable medical cause of the short stature can be found. Often children with CGD experience a delayed onset of pubertal development and usually obtain normal or near normal adult height (Plotnick, 1990). Neither FSS nor CGD is considered to be due to medically determinable causes in most cases (Attie, 2000). Since it can be difficult to differentiate between these two conditions, the term isolated short stature (ISS), is often used interchangeably for both FSS and CGD.

Medically determinable causes of short stature include abnormalities in the growth hormone axis such as decreased growth hormone production and diminished response to growth hormone. Other endocrine abnormalities such as hypothyroidism and Cushing disease may lead to short stature (Bacon, Spencer, Hopwood, et al., 1990). A variety of genetic disorders including chromosomal disorders,

metabolic disorders and single gene disorders can also result in short stature (Bacon, Spencer, Hopwood, et al., 1990).

Skeletal dysplasias are genetic disorders that result in abnormal formation of part or all of the skeleton. Not all skeletal dysplasia will result in short stature. The skeletal dysplasias most likely to lead to short stature are those that involve formation and growth of the long bones and/or the spine. The most common skeletal dysplasias that typically result in short stature include achondroplasia, hypochondroplasia, and osteogenesis imperfecta (Taybi and Lachman, 1996). There are more than 200 described skeletal dysplasias, many of which may lead to short stature, but each of these conditions individually is quite rare (Online Mendelian Inheritance in Man, 2002).

The presence of a chronic disease in a child has long been known to be a risk factor for decreased growth to a varying degree (Plotnick, 1990). However, the underlying cause of the decreased growth has not been determined in all chronic diseases. Diseases that affect a child's nutritional status (inflammatory bowel disease, celiac disease) may lead to a decrease in growth velocity secondary to caloric and general nutritional insufficiency (Kelts, Grand, Shen, et al., 1979; Oliva and Lake, 1996). Other diseases such as asthma, which do not appear to directly affect nutritional status, have also been reported to lead to decreased growth velocity (Abrams, 2001).

Definition of Disability

The definition of disability in children used for the purposes of this report came from the SSA and was based on a definition passed by Congress in 1996. Under Title XVI, a child under age 18 years will be considered disabled if he or she has a medically determinable physical or mental impairment or combination of impairments that causes marked and severe functional limitations, and that can be expected to cause death or that has lasted or can be expected to last for a continuous period of not less than 12 months (Disability evaluation under Social Security, 1999).

Specific areas of functioning include: 1) acquiring and using information, 2) attending and completing tasks, 3) interacting and relating with others, 4) moving about and manipulating objects, 5) caring for yourself, 6) health and physical well-being. Disability is based on the degree to which the above functions are interfered with. Disability is established if there are marked limitations in at least two areas or there is an extreme limitation in one area of functioning. Where standardized tests of function exist, the regulations define a "marked" degree of functional limitation as more than two but less than three standard deviations below the mean and an "extreme" limitation as three or more standard deviations below the mean. (Disability evaluation under Social Security, 1999).

However, SSA's definition of disability is an administrative one, which is not commonly used by clinicians or researchers. In general, disability is defined differently by different researchers for different diseases. Furthermore, studies of children with short stature frequently focus on differences of ability, rather than on disability per se. Thus, any analysis of the literature to evaluate disability for SSA will be limited by the fact that few studies have primary analyses of disability that correspond to SSA's definition.

Evaluation of children with short stature due to a medically determinable cause

The evaluation of the association of short stature due to medically determinable causes with disability is complicated by the fact that it is often hard to distinguish whether the disability is due directly to short stature or to the underlying medical problem. As an example, Turner syndrome, which is caused by the absence of part or all of one X chromosome in a female, results in short stature in the majority of girls affected. These girls often have difficulties in visual-spatial relationships, but these difficulties are believed to be secondary to their genetic defect and not related to their short stature (Ross, Stefanatos, Roeltgen, et al., 1995). Similarly in Down syndrome, which is caused by chromosome 21 trisomy, children generally have short stature; however the significant mental retardation in these children is not thought to be secondary to their stature (Tolmie, 1997).

Evaluation of children with short stature may be done by a variety of medical specialties including endocrinology, gastroenterology, and genetics and depending on the specialty, different evaluations may be done. In general, research done on children with short stature has tended to focus on intelligence and psychological concerns, which fall into the first three areas of functioning discussed above (acquiring and using information, attending and completing tasks, and interacting and relating with others).

Evaluation of disability among children with short stature due to medically determinable causes is limited in that few studies examine disability per se, but instead compare different levels of ability (e.g. cognitive ability). In addition, direct associations between ability and height are often not reported.

Evaluation of children with short stature secondary to a skeletal dysplasia

Skeletal dysplasias are a relatively heterogeneous group of diseases that cause abnormalities in development of one or more parts of the skeleton. For the most part skeletal dysplasias tend to affect only bony development, specifically metaphyseal or epiphyseal development. However, certain skeletal dysplasias may also have other associated anomalies, such as severe myopia and cleft palate in diastrophic dysplasia, which may impact on a disability evaluation. Most, but not all, skeletal dysplasias will lead to stature below the third percentile. The most common skeletal dysplasias include achondroplasia, hypochondroplasia, osteogenesis imperfecta, and diastrophic dysplasia (Taybi and Lachman, 1996). The research on disability and skeletal dysplasia has tended to focus on structural abnormalities of the bones and short stature and has looked at problems such as difficulties in acquiring and using information, moving about and manipulating objects, caring for self, and health and physical well-being.

Evaluation of disability among children with skeletal dysplasia, as with children with short stature due to medically determinable causes, is limited in that few studies examine disability per se, but instead compare different levels of ability (e.g. cognitive ability). The main exception to this are studies of ambulation and mobility. In addition, direct associations between ability and height and between severity of short stature within a particular skeletal dysplasia are often not reported.

Evaluation of children with decreased growth velocity secondary to chronic disease

Some chronic diseases (e.g., inflammatory bowel disease, asthma, congenital heart disease) have been associated with poor growth in the affected child. The poor growth may lead to height less than the third percentile in some, or the height may stay within the normal range but with a decreased growth velocity (Mahoney, 1987). Of interest is whether decreased growth velocity can be used as a marker to indicate worsening severity of disease. This question does not directly relate to disability.

Certain chronic diseases, such as diabetes or chronic kidney disease, have clearly defined methods of measuring severity of disease (i.e., $HgbA_{1c}$ and glomerular filtration rate, respectively). However, most chronic diseases have less well-defined measures of severity (e.g., asthma, congenital heart disease, sickle cell anemia). Therefore, different studies use different, non-standard definitions of severity, making comparisons across studies difficult. For some chronic diseases, severity of disease may just be a proxy for different categories or sub-types of the disease (e.g., congenital heart disease, juvenile rheumatoid arthritis). Growth may be affected differently by the different categories of the chronic disease, which may not be associated with the "severity" of the disease.

To properly evaluate the association between chronic disease severity and growth, studies must be longitudinal and measure height velocity. However, much of the research on severity of chronic disease has been cross-sectional. Therefore, height, rather than height velocity, has frequently been analyzed.

Chapter 2. Methodology

This evidence report is based on a systematic review of the literature. A series of teleconferences was held with the science partner representatives from the Social Security Administration (SSA), the American Academy of Pediatrics (AAP), the internal technical experts from the Evidence-based Practice Center (EPC), and a representative of the Disability Law Center to formulate the key questions addressed by this report. A comprehensive search of the medical literature was conducted to identify the evidence available to address the questions.

Detailed information about each study used in the systematic review was abstracted. The results are presented in evidence tables. Information directly pertinent to answer each aspect of the key questions addressed is presented in summary tables within the Results section (Chapter 3). A list of abbreviations is presented in Appendix 2.

Key Questions Addressed by the Evidence Report

The EPC staff, pediatric experts, and representatives of SSA arrived at consensus on three key questions following discussions and between-meeting solicitation of comments from the group members. The key questions were refined to ensure that the answers would be useful to SSA, would be of interest to the technical experts, would be appropriate for literature review, and would likely be available in the literature. The final key questions are:

1. Is short stature (height $< 5^{th}$ 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?

2. What is the evidence that short stature (height $< 5^{th}$ 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?

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?

For all key questions, the populations of interest are boys and girls under age 18 years who have short stature. Children of all ethnicities, nationalities, racial, and socioeconomic groups were included.

For key questions 1 and 2, short stature was defined as height less than the 5th percentile (or less than –1.67 standard deviations (SD) below the mean) for age. However, given the variability of definitions of short stature in the literature, we accepted definitions of short stature up to the 25th percentile.

For key questions 1 and 2, disability was defined based on SSA definitions published in "Disability Evaluation Under Social Security" (Disability Evaluation Under Social Security, 1999), as discussed in the Introduction. The list of impairments provided by SSA was reviewed to determine the possible disabilities of interest. However, SSA's definition of disability is based on a need to determine an administrative definition to comply with Federal law. Clinicians and researchers, though, use various definitions of ability and disability to care for patients. Thus,

very few studies have examined the association between short stature and (SSA-defined) disability, per se. This report therefore focuses on assessments of functional limitations, as defined by study authors. Objective and teacher- or clinician-scored assessments were included. Parent or child determinations of functional ability were excluded.

Question 1. Definition of short stature as a result of medically determinable impairment.

The primary categories (or causes) of short stature considered included isolated or idiopathic short stature, constitutional growth delay, growth hormone deficiency, multiple hormone deficiency, Russell-Silver syndrome, and Turner syndrome. No predetermined definitions for each of the causes of short stature were used; instead, definitions used by study authors were accepted. Studies that focused on children with Down syndrome were not reviewed as SSA already defines such children as disabled from birth.

The associations between short stature due to medically determinable impairment and functional ability included academic achievement, intelligence, academic advancement, visual motor skills, psychomotor development, and teacher-graded behavioral problems.

Question 2. Definition of short stature as a result of skeletal dysplasia.

The primary skeletal diseases resulting in short stature considered included osteogenesis imperfecta, achondroplasia, diastrophic dysplasia, and other skeletal dysplasias. No predetermined definitions for each skeletal dysplasia were used; instead, definitions used by study authors were accepted.

The associations between short stature due to skeletal dysplasia and functional ability included 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.

Question 3. Chronic disease and linear growth velocity

Attention was paid to addressing the association between disease severity and decreased linear growth velocity. Thus, only studies that categorized children with chronic diseases by disease severity and that also directly compared height to disease severity were included. Studies that investigated only the association between disease presence and height were not reviewed. No predetermined definitions of disease severity were used; instead definitions used by study authors were accepted. To capture the full range of data available on growth in children with chronic disease, we included both studies that evaluated height velocity as well as height alone.

The review focused on chronic diseases that either are associated with, or may result in, disability, as defined by SSA. We did not review studies that evaluated the association between treatment for chronic disease and height, unless sufficient data were available to answer the primary question. Thus, studies of steroid use for gastrointestinal and most other diseases were generally excluded. For studies of children with asthma, we excluded those that explicitly examined the effect on growth of steroid use. However, we included studies that used medication

requirement (including steroids) as a marker of severity, since this was a common method of analysis. Cancer and cardiac diseases requiring surgery were not considered because separating the effect on height of treatment from the underlying disease is not possible.

Search Strategies

Systematic searches were performed for full journal articles of original data. The primary search for the literature review consisted of a MEDLINE® search from 1966 through February 2001, with updates through October 2001. Supplemental searches were also performed in ERIC, PsycInfo, Healthstar and Embase. Additional studies were identified from reference lists of review and primary articles, and from domain experts.

Development of the search strategies was an iterative process that included input from domain experts. Keywords from known relevant studies were used to refine and focus the final search strategies used.

The details of the literature searches performed in MEDLINE® are presented in Appendix 1. The primary search strategy for key questions 1 and 2 retrieved articles with the keywords or text words developmental bone diseases, growth disorders, body height, or short stature, along with variations of disability, limitation, handicap, or impairment (Appendix Table 1, lines 1-11). The primary search strategy for key question 3 retrieved articles with the keywords or text words developmental bone diseases, short stature, skeletal dysplasia, growth velocity, retardation, delay and restriction, and growth disorders (Appendix Table 1. lines 12-50). Studies that focused on growth disorders that do not cause short stature, that affect neonatal development or that are rapidly fatal were not included. These topics included fetal development, pregnancy, failure to thrive, facial bones, thanatropic dysplasia, and various forms of gigantism or other bone diseases that do not cause short stature. To capture additional studies of common chronic diseases that affect growth, supplemental searches were performed for heart diseases, arthritis, and asthma in children, as summarized in Appendix Table 2.

Only articles that included human children under age 18 years and that were published in English were included. Case reports, review articles, commentaries, letters, and abstracts were excluded.

Study Selection

Pediatrician domain experts and EPC staff manually screened the titles and abstracts of the search results to identify potentially useful articles to address each of the key questions. A set of minimum inclusion criteria were used in this initial screening: primary articles reporting original data on at least 10 children that provided primary or secondary evaluation of growth failure and had a primary or secondary outcome of a potential functional limitation. Studies could be cross-sectional or longitudinal, prospective or retrospective, comparative or not. Full articles of abstracts found potentially useful were retrieved for more careful evaluation.

Data Abstraction

Data abstraction forms were developed in an iterative process by EPC staff with the pediatrician experts. The forms were designed to capture information of various aspects of the

primary articles. Individual forms were developed for each key question. Forms included study setting, demographics (including such information as age, height, sex, race, and socioeconomic status), eligibility criteria, number of subjects, study design, funding source, relevant measurements and outcomes evaluated, statistical methodology, results, potential biases, and study quality.

Pediatrician domain experts performed all the data abstraction. Abstractors were trained by the EPC staff. As part of the training, each Team Member abstracted three studies in duplicate with the Team Leader and meetings were held to discuss discrepancies. After training, all remaining studies were abstracted by one pediatrician. All abstracted data were reviewed by two members of the EPC staff when data were transferred to evidence and summary tables.

Articles that reported data on the same or overlapping sets of children were grouped together in the evidence and summary tables, or noted to contain duplicate data, to avoid duplication of results. One study author (RHH Engelbert) was contacted by email to clarify the overlap of a number of studies.

Summary Tables

Summary tables were created to describe studies reviewed for each topic. The tables describe the strength of the evidence according to four dimensions: study size, study sample applicability, results, and methodological quality. For questions 1 and 2, studies are grouped first by study sample disease type. Within each section, studies are ordered first by methodological quality (best to worst), then by study size (largest to smallest). For question 3, studies are grouped first by methodological quality, then by applicability of study sample to children with the given chronic disease, then by study size.

Study Quality

Methodological quality (also known as internal validity) refers to the design, conduct, and reporting of the clinical study. Because studies with a variety of design types were evaluated, a three-level classification of study quality, used in previous reports, was modified. All studies were graded on the following scale:

- ● Good quality. Least bias. Results are valid. A study that mostly adheres to the commonly held concepts of high quality, including the following: a formal study; prospective design, clear description of the population and setting; proper measurement techniques; appropriate statistical and analytic methods; no reporting errors; no obvious bias.
- ◉ Fair quality. Susceptible to some bias, but not sufficient to invalidate the results. A study that does not meet all the criteria of category A. It has some deficiencies but none likely to cause major bias.
- ○ Poor quality. Significant bias likely that may invalidate the results. A study with serious errors in design or reporting. These studies may have large amounts of missing information or discrepancies in reporting.

In general, studies that reported data relevant to multiple topics of interest were given the same quality rating for each topic; however, some studies were rated differently for different topics, depending on the quality of the data for each topic. For example, a study may have

performed a complete and valid statistical analysis of intelligence but may not have performed a statistical analysis of academic achievement. The study may therefore receive a lower quality rating for its analysis of academic achievement than for intelligence.

Applicability

Applicability (also known as generalizability or external validity) addressed the issue of whether the study sample is sufficiently broad so that the results of the study can be generalized to the population of interest at large. The study population is typically defined by the eligibility criteria. Restrictive eligibility criteria (e.g., single sex, limited range of disease severity) or small sample size may reduce the applicability of a given study.

For questions 1 and 2 the applicability of each study is described by the type of disease causing short stature. The few studies that had particularly restrictive eligibility are noted in each table's footnotes. For certain disability topics (e.g., hearing loss and ambulation) where separate results are reported for different sub-populations of children, columns were added to the tables to describe the populations. For each study, the mean, median, or threshold height (generally expressed in age and sex standard deviations from the mean, or standard deviation score (SDS) were recorded.

For question 3, where all studies within a given table evaluate children with the same (or similar) diseases, a designation for applicability was assigned to each article, according to the following three-level scale:

   ♟♟♟   Study is representative of all children with the given chronic disease. Study sample includes both sexes, the full range of disease severity, a sufficient number of subjects. There are no substantial eligibility restrictions.

   ♟♟   Sample is representative of a relevant sub-group of children with the given chronic disease. There were eligibility restrictions that may limit the applicability, such as single sex, disease severity, or co-morbidities.

   ♟   Sample is representative of a narrow subgroup of children with the given chronic disease. There were substantial eligibility restrictions that limit applicability.

To complement the applicability scale, each table has a column describing the diseases of the study population.

Study Size

The study (sample) size is used as a measure of the weight of the evidence. In general, large studies provide more precise estimates of prevalence and associations. In addition, large studies are more likely to have wide applicability, depending on eligibility criteria. However, large study size does not guarantee applicability.

Results

The type of results available is determined by each study's design, the purpose of the study, and the question(s) being asked. Therefore, the results presented vary across summary tables. For

questions 1 and 2 most summary tables present either the mean test results of a given test or the prevalence of a given condition. When necessary, the test or condition evaluated in each study is included. When available, the results for a control group are also included. Summary tables for question 3 include separate columns for association of disease severity with height and with height velocity. For appropriate topics in questions 1 and for all topics in question 3, associations are described with the following arrows:

⬆ Statistically significant positive association between severity of chronic disease and height or height velocity. More severe chronic disease associated with growth retardation. If statistical analysis was not reported, but a large clinical difference in growth based on disease severity was, statistical significance was assumed to be likely. This symbol was used only in studies evaluated for question 3.

⬇ Statistically significant negative association between ability and disease causing short stature. This symbol was used only in studies evaluated for visual-motor skills in question 1.

⇧ Trend toward positive association between severity of chronic disease and height or height velocity. Some indication that children with more severe chronic disease may be associated with growth retardation. However, association either is not statistically significant or statistical analysis was not reported. This symbol was used only in studies evaluated for question 3.

⇔ No association between severity of chronic disease and height or height velocity. This symbol was used only in studies evaluated for question 3.

Limitations

While literature searches were intended to be comprehensive, they may not have been exhaustive. As noted above, search strategies were limited to focus on studies likely to be relevant. Searches were limited to English language publications. Hand searches of journals were not performed, and review articles and textbook chapters were not systematically searched. However, important studies known to the domain experts and studies found in reference lists were included in the review.

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			Bias [a]	Quality [b]
			Full	Verbal	Performance		
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	Mean IQ Verbal	Mean IQ 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	**– 2 y 1 mo** [b]	◉
			Beery Visual Motor Integration	**–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	Math	Reading	Compre-hension	Spelling	Bias [a]	Quality [b]
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			Bias [a]	Quality [b]
			Full	Verbal	Performance		
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	4.5	◉
	Type III	11		3.5	
	Type IV	12	0=None	4.5	
	Type I	17	5=Normal	4.8	
	Type III	11	Leg strength score	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 (%)								Wheelchair	Quality [a]
			Without Assistance				Assistance Needed					
			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	

Author Year	Sample N	Population	Result [g]	Scale		Quality [a]
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			

	9 [i]	Type IV [i]	Self-care = 41			
			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		Kyphosis		Quality [a]
			Cobb Angle	% of Subjects	Cobb Angle	% of Subjects	
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]					⚪
Osteogenesis Imperfecta								
Falvo, 1973	10	All	85 [c]	119 [c]	99	88	35	⚪

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]	○
			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…

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	Generalizability [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 β-Thalassemia with Decreased Growth Velocity

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

Chapter 4. Conclusions

Overview

In this chapter, we discuss the conclusions resulting from our evaluation of the three questions asked by the Social Security Administration (SSA). We also describe the limitations of the existing studies related to disability and short stature as well as the relationship between chronic disease and decreased growth.

This report summarizes the scientific evidence in regard to three questions attempting to determine if children with short stature are disabled because of their short stature, if children with short stature secondary to a skeletal dysplasia are disabled and if decreased growth velocity can be related to severity of chronic disease.

The results presented in Chapter 3 are based on the screening of 13,537 MEDLINE® citations and the review of 825 full articles.

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?

There were 23 studies that provided information on functional abilities among children with short stature due to medically determinable impairments. Fifteen were prospective cross-sectional studies; seven were prospective longitudinal studies; and one was a retrospective longitudinal study. Two were of good quality, eleven were of fair quality, and nine were of poor quality. One study was of fair quality in its analysis of intelligence, but of poor quality in its analysis of academic achievement.

Based on the reviewed articles, no severe functional limitations were found in children with short stature due to growth hormone deficiency, multi-hormone deficiency, Turner syndrome, Russell-Silver syndrome or isolated short stature. These specific causes of short stature were chosen because they allowed us to isolate the effect of short stature and thus enabled us to determine if there was an increased risk for disability-related problems due just to short stature. The articles focused on intelligence, academic achievement, behavior, visual-motor perception, and psychomotor development. In each of these categories, children with short stature either had testing that was not significantly different from the controls or from the population mean, or if the testing were significantly poorer it was still for the most part within 1 standard deviation (SD) of the population mean.

Academic Achievement

Eleven studies evaluated the relationship between academic achievement and short stature. Five of the studies found that children with short stature had academic achievement scores at or above the population norm. The other six studies found scores below the population norm but the great majority of subjects were still within 1 SD of the mean. These results imply that children

with short stature do not have enough difficulties with academic achievement to qualify as a disability. A major limitation in five of the studies was the exclusion of children with a low intelligence quotient (IQ). Further studies that look at academic achievement in a large unselected population of children with short stature and compares them to matched controls are needed to more clearly delineate this relationship.

Intelligence

Intelligence was evaluated in 21 studies of children with short stature. Fifteen studies found short stature children to have IQs at or above the population mean, while the remaining studies reported IQs for the most part less then 1 SD below the mean. Three of the studies that found IQs at or above the mean excluded children with low IQs. The studies were limited by the IQ exclusion and also by an absence of a control population in many of the studies. Future studies are needed to better delineate this question.

Visual-Motor Skills

Only three studies could be found that evaluated visual-motor perception in children with short stature. All three found significantly lower visual-motor skills in the evaluated children. These studies, however, were limited by their reporting of the data. Furthermore, it is not clear how a decrease in visual-motor skill can be correlated with the SSA definition of disability. Future studies are needed to evaluate disabilities caused by functional limitations in visual-motor skills.

Developmental Skills

Only one study evaluated developmental skills in a group of children with short stature. These children, who had Russell-Silver syndrome, were found to have delays in meeting their developmental landmarks. However, the value of this finding in relation to disability is questionable since the children did eventually meet their developmental landmarks (e.g., walking). Future studies are needed to determine the significance of these findings.

Behavior

Teacher-based evaluation of behavior in children with short stature was reported in seven studies. In general, behavior in the children with short stature was not significantly different from the controls. Exceptions to this were increased hyperactivity reported in one study, increased locus of control in another study, and general increased behavior problems in a third study. It is difficult to extrapolate behavior in general from these studies since they tended to use different tests, and the test results do not always overlap. In addition, sub-group results were not given for each study. Furthermore, the value of behavioral impairments for determining a child's level of disability is questionable. Further studies are needed that evaluate large groups of non-selected short stature children, use the same behavior based test, compare results to matched controls, and determine likelihood of disability.

Question 2. What is the evidence that short stature (height less than the 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?

There were 31 papers from 25 study groups that provided information on functional abilities among children with short stature due to skeletal dysplasia. Of the studies, 22 were prospective cross-sectional studies; five were prospective longitudinal studies; two were retrospective longitudinal; and two were retrospective cross-sectional. One was of good quality, 16 were of fair quality, and 12 were of poor quality. One study was of good quality in its analysis of academic achievement, but of fair quality in its analysis of ambulation and mobility. One study was of fair quality in its analysis of neuromuscular function and range of motion, but of poor quality in its analysis of ambulation and mobility.

Based on the articles reviewed, children with skeletal dysplasias were not at increased risk of having severe impairments in intelligence, academic achievement, or psychological outcome. There was an increased risk for delay in achievement of motor skills in children with achondroplasia and osteogenesis imperfecta, and decreased ambulation, range of motion and mobility in children with more severe forms of osteogenesis imperfecta. The results for hearing impairment, respiratory dysfunction and spinal curvature appear to indicate an increased risk for impairment in these three areas, but the studies were limited in the number of children evaluated and how the samples were selected, thus making it difficult to arrive at a definitive conclusion in these areas.

Academic Achievement

Three studies examined academic achievement among children with achondroplasia or osteogenesis imperfecta. In two studies, achondroplasia patients scored lower than control groups, yet remained in the normal range. Further studies on this issue are needed to evaluate a larger population of children with achondroplasia, osteogenesis imperfecta and other types of skeletal dysplasias.

Intelligence

Five studies evaluated intelligence in children with achondroplasia, osteogenesis imperfecta and other skeletal dysplasias. No evidence of significantly impaired intelligence was found in any of the skeletal dysplasias by intelligence testing with all scores either above the population norm or within 0.5 SD of the norm. These studies were generally small for the comparisons made. Further studies on this issue are needed to evaluate a larger population with skeletal dysplasias clearly defined by up-to-date standards.

Psychomotor Development

Six studies found generally delayed achievement of psychomotor abilities or development in children with achondroplasia and osteogenesis imperfecta. Each group evaluated was small, used different testing instruments, and had varying ages of subjects. Furthermore, none was followed longitudinally. Clinically useful conclusions about ultimate motor function in children with

skeletal dysplasias cannot be made from these studies. Larger, longitudinal studies are needed that test psychomotor functional abilities.

Neuromuscular

From review of the available literature, children with short stature due to various skeletal dysplasias appear to be at risk for neuromuscular abnormalities. Six studies evaluated neuromuscular function in children with skeletal dysplasias. The four studies that looked solely at children with achondroplasia found varied abnormalities. The three that measured strength found substantial weakness and hypotonia. Asymmetry, sensory deficits, poor coordination, and seizures were found in frequencies higher than controls or than are expected in the healthy population. All studies highlighted the significant risk of often occult cervical cord compression in these young children. The one paper that evaluated osteogenesis imperfecta found substantial muscle weakness in children who are moderately to severely affected their disease. The one paper that reviewed other skeletal dysplasias found cervical cord complications in children with Morquio disease. Further studies of children with skeletal dysplasias, especially achondroplasia, are needed to better delineate the extent of neuromuscular impairment.

Ambulation and Mobility

Of the eight papers considering ambulation and mobility in children with short stature due to skeletal dysplasia, all considered children with osteogenesis imperfecta. All found significant impairment in ambulation, with greater impairment, as expected, in patients with more severe disease. Children with the less severe types of osteogenesis imperfecta (tarda, Type I, Type IV) were more likely to attain some walking capability, although a substantial proportion of these children did require assistance. Orthopedic abnormalities such as scoliosis, decreased range of motion, decreased muscle strength and fracture contribute to limitations of ambulation. All of the studies were of small size; although given the rarity of osteogenesis imperfecta, the studies were of reasonable size. Definitions of levels of ambulation were consistent and fairly objective. Studies of ambulation and mobility disabilities are necessary for children with skeletal dysplasias other than osteogenesis imperfecta.

Limb Range of Motion

Two studies evaluated upper and lower range of motion (ROM) abnormalities in children with various types of osteogenesis imperfecta and with achondroplasia. Decreased ROM was found in children with osteogenesis imperfecta, but no such correlation was seen in children with achondroplasia. Decreased lower extremity ROM may impact on ability to independently ambulate. Decreased upper extremity ROM may limit an individual's independence by reducing his or her ability to engage in self-care. Further studies are necessary to better delineate the connection between limb ROM and various skeletal dysplasias.

Spinal Curvature

Four papers assessed spinal deformities in children with short stature due to skeletal dysplasia. Three studied children with osteogenesis imperfecta, and one studied children with

diastrophic dysplasia. A high prevalence of scoliosis was found in children with both conditions. One study also found a high prevalence of pathologic kyphosis. All studies, however, likely represent a selected, perhaps more severe, population of patients followed by academic medical centers. Thus to find prevalence in the general population of individuals with skeletal dysplasias, it will be necessary to evaluate scoliosis and kyphosis in a group of unselected individuals with skeletal dysplasias.

Hearing Loss

Of the six studies that reported on hearing loss in children with skeletal dysplasia, only three performed objective hearing testing. All papers that reported actual hearing testing in young osteogenesis imperfecta patients reported a sizable proportion with hearing loss, although the prevalences varied due to selection and cohort size differences. Subjective reports of hearing problems in achondroplasia patients were common. One study did not show a high level of self-report of hearing in patients with a mix of skeletal dysplasias, including achondroplasia. The available literature supports that children with at least some skeletal dysplasias, specifically achondroplasia and osteogenesis imperfecta, are at risk for hearing problems. Further studies with a larger, unselected population of children with skeletal dysplasia are needed to better define the extent, severity and type of hearing loss.

Sleep Apnea and Respiratory Dysfunction

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 numbers of children. Two of the groups contained patients referred for their respiratory or neurologic symptoms, and therefore may not represent the general achondroplasia population. Further studies that look at larger groups of non-selected achondroplasia patients are needed to define the prevalence of apnea in this population.

Little information on pulmonary function in children with skeletal dysplasia was found. One group found abnormal pulmonary function in a small group of children with achondroplasia, and one found no significant abnormality in a smaller group of children with osteogenesis imperfecta. More data are required before meaningful conclusions can be drawn.

Psychology

Only one paper was found that adequately studied the association of short stature due to skeletal dysplasia with psychological outcomes. The study found no evidence for increased rates of depression or anxiety in children with skeletal dysplasia. Further studies that evaluate psychological problems such as depression and anxiety are needed to validate these results.

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?

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. Nineteen were prospective longitudinal studies, 19 were retrospective longitudinal studies, 10 were prospective cross-sectional studies, and five were retrospective cross-sectional studies. Four were of good quality, 29 were of fair quality, and 20 were of poor quality. The evidence from four conditions (congenital heart disease, juvenile rheumatoid arthritis, Crohn's disease and (human immunodeficiency virus infection (HIV)) 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, atopic dermatitis, diabetes, ß-thalassemia, and chronic kidney failure. There was only one study for sickle cell disease, congenital adrenal hyperplasia and cerebral palsy 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.

Asthma

Eleven studies evaluated the relationship between the severity of asthma and growth retardation. Overall, the studies did not find a consistent result. Six of the studies found no association between severity of asthma and growth retardation. No study found an association between mild asthma and growth retardation.

Studies were limited by poorly defined samples, limited data and analysis, missing data and, frequently, by the fact that severity of disease was measured by steroid treatment. These studies do not clearly provide evidence that a sustained decrease in linear growth velocity can be used as a marker of severity of asthma or whether a decrease in growth velocity is likely to be disabling. Future well-designed studies are needed.

Congenital Heart Disease

There were six studies that evaluated the relationship between congenital heart disease and growth retardation. Many studies were limited by incomplete data and statistical analysis and some studies were limited because they excluded children with the most severe congenital cardiac defects. Given the limitations, the results do suggest that height and height velocity retardation is seen in children with severe congenital heart defects and may be a marker for more severe disease. Whether the decrease in height or height velocity in itself is disabling is not answered.

Diabetes Mellitus

Eleven studies evaluated the relationship between growth retardation and control or severity of insulin dependent diabetes mellitus. Overall, the studies showed mixed results with five studies demonstrating a positive relationship between poor diabetes control or increased severity of disease and decreased growth velocity. Several studies associated growth deceleration with

peripubertal onset of illness. Some studies were limited because they did not use a well-defined, objective measure, such as glycohemoglobin (Hgb A_{1c}), to assess severity or control. Some studies were limited by unclear statistical analysis, lack of specific data included or summary results. These studies did not find clear evidence that a sustained decrease in linear growth velocity can be used as a marker of severity of diabetes or whether a decrease in linear growth velocity is in itself disabling. Further prospective, longitudinal studies of the linear growth of children with diabetes mellitus, using objective measure of control like Hgb A_{1c}, are needed to clarify whether a decrease in linear growth velocity may be a marker for severity of disease.

β-Thalassemia

There were three studies that evaluated the relationship between growth retardation and severity of anemia in ß-thalassemia. One study showed a relationship between increased severity of anemia and reduced height and one study showed a trend toward increased severity of disease and decreased growth. The studies were limited by incomplete data reporting and by inconsistent definitions of severity. These studies do not show clear evidence that a sustained decrease in linear growth velocity can be used as a marker of the severity of the disease. Prospective longitudinal cohort studies with clear definitions of severity (i.e. hemoglobin levels) and measurements of height velocity may answer the question.

Inflammatory Bowel Disease

There were three studies evaluating the relationship between growth retardation and the severity of inflammatory bowel disease. Two studies included only children with Crohn's disease. The other two studies included children with both Crohn's disease and ulcerative colitis. Disease severity was associated with height velocity among children with both Crohn's disease and ulcerative colitis; however, height was not significantly associated with disease severity in any study. There are no data presented to suggest that the process of growth failure is likely to be disabling. Further prospective longitudinal studies that include both larger numbers of patients with ulcerative colitis patients and Crohn's disease and that compare both to population standards and to each other may clarify whether growth retardation is a marker associated with severity of all inflammatory bowel diseases, or is related to one in particular.

Juvenile Rheumatoid Arthritis

Three studies evaluated the relationship between growth retardation and the subtypes or severity of juvenile rheumatoid arthritis. All studies indicated an association between decreased growth velocity and increased severity of the disease. One study noted that height velocity normalized after the first year of treatment. The studies were limited in two cases by excluding children with the most severe disease, by incomplete statistical analyses in one, and by poorly defined outcomes in another. With these caveats, the studies suggest that a decrease in linear growth velocity is associated with more severe disease and may serve as a marker of severity of the underlying disease. There are no data reported addressing the question of whether decreased growth velocity is in itself disabling. Future well-designed studies with broad inclusion criteria are needed to clarify the issue.

Chronic Kidney Disease

Ten studies evaluated the relationship between growth retardation and severity of chronic kidney disease. Eight of the studies found a positive relationship between increased severity of kidney failure and decreased height or height velocity. Single studies of sub-populations of children with autosomal recessive polycystic kidney disease (ARPKD) and very young children with chronic kidney disease found no association of disease severity with height velocity. There was conflicting evidence about the role of steroid use in causing growth retardation. Some studies were limited by using a severity marker other than glomerular filtration rate, by small sample sizes, or by incomplete data reporting. Overall, the studies suggest that a decrease in linear growth velocity is associated with the severity of the underlying disease but this finding was not universal. No data were available to assess if a decreased height velocity is in itself disabling. Additional prospective, longitudinal studies that evaluate whether a decrease in linear growth velocity can be used as a marker of severity of underlying kidney disease are needed.

Human Immunodeficiency Virus Infection

There were two studies evaluating the relationship between growth retardation and progression to disease in HIV positive children. Both studies found that linear growth retardation is a marker for progression to active disease in HIV positive children and linear growth deceleration may precede the onset of symptoms of active disease. These studies were limited by incomplete data reporting and poorly defined methods, predictors and outcomes. Despite the limitations, the studies do 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. Larger, prospective, longitudinal studies of the relationship between decreasing linear growth velocity and progression of disease could confirm the usefulness of decreased linear growth velocity as a marker for increasing severity of disease.

Atopic Dermatitis

Two studies evaluated the relationship between growth retardation and severity of atopic dermatitis. The studies reported conflicting results with one study reporting a positive association between increased severity and decreased height and the other study showing no association between increased severity and decreased height or height velocity. In the first study the more severely affected group had higher steroid use and some used systemic steroids. In the second study, those using systemic glucocorticoids were excluded from analysis. This study was also limited by a failure to report complete results and a failure to report statistical analyses. 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. No data were provided that look at whether the process of a decreasing linear growth velocity is in itself disabling. Further prospective longitudinal studies are needed to clarify whether growth velocity is affected by the severity of atopic dermatitis, or whether the apparent effect is related to steroid treatment.

Cerebral Palsy

There was only one study with 81 subjects that looked at the relationship between growth retardation and cerebral palsy. The study did not find a significant association between the type of cerebral palsy and decreased growth velocity but cognitive impairment and non-ambulatory status were associated with decreased growth velocity. This suggests that those more severely affected by both motor and non-motor neurological deficits have decreased growth velocity. This study was limited by the exclusion criteria, which likely excluded the most severely affected children. No data were presented to answer the question about whether the process of having a decreasing linear growth velocity is in itself disabling. Further prospective longitudinal studies of children with varying severity of cerebral palsy are needed to confirm whether a decreasing linear growth velocity is a marker for the severity of the underlying disorder.

Sickle Cell Disease

There was only one study with 24 subjects that evaluated the association of growth retardation with the severity of sickle cell disease. That study found a positive association between severe sickle cell disease (measured by need for transfusions and the number of crises) and decreased height percentile compared to controls. The study was small and did not explicitly compare less severe sickle cell disease to more severe disease. The study also did not look at height velocity as a predictor of more severe disease. Further prospective longitudinal studies that compare larger numbers of patients with mild, moderate and severe sickle cell disease are needed to determine if a decreasing linear growth velocity can serve as a marker for the severity of the underlying disease.

Congenital Adrenal Hyperplasia

There was only one study with 9 subjects that looked at the relationship between growth retardation and congenital adrenal hyperplasia. It did not find an association between number of escapes (more severe disease) and decreased growth velocity. The study was limited by its small size and by its reporting of results in graphic form only. There is not clear evidence that a decreasing linear growth velocity can be used as a marker for the underlying severity of congenital adrenal hyperplasia. No data were presented that look at whether the process of a decreasing linear growth velocity is in itself disabling. Further prospective longitudinal studies of larger numbers of patients with congenital adrenal hyperplasia are needed to answer the question of whether decreasing linear growth velocity can be used as a marker for severity of the underlying disease.

Limitations

There were several limitations encountered in evaluating Questions 1 and 2. Very few studies looked specifically at disability as defined by SSA. Most studies in fact were looking at functional ability such as IQ or academic achievement. Such areas are focused on in the published literature because they allow for acquisition of data that can be compared to published norms. Results from such studies have to be extrapolated to determine if the children evaluated meet the SSA definition of disability. For example, one SSA criterion of disability includes

acquiring and using information. A significantly reduced IQ in a child may lead to such limitations, but there is not a clear relationship between IQ and difficulties in acquiring and using information. Even those studies that evaluated functional impairment, such as those that evaluated inability or limitation of walking, do not necessarily correlate directly with SSA's definitions of disability. A further limitation to evaluation of intellectual function for Questions 1 and 2 is that many relevant articles excluded children with limited IQ. Similar biases due to eligibility criteria and sample choices limit the generalizability of many of the studies.

One limitation to evaluating Question 3 relates to difficulties in trying to correlate the severity of disease with decreasing growth velocity. Frequently a report that details height in a specific disorder does not directly correlate this with severity of disease. Also the way in which severity of disease was reported may vary between reports discussing the same disease. The same problem was seen with the reporting of growth data, which is given in a variety of different formats (e.g., one-time height, growth velocity, and standard deviation from the mean). This makes it more difficult to determine the overall validity of the results.

Chapter 5. Future Research

Questions 1 and 2

If the relationship between short stature and disability is to be elucidated, future research is needed. This is true for both short stature caused by medical conditions and skeletal dysplasia. Such research would be most beneficial if it focused on functional deficits (including disability, as defined by the Social Security Administration). Especially helpful would be studies that look at physical limitations related to short stature such as difficulties in using public restrooms due to the height of the toilet or difficulties in climbing stairs. Such studies may need to focus more on more extreme short stature (i.e. 5 to 7 standard deviations below the mean) to see a significant difference. Also studies on short children have tended to focus on functional ability and have not specifically evaluated functional deficits. For example, many studies evaluated intelligence in children with short stature but few have evaluated the proportion of short children who have mental retardation.

Question 3

To properly answer the question of whether a decreasing growth velocity may indicate worsening severity of disease, prospective, longitudinal studies are needed. Studies should be prospective to minimize bias related to treatment, severity of disease and to allow accurate and consistent measurement of disease severity and growth. Longitudinal studies will allow accurate measurement of growth velocity and avoid using height as a proxy. Studies are also needed of children at various ages including puberty to account for different growth rates at different ages. The severity of disease in such studies needs to be clearly defined. In classifying children by severity of disease, researchers should clearly define the severity categories and use well-established definitions of severity. The severity definitions should not be confounded by treatment or management decisions. Finally other factors that affect height should be controlled for such as parental height, age and socioeconomic status. This is also why growth velocity is the best way to evaluate growth in an individual since it tends to remove the influence of some of these confounding factors, especially parental height.

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Evidence Table 1. Studies Evaluating Short Stature Secondary to Medical Impairment

Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Abbott 1982 82277019	Location: US Setting: In-patient Mean age: 11±3 y Age range: 4-18 y Mean height: ND Height range: 81-132 cm Male: 64% Race: White 82%, Black 18% Enrolled: ND Evaluated: 11 Number of sites: 1	Short stature due to growth hormone deficiency and/or other pituitary hormone deficiency	None	Isolated short stature	Prospective cross-sectional cohort
Angehrn 1979 80093987	Location: Switzerland Setting: ND Mean age: 4±2.2 y Age range: ND Mean height, SDS: −4.4±1.0 Male: 80% Race: ND Enrolled: ND Evaluated: 20 Number of sites: 1	Russell-Silver syndrome: Height < 2 SDS Low normal growth velocity Low birth weight Moderate bone age retardation Small triangular face and skull of large appearance	None	RSS	Prospective longitudinal cohort

Evidence Table 1. Studies Evaluating Short Stature Secondary to Medical Impairment

Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Frisch 1990 90350511	Location: Austria Setting: Clinic Mean age: 12±3 y Age range: 6.8-15.7 y Mean height, SDS: –2.5±0.9 Height range, SDS: –4.5 to –0.9 Male: 67% Race: ND Enrolled: ND Evaluated: 23 Number of sites: 1	Isolated GH deficiency, or Multi-pituitary hormone deficiency	None	GH deficiency	Prospective cross-sectional

Gordon 1984 84214634
 	
Gordon 1982 82268405
	Location: US
	Setting: Pediatric endocrinology clinic
	Mean age:
	  Cases 10±2.2 y
	  Controls 10±2.1 y
	Age range:
	  Case 6-12 y
	  Control 6-12 y
	Mean height, SDS: <5th percentile
	Male: 83%
	Race: ND
	Mean SES: 3.5 (Hollinghead)
	Enrolled: ND (23 controls)
	Evaluated: 24 (23)
	Number of sites: 1
		Cases - Constitutional short stature < 5th percentile height
		  Skeletal maturation delayed > 13 months
		  Height velocity > 4 cm/y
		Controls - Normal height
		  Matched for age, IQ, SES and sex
			Cases - Abnormal GH studies
			  Psychiatric history
			Controls - Psychiatric history
				Isolated short stature	Prospective cross-sectional cohort

Evidence Table 1. Studies Evaluating Short Stature Secondary to Medical Impairment
Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Holmes 1986 Holmes 1985 86060101	Location: US Setting: Pediatric endocrinology clinic Mean age, initial: 12 y Mean age, follow-up: 15 y Age range: ND Mean height, SDS: < –2 Male: ND Race: ND SES: Middle class 21% Enrolled: 76 Evaluated: 47 Number of sites: 1	Height < –2 SDS Patients at pediatric endocrinology clinic	Additional medical diagnoses (e.g., IDDM)	Isolated short stature: GH deficiency (17) Constitutional delay (21) Turner syndrome (9)	Prospective longitudinal cohort (Mean 3.1 y Range 2.2-4.0 y)

Kranzler 2000 20102780	Location: US
	Setting: Region
	Mean age: 10±1.4 y
	Age range: 6-12 y
	Mean height, SDS:
	  Referred –2.7±1.0
	  Non-referred –1.7±0.5
	  Controls +0.1±0.4
	Height range, SDS:
	  Referred –4.5 to –1.3
	  Non-referred –3.2 to –1.3
	  Controls –0.7 to +0.7
	Male: 51%
	Race: ND
	Enrolled: ND
	Evaluated: 61 (29 controls)
	Number of sites: 2
		Referred Cases - Height < 5th percentile
		  Pediatric endocrinology clinics
		  (n=27)
		Non-referred - Identified in local public schools as shortest 10% of class
		  (n=34)
		Controls - Height in middle 50%
		  At local public schools.
			IQ < 75
			Serious psychiatric or medical problem
			English not primary language
				Isolated short stature	Prospective cross-sectional cohort

Evidence Table 1. Studies Evaluating Short Stature Secondary to Medical Impairment
Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Lai 1994 95243689	Location: UK Setting: Clinic Mean age: 9±2 y Age range: ND Mean height, SDS: −2.2±1.5 Male: 80% Race: White 95%; West Indian 5% SES: 80% Middle-class or higher Enrolled: 30 Evaluated: 25 Number of sites: 3	Russell-Silver Syndrome (met 3 of 5 criteria) Age 6-12 y	None	RSS	Prospective cross-sectional

McCauley 1987 87161055
 	
McCauley 1986 86141341
	Location: US
	Setting: Pediatric endocrinology clinic
	Mean age:
	  Turner 13±2.4 y
	  SS 13±2.8 y
	Age range: ND
	Mean height:
	  Turner 52±5.0 in
	  SS 53±4.5 in
	Male: 0%
	Race: White 94%, Black 6%
	SES:41±16 (Hollingshead revised)
	Enrolled: 23 (22 controls with SS)
	Evaluated: 33 total
	Number of sites: 1
		<u>Cases</u> - Turner syndrome
		  Followed at Endocrine and
		  Genetics Clinics
		<u>Controls</u> - Girls with height < 5th percentile from cause other than Turner syndrome
		  Followed at Endocrine and
		  Genetics Clinics
			Verbal IQ < 79-80	Turner syndrome (17)
				Isolated short stature (16)
					Prospective cross-sectional cohort

Evidence Table 1. Studies Evaluating Short Stature Secondary to Medical Impairment

Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)

Meyer-Bahlburg 1978 78184456	Location: US
	Setting: Pediatric endocrine clinic
	Mean age:
	  GH def 12 y
	  Multi-hormone def 13 y
	Age range:
	  GH def 4-18 y
	  Multi-hormone def 6-18 y
	Mean height, SDS:
	  GH def –3.6
	  Multi-hormone def –3.9
	Height range, SDS:
	  GH def –4.8 to –2.4
	  Multi-hormone def –6.0 to –1.9
	Male: 73%
	Race: ND
	Enrolled: 29
	Evaluated: 22 (age ≤ 18 y; 29 total)
	Number of sites: 1
		Isolated growth hormone deficiency, or
		Multiple hormone deficiency
			None	Isolated growth hormone deficiency (9 total)
				Multiple hormone deficiency (13 total)
					Prospective cross-sectional cohort

Pollitt 1964	Location: US Setting: Endocrine clinic Mean age: ND Age range: 3-16 y Mean height: ND Height range: 70-126 cm Male: 40% Race: ND Enrolled: ND Evaluated: 15 Number of sites: 1	Significant short stature thought to be due to growth hormone deficiency – either pan-hypopituitary or isolated Pediatricians thought were well-adjusted psychologically and had cooperative parents	None	Isolated short stature	Prospective cross-sectional cohort

Evidence Table 1. Studies Evaluating Short Stature Secondary to Medical Impairment

Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Robinson 1983 84052395	Location: US Setting: Region Mean age: ND Age range: 7-15 y Mean height: ND Male: 0% Race: ND Enrolled: 9 Evaluated: 9 Number of sites: ND	Monosomy X karyotype (45, X) and partial monosomy X	None	Turner Syndrome Monosomy (6) Partial monosomy (3)	Prospective cross-sectional cohort
Ross 1997 97320537	Location: US Setting: ND Mean age: 9.5 y Age range: ND Mean height: ND Male: 0% Race: 87% White SES: 47 (Hollingshead) Enrolled: ND Evaluated: 40 Number of sites: 2	Turner syndrome, confirmed by karyotyping Age ≥5 and <12 y	Estrogen treatment Androgen treatment	Turner syndrome	Prospective cross-sectional cohort (derived from RCT of GH treatment)
Rovet 1985	Location: Canada Setting: Clinic Mean age: 14±1 y Age range: ND Mean height: 139±9 cm Male: 100% Race: ND Enrolled: 27 Evaluated: 25 Number of sites: 1	Height more than 2 SD below mean	History of familial short stature	Isolated short stature	Prospective cross-sectional

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Evidence Table 1. Studies Evaluating Short Stature Secondary to Medical Impairment

Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)

Siegel 1986	Location: US
	Setting: Endocrinology clinic
	Mean age: 12±2.3 y
	Age range: 6-16 y
	Mean height, SDS: < –2
	Male: 71%
	Race: ND
	SES, Social position: High 5%, High
	  average 21%, Average 31%,
	  Low average 33%(14), Low
	  10%
	Enrolled: 53
	Evaluated: 42
	Number of sites: 2
		Idiopathic hypopituitarism	Deprivation dwarfism
			Craniopharyngioma
			Age < 6 y
			IQ < 30
				Isolated short stature
				  GH def (28)
				  Multiple hormone def
				  (14)
					Prospective cross-sectional cohort

Siegel 1994	Location: US
	Setting: Endocrinology clinic
	Mean age:
	  GHD 11±2.7 y
	  ISS 11±2.6 y
	  Control 11±2.8 y+
	Age range: ND
	Mean height, SDS:
	  GHD –2.7±0.6
	  ISS –2.8±0.6
	  Control +0.1±0.9
	Male: 75%
	Race: White 91%
	Enrolled: 177 (90 controls)
	Evaluated: 177 (90)
	Number of sites: 27
		<u>Cases</u> - Height < 3rd percentile
		<u>Controls</u> - Normal height
			Known mental impairment
			Severe psychiatric
			Chronic medical illness
			Non-English speaking
			Short stature secondary to
			  systemic disease, tumor,
			  or genetic abnormalities
				Isolated short stature
				  GH Def (87)
				  Idiopathic SS (90)
					Prospective cross-sectional cohort

Evidence Table 1. Studies Evaluating Short Stature Secondary to Medical Impairment

Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)

Siegel 1998 98356098	Location: US
	Setting: Clinic
	Initial mean age: 10 y
	  Control 11 y
	Initial mean height:
	  TS 120±13 cm
	  GHD/ISS 125±12 cm
	  Control 145±17 cm
	Male: 0%
	Race: ND
	Enrolled: 88 (Controls 67)
	Evaluated: 47 (25)
	Number of sites: ~27
		<u>Cases</u> - Girls with Turner syndrome, GH deficiency, or idiopathic short stature
		<u>Controls</u> - Matched for age and socioeconomic status
			Did not follow through with 3 y of GH therapy	Turner syndrome (22)
				GH deficiency (13)
				Idiopathic short stature (12)
					Prospective longitudinal cohort
					
					(3 y)

Skuse 1997
 	
Gilmour 1996 96408881
 	
Skuse 1994 95252652
	Location: UK
	Setting: Growth clinics
	Mean age:
	  Case 8±1.5 y
	  Control 9±1.4 y
	Age range:
	  Case 6-11 y
	  Control 2-11 y
	Mean height, SDS :
	  Case –2.5±0.3
	  Control –0.3±1.1
	Male: 72%
	Race: ND
	SES (Parent profession): 59% advantaged/professional ; 14% clerical/craft; 14% manual
	Enrolled: 31 (25 controls)
	Evaluated: 22 (22)
	Number of sites: 2
		<u>Cases</u> - Height < 5th percentile (< –2 SDS)
		  Height velocity over the last year above –1.5 SDS
		  Age 6-11 y
		  Prepubertal
		<u>Controls</u> - From each case's school class, matched for age, sex, and SES
			<u>Cases</u> - Bone age delayed > 2 y
			Medical treatment for growth retardation
			  Russell-Silver children who had IQ < 72
				Isolated short stature (15)
				Russell-Silver syndrome (7)
					Prospective cross-sectional cohort

Evidence Table 1. Studies Evaluating Short Stature Secondary to Medical Impairment
Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)

Stathis 1999 20099119	Location: Australia
	Setting: Region
	Mean age: 5.5 y
	Age range: 4-6 y
	Mean height: <3rd percentile
	Male: 53%
	Race: ND
	Enrolled: ND
	Evaluated: 113 (3,178 controls)
	Number of sites: 1
		<u>Cases</u> - Height < 3rd percentile
		  Age 4-6 y
		<u>Controls</u> - Height between 10th and
		  90th percentile
		  Age 4-6 y
			PPVT-R score < 50
			Cerebral palsy
			Other serious neurological
			  disorder
				Isolated short stature	Prospective cross-sectional cohort

Steinhausen 1976 77086274	Location: Germany
	Setting: Inpatient
	Mean age:
	  SS 14±2.7 y
	  Control 14±2.6 y
	Age range:
	  SS 9-18 y
	  Control 9-18 y
	Mean height, SDS: <3rd percentile
	Male: 81%
	Race: ND
	SES: Lower class 59%, Middle
	  class 41%
	Enrolled: ND
	Evaluated: 32 (32 controls)
	Number of sites: 1
		<u>Cases</u> - Height < 3rd percentile
		<u>Controls</u> - Age and sex matched
		  from local schools with "normal"
		  stature
			None	Isolated short stature
				  GH deficiency (16)
				  Constitutional delay
				  (16)
					Prospective cross-sectional cohort

Evidence Table 1. Studies Evaluating Short Stature Secondary to Medical Impairment
Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Tanner 1975 75217260	Location: UK Setting: Growth disorder clinic Mean age: ND Age range: 1.4-10 y Mean height, SDS: –3.6 Height range, SDS: –6.3 to –2.2 Male: 56% Race: ND Enrolled: 39 Evaluated: 39 Number of sites: 1	Russell-Silver syndrome Height < –2 SDS Adjusted birth weight ≥ 2 SD below the mean of the Tanner-Thomson standard	None	RSS	Unclear

Voss 1994 Voss 1991 92151680
 	
Downie 1997 97159125
Downie 1996 96408882
	Location: UK
	Setting: Region
	Mean age: ND
	Age range: Data at ages 5-6 y, 7-9 y, 11-13 y, mean 13 y (see comments)
	Mean height (age 5-6 y), SDS:
	  Case –2.3±0.3
	  Control +0.1±0.6
	Mean height (mean age 13, No GH): Case 139 cm
	  Control 155 cm
	Male: 54%
	Race: ND
	SES: Class I/II 20%; Class III 49%; Class IV/V 31%; 25% unemployed fathers
	Enrolled: 140 (140 controls)
	Evaluated: 140 (140)
	  (See comments)
	Number of sites: 1
		Cases - Height <3rd percentile, starting school between 1985 and 1986
		Controls - From same school class Height between 10th and 90th percentile
		Matched for age, sex and school class
			Cases - Organic disease (e.g., Turner syndrome or celiac disease); Immigrant parents
			Controls - None
				Isolated short stature	Prospective longitudinal cohort (up to 9 y)

Evidence Table 1. Studies Evaluating Short Stature Secondary to Medical Impairment

Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Disease/Condition Type (N)	Study Design (Duration)
Wilson 1986	Location: US Setting: ND Mean age: ND Age range: 6-17 y Mean height, SDS: ND Male: ND Race: ND Enrolled: ND Evaluated: 6,768-7,119 (all heights) Number of sites: ND	National Health Examination Survey (NHES): 1963-1965: 7,119 children 6-11 y 1966-1970: 6,768 adolescents 12-17 y	None	Isolated short stature	Prospective cross-sectional cohort
Young-Hyman 1986	Location: US Setting: Endocrine clinic Mean age: 12 y Age range: ND Mean height, SDS: ND Male: 78% Race: ND SES: Upper middle class Enrolled: 27 Evaluated: 27 Number of sites: 1	Children with SS who presented to endocrine clinics for evaluation	Chronic health problem Mental disability	Isolated short stature	Prospective cross-sectional cohort

Evidence Table 1. Studies Evaluating Short Stature Secondary to Medical Impairment

Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Abbott 1982 82277019	Isolated short stature	ND	Cognitive/Academic	IQ (WISC) Academic achievement (WRAT) Visual-motor skills (Developmental Test of Visual-Motor Integration)
Angehrn 1979 80093987	Russell-Silver syndrome	Height < –2 SDS, low normal growth velocity, low birth weight for gestational age, moderate bone age retardation, typical small triangular face, and large skull	Cognitive/Academic Psychomotor	IQ (ND) Psychomotor development (Denver developmental screening test)
Frisch 1990 90350511	Isolated short stature/GH deficiency Hypopituitary GH deficiency	GH peak < 5 ng/ml in 2 stimulation tests	Cognitive/Academic Behavioral/Psychological	IQ (HAWIK & HAWIE, German version of Wechsler IQ test) Academic performance (Repetition of grade) Personality structure tests (Freiburger Personality Questionnaire, Giessen Test) Sociability, Social activity, Neuroticism (Hamburger Neuroticism-Extroversion Scales)
Gordon 1984 84214634 Gordon 1982 82268405	Isolated short stature	Height < 5th percentile	Cognitive Behavioral	IQ (WISC-R) Math, reading, comprehension (PIAT) School adjustment, Internalization (CBCL – Teacher)
Holmes 1986 Holmes	Isolated short stature: CGD (21) GHD (17)	Retarded bone age, growth velocity within 2 SD of normal for age, projected adult height normal Maximum GH ≤ 7 ng/ml on 9 samples	Cognitive/Academic	IQ (WISC-R)

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Evidence Table 1. Studies Evaluating Short Stature Secondary to Medical Impairment
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
1985 86060101	TS (9)	ND		
Kranzler 2000 20102780	Isolated short stature	Referred: Height < 5th percentile Non-referred: Height < 10th percentile of class	Cognitive/Academic	Verbal and non-verbal intelligence (K-BIT) Educational achievement (KTEA brief form)
			Behavioral	Adaptive and problem behaviors (BASC – Teacher)
Lai 1994 95243689	Isolated short stature	Russell-Silver syndrome	Cognitive/Academic	IQ (WISC) Reading comprehension (Neale Analysis of Reading Ability) Arithmetic comprehension (ND) Cognitive processing (Matching Familiar Figure Test) Special educational needs
McCauley 1987 87161055	Turner syndrome	Karyotype showing absence of all or part of an X chromosome	Cognitive	IQ (WISC)
			Behavioral	Behavior factor (Piers-Harris Scale – Children self-report)
McCauley 1986 86141341	Isolated short stature	Height < 5th percentile	Psychological	Depression (Children's Depression Inventory)
Meyer-Bahlburg 1978 78184456	Isolated growth hormone deficiency, and multiple hormone deficiency	GH deficient or panhypopituitary	Cognitive	IQ (WISC)

Evidence Table 1. Studies Evaluating Short Stature Secondary to Medical Impairment
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Pollitt 1964	Hypopituitary short stature	Panhypopituitary Isolated GH deficiency Turner syndrome Primordial Undiagnosed	Cognitive	IQ (WISC Scale for Children – age > 5 y)
Robinson 1983 84052395	Turner Syndrome	45, X monosomy or partial monosomy on karyotype from chromosomal exam of amniotic membrane	Cognitive	IQ (Wechsler Preschool and Primary Scale of Intelligence) Language development ("A comprehensive speech and language evaluation")
			Physical Development	Neuromuscular maturation (Bruininks-Oseretsky Test of Motor Proficiency)
Ross 1997 97320537	Turner syndrome	Karyotype 45,X	Cognitive/Academic	IQ (WISC-R) Academic achievement (WART - reading)
Rovet 1985	Isolated short stature	SD from mean	Cognitive	IQ (WISC)
Siegel 1986	Hypopituitary isolated short stature	GH secretion < 7 ng/dL, delayed bone age, growth < 4 cm in past year, height < –2 SDS or below the 3rd percentile	Cognitive/Academic	IQ (WISC-R) Academic achievement (WRAT) Visual-motor integration skills (Bender Visual-Motor Gestalt Test: a significant visual-motor integration deficit was defined as if the developmental score was < 16th percentile, and four or more errors were significant indicators of brain injury)

Siegel 1994	Isolated short stature
	  GH deficient
	  Idiopathic short stature
		Height < 3rd percentile	Cognitive/Academic	IQ (Slosson Intelligence Test)
				Academic achievement (WRAT - revised)

Evidence Table 1. Studies Evaluating Short Stature Secondary to Medical Impairment

Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Siegel 1998 98356098	Isolated short stature	Turner syndrome GHD/ISS	Cognitive/Academic	IQ (Slosson Intelligence Test) Academic achievement (WRAT - revised)
Skuse 1997 Gilmour 1996 96408881 Skuse 1994 95252652	Isolated short stature and Russell-Silver syndrome	Height < –2 SDS	Cognitive Behavioral	IQ (WISC for children – version III) Competence and self-concept (Harter Self Perception Profile for Children, Harter Pictorial Scale of Perceived Competence and Social Acceptance for Young Children, CHIPS)
Stathis 1999 20099119	Isolated short stature	Height < 3rd percentile	Cognitive	Receptive vocabulary (PPVT-R, which correlates closely with intellectual ability)
Steinhausen 1976 77086274	Isolated short stature	Height < 3rd percentile GH deficiency or no endocrine disease	Cognitive/Academic Behavior	Primary mental abilities (LPS) IQ (WISC) Academic performance (Grade level for age) School achievement (ND) Extraversion and Neuroticism (Hamburg Neuroticism Extraversion Scale)
Tanner 1975 75217260	Russell-Silver syndrome	Height < –2 SDS, adjusted birth weight< –2 SDS, no other obvious cause of short stature	Cognitive/Academic	IQ (ND) Academic achievement (Grade repetition)

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Evidence Table 1. Studies Evaluating Short Stature Secondary to Medical Impairment
Part II

Author, Year	Predictors	Predictor Measures	Outcomes	Outcome Measures
Voss 1994 Voss 1991 92151680	Isolated short stature	Height < 3rd percentile	Cognitive/Academic	IQ (Short form IQ scale of the British Ability Scales) Attainment (Word reading and basic number skills scales of British Ability Scales)
Downie 1997 97159125 Downie 1996 96408882			Behavioral	Behavioral problems (Rutter's Behavior Questionnaire – Teacher) Locus of control (Nowicki and Strickland scale)
Wilson 1986	Isolated short stature	Height < 5th percentile	Cognitive/Academic	IQ (WISC) Academic achievement (WRAT)
Young-Hyman 1986	Isolated short stature	ND	Cognitive	IQ (WISC-R) Visual-motor integration skills (Bender Visual-Motor Gestalt Test)

Evidence Table 1. Studies Evaluating Short Stature Secondary to Medical Impairment

Part III

Author, Year	Associations found	Potential Biases	Comments
Abbott 1982 82277019	Mean (SD) IQ of children with SS due to pituitary hormone deficiency (n=11) was Full Scale = 88 (17), Verbal = 89 (20), Performance = 89 (16), Reading = 88 (17), Spelling = 85 (14), and Arithmetic = 83 (15) Mean (SD) WRAT scores for children with SS (n=11) were Reading = 88 (17), Spelling = 85 (14), and Math = 83 (15) Visual-Motor Integration skills were significantly below average among children with SS	Compared to population norms	Study was government and hospital funded
Angehrn 1979 80093987	Mean (range) IQ for children with SS due to RSS (n=9) was 91 (38 to 110); 3 subjects had low IQs of 85, 83, and 38; an additional 5 subjects were "probably of normal intelligence" Of subjects with RSS, 3 of these children had microcephaly; 3 children had sub-normal IQ, 2 of whom had microcephaly More than half of the psychomotor activities on the Denver developmental screening test occurred at an age > 90th percentile in subjects with RSS (n=14)	Incomplete testing IQ test used not reported Incomplete and unclear reporting Small sample size for IQ data	No data on funding source
Frisch 1990 90350511	The median (range) IQ of children with GHD (n=23) were Full Scale = 115 (68-131), Performance = 114 (61-136), Verbal = 104 (72-128); full score and performance IQ were significantly higher than population norms; verbal IQ was similar to population norms Performance Behavior (zeal and school aversion) was similar in children with GHD (n=20) compared to population norms Sociability in children with GHD (n=20) than population norms; Social activity in children with GHD was similar to population norms (No further data) Emotional Stability (including mood, control, depression) in children with GHD was similar to population norms (No further data) Delayed Schooling was more common in children with multiple pituitary hormone deficiencies and SS (33%) than normal population (2.1%)	Compared to population norms Reporting incomplete	No data on funding source

Evidence Table 1. Studies Evaluating Short Stature Secondary to Medical Impairment

Part III

Author, Year	Associations found	Potential Biases	Comments
Gordon 1984 84214634 Gordon 1982 82268405	Mean (SD) IQ for children with SS due to constitutional delay (n=24) were total 108 (14), verbal 107 (16), and performance 108 (14). Mean (SD) scores on PIAT for children with SS (n=24) were math 103 (16), reading recognition 102 (11), and comprehension 102 (11); these were, similar to scores among children with normal stature who were matched by IQ (n=23): 103 (9.6), 102 (7.5), and 103 (10), respectively Mean (SD) teacher CBCL scores for children with SS (n=24) were total 31.2 (26.5) and for controls (n=23) 27.5 (27.6); conduct problem scores were 22.6 (4.3) and 24.1 (6.8), respectively; inattentive/passive 12.7 (4.8) and 12.1 (4.8), respectively; hyperactive 13.7 (5.9) and 11.9 (4.3), respectively; and socialization 14.7 (2.5) and 14.3 (3.0), respectively	Comparisons of cognitive function between short children and controls of questionable value since controls were matched for overall IQ No outline of the statistical analyses used in the paper; therefore, it is hard to evaluate the significance	Study was government and private funded There is no evidence that these behavior problems constitute a disability The subjects and controls were matched for IQ and had equal school performance
Holmes 1986 Holmes 1985 86060101	Mean (SD) Verbal IQ in children with isolated SS (n=47) was 102 (13); among these children, those with GH deficiency (n=17) verbal IQ was 97 (13), those with constitutional delay (n=21), 104 (14) and those with TS (n=9), 103 (14); these were all similar to population norms	40% non-participation rate Those declining participation more likely to have constitutional delay and to have received optimal treatment benefits Study presented only partial data, focusing on significant results IQ compared only to population norms	No data on funding source

Evidence Table 1. Studies Evaluating Short Stature Secondary to Medical Impairment
Part III

Author, Year	Associations found	Potential Biases	Comments
Kranzler 2000 20102780	Mean (SD) IQ scores of referred children with SS (n=27) were Verbal = 101 (16), Matrices = 106 (14), and Composite = 103 (14); of non-referred children with SS (n=34) were Verbal = 104 (15), Matrices = 105 (14), and Composite = 105 (14); and of normal controls (n=29) were verbal = 110 (12), matrices = 110 (17), and composite = 112 (13); Post hoc analysis found that referred short children had significantly lower Verbal IQ than normal controls; other comparisons were statistically similar Mean (SD) composite and spelling Educational Achievement (KTEA) scores were similar for referred short children, 106 (18) and 105 (15), non-referred short children, 107 (19) and 104 (19); and, controls, 114 (17) and 102 (17). Mean (SD) mathematics and reading KTEA scores were lower for referred short children, 107 (21) and 104 (15) and for non-referred short children, 105 (19) and 106 (18) than for controls, 121 (20) and 115 (18). Teacher ratings on BASC for Externalizing behavior, Internalizing behavior, School Problems composite, Behavior symptoms index and Adaptive Skills composite were each similar among referred short children, non-referred short children and normal controls	Study of cognitive skills excluded children with low IQ Definition of non-referred short children sample vague Predominantly post hoc analyses	Study was government, privately and pharmaceutical funded
Lai 1994 95243689	The mean (SD) IQ of children with RSS (n=25) were Full Scale = 86 (24), range 46-130, Verbal = 89 (23), range 52-141, and Performance = 84 (24), range 47-127; these were significantly lower than population norm, 100 (15) In children with RSS, larger Head Circumference was significantly associated with higher IQ (r=0.5-0.6) Reading Comprehension in children with RSS was delayed by a mean of 15.4 months; Arithmetic Competence was delayed by a mean of 7 months Cognitive Processing, measured by reaction time and error scores in children with RSS (n=22) was similar to normal controls from an earlier study (n=90) Special Education needs were necessary in 9 (36%) children with RSS, primarily in reading and language skills; 12 (48%) children received speech therapy	Compared to population norms and controls from prior study	No data on funding source

Evidence Table 1. Studies Evaluating Short Stature Secondary to Medical Impairment

Part III

Author, Year	Associations found	Potential Biases	Comments
McCauley 1987 87161055 McCauley 1986 86141341	Mean verbal and performance IQ (SD) for girls with TS (n=17) were 95 (11) and 91 (10), respectively; those IQ (SD) scores for girls with SS not due to TS (n=16) were 100 (12) and 108 (14), respectively. The difference in performance IQ between the groups was significant; however, both groups had verbal and performance IQ scores within 1 SD of the mean Girls withth TS had significantly lower performance on arithmetic, digit span, picture completion, object assembly, and coding subscales than girls with SS; performance on other subscales were similar for the two groups Self-reported Piers-Harris behavior factor and Children's Depression Inventory scores were similar in girls with TS and girls with SS; "Although the TS children indicated low self-concept they did not endorse features of clinical depression."	Excluded children with low IQ	Study was hospital funded
Meyer-Bahlburg 1978 78184456	Mean IQ of children with isolated GHD (n=13) was 101, and of children with multiple hormone deficiency (n=9) was 102 Patients with multiple hormone deficiencies have somewhat lower IQs than patients with isolated GHD, after controlling for SES	Compared to population norms	No data on funding source
Pollitt 1964	Mean (SD) IQ for children over age 5 with SS (n=13) were total 103 (16), verbal 103 (15), and performance 102 (16); These IQ scores were not significantly different than normal IQ	Compared to population norms	No data on funding source Descriptive study
Robinson 1983 84052395	Mean (SD) IQ of girls with TS (n=9) were Full Scale = 87 (20), Verbal = 93 (25), and Performance = 83 (12). Siblings (n=17) had significantly higher Full Scale IQ = 111 (15) and Performance IQ = 107 (14), but similar Verbal IQ =113 (15). The TS girls were at non-significantly greater risk of developing Language Disorders than their unaffected siblings	Small sample Handwriting problems not defined Methods and results not fully reported Most analyses were done for all subjects (girls and boys with various sex chromosomal anomalies) together	No data on funding source

Evidence Table 1. Studies Evaluating Short Stature Secondary to Medical Impairment
Part III

Author, Year	Associations found	Potential Biases	Comments
Ross 1997 97320537	Mean (SD) Full scale IQ in girls with TS with GH treatment (n=20) was 98 (14) and without GH (n=20) was 99 (15) Mean (SD) Academic Achievement (WART) reading score in girls with TS with GH treatment (n=20) was 100 (14) and without GH treatment (n=20) was 97 (17), similar to population norms	Indirectly compared to population norms	Study was government funded
Rovet 1985	The mean IQ of boys with SS (n=25) were Verbal = 98, Performance = 102, and Full Scale = 101	Compared to population norms	Study was hospital funded
Siegel 1986	Mean (SD) IQ for children with hypopituitary SS (n=42) were verbal 94 (18), range 52 to 127, and performance 94 (16), range 49-123; Both the verbal and performance IQ were significantly below normal IQ Mean (SD) WRAT scores for children with hypopituitary SS (n=42) were reading 96 (16.9), range 52 to 131, and math 85 (13.9), range 52-126; The WRAT reading score was in normal range, but the WRAT math score was significantly below the normal score (100) Significant visual-motor integration deficits occurred in 11 (26%) of children with hypopituitary SS (n=42), indicating "a significant number of hypopituitary youngsters have visual-motor integration problems."	Compared to population norms Excluded children with severe mental retardation	Study was hospital funded
Siegel 1994	Mean (SD) IQ for children with GHD (n=87) was 110 (16) for children with ISS (n=90) was 107 (19); compared to 116 (15) for control children (n=90); Significantly more GHD children (9%) and ISS children (18%) had IQs < 90, than control children (3%) Mean (SD) WRAT scores for children with GHD (n=87) were reading 103 (18), spelling 98 (17), and math 99 (17); for children with ISS (n=90) were reading 102 (18), spelling 98 (17), and math 96 (21); and for control children (n=90) were reading 105 (14), spelling 103 (14), and math 105 (16) Significantly more ISS children (22%) had a skill deficit in math (score < 80) compared to GHD (10%) and normal children (7%)	Excluded children with "known mental impairment"	No data on funding source

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Evidence Table 1. Studies Evaluating Short Stature Secondary to Medical Impairment

Part III

Author, Year	Associations found	Potential Biases	Comments
Siegel 1998 98356098	The mean IQ of girls with TS (n=22) was 102 (11), and with GHD/ISS (n=25) was 105 (15); these were not significantly different than controls (n=25) with 109 (17). Mean (SD) WRAT scores for children with TS (n=22) were reading 98 (15), spelling 95 (19), and math 90 (16); for children with GHD/ISS (n=25) were reading 105 (18), spelling 99 (21), and math 102 (22); and for control children (n=25) were reading 98 (16), spelling 100 (15), and math 99 (20). No significant differences among groups.	CBCL completed by parent, typically mother	Study was pharmaceutical company funded
Skuse 1997 Gilmour 1996 96408881 Skuse 1994 95252652	Mean (SD) IQ of children with SS (n=22) were Full Scale = 96 (19), Verbal = 95 (20), and Performance = 97 (17); for normal children (n=22), Full Scale = 107 (17), Verbal = 105 (17), and Performance = 108 (17); Children with SS had statistically lower Full Scale IQ and Performance IQ than controls, but statistically similar Verbal IQ Conduct, Global, Physical, Athletic, Social, and Scholastic competencies measured by Teacher CBCL were similar among SS children (n=17) and controls	Excluded Russell-Silver Syndrome children who had low IQ Incomplete reporting of results. Teacher CBCL completed only on subset of subjects	Study was pharmaceutical funded
Stathis 1999 20099119	Mean receptive vocabulary score on PPVT-R test for boys with SS (n=60) was 92, which was significantly lower for normal height boys, 98 (n=1,660) Mean receptive vocabulary score on PPVT-R test for girls with SS (n=53) was 92, which was significantly lower for normal height girls, 95 (n=1,508)	Study of correlation of PPVT-R score to height excluded those with score < 50	No data on funding source PPVT-R score was adjusted for maternal age, education, non-English speaking background, age at evaluation, maternal depression at birth and maternal height

Evidence Table 1. Studies Evaluating Short Stature Secondary to Medical Impairment
Part III

Author, Year	Associations found	Potential Biases	Comments
Steinhausen 1976 77086274	Mean IQ for children with SS (n=32) were total 103, verbal 102, and performance 103. Primary mental abilities on LPS intelligence test were significantly different among children with SS (n=32) and controls (n=32) for only 2 of 14 measures of intelligence; Spatial orientation was 4.7 for SS children and 6.2 for controls; Speed of closure was 4.4 for SS children and 5.3 for controls Grade level was appropriate in 59% of children with SS (n=17); Academic achievement was adequate in 48% of SS children Among children with short stature (n=32) mean extraversion and neuroticism scores on HANES were 11.4 and 12.9, respectively. These were similar to controls (11.6 and 15.6, respectively).	Not all of the psychological tests are published and validated; the one well-known test (WISC) was used without data in control group Many comparisons with some statistical significance but questionable clinical significance; the intelligence (LPS) and personality (CPQ) variables are not well defined No statistical comparison was done for social and coping behavior; and, school performance; Average scores only No outline of how the subset 17 kids were selected School achievement not defined	No data on funding source
Tanner 1975 75217260	Mean (SD) IQ for children with SS due to RSS (n=11) was 103 (21), range 70-130 Of subjects with RSS and head circumference < 3rd percentile (n=18), 83% were at "normal" schools, 17% were at schools for educationally subnormal children ("usually IQ < 80"); Of subjects with head circumference > 3rd percentile (n=19), all were at normal schools	IQ test not described and performed in only a sub-sample	No data on funding source

Evidence Table 1. Studies Evaluating Short Stature Secondary to Medical Impairment
Part III

Author, Year	Associations found	Potential Biases	Comments
Voss 1994 Voss 1991 92151680 Downie 1997 97159125 Downie 1996 96408882	Mean (SD) IQ in children aged 7-9 y with SS (n=140)was 102 (15.2) and for controls with normal height (n=140), IQ was 104 (14.1); there was no significant difference between the two groups; there was also no significant difference in Verbal scales, Non-verbal scales, Speed of Information Processing, or Reading or Number Attainment, after controlling for SES Behavior Disturbance (total Teacher RBQ score > 9) occurred in 29% of children aged 7-9 y with SS (n=132), and in 21% of control children (n=132); the difference was not significant; Hyperactivity (Activity subscale score ≥ 3) occurred in 16% of SS children compared to 8% of control children (p=0.003); Mean (SD) Total Behavior scale score for children with SS was 6.2 (6.2), compared to 5.1 (6.5) for control children (NS) Conduct subscale score was 1.2 (2.3) for children with SS, compared to 1.0 (2.1) for control children (NS) Emotional subscale score was 1.2 (1.4) for children with SS, compared to 1.2 (1.7) for control children (NS) Activity subscale score was 1.7 (2.1)for children with SS, compared to 1.1 (1.6) for control children (NS after controlling for SES) Mean (SD) IQ in children aged 13 y with SS, not treated with GH, (n=84-106 for different tests) and controls (n=93-119), were 103 (17) and 109 (16), respectively (p=0.005); Reading Attainment of 44.3 (8.8) and 47.9 (8.5), respectively (p=0.002); Math Attainment of 40.2 (7.2) and 43.5 (9.2), respectively (p=0.003); Locus of Control score of 16.6 (5.0) and 14.3 (5.1), respectively (p=0.001), Behavior score of 6.8 (7.5) and 5.3 (6.8), respectively (NS); The statistical significance of these differences were reduced, but remained significant, after controlling for SES	None noted	Studies were hospital and pharmaceutical funded Downie studies included subsets of subjects in Voss studies; one examined subjects treated with GH; one examined untreated subjects Different sized subsets of subjects, at different ages, analyzed in different articles

Evidence Table 1. Studies Evaluating Short Stature Secondary to Medical Impairment

Part III

Author, Year	Associations found	Potential Biases	Comments
Wilson 1986	Mean IQ (WISC) for children with SS, aged 12-17 (N~350) was 92 Mean IQ (WRAT) for children with SS, aged 12-17 (N~350) was 91 Among children of all heights, aged 6-11 (n=7,119), both WISC and WRAT scores showed a significant but small correlation with height (r=0.18, WISC; r=0.17, WRAT) Among children of all heights, aged 12-17 (n=6,768), both WISC and WRAT scores showed a significant but small correlation with height (r=0.20, WISC; r=0.19, WRAT) "The association between height and IQ scores is less among the subjects with a high family income"	Prevalence and correlation data only Incomplete reporting	Study was government funded
Young-Hyman 1986	Mean (SD) IQ for children with SS (n=27) was 110 (16), range was 85 to 142 Mean (SD) perceptual-motor skill for children with SS (n=27) was significantly delayed at 9.2 y (1.2 y), compared to chronological age 11.8 y	How significance was defined for perceptual-motor skill test was not outlined in the paper	No data on funding source

Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia
Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Disease / Condition Type	Study Design Mean Duration (Range)
Alston 1983	Location: UK Setting: Brittle Bone Society, Health Authorities Mean age: ND Age range: 5-16 y Mean height: ND Male: ND Race: ND Enrolled: 40 (40 controls) Evaluated: 40 (40) Number of sites: ND	<u>Cases</u> - Osteogenesis imperfecta <u>Controls</u> - Same school class or neighborhood as cases, matched for age, sex and social class	None reported	Osteogenesis imperfecta	Prospective cross-sectional cohort
Apajasalo 1998 98163312	Location: Finland Setting: Clinic Mean age: ND Age range: 12-15 y Mean height: ND Male: 42% Race: ND Enrolled: 21 (239 controls) Evaluated: 19 (239) Number of sites: 1	<u>Cases</u> - Diagnosis of skeletal dysplasia Age 12-15 y <u>Controls</u> – Age-matched Helsinki elementary school pupils who completed the HRQOL questionnaire Age 12-15 y	<u>Cases</u> – Incomplete questionnaires	Skeletal dysplasia Achondroplasia Cartilage hair hypoplasia Diastrophic dysplasia	Prospective cross-sectional

Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia

Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Disease / Condition Type	Study Design Mean Duration (Range)
Bailey 1971 72080259	Location: US Setting: Clinic Mean age: ND Age range: 3 days - 72 y Mean height: ND Male: 51% Race: ND Enrolled: ND Evaluated: 41 (no data on number < 21 y) Number of sites: 1	Diagnosis of achondroplasia	None reported	Achondroplasia	Retrospective cross-sectional
Benson 1978 79027354	Location: US Setting: Shriner's Hospital Mean age: ND Initial age range: 1 mo - 16 y Mean height: ND Male: 44% Race: White 94%; Black 6% Enrolled: 143 Evaluated: 126 Number of sites: 1	Diagnosis of osteogenesis imperfecta from 1924 to 1974	Spine X-ray films not available	Osteogenesis imperfecta	Retrospective longitudinal case series (Mean [Range] 5 [0-17] y)

Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia
Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Disease / Condition Type	Study Design Mean Duration (Range)
Bleck 1981 82026195	Location: US Setting: ND Initial mean age: 9y Follow-up mean age: 13 y Initial age range: 3 mo - 21 y Follow-up age range: 4-26 y Mean height: ND Male: ND Race: ND Enrolled: 30 Evaluated: 24 Number of sites: ND	Diagnosis of osteogenesis imperfecta: congenita or tarda	Death Too young to enable a satisfactory follow-up Moved out of the state	Osteogenesis imperfecta	Prospective longitudinal cohort (Mean [Range] 4 [1-15] y)
Brinkmann 1993 94091382	Location: Germany Setting: Clinic Mean age: 9 y Age range: ND Mean height: ND Male: 47%% Race: ND SES: Primarily middle-class Enrolled: 30 (90 controls) Evaluated: 30 (90) Number of sites: 1	Cases - Clinical and radiographic diagnosis of achondroplasia Controls - Closest sibling; Other causes of short stature Matched for age, sex and SES Normal height children, matched for age, sex and SES	None reported	Achondroplasia	Prospective cross-sectional

Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia
Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Disease / Condition Type	Study Design Mean Duration (Range)
Cox 1982 83016754	Location: US Setting: Dept of Communicative Disorders Mean age: 10 y Age range: 4-17 y Mean height: ND Male: 53% Race: ND Enrolled: 30 Evaluated: 30 (15 met criteria for current review) Number of sites: 1	Medically diagnosed osteogenesis imperfecta, types I, III or IV	History of head injury Prior surgery Treatment for ear disease Noise exposure (For current review, excluded those age ≥ 18 y)	Osteogenesis imperfecta	Prospective cross-sectional cohort
Daly 1996 96219608	Location: UK Setting: Osteogenesis imperfecta clinic Mean age: 7.4 y Age range: 3.5-16.3 y Mean height: ND Male: 49% Race: ND Enrolled: 59 Evaluated: 51 Number of sites: 1	Patients registered at OI clinic who had been recently seen	No reply to the questionnaire	Osteogenesis imperfecta	Prospective cross-sectional cohort

Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia
Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Disease / Condition Type	Study Design Mean Duration (Range)

Engelbert 1997
 	
Possible overlap with Engelbert 1998, Engelbert 1999 Engelbert 2000 Engelbert 2001
	Location: Netherlands
	Setting: Children's hospital
	Mean age:
	  Type I OI: 7.3±3.5 y
	  Type III OI: 6.5±2.9 y
	  Type IV OI: 9.1±5.0 y
	Age range:
	  Type I OI: 2-16 y
	  Type III OI: 2-12 y
	  Type IV OI: 1-17 y
	Mean height: ND
	Male: 54%
	Race: ND
	Enrolled: 68
	Evaluated: 61
	Number of sites: 1
		Diagnosis of osteogenesis imperfecta
		Visit source hospital = 1 per year
			Parents declined to participate	Osteogenesis imperfecta	Prospective cross-sectional cohort

Engelbert 1998 98366964
 	
Possible overlap with Engelbert 1997, Engelbert 1999 Engelbert 2000 Engelbert 2001
	Location: Netherlands
	Setting: Children's hospital
	Mean age: 8 y
	Age range: 1-15 y
	Mean height, SDS:
	  Type I OI –1.6±1.3
	  Type III OI –8.0±2.0
	  Type IV OI –2.8±1.7
	Male: 47%
	Race: ND
	Enrolled: 47
	Evaluated: 47
	Number of sites: 1
		Children with osteogenesis imperfecta who regularly attended a referral center	None reported	Osteogenesis imperfecta	Prospective cross-sectional cohort

Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia
Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Disease / Condition Type	Study Design Mean Duration (Range)

Engelbert 1999 99381568
 	
Possible overlap with Engelbert 1997, Engelbert 1998 Engelbert 2000 Engelbert 2001
	Location: Netherlands
	Setting: Children's hospital
	Mean age:
	  Initial: 7.3±3.8 y
	  Follow-up: 9.4±3.6 y
	Age range:
	  Initial: 1-15 y
	  Follow-up: 3-17 y
	Mean height: ND
	Male: 50%
	Race: ND
	Enrolled: 54
	Evaluated: 44
	Number of sites: 1
		Diagnosis of osteogenesis imperfecta	Intramedullary fixation surgery within 6 months
			Any other disability or impairment
			Parents' refusal in follow-up
			Unable to be reached
			Surgical interventions in the last half year of the study
				Osteogenesis imperfecta	Prospective longitudinal cohort (Mean [Range] 1.2 [0.7-1.8] y)

Engelbert 2000 20429012
 	
Possible overlap with Engelbert 1997, Engelbert 1998 Engelbert 1999 Engelbert 2001
	Location: Netherlands
	Setting: Children's hospital
	Mean age: 11.2±5.2 y
	  Type I OI: 10.8±5.8 y
	  Type III OI: 9.4±2.9 y
	  Type IV OI: 13±4.6 y
	Age range: 1-28 y
	  Type I OI: 1-28 y
	  Type III OI: 5-15 y
	  Type IV OI: 4-20 y
	Mean height: ND
	Male: 45%
	Race: ND
	Enrolled: 98
	Evaluated: 70
	Number of sites: 1
		Diagnosis of osteogenesis imperfecta
		Completed questionnaire
			Too young to expect walking	Osteogenesis imperfecta	Retrospective cross-sectional cohort

Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia
Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Disease / Condition Type	Study Design Mean Duration (Range)
Engelbert 2001 21334060 Possible overlap with Engelbert 1997, Engelbert 1998 Engelbert 1999 Engelbert 2000	Location: Netherlands Setting: Hospital Mean age: 12.6±3.2 y Age range: 8-16 y Mean height: ND Male: 50% Race: ND Enrolled: 40 Evaluated: 40 Number of sites: 1	Diagnosis of osteogenesis imperfecta	None reported	Osteogenesis imperfecta	Prospective cross-sectional cohort
Falvo 1973 74013834	Location: US Setting: ND Mean age: 13.5 y Age range: 4-34 y Mean height: ND Male: 27% Race: ND Enrolled: ND Evaluated: 11 Number of sites: 1	Diagnosis of osteogenesis imperfecta	None reported	Osteogenesis imperfecta	Unclear

Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia
Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Disease / Condition Type	Study Design Mean Duration (Range)
Fowler 1997 97356792 Possible overlap with Pauli 1995	Location: US Setting: Bone dysplasia clinic Mean age: ND Age range: 1-60 months Mean height: ND Male: 48% Race: White 88%, Black 2%, Hispanic 3%, Korean/Asian/Indian 5% Enrolled: 93 Evaluated: 37 Number of sites: 1	Diagnosis of achondroplasia	None reported	Achondroplasia	Prospective cross-sectional
Pauli 1995 95193803 Possible overlap with Fowler 1997	Location: US Setting: Bone clinic Mean age: ND Age range: Infants, young children Mean height: ND Male: 52% Race: White 85%; Black 3%; Hispanic 4%; Korean 7%; Asian Indian 1% Enrolled: 75 Evaluated: 75 Number of sites: 1	Clinical diagnosis of achondroplasia	None reported	Achondroplasia	Prospective longitudinal (N = 53) and cross-sectional (N = 22) cohorts (To age > 1 y)

Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia
Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Disease / Condition Type	Study Design Mean Duration (Range)
Hecht 1991 92152267	Location: US Setting: Clinic Mean age: 15±5 mo Age range: 8.5-26 mo Mean height: ND Male: 46% Race: ND Enrolled: 13 Evaluated: 13 Number of sites: ND	Infants with clinical diagnosis of achondroplasia	None reported	Achondroplasia	Prospective cross-sectional cohort
Hunter 1998 98299528	Location: Multinational Setting: Clinic Mean age: ND Age range: ND Mean height: ND Male: 49% Race: White 100% Enrolled: 55 (37 controls) Evaluated: 55 (37) Number of sites: 6	Cases - Diagnosis of primary skeletal dysplasia Age < 16-18 y old (by site) Controls - Unaffected siblings	None reported	Skeletal dysplasia	Prospective cross-sectional
Kuurila 2000 20379515	Location: Finland Setting: Dept of clinical genetics Mean age: 10 y Age range: 4-16 y Mean height: ND Male: 42% Race: White Enrolled: 60 Evaluated: 45 Number of sites: 1	Diagnosis of osteogenesis imperfecta Age 4-16 y	Insufficient cooperation No audiometry performed Moderate mental retardation.	Osteogenesis imperfecta	Prospective cross-sectional cohort

Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia
Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Disease / Condition Type	Study Design Mean Duration (Range)
Norimatsu 1982 82163323	Location: Japan Setting: Children's Hospital Initial mean age: ND Follow-up mean age: 15.5 y Initial age range: 12 d - 14 y Follow-up age range: 4-28 y Mean height: ND Male: 68% Race: (Japanese) Enrolled: 30 Evaluated: 22 Number of sites: 1	Osteogenesis imperfecta Treated from 1959 to 1980 Followed by spinal x-ray	None reported	Osteogenesis imperfecta (congenita and tarda)	Retrospective longitudinal case series (Mean [Range] 7.6 [1-20] y)
Poussa 1991 92054945	Location: Finland Setting: Genetics and bone clinics Mean age: ND Age range: 6-20 y Mean height: ND Male: ND Race: White Enrolled: 101 Evaluated: 38 Number of sites: 2	Diagnoses of diastrophic dysplasia Age ≤ 20 y	None reported	Diastrophic dysplasia	Prospective longitudinal cohort 13.5 y

Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia
Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Disease / Condition Type	Study Design Mean Duration (Range)
Reid 1988 89193370 Possible overlap with Stokes 1988	Location: US Setting: Genetics clinic Mean age: ND Age range: < 7 y Mean height: ND Male: ND Race: ND Enrolled: 62 Evaluated: 26 Number of sites: 1	Achondroplasia Age < 7 y Seen in genetics clinic	Seen only in orthopedics clinic (not in genetics clinic)	Achondroplasia	Prospective longitudinal cohort 20-45 mo
Stokes 1988 88110722 Possible overlap with Reid 1988	Location: US Setting: Hospital, genetics clinic, LPA convention Mean age: ND Age range: ND Mean height: ND Male: 50% Race: ND Enrolled: 102 (including adults) Evaluated: 24 children Number of sites: 1	Achondroplasia	Acute medical or surgical problems Hypochondroplasia Technically unsatisfactory spirometry Too young to cooperate with spirometry	Achondroplasia	Prospective cross-sectional cohort
Reite 1972 72182015	Location: US Setting: Clinic Mean age: ND Age range: 6-17 y Mean height: ND Male: ND Race: ND Enrolled: ND Evaluated: 12 Number of sites: 2	Children with "severe" osteogenesis imperfecta	None reported	Osteogenesis imperfecta	Retrospective cross-sectional

Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia

Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Disease / Condition Type	Study Design Mean Duration (Range)
Rogers 1979 79200737	Location: US Setting: Pediatric clinic research unit Mean age: ND Age range: 5 mo – 15 y Mean height: ND Male: ND Race: ND Enrolled: 68 Evaluated: 68 Number of sites: 1	Diagnosis of skeletal dysplasia leading to short stature	Syndromes of low-birth-weight dwarfism Multiple malformations Mucolipidosis or mucopolysaccharidosis Cardiac arrest	Skeletal dysplasia and achondroplasia	Prospective cross-sectional cohort
Ruiz-Garcia 1997 97346439	Location: Mexico Setting: Genetics clinic Mean age: 4.5 y Age range: 3 mo - 17 y Mean height: ND Male: 49% Race: ND Enrolled: 39 Evaluated: 39 Number of sites: 1	"Classical" achondroplasia diagnosed in Genetics Department	History of neurosurgical procedures	Achondroplasia	Prospective cross-sectional cohort

Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia
Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Disease / Condition Type	Study Design Mean Duration (Range)
Shurka 1976	Location: Israel Setting: Pediatric endocrinology clinic Mean age: 15 y Age range: 9-17 y Mean height: 134 cm Height range: 104-157 cm Male: 46% Race: ND SES: Primarily average or high Enrolled: 12 Evaluated: 11 (7 met criteria for current review) Number of sites: 1	Dwarfism due to bone disease	(For current review, age ≥ 18 y)	Bone disease (External chondromatosis, Achondroplasia, Undefined)	Prospective cross-sectional cohort
Skeletal Dysplasia Group 1989 89192477	Location: UK Setting: Workgroup's registers Mean age: ND Age range: 1-15 y Mean height: ND Male: 49% Race: ND Enrolled: 182 Evaluated: 15 (children with Morquio disease) Number of sites: ND	Diagnosis of skeletal dysplasia Adequate cervical spine films (Morquio disease: other disease sub-groups did not meet criteria for current review)	Osteogenesis imperfecta Sclerosing bone dysplasias or tumor-like disorders Malformation syndromes	Morquio disease	Retrospective cross-sectional case series

Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia

Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Disease / Condition Type	Study Design Mean Duration (Range)
Stewart 1989 90125184	Location: Scotland Setting: Dep. Of medical genetics Mean age: ND Age range: 10-19 y Mean height: ND Male: 43% for the larger group Race: ND Enrolled: 56 Evaluated: 56 (13 met criteria for current review) Number of sites: ND	Diagnosed based on their history of spontaneous fractures. Contacted via Brittle Bon Society. For current review, only children aged 10-19 were included	None reported	Osteogenesis imperfecta	Prospective cross-sectional cohort

Thompson 1999 99221075	Location: US
	Setting: Genetics clinic
	Mean age:
	  Cases: 89 mo
	  Premature: 107 mo
	  Controls: 111 mo
	Age range: ND
	Mean height: ND
	Male: 52%
	Race: White 74%, Black 6%, Hispanic 13%, Other 7%
	SES: Low 31%, Middle 19%, High 50%
	Enrolled: 16 (21 premature, 17 controls)
	Evaluated: 16 (21, 17)
	Number of sites: 1
		Cases - clinical and radiographic diagnosis of ACH
		Premature controls- premature infants with hydrocephalus
		Normal controls - normally developing children of average stature
		All - IQ>69
			Severe psychiatric disorder
			Uncontrolled seizure
			Other neurological disorder
			Child abuse
			Sensory deficit
			Unable to speak English
				Achondroplasia	Prospective cross-sectional cohort

Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia

Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Disease / Condition Type	Study Design Mean Duration (Range)
Waters 1993 94029092	Location: Australia Setting: Sleep lab and clinic Mean age: ND Age range: 1-31 y Mean height: ND Male: 50% Race: ND Enrolled: 20 Evaluated: 20 Number of sites: 1	Patients with dysplasia (implied)	Refusal to participate	Achondroplasia	Prospective cross-sectional cohort

Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia

Part II

Author, Year	Predictors	Predictor Measures / Definitions	Outcomes	Outcome Measures
Alston 1983	Osteogenesis imperfecta	ND	Cognitive/Academic	Non-verbal intelligence (Raven's Matrices) Reading (Primary Reading Test, Wide Span Reading Test, or Gapadol Reading Test) Spelling (Graded Word Spelling Test) Writing speed (Number of words written in 5 minutes)
			Motor function	Mobility (Walk vs wheelchair)
Apajasalo 1998 98163312	Achondroplasia	Disproportionate short limbed short stature, characteristic facial features and joint and spine disorders	Physical development	Overall quality of life (Health related quality of life, 16 dimensions) Mobility dimension Vision dimension Hearing dimension
	Cartilage-hair hypoplasia	Congenital disproportionate short-limbed short stature, thin/sparse hair, defective immunity		
	Diastrophic Dysplasia	Severe physical handicap due to short-limbed short stature, progressive joint limitations, kyphoscoliosis, foot deformities		
Bailey 1971 72080259	Achondroplasia	ND	Motor function	Elbow flexion (Angle, Self-reported disability)
Benson 1978 79027354	Osteogenesis imperfecta, mild	Thicker cortical bone with visible trabeculae, not severe osteoporosis of vertebrae	Motor function	Walking ability (Independent walkers, Walked with appliance, Sitter) Scoliosis (spinal curvature on spine radiography)
	Osteogenesis imperfecta, moderate	ND		
	Osteogenesis imperfecta, severe	Thin osteoporotic long bones and severe osteoporosis of vertebrae		

Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia

Part II

Author, Year	Predictors	Predictor Measures / Definitions	Outcomes	Outcome Measures
Bleck 1981 82026195	Osteogenesis imperfecta congenita	Severe type	Physical development/Motor function	Independence (0 = No achievement possible 1 = Complete dependence 2 = Partial dependence 3 = Independence through technical help 4 = Completely independent, but not normal in timing, effort expenditure, or external appearance 5 = Normal activity) Mobility efficiency (0 = None 1 = Mobility not functional enough to be used 2 = Moves about immediate surroundings 3 = Travels in the community 4 = Travel beyond the community Activities of daily living (ADL: 0 = No ADL possible 1 = Meets own essential needs 2 = Completes personal care 3 = Household activity possible 4 = Normal ADL) Ambulation (0 = None 1 = Walking possible but not functional enough to be useful 2 = Household walker 3 = Walk outside home but limited to neighborhood 4 = Community walker)
	Osteogenesis imperfecta tarda	ND		

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Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia

Part II

Author, Year	Predictors	Predictor Measures / Definitions	Outcomes	Outcome Measures
Brinkmann 1993 94091382	Achondroplasia	Short limbs and characteristic skull changes with macrocephaly	Cognitive	Cognitive Abilities Test, German version Verbal component Arithmetic component Reasoning component
			Physical development	Motor development (Months to sit, stand, walk alone) Delayed speech (parental report)
			Sensory	Hearing deficit (parental report)
			Pain	Limb, joint, back pain
Cox 1982 83016754	Osteogenesis imperfecta	Idiopathic bone fragility, blue sclerae, hearing impairment	Sensory	Hearing loss (Pure tone thresholds > 30 dB hearing loss at 250-1,000 Hz and/or > 25 db hearing loss at 2,000-6,000 Hz)
Daly 1996 96219608	Osteogenesis imperfecta Shapiro classification: Congenita A	Fractures at birth, bones radiographically abnormal	Physical development/Motor function	Mobility (Wheelchair, Aided walker, Independent) Patterns of development (Abnormal arrested, Delayed arrested, Normal arrested, Delayed, Normal)

Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia

Part II

Author, Year	Predictors	Predictor Measures / Definitions	Outcomes	Outcome Measures
	Congenita B	Fractures at birth, bones radiographically normal		
	Tarda A	First fracture by walking stage, bones narrow, osteopenic		
	Tarda B	First fracture after walking, bones radiographically normal		
	Osteogenesis imperfecta Sillence classification: I A	Autosomal dominant, normal stature, blue sclerae		
	I B	IA plus dentinogenesis imperfecta		
	III	Autosomal recessive, multiple fractures at birth, progressively deforming		
	IV A	Autosomal dominant, bone fragility, normal sclerae		
	IV B	IV A plus dentinogenesis imperfecta		
Engelbert 1997	Osteogenesis imperfecta I, III and IV	Classified according to Sillence method (see Daly 1996, above)	Motor function	Self-care (Pediatric Evaluation of Disability Inventory, PEDI, range 0-100, median 50. Score scaled for children older than 7.5 years such that normal score=100) Mobility (PEDI)
Engelbert 1998 98366964	Osteogenesis imperfecta I, III and IV	Classified according to Sillence method (see Daly 1996, above)	Motor function	Scoliosis (Cobb angle > 40°) Kyphosis (Cobb angle < 10° or > 40°)
Engelbert 1999 99381568	Osteogenesis imperfecta I, III and IV	Classified according to Sillence method (see Daly 1996, above)	Motor function	Level of ambulation (Bleck classification)
Engelbert 2000 20429012	Osteogenesis imperfecta I, III and IV	Classified according to Sillence method (see Daly 1996, above)	Motor function	Level of ambulation (Bleck classification)

Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia

Part II

Author, Year	Predictors	Predictor Measures / Definitions	Outcomes	Outcome Measures
Engelbert 2001 21334060	Osteogenesis imperfecta I, III and IV	Classified according to Sillence method (see Daly 1996, above)	Motor function	Self-care (Pediatric Evaluation of Disability Inventory, PEDI, range 0-100. Score scaled for children older than 7.5 years such that normal score=100) Mobility (PEDI) Level of ambulation (Bleck classification)
			Motor function	Joint range of motion: arms, legs (0=normal, 4=maximally decreased) Muscle strength: arms, legs (0=no muscle activity, 5=normal muscle strength)
Falvo 1973 74013834	Osteogenesis imperfecta	Generalized osteoporosis, blue sclerae, dentinogenesis imperfecta, history of fracture	Pulmonary	Pulmonary function tests (Vital capacity (VC), Residual volume (RV), 1-second forced expiratory volume divided by forced vital capacity (FEV_1/FVC)) Arterial blood analysis (Oxygen partial pressure, carbon dioxide partial pressure)
	Mild	No noticeable deformity of long bones		
	Moderate	Bowing of lower extremity long bones only		
	Severe	Bowing of all long bones		
Fowler 1997 97356792	Achondroplasia	ND	Physical development	Motor development (Denver Developmental Screening Test: Months to sit, stand, walk alone)
Pauli 1995 95193803	Achondroplasia	ND	Neurological	Neurological examination (Truncal tone, Limb tone, Arm strength, Leg strength) Neurological history (Developmental delays, Asymmetry, Weakness, Sensory abnormality, Arching / opisthotonus, Clonus, Seizure, Apnea)
			Pulmonary	Polysomnography (Central apnea, Central hypopnea, Obstructive apnea)

Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia
Part II

Author, Year	Predictors	Predictor Measures / Definitions	Outcomes	Outcome Measures
Hecht 1991 92152267	Achondroplasia	ND	Cognitive	Mental development index (Bayley Scales of Infant Development) Psychomotor development index (Bayley)
			Pulmonary	Sleep apnea
Hunter 1998 98299528	Chondrodysplasia	ND	Psychological	Depression (Beck Depression Inventories) Anxiety (Speilberger State-Trait Anxiety Inventories)
Kuurila 2000 20379515	Osteogenesis imperfecta I, III and IV	Classified according to Sillence method (see Daly 1996, above)	Sensory	Hearing loss (Pure tone < 20 dB, Conductive < 15 dB)
Norimatsu 1982 82163323	Osteogenesis imperfecta Mild, Moderate, Severe	Per Falvo 1973 (see above)	Motor function	Walking ability (Wheelchair bound, ambulates with assistance) Scoliosis (Mild <30°; Moderate 30°-50°; Severe > 50°, by Cobb's method)
Poussa 1991 92054945	Diastrophic dysplasia	Short-limbed short stature, joint limitations, spinal and foot deformities, dysmorphic earlobes, cleft palate	Motor function	Scoliosis (>10° by Cobb's method)
Reid 1988 89193370	Achondroplasia	ND	Pulmonary	Obstructive sleep apnea (>5 obstructive or >2 central apneas per hour)
			Neurological	Paresis (not defined)
Stokes 1988 88110722	Achondroplasia	Rhizomelia, macrocephaly with midfacial hypoplasia, spinal canal narrowing	Pulmonary	Forced vital capacity
Reite 1972 72182015	Osteogenesis imperfecta	ND	Cognitive	IQ (WISC)

Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia

Part II

Author, Year	Predictors	Predictor Measures / Definitions	Outcomes	Outcome Measures
Rogers 1979 79200737	Achondroplasia Other skeletal dysplasia	ND Multiple diagnoses	Cognitive	IQ (Age< 2 y: Bayley Scales of Infant Development; Age 2-6 y: Stanford-Binet Intelligence Scale; Age 6-15 y: WISC)
Ruiz-Garcia 1997 97346439	Achondroplasia	Autosomal dominant, abnormally short stature, macrocephaly, rhizomelia	Neurological	Neurological examination (Quadriparesis, Weakness, Sensory deficit) Compressive neural syndrome (craniocervical compression, lumbar compression)
			Hearing Loss	Brainstem auditory evoked response
Shurka 1976	Skeletal dysplasia	External chondromatosis, achondroplasia, or undefined	Cognitive	IQ (WISC)
Skeletal Dysplasia Group 1989 89192477	Morquio disease	ND	Neurological	Neurological complications (ND)
Stewart 1989 90125184	Osteogenesis imperfecta	ND	Sensory	Hearing loss (Pure tone < 30 dB, conductive < 15 dB)
Thompson 1999 99221075	Achondroplasia	ND	Cognitive	IQ (WISC-R) Academic achievement (WRAT-R)
			Motor function	Gross motor arm and leg coordination (McCarthy Scales)

Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia

Part II

Author, Year	Predictors	Predictor Measures / Definitions	Outcomes	Outcome Measures
			Visual-motor skills	Motor-based design copying task (Beery Test of Visual Motor Integration)
				Motor-free spatial matching task (Judgment of Line Orientation)
				Fine motor skills
Waters 1993 94029092	Achondroplasia	ND	Pulmonary	Sleep apnea (> 5 apneic episodes per hour)

Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia

Part III

Author, Year	Associations found	Potential Biases	Comments
Alston 1983	In children with osteogenesis imperfecta (n=40) mean non-verbal intelligence (104), reading ability (100) and spelling ability (102) were similar to control children (n=40, 105, 102, 104, respectively). Writing speed was significantly slower (51 words in 5 minutes) compared to controls (61 words). Of children with osteogenesis imperfecta (n=40), 38% required wheelchair use.	None noted	Study was privately funded
Apajasalo 1998 98163312	Among adolescents with skeletal dysplasia (n=19), overall quality of life (HRQOL=92) was significantly lower than in controls (n=239, 95) in univariate and multivariate analyses. Among adolescents with skeletal dysplasias (n=19), the quality of life dimension mobility was significantly lower than for normal children. Children with diastrophic dysplasia and achondroplasia had mean scores of ~81 (from graph); those with cartilage-hair hypoplasia had a mean score of 100. Those with skeletal dysplasia had similar scores to normal children for vision and hearing. Children with diastrophic dysplasia had mean scores of 94 for vision and 93 for hearing; those with achondroplasia had mean scores of 96 and 95, respectively; those with cartilage-hair hypoplasia had mean scores of 96 and 85, respectively. In the analysis of 16 dimensions of quality of life, there were no statistically significant differences among the different groups of children with skeletal dysplasia.	Few definitions of outcome measures Reporting of analyses incomplete	No data on funding source
Bailey 1971 72080259	Infants with achondroplasia, aged 0-2 years, had mean elbow flexion deformity of 11°, ranging from 5°-25°; Children, aged 3-12 years, had mean elbow flexion of 19°, ranging from 10°-40°; adolescents, aged 13-20 years, had mean elbow flexion of 23.5°, ranging from 0°-40°.	No data on actual disability due to limited joint movement specifically in children. Unknown number of subjects in relevant age ranges.	No data on funding source

Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia

Part III

Author, Year	Associations found	Potential Biases	Comments
Benson 1978 79027354	Among children with osteogenesis imperfecta (n=126) 48% were wheelchair bound (sitters), 25% walked with appliances, and 28% were independent walkers. Among those children with osteogenesis imperfecta who had spine radiography performed (n=103), 38% had straight spines, 7% had scoliosis between 0°-9°, 19% had scoliosis between 10°-19°, 14% had scoliosis between 20°-49°, 14% had scoliosis between 50°-79°, and 9% ≥ 80°.	Incomplete data available. Incomplete reporting	No data on funding source
Bleck 1981 82026195	Among children with osteogenesis imperfecta congenita, severe type (n=12), mean independence, mobility, activities of daily living, and ambulation scores after orthotic and mobility management were 2.6 (partial dependence-independence through technical help), 3.0 (travels in community), 2.5 (completes personal care-household activity possible), and 0.7 (no ambulation-walking possible but not functional), respectively. Among children with osteogenesis imperfecta tarda (n=12), mean independence, mobility, activities of daily living, and ambulation scores after orthotic and mobility management were 3.4 (independence through technical help-completely independent but not normal), 3.8 (almost travel beyond community), 3.7 (almost normal activities of daily living), and 2.8 (almost walk outside home but limited to neighborhood), respectively.	No statistical analysis.	No data on funding source. No statistical comparison.

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Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia

Part III

Author, Year	Associations found	Potential Biases	Comments
Brinkmann 1993 94091382	Among children with achondroplasia (n=30), mean Cognitive Abilities Scores were Total 48, Verbal 46, Arithmetic 49, and Reasoning 51. Compared to normal controls (n=30), Total (56), Verbal (54) and Arithmetic (55), children with achondroplasia had significantly lower scores; Reasoning scores (control 55) were not significantly different. Overall comparisons to siblings (n=30) and other short children (n=30) were similar. Children with achondroplasia (n=30) were able to sit alone at a median of 12 months (compared to 7 months for normal controls, n=30), according to parental reports, to stand alone at 14 months (10 months), and to walk alone at 18 months (12 months). Siblings (n=30) and short controls (n=30) had motor development similar to other controls. No statistical analysis reported. Among children with achondroplasia (n=27) 63% were reported by their parents to have hearing deficits, compared to 18% of short controls (n=28) and 19% of normal controls (n=27). Among children with achondroplasia (n=27) 41% were reported by their parents to have delayed speech development, compared to 14% of short controls (n=28) and 7% of normal controls (n=27). Among children with achondroplasia (n=30) limb, joint or back pain was present by parental report in 80%, compared to 43% of short controls (n=30) and 10% of normal controls (n=30).	Limited statistical analyses. No data on sibling controls for factors that were reported by parents.	Study was government funded
Cox 1982 83016754	Of children with osteogenesis imperfecta (n=15) 33% had hearing loss	All subjects from 5 families with history of osteogenesis imperfecta. Limited data on hearing function	Study was university funded

Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia

Part III

Author, Year	Associations found	Potential Biases	Comments
Daly 1996 96219608	Among children with osteogenesis imperfecta classified by Shapiro as congenita B (n=31) 19% had abnormal arrested development, 19% had delayed arrested development, 29% had normal arrested development, 29% had delayed development, and 3% had normal development. Among these children, 87% were wheelchair bound and 13% were independent walkers. Among children with osteogenesis imperfecta tarda A (n=15) none had abnormal arrested development, 27% had delayed arrested development, 7% had normal arrested development, 20% had delayed development, and 47% had normal development. Among these children, 27% were wheelchair bound, 13% were aided walkers, and 60% were independent walkers. Too few children had osteogenesis congenita A (n=1) or tarda B (n=4) for analysis. Among (the same sample of) children with osteogenesis imperfecta classified by Sillence as Type I (n=15) none had abnormal arrested or delayed arrested development, 7% had normal arrested development, 27% had delayed development, and 67% had normal development. Among these children, 7% were aided walkers and 93% were independent walkers. Among children with osteogenesis imperfecta Type III (n=29) 21% had abnormal arrested development, 34% had delayed arrested development, 28% had normal arrested development, 17% had delayed development, and none had normal development. Among these children, 97% were wheelchair bound and 3% were independent walkers. Among children with osteogenesis imperfecta Type IV (n=7) none had abnormal arrested development, 14% had delayed arrested development, 14% had normal arrested development, 43% had delayed development, and 29 had normal development. Among these children, 57% were wheelchair bound, 14% were aided walkers and 29% were independent walkers.	Only a parental questionnaire No statistical analysis. Definitions of development unclear	No data on funding source

Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia

Part III

Author, Year	Associations found	Potential Biases	Comments
Engelbert 1997	Among children aged ≤ 7.5 years with osteogenesis imperfecta Type I (n=16) mean Self-care Functional Skills score on PEDI (normal median 50) was 39 and mean Mobility score was 31. Among children with Type III (n=8) mean Self-care score was 31 and Mobility score was 5. Among children with Type IV (n=6) mean Self-care score was 37 and Mobility was 48. Among children aged > 7.5 years with osteogenesis imperfecta Type I (n=16) mean Self-care Functional Skills score on PEDI (normal = 100) was 100 and mean Mobility score was 100. Among children with Type III (n=6) mean Self-care score was 70 and mean Mobility was 41. Among children with Type IV (n=9) mean Self-care score was 93 and Mobility was 62.	Interpretation of scales difficult due to different norms used and unclear description of scales No explicit comparison to normal children Unclear how much overlap in sample with other Engelbert papers.	No data on funding source
Engelbert 1998 98366964	Among children with osteogenesis imperfecta scoliosis > 10° was present in 12% of those with Type I (n=17), 63% with Type III (n=16), and 71% with Type IV (n=14). Among children with osteogenesis imperfecta kyphosis < 10° was present in 6% of those with Type I (n=17), 38% with Type III (n=16), and 14% with Type IV (n=14). Among children with osteogenesis imperfecta kyphosis > 40° was present in 6% of those with Type I (n=17), 38% with Type III (n=16), and 14% with Type IV (n=14).	No comparison with normal controls Unclear how much overlap in sample with other Engelbert papers.	No data on funding source
Engelbert 1999 99381568	At follow-up, of children with osteogenesis imperfecta Type I (n=19) 53% were community walkers, 26% were neighborhood walkers, 16% were household walkers, and 5% were exercise walkers. Of children with Type III (n=13) 31% were household walkers, 8% were exercise walkers, 38% were bottom shufflers, 15% could sit unsupported, and 8% could only sit supported. Of children with Type IV (n=10) 10% were community walkers, 10% were neighborhood walkers, 10% were household walkers, 40% were exercise walkers, 20% could weight bear on feet, and 10% were bottom shufflers.	No children with recent intramedullary fixation surgery or other disability or impairments. PEDI scale scores reported for small to very small samples of children. Appears to be earlier subset of data reported earlier in Engelbert 1997. Not analyzed here. Unclear how much overlap in sample with other Engelbert papers.	No data on funding source

Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia

Part III

Author, Year	Associations found	Potential Biases	Comments
Engelbert 2000 20429012	At follow-up, of children with osteogenesis imperfecta Type I (n=41) 59% were community walkers without aides, 5% were community walkers with aides, 10% were neighborhood walkers without aides, 12% were household walkers without aides, 7% were household walkers with aides, and 7% were therapy walkers with aides. Of children with Type III (n=11) 9% were neighborhood walkers with aides, 27% were household walkers with aides, 19% were therapy walkers with aides, and 45% were non-walkers. Of children with Type IV (n=18) 28% were community walkers without aides, 11% were community walkers with aides, 6% were neighborhood walkers with aides, 11% were household walkers with aides, 22% were therapy walkers with aides, and 22% were non-walkers.	Unclear how much overlap in sample with other Engelbert papers. No comparison with normal children	No data on funding source.

Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia

Part III

Author, Year	Associations found	Potential Biases	Comments
Engelbert 2001 21334060	Among children aged > 8 years with osteogenesis imperfecta Type I (n=17) mean Self-care Functional Skills score on PEDI (normal = 100) was 100 and mean Mobility score was 92. Among children with Type III (n=11) mean Self-care score was 81 and mean Mobility was 55. Among children with Type IV (n=12) mean Self-care score was 100 and Mobility was 67. Among children with osteogenesis imperfecta Type I (n=17) the average child was a community walker without aides. Among children with Type III (n=11) the average child was a therapy walker with aides. Among children with Type IV (n=12) the average child was a household walker without aides. Among children with osteogenesis imperfecta Type I (n=17), the average joint range of motion on a scale of 0 (normal) to 4 (maximally decreased) was 0.5 for arms and 0 for legs. Among children with Type III (n=11) the average arm range of motion was 1.8 and leg range of motion was 3.3. Among children with Type IV (n=12) the average arm range of motion was 1.3 and leg range of motion was 1.7. Among children with osteogenesis imperfecta Type I (n=17), the average muscle strength on a scale of 0 (no muscle activity) to 5 (normal muscle strength) was 4.5 for arms and 4.8 for legs. Among children with Type III (n=11) the average arm strength was 3.5 and leg strength was 3.6. Among children with Type IV (n=12) the average arm strength was 4.5 and leg strength was 3.8.	Unclear how much overlap in sample with other Engelbert papers, especially those with PEDI analyses (1997 and 1999) No comparison to normal children. Meaning of scales unclear.	No data on funding source.
Falvo 1973 74013834	Among children with osteogenesis imperfecta mean pulmonary vital capacity was 85% of predicted normal (n=10), mean residual volume was 119% of predicted normal (n=10), mean FEV_1/FVC was 99% of predicted normal (n=10), mean arterial oxygen partial pressure was 88 mm Hg (n=8), and mean arterial carbon dioxide partial pressure was 35 mm Hg (n=8). "No patient had severe hypoxemia or hypercapnea. Reduction of VC and increase in RV were found only in patients with kyphoscoliosis. Other parameters of pulmonary function were within normal limits."	Limited analyses	Study was government and privately funded.

Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia

Part III

Author, Year	Associations found	Potential Biases	Comments
Fowler 1997 97356792	Among children with achondroplasia, by parental report, the mean age of sitting unsupported was 12 months (n=37), the mean age of standing alone was 19 months (n=21), and the mean age of walking alone was 18 months (n=24). "Virtually all fine motor skills were delayed when compared with children without achondroplasia."	Includes subjects in Pauli 1995 Data on motor development from few subjects enrolled in study	No data on funding source
Pauli 1995 95193803	Among children with achondroplasia, 72% had decreased truncal tone (n=39), 70% had decreased limb tone (n=44), 32% had abnormal arm strength (n=40), and 50% had abnormal leg strength (n=40). No child had marked abnormalities in neurological examination. Among children with achondroplasia (n=52) 42% had an abnormality by neurological history. These included disproportionate developmental delays (10%), asymmetries (21%), weakness (14%), sensory abnormalities (4%), arching/opisthotonos (10%), clonus (8%), seizures (8%), and apnea (27%). Among children with achondroplasia (n=35) by polysomnography 40% had mild to severe central apnea, 66% had mild to severe central hypopnea, and 23% had mild obstructive apnea	Earlier subset of subjects in Fowler 1997	Study was hospital funded
Hecht 1991 92152267	Among infants with achondroplasia (n=13) mean BSID Mental Development Index score was 97 (1 or 2 infants had scores <70, text and table disagree) and mean Psychomotor Development Index score was 63 (62% scored <50). Among infants with achondroplasia (n=13) 77% had normal polysomnography. Two infants (15%) had obstructive apnea, 1 had hypoxemia and respiratory acidosis.	5 of 13 patients were initially seen (and thus included) for apnea, motor delay or neurological complication Reporting errors	Study was government funded

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Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia

Part III

Author, Year	Associations found	Potential Biases	Comments
Hunter 1998 98299528	Among children with chondroplasias (n=55) 7% had moderate or severe depression per the Beck Depression Inventories, which was not significantly different than among normal siblings (11%, n=35). Among children with chondroplasias (n=55) the mean Speilberger Child State Anxiety score was 28.4 and Trait Anxiety score was 32.5, which were significantly lower (implying *less* anxiety) than general population means for boys (31.0 and 36.7, respectively) and girls (30.7 and 38.0, respectively).	None noted	No data on funding source
Kuurila 2000 20379515	Among children with osteogenesis imperfecta (n=45), 7% had hearing loss: 2 children had conductive hearing loss and 1 had sensorineural deafness.	Descriptive study only	No data on funding source.
Norimatsu 1982 82163323	Among children with osteogenesis imperfecta congenita (n=8) 38% were wheelchair bound; the remainder walked with assistance. Among children with osteogenesis imperfecta tarda (n=14) 14% were wheelchair bound; the remainder walked with assistance. Among children with osteogenesis imperfecta congenita (n=8) 88% had severe scoliosis (59°-139°; one had mild scoliosis (17°). Among children with osteogenesis imperfecta tarda (n=14) 21% had severe scoliosis (55°-125°), 14% had moderate scoliosis (32° & 33°), 64% had mild scoliosis (5°-28°).	Multiple subjects were closely related. Descriptive study only	No data on funding source
Poussa 1991 92054945	Among children with diastrophic dysplasia (n=38) 29% had scoliosis. Of those ≤ 10 years (n=17) 6% had scoliosis; of those between 11 and 20 years (n=21) 48% had scoliosis. Those with scoliosis (n=11) had a mean magnitude of curvature of 39° (range 15°-80°).	Descriptive analysis only	No data on funding source. Subjects are part of the study. Descriptive data only.
Reid 1988 89193370	Among children with achondroplasia (n=26) 85% had a history of respiratory abnormalities including pneumonia, loud snoring, cyanotic spells or apnea in the preceding 6 months; 35% had obstructive sleep apnea. Among children with achondroplasia (n=26) 42% had paresis.	Descriptive study only No specific definitions of conditions reported Appears to be subgroup of subjects included in Stokes 1988	No data on funding source

Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia

Part III

Author, Year	Associations found	Potential Biases	Comments
Stokes 1988 88110722	Among children with achondroplasia (n=24) mean forced vital capacity was 72% of predicted, significantly lower than population norms.	Limited details of pediatric sub-sample. Appears to include subjects in Reid 1988	Study funded by government, hospital and private sources
Reite 1972 72182015	Among children with osteogenesis imperfecta (n=12) the mean IQ was 107, ranging from 78-133.	Only children with "severe" osteogenesis imperfecta Incomplete data reported	Study was government and privately funded.
Rogers 1979 79200737	Among school aged children with achondroplasia (n=19) mean Full scale IQ was 96, Verbal IQ was 95, and Performance IQ was 100; 5% had IQ<70. Among preschool aged children with achondroplasia (n=15) mean Full scale IQ was 97; 13% had IQ<70. Among school aged children with other skeletal dysplasias (n=22) mean Full scale IQ was 104, Verbal IQ was 104, and Performance IQ was 103; none had IQ<70. Among preschool aged children with other skeletal dysplasias (n=12) mean Full scale IQ was 100; none had IQ<70.	Descriptive study only	Study was government funded
Ruiz-Garcia 1997 97346439	According to summary table, among children with achondroplasia (n=39) 59% had hypotonia, 15% had quadriparesis, 31% had weakness, and 10% had a sensory deficit. According to text, 49% had hypotonia, 13% had quadriparesis, 26% had weakness, and 5% had sensory deficit. In additon, 31% had compressive neural syndromes (18% craniocervical, 13% lumbar). According to the text, among children with achondroplasia (n=32), 50% had abnormal hearing as tested by brainstem auditory evoked response.	No definitions of outcomes Results reported in text differ from results reported in table Descriptive study only.	No data on funding source
Shurka 1976	Among children with skeletal dysplasias (n=7) mean Full scale IQ was 102, Verbal IQ was 103, and Performance IQ was 99.	Very small sample size. Multiple, poorly defined causes of dwarfism.	No data on funding source

Evidence Table 2. Studies Evaluating Short Stature Secondary to Skeletal Dysplasia
Part III

Author, Year	Associations found	Potential Biases	Comments
Skeletal Dysplasia Group 1989 89192477	Among children with Morquio disease (n=15) 33% had "known neurological complications."	Limited data reported Conditions and outcomes not defined Only subset met criteria for inclusion in SSA report	No data on funding source
Stewart 1989 90125184	Among children with osteogenesis imperfecta (n=13), 15% had hearing loss.	Incomplete reporting Descriptive only	Study was private funded
Thompson 1999 99221075	Among children with achondroplasia mean WISC-R Verbal IQ was 94 (n=16), Performance IQ was 101 (n=16), WRAT-R Spelling score was 88 (n=14), Arithmetic was 89 (n=15), and Sentence writing was 80 (n=12). These scores were all statistically similar to normal controls (IQ ND, Spelling 97, Arithmetic 96, Sentence writing 95, n=17). Among children with achondroplasia (n=13) Gross Motor Arm Coordination score on McCarthy Scales was 73 and Leg Coordination was 79, significantly lower than normal controls (93, 104, respectively; n=13). Among children with achondroplasia (n=13) visual motor skills were significantly lower (Beery 82, JLO 85) than among normal controls (Beery 92, JLO 100, n=12). Various measures of fine motor skills were similar between the two groups.	Biased sample as some children dropped who were unable to complete the testing for many measures and excluded children with IQ<69.	Study was government funded. Subjects were recruited as part of larger previous study of hydrocephalus
Waters 1993 94029092	Among children with achondroplasia (n=20) 75% had > 5 apneic episodes per hour of sleep.	Descriptive study only	No data on funding source

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Asthma – Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Types of Diseases / Conditions	Study Design (Duration)
Balfour-Lynn 1986 87074993	Location: UK Setting: Pediatric asthma clinic Initial mean age: 7.5 y Initial age range: 2-12 y Follow-up mean age: 21 y Follow -up age range: 13-26 y Mean height: ND Male: 68% Race: ND SES: ND Enrolled: 66 Evaluated: 66 Number of sites: 1	Chronic perennial asthma	None reported	Asthma	Prospective longitudinal cohort (Mean 8.9 y)
Cernelc 1975 76016195 [Also in cardiac section]	Location: Yugoslavia Setting: Clinic Mean age: ND Mean height: ND Male: ND Race: ND SES: ND Enrolled: ND Evaluated: 337 Number of sites: ND	Asthmatic children with normal or pathological lung function tests	None reported	Asthma	Prospective cross-sectional

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Asthma – Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Types of Diseases / Conditions	Study Design (Duration)
Ferguson 1982 82190765	Location: Canada Setting: Regional Mean age: ND Age range: ~3-17 y Mean height: ND Male: 89% Race: ND SES: ND Enrolled: 36 Evaluated: 36 Number of sites: 1	Children with a diagnosis of asthma and short stature (height < 3rd percentile)	None reported	Asthma	Preliminary study of a prospective longitudinal study
Hauspie 1979 80114229	Location: Belgium and Hungary Setting: Sanatorium; Asthma clinic Mean age: ND Age range: 3-16 y Mean height: ND Male: 100% Race: ND SES: ND Enrolled: 1107 Evaluated: 1107 Number of sites: 2	Hungary : asthmatic boys residing in the National Sanatorium for Children Belgium: boys with chronic aspecific respiratory affection, asthma or asthma and eczema.	None reported	Asthma /Respiratory disease	Retrospective cross-sectional cohort

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Asthma – Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Types of Diseases / Conditions	Study Design (Duration)
Klein 1991 91314975	Location: US Setting: Clinic Mean age: 8.5 y Age range: 2-15 y Mean height: ND Male: ~ 69% Race: ND SES: ND Enrolled: 176 Evaluated: 176 Number of sites: 4	Children with moderately severe, non-steroid-dependent asthma	> 6 short courses of steroids during previous year	Asthma	Prospective cross-sectional
Martin 1981 82110081	Location: Australia Setting: Region Initial age: 7 y Follow-up ages: 10 y, 14 y, 21 y Mean height: ND Male: 63% Race: ND SES: ND Enrolled: 375 Evaluated: 315 Number of sites: 1	Asthmatic children Aged 7 y in 1964	None reported	Asthma	Prospective longitudinal cohort (14 y follow-up)

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Asthma – Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Types of Diseases / Conditions	Study Design (Duration)
McNicol 1970 71076839	Location: Australia Setting: Unclear Ages: 7 and 10 y Mean heights: 123 cm (age 7 y); 138 cm (age 10) Male: ND Race: ND SES: ND Enrolled: 226 Evaluated: 226 Number of sites: ND	Asthmatic children	None reported	Asthma	Prospective longitudinal cohort (Ages 7 and 10)
Neville 1996 96427603	Location: UK Setting: Pediatric practices Mean age: ND Age range: 3.5-13 y Mean height: ND Male: 57% Race: ND SES: "Broad range" Enrolled: 2915 Evaluated: 699 Number of sites: 12	Tayside Childhood Asthma Project (1990-92) Possible asthma, based on medication prescriptions, from chart review Age 3.5-13 y Height and weight measurements available	Loss to follow-up	Asthma	Secondary analysis of prospective longitudinal cohort

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Asthma – Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Types of Diseases / Conditions	Study Design (Duration)
Rona 1980 81025712	Location: UK Setting: Schools Mean age: ND Age range: 5-11 y Mean height: ND Male: 68% Race: ND SES: Proportionally more lower SES areas Enrolled: 102 Evaluated: 102 Number of sites: 28	Parental reporting of asthma in last 12 months	None reported	Asthma	Retrospective cross-sectional cohort
Sant'Anna 1996 97295750	Location: Brazil Setting: Pediatric immunology clinic Mean age: ND Age range: 6 mo - 16 y Mean height: ND Male: 58% Race: ND SES: ND Enrolled: 514 Evaluated: 514 Number of sites: 1	Children with asthma followed in Division of Allergy, Clinical Immunology and Rheumatology	Phenotypical deviations Clear changes in body proportions Other chronic diseases Rash and/or atopic dermatitis	Asthma	Retrospective cross-sectional case series

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease

Asthma – Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Types of Diseases / Conditions	Study Design (Duration)
Spock 1965	Location: US Setting: Pediatrics department Mean age: 7 y Age range: 4-12 y Mean height: ND Male: 65% Race: White SES: ND Enrolled: 200 Evaluated: 200 Number of sites: 1	Children with bronchial asthma Age > 4 y at the first visit Followed for minimum of 3 y	Concomitant chronic illness Cyproheptadine use	Asthma	Retrospective longitudinal cohort (19 y)

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease

Asthma – Part II

Author, Year	Severity of Illness Groups	Outcomes
Balfour-Lynn 1986 87074993	Treatment required to control asthma • Bronchodilators alone or children whose asthma resolved before puberty • Sodium cromoglycate and bronchodilators in children whose asthma did not improve at puberty • Steroids and bronchodilators	Initial growth retardation (not defined) Growth along centile lines Final adult height Percentile, based on Tanner and Whitehouse growth chart
Cernelc 1975 76016195	Pulmonary function tests • Normal • Pathological (not defined)	Height by age (linear regression) Compared to normal values for Slovenian children
Ferguson 1982 82190765	Asthma symptom score, based on frequency of wheezing in past year, duration of wheezing, level of therapy required, and bronchodilator medication days in past year (16 point scale) • Mild: score 1-7 • Moderate: score 8-12 • Severe: score 13-16	Height Percent average height for age
Hauspie 1979 80114229	Hungarian sample: Ovsáth's system, based on based on frequency of attacks, seriousness of dyspnea, duration of dyspnea, and number of symptom-days per year • Class II: Less severe • Class III: More severe • Class IV: Most severe Belgian sample: Disease diagnosis • Chronic aspecific respiratory affection • Asthma • Asthma and eczema Belgian sample: Treatment required to control asthma: • No corticotherapy • Interrupted corticotherapy • Continuous corticotherapy for at least 6 months	Height Z-scores
Klein 1991 91314975	Asthma severity score (by event), based on hospitalization and medication requirements in previous year (score: 0-60) • Mild: score < 25 • Moderate/severe ≥ 25	Height Height percentile Based on National Center for Health Statistics Growth Chart

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease

Asthma – Part II

Author, Year	Severity of Illness Groups	Outcomes
Martin 1981 82110081	Asthma grade, based on frequency and recency of wheezing • Grade A: ≤ 5 episodes of wheezing • Grade B: > 5 episodes of wheezing but no wheezing within 12 months of exam • Grade C: Episodic asthma over a number of years and wheezing within 12 mo of exam • Grade D: Very frequent or chronic unremitting asthma	Percentage of subjects <10th percentile Based on Australian Department of Health Anthropometric tables At ages 10, 14, and 21 y
McNicol 1970 71076839	Asthma grade, based on frequency and recentness of asthma episodes • Grade I: ≤ 5 episodes of asthma • Grade II: ≤ 20 episodes of asthma or no asthma within 12 mo of exam • Grade III: >20 episodes and still having asthma within 12 mo of exam	Height
Neville 1996 96427603	Asthma severity (British Thoracic Society treatment steps), based on medication requirements • Step 1: Beta-agonist only in past year • Step 2: Beta-agonist and cromoglycate • Step 3: Beta-agonist and low dose inhaled steroid • Step 4: Beta-agonist and > 400 µg/day inhaled steroid	Height SDS, based on control group within study
Rona 1980 81025712	Frequency of asthma episodes • ≤ 2 episodes in the past year • ≥ 3 episodes in the past year Hospitalization for asthma	Height SDS, based on Scottish and English norms • Unadjusted • Adjusted for parents' height, social class, number of siblings Height gain, cm/year • Unadjusted • Adjusted
Sant'Anna 1996 97295750	Asthma severity, based on the International Consensus Report on Diagnosis and Treatment of Asthma • Mild • Moderate • Severe	Percentage with short stature < 3rd percentile, based on National Center of Health Statistics, US, 1977

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease

Asthma – Part II

Author, Year	Severity of Illness Groups	Outcomes
Spock 1965	Clinical status (not defined) • Poor • Fair • Good • Excellent	Linear growth rate Percentage of normal, based on Stuart and Wetzel's anthropometic charts

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Asthma – Part III

Author, Year	Associations found	Potential Biases	Comments
Balfour-Lynn 1986 87074993	Comparing children whose asthma was controlled with bronchodilators alone or had resolved at puberty (n=18, Group I) with those whose asthma required sodium cromoglycate and had not resolved at puberty (n=19, Group II), and with those whose asthma required treatment with steroids (n=29, Group III), there was no statistical difference in growth retardation at the start of the study. However, "growth retardation" was not defined. Of children in Group I, 2 of 18 (11%) had initial height < 10th percentile. Of children in Group II, 1 of 19 (5%) had initial height < 10th percentile. Of children in Group III, 3 or 29 (10%) had initial height < 10th percentile. No child had height < 3rd percentile. All children "grew along expected centile lines without appreciable deviation, from initial age (mean 7.5 y) until age 10 y, regardless of treatment required. 30 of 66 (45%) children had "physiological decelerating growth velocity pattern of delayed puberty." No data are reported regarding association with asthma severity. Comparing the three groups of asthmatic children, based on treatment requirements, no statistical difference was found in final adult height. Possible minor trend toward taller adult height from Group I to II to III seen in graph.	Severity of asthma based on treatment used, not objective measures Reported data incomplete Study sample poorly defined 6 subjects lost to follow up prior to obtaining final adult height but were followed for mean 8.3 years (6.3-14.6 y)	No data on funding source
Cernelc 1975 76016195	Asthmatic children with normal pulmonary function tests (n=225) were not significantly different in height for age compared to asthmatic children pathological pulmonary function tests (n=112). No data on growth velocity.	Limited data and analysis Study sample poorly defined	No data on funding source Data on asthmatic children with bronchiectasis (n=22) not included because children reported to be both significantly and not significantly more likely to have growth retardation
Ferguson 1982 82190765	The percentages of average normal height for age (50th percentile) of short children whose asthma was mild (n=19, 90.7%), moderate (n=13, 90.2%) and severe (n=4, 88.5%) were not significantly different among the three groups. No significant correlation was found between symptom score and percentage of average normal height for age of individual subjects (r=0.20). No data on growth velocity	Study limited to children with height < 3rd percentile, however results reported as percentage of average normal height	Study was government and private funded.

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Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease

Asthma – Part III

Author, Year	Associations found	Potential Biases	Comments
Hauspie 1979 80114229	Mean height of Class II (relatively mild) Hungarian asthmatic boys (n=222) is normal (~ 0 SDS, from graph). The mean height of Class III asthmatic boys (n=253) was significantly lower (~ –0.3 SDS) and that of Class IV asthmatic boys (n=25) was even lower (~ –0.9 SDS). "A gradually increasing degree of growth retardation in relation to the seriousness of the disease can be observed." In a separate sample of Belgian asthmatic boys, those with chronic aspecific respiratory affection (n=204) had normal mean height (~ –0.1 SDS, from graph). Those with asthma (n=323) were statistically significantly but minimally shorter (~ –0.2 SDS) and those with asthma and eczema (n=80) were even shorter (~ –0.4 SDS). Belgian asthmatic boys requiring no corticotherapy (n=245) and requiring interrupted corticotherapy (n=130) had normal mean height (~ –0.1 SDS, from graph). Those who required continuous corticotherapy (n=16) were statistically shorter (~ –0.5 SDS). No data on growth velocity.	Chronic aspecific respiratory affection includes illnesses other than asthma. Data reported mostly in graphical format only Study limited to boys	No data on funding source.
Klein 1991 91314975	Children (n=176 total) with mild asthma (ND on n) had mean ± SD height of 145±10 cm; those with moderate asthma were on average 148±10 cm. The height difference was not significantly different. No data reported on children with severe asthma. "There was no relationship between the severity of asthma (as assessed by a clinical and medications score) and the height percentile." Reported data are incomplete. No data on growth velocity	Reported data very incomplete. Mean heights reported as 44.8 cm and 47.8 cm. We understood this to mean 144.8 cm and 147.8 cm, however, reported numbers may refer to percentiles. Children requiring > 6 short courses of steroids within previous year excluded.	No data on funding source

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Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Asthma – Part III

Author, Year	Associations found	Potential Biases	Comments
Martin 1981 82110081	The prevalence rates of height < 10th percentile in 10 years old children whose asthma was rated Grade A (mild, n=64), Grade B (moderate, n=88), Grade C (severe, n=106), and Grade D (very severe, n=57) were 9%, 8%, 8%, and 15% respectively. Only children with very severe asthma had significant higher prevalence of height < 10th percentile at age 10 y compared to non-asthmatic children (n=62, 4%). The prevalence of short stature in the asthmatic children when they were 14 years old was similar to when they were 10 years old. Height < 10th percentile in Grade A asthmatics was 6%, Grade B 5%, Grade C 5%, and Grade D 17%. Only children with very severe asthma had significant higher prevalence of height < 10th percentile at 14 years of age compared to non-asthmatic children (1%). At age 21 years, the prevalence of short stature was similar among all asthma grades. Height < 10th percentile Grade A asthmatics was 15%, Grade B 15%, Grade C 9%, and Grade D 19%. There was no difference in the prevalence of height < 10th percentile at 21 years of age, between the 4 groups and non-asthmatic children (12%). No direct data on growth velocity	None noted.	No data on funding source
McNicol 1970 71076839	The mean heights of children at both ages 7 and 10 years were the same (123-124 cm at age 7 years; 137-139 cm at age 10 years) regardless of frequency of asthmatic episodes among 276 asthmatic children and 94 non-asthmatic controls. No significant difference was found between controls and any degree of asthma severity. No data on growth velocity	None noted	No data on funding source
Neville 1996 96427603	Asthmatic children who used only beta agonists (n=537) had a mean height of +0.04 SDS. Those who used beta agonists and cromoglycate (n=64) had a mean height of +0.04 SDS. Those who used beta agonists and low dose inhaled steroids (n=39) had a mean height of +0.08. Those who used beta agonists and > 400 µg/day inhaled steroids (n=59) had a mean height of –0.38. Only those on high dose inhaled steroids were significantly shorter than normal. No data on growth velocity.	Large number of potential subjects excluded due to missing height data. Statistical analysis implied only. Asthma severity based on medication use	Study was government, privately, and pharmaceutical funded

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Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Asthma – Part III

Author, Year	Associations found	Potential Biases	Comments
Rona 1980 81025712	Among children with asthma episodes, those with ≤ 2 episodes in previous year (n=33) were not significantly shorter (–0.1 SDS, – 0.2 SDS, respectively) than controls (n=4334) in both unadjusted model and model adjusted for parental height, social class, and number of siblings. Those with ≥ 3 asthma episodes in previous year (n=69) were significantly shorter (–0.4 SDS) than controls in both models. Overall, "there was a highly significant negative relationship between unadjusted [and adjusted] height and number of [asthma] episodes. "Hospitalization for asthma was more closely associated with shorter stature for boys than for girls, but the number of children hospitalized was too small for useful analysis." In adjusted model, height velocity was non-significantly lower in boys with ≤ 2 asthma episodes per year (n=22, 5.34 cm/y) and with ≥ 3 episodes per year (n=41, 5.57 cm/y) than non-asthmatic boys (n=1873, 5.72 cm/y), and in girls with ≤2 episodes per year (n=9, 5.67 cm/y) and with ≥ 3 episodes per year (n=16, 5.50 cm/y) than non-asthmatic girls (n=1552, 5.93 cm/y).	Retrospective survey of parents (for medical history) and school records Logic of adjusting for number of siblings unclear.	Study was government funded.
Sant'Anna 1996 97295750	The prevalence of short stature (< 3rd %tile) in children with mild asthma (n=211, 6%) was non-significantly lower than those with moderate asthma (n=154, 11%) and severe asthma (n=149, 11%). No data on growth velocity	Multiple height-related exclusion criteria	No data on funding source
Spock 1965	The mean linear growth rate in percentage of normal was 109% for asthmatic patients with excellent clinical status (n=68), 107% for asthmatic patients with good clinical status (n=86), 102% for asthmatic patients with fair clinical status (n=30), and 97% for asthmatic patients with poor clinical status (n=16). The correlation between severity of clinical status and the linear growth rate in percentage of normal was not statistically significant. "No statistically significant correlation was found between the duration and/or severity of asthmatic symptoms and growth impairment for height or weight."	Degree of clinical status not defined The percentage of children requiring steroids was unusually low at 12%	No data on funding source.

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Cardiac Disease – Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Types of Diseases / Conditions	Study Design (Duration)
Baum 1980 81065058	Location: US Setting: Clinic Mean age: 3.8±1.0 y Age range: ND Mean height: 99 cm Male: 77% Race: ND SES: ND Enrolled: 26 Evaluated: 26 Number of sites: 1	Diagnosis of acyanotic congenital heart disease Age 2 to 6 y	None reported	Congenital heart disease: Patent ductus arteriosus Ventricular septal defect Atrial septal defect Pulmonic stenosis Aortic stenosis Atrioventricular canal Pulmonary artery band Right ventricular band Mitral stenosis Mitral insufficiency	Prospective cross-sectional cohort
Cernelc 1975 76016195 [Also in asthma section]	Location: Yugoslavia Setting: Clinic Mean age: ND Mean height: ND Male: ND Race: ND SES: ND Enrolled: ND Evaluated: 22 Number of sites: ND	Children with congenital heart disease with or without cyanosis	None reported	Congenital heart disease: Not defined	Prospective cross-sectional

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Cardiac Disease – Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Types of Diseases / Conditions	Study Design (Duration)

Feldt 1969 69176079	Location: US
	Setting: Clinic
	Mean age: ND
	Age range: 1 wk - 17 y
	Mean height: ND
	Male: ND
	Race: ND
	SES: ND
	Enrolled: 463
	Evaluated: 311
	Number of sites: 1
		Diagnosis of congenital heart disease	Trisomy 21
			Gonadal dysgenesis
			Clinically recognized maternal rubella syndrome
				Congenital heart disease:
				  Ventricular septal defect
				  Tetralogy of Fallot
				  Aortic stenosis
				  Pulmonary stenosis
					Prospective longitudinal cohort (5 mo)

Levy 1977 78125814	Location: US Setting: Cardiology clinic Mean age: ND Age range: ND Mean height: ND Male: 50% Race: ND SES: ND Enrolled: 1,210 Evaluated: 777 Number of sites: ND	Diagnosis of ventricular septal defect	None reported	Ventricular septal defect	Retrospective longitudinal cohort (mean[range] 6.4 [4-8] y)

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Cardiac Disease – Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Types of Diseases / Conditions	Study Design (Duration)
Strangway 1976 76101945	Location: Canada Setting: Cardiology clinic Mean age: ND Age range: < 2-11 y Mean height: ND Male: ND Race: ND SES: ND Enrolled: 568 Evaluated: 568 Number of sites: 1	Diagnosis of congenital heart disease	Additional major congenital lesion Mental retardation Undergone corrective surgery Acute or chronic intercurrent illness	Congenital heart disease: Tetralogy of Fallot Ventricular septal defect Atrial septal defect Pulmonary stenosis Aortic stenosis Coarctation of aorta Patent ductus arteriosus Arterioventricular canal MIscellaneous	Retrospective longitudinal cohort (5 y)
White 1970 72024496	Location: US Setting: Adolescent cardiac clinic Mean age: ND Age range: 12-18 y Mean height: ND Male: ND Race: White 96% SES: Generally middle class Enrolled: 80 Evaluated: 80 Number of sites: 1	Diagnosis of congenital heart disease Age < 19 y	Tetralogy of Fallot with total corrective surgery	Congenital heart disease: Ventricular septal defect Atrial septal defect Patent ductus arteriosus Pulmonary stenosis Aortic stenosis Coarctation of aorta Aortic insufficiency Undiagnosed acyanotic	Prospective cross-sectional

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Cardiac Disease – Part II

Author, Year	Predictors (N)	Outcomes

Baum
1980
81065058
	Heart Failure (not defined)	Height by age (linear regression)
		Height percentile
		    Based on National Center for Health Statistics growth
		    charts

Cernelc 1975 76016195 [Also in asthma section]	Cyanosis	Height by age (linear regression) Compared to normal values for Slovenian children

Feldt
1969
69176079
	Pulmonic valve pressure gradient
	Aortic valve pressure gradient
	Tetralogy of Fallot lesion severity
	    • Hematocrit
	    • Oxygen saturation (cyanosis)
	    • Magnitude of right to left shunt
	    • History of hypoxemia
	Ventricular septal defect shunt severity
	    • Pulmonary vascular disease (pressure)
		Growth failure
		    preoperative height (and weight) $\leq$ –2 SDS
		Height SDS
		    based on Reed and Stuart, 1959

Levy
1977
78125814
	Ventricular septal defect severity
	    • I: Trivial to mild, pulmonary artery mean pressure < 20 mm Hg
	    • II: pulmonary artery mean pressure $\geq$ 20 mm Hg and pulmonary to systemic resistance ratio
	        < 0.20
	    • III-IV: Severe: pulmonary artery mean pressure $\geq$ 20 mm Hg and pulmonary to systemic
	        resistance ratio $\geq$ 0.20
		Height SDS

Strangway
1976
76101945
	Cardiac problems
	    • Cyanosis
	    • Cardiac enlargement (cardiothoracic ratio > 59% age < 2 y, > 55% age >2 y)
	    • Congestive heart failure
		Height velocity
		    fraction of the normal mean for the same age and
		    sex

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Cardiac Disease – Part II

Author, Year	Predictors (N)	Outcomes
White 1970 72024496	Cyanosis	Short stature, height < 2nd percentile

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Cardiac Disease – Part III

Author, Year	Associations found	Potential Biases	Comments
Baum 1980 81065058	Children with congenital heart disease with early heart failure (n=12) were significantly shorter for age than asymptomatic children (n=14). On average, children age 2-6 years with heart failure were 5-9 cm shorter than those without. The differences in height were greater with older age. Six (50%) of the 12 children with early heart failure had height below the 5th percentile, while none of the 14 asymptomatic children had height below the 10th percentile. No data on growth velocity.	None noted	No data on funding source.
Cernelc 1975 76016195 [Also in asthma section]	Children with congenital heart disease and cyanosis (n=11) were significantly more likely to be short for age than normal population, as opposed to children with congenital heart disease without cyanosis (n=11) who were not significantly different in height for age than normal population.	Limited data and analysis Study sample poorly defined	No data on funding source
Feldt 1969 69176079	Among children with aortic or pulmonary stenosis (n=73), those "with mild pressure gradients (< 50 mm Hg) across either the pulmonic or the aortic valve usually were of normal weight and height. In contrast, patients with severe valvular gradients were more likely to have severe growth failure." The severity of growth failure of children with Tetralogy of Fallot (n=83) "was not related to any criteria for seveity of the lesion such as hemaglobin value, oxygen saturation..., magnitude of right to left shunt, or history of hypoxemic spells." Specifically height SDS was not associated with hemoglobin level. Among children with ventricular septal defect (n=155) "there was no correlation between the extent of growth failure and the degree of pulmonary vascular disease assessed either at cardiac catheterization of from pressure measurements taken at the time of operation." No data correlated height velocity to severity of disease.	No statistical analyses Growth retardation included both short stature and low weight	Study was government funded.
Levy 1977 78125814	For children with ventricular septal defect, the mean initial height SDS for those with mild disease (n=492) was –0.23 SDS, for those with moderate disease (n=170) –0.63 SDS, and for those with severe disease (n=115) –0.86. The height of children in each category was statistically significantly lower than normal children. The statistical significance of the association between height and severity of disease is implied only.	Reporting of statistical analyses unclear and incomplete	Study was government funded.

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease

Cardiac Disease – Part III

Author, Year	Associations found	Potential Biases	Comments
	No data on growth velocity		
Strangway 1976 76101945	Among children aged 0 to 2 years with congenital heart disease (n=181), height velocity percentile was significantly lower in children with cyanosis (–14%) than those without cyanosis (+7%), was similar in children with cardiac enlargement (+2%) as without cardiac enlargement (+1%), and was non-significantly lower in children with congestive heart failure (–20%) than without congestive heart failure (+2%). Among children aged 2 to 11 years with congenital heart disease (n=387), height velocity percentile was similar in children with cyanosis (+10%) as those without cyanosis (+7%), was similar in children with cardiac enlargement (+15%) as without cardiac enlargement (+6%), and was non-significantly lower in children with congestive heart failure (–13%) than without congestive heart failure (+7%).	Because of the calculation of height velocity, some subjects missing follow-up measures of height were excluded from analyses.	Study was government funded.
White 1970 72024496	Among children with congenital heart disease, height < 2nd percentile was more common among those with cyanosis (n=27, 19%) than those without cyanosis (n=53, 2%)	No statistical analyses performed Reporting of data unclear	Study was partial government funded.

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Insulin Dependent Diabetes Mellitus – Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Types of Diseases / Conditions	Study Design (Duration)
Arreola 1991 93191566	Location: Mexico Setting: Outpatient diabetes clinic Mean age: ND Age range: 1-16 y Mean height: ND Male: ND Race: ND SES: ND Enrolled: 198±8 each year (1984-1988) Evaluated: 198±8 each year Number of sites: 1	Patients with type I diabetes seen at outpatient diabetes clinic from 1984 to 1998 Age 1-16 y	None reported	Insulin dependent diabetes	Retrospective longitudinal cohort (4-5 y)
Court 1982 83021090	Location: UK Setting: Region Mean age: 13±3.7 y Age range: ND Mean height, SDS: –0.69 Male: 54% Race: ND SES: ND Enrolled: 121 Evaluated: 111 Number of sites: ND	Children with diabetes attending clinics in the Newcastle region	None reported	Diabetes (implied insulin dependent)	Retrospective cross-sectional cohort

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Insulin Dependent Diabetes Mellitus – Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Types of Diseases / Conditions	Study Design (Duration)
Herber 1988 88180314	Location: UK Setting: Pediatric diabetic clinic Initial mean age: 10 y Follow-up mean age: 13 y Age range: ND Initial height, SDS: –0.24±1.16 Follow-up height, SDS: –0.20±1.08 Male: 64% Race: ND SES: ND Enrolled: 67 Evaluated: 67 Number of sites: 1	Patients with Type I diabetes who have attended the pediatric diabetic clinic for at least 3 years	None reported	Insulin dependent diabetes	Retrospective longitudinal cohort (3 y)
Izumi 1995 96105591	Location: Japan Setting: Summer camp Initial mean age: ND Follow-up mean age: 14 y Age range: ND Mean height: ND Male: 40% Race: ND SES: ND Enrolled: 385 Evaluated: 107 Number of sites: ND	Children participated in Summer camp program More than 3 determinations of Hgb_A1c Age < 18 y at final examination.	None reported	Insulin dependent diabetes mellitus	Retrospective longitudinal cohort (18 y)

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Insulin Dependent Diabetes Mellitus – Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Types of Diseases / Conditions	Study Design (Duration)
Jivani 1973 73134278	Location: UK Setting: Children's hospital Mean age: ND Age range: 9 mo - 13 y Mean height: ND Male: 46% Race: ND SES: ND Enrolled: 116 Evaluated: 104 Number of sites: 1	Children with diabetes > 3 y follow-up	Other condition which might have affected growth (12 subjects with fair control were not analyzed)	Diabetes (implied insulin dependent)	Retrospective longitudinal cohort (mean [range] 7 [3-13] y)
Pitukcheewanont 1995 96136504	Location: US Setting: Clinic Mean age: 11.5±3.8 y Age range: ND Mean height: ND Male: 49% Race: White 100% SES: ND Enrolled: 82 Evaluated: 82 Number of sites: 1	Type I diabetes	< 3 visits during study Other problems that might affect growth (thyroid disease, cerebral palsy, foster care placement, methylphenidate therapy) Precocious or delayed puberty	Insulin dependent diabetes	Retrospective longitudinal cohort (6 y)

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease

Insulin Dependent Diabetes Mellitus – Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Types of Diseases / Conditions	Study Design (Duration)
Rosenbloom 1982 83032889	Location: US Setting: Clinic Mean age: ND Age range: ND Mean height: ND Male: ND Race: ND SES: ND Enrolled: 309 Evaluated: 142 Number of sites:8	Children with Type I diabetes Pre-puberty Duration of DM >3 y	None reported	Insulin dependent diabetes mellitus	Prospective longitudinal cohort (ND)
Salardi 1987 87127000	Location: Italy Setting: Pediatric clinic Mean age: 7.4±3.6 y Age range: 0.7-15 y Mean height: ND Male: 44% Race: ND SES: ND Enrolled: 79 Evaluated: 79 Number of sites: 1	Children with Type I diabetes	None reported	Insulin dependent diabetes mellitus	Prospective longitudinal cohort (Mean [Range] 4.5 [1-10.7] y)

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease

Insulin Dependent Diabetes Mellitus – Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Types of Diseases / Conditions	Study Design (Duration)
Soliman 1996 96412723	Location: Oman Setting: Diabetes clinic Mean age: 9 y Age range: 2-12 y Mean height: ND Male: ND Race: ND SES: ND Enrolled: 47 Evaluated: 45 Number of sites: 1	Prepubertal children with diagnosis of Type I diabetes mellitus	Intra-uterine growth retardation Systemic or endocrine disease Dysmorphic trait Central nervous system irradiation Hypothyroid	Insulin dependent diabetes mellitus	Prospective longitudinal cohort (1 y)
Vanelli 1992 93052062	Location: Italy Setting: Diabetes unit Mean age: ND Age range: 1.5-21 y Mean height: ND Male: 0% (analyzed) Race: ND SES: ND Enrolled: 204 Evaluated: 42 Number of sites: 1	Diabetic children referred to diabetes clinic at diagnosis Treated with daily insulin Subset analysis of girls who became diabetic at onset of puberty	Endocrinological disease affecting linear growth	Insulin dependent diabetes mellitus	Prospective longitudinal cohort (ND)

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Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease

Insulin Dependent Diabetes Mellitus – Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Types of Diseases / Conditions	Study Design (Duration)
Wise 1992 92387067	Location: US Setting: Pediatric diabetes clinic Mean age: ND Age range: ND Mean height: ND Male: ND Race: ND SES: ND Enrolled: 122 Evaluated: 122 Number of sites: 1	Children and adolescents with diabetes	Other problems that might affect growth (thyroid disease, cerebral palsy, foster care placement, methylphenidate therapy, or precocious or delayed onset of puberty)	Insulin dependent diabetes mellitus	Prospective longitudinal cohort

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Insulin Dependent Diabetes Mellitus – Part II

Author, Year	Severity of Illness Groups	Outcomes
Arreola 1991 93191566	Diabetes control • HgbA1c • Poor control: HgbA1c > 11% • Good control: HgbA1c < 11%	Height velocity cm/month
Court 1982 83021090	Diabetes control (text unclear) • Poor control: Glucosuria (>2%) frequency >75% or 24 hour urine glucose > 50 g • Good control: Glucosuria frequency < 10% or 24 urine glucose < 20 g	Height SDS, based on Tanner 1976 Growth velocity SDS
Herber 1988 88180314	HgbA1c	Change in height SDS
Izumi 1995 96105591	HgbA1c category • <10.0% • 10.0-12.4% • ≥12.0% (unclear why overlap)	Height SDS, based on Japanese Ministry of Education statistics
Jivani 1973 73134278	Diabetes control • Poor: Ketonuria, glycosuria up to 5% at clinic, BS > 250 mg/dL, severe or frequent hypoglycemic reactions • Good: No ketonuia, ≤ 1% glycosuria at clinic, blood sugar < 150 mg/dL, rare mild hypoglycemic reactions	Height percentile, based on Tanner, 1966
Pitukcheewanont 1995 96136504	HgbA1c	Height SDS, based on National Center for Health Statistics Height velocity, SDS
Rosenbloom 1982 83032889	Limited joint mobility ("associat[ed with] early microvascular complications) • None • Mild: Involving 1 or 2 interphalangeal joints, 1 large joint, or only the metacarpophalangeal joints bilaterally • Moderate/Severe: Involving 3 or more interphalangeal joints or 1 finger joint and 1 large joint bilaterally or cervical spine involvement or obvious hand deformity at rest	Height percentile, based on National Center for Health Statistics < 25%

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Insulin Dependent Diabetes Mellitus – Part II

Author, Year	Severity of Illness Groups	Outcomes
Salardi 1987 87127000	HgbA1c	Height SDS, based on Tanner's centiles Height velocity SDS, based on Tanner's centiles
Soliman 1996 96412723	Diabetes control • HgbA1c < 10% • HgbA1c > 10%	Height velocity SDS, based on age-matched population
Vanelli 1992 93052062	Diabetes severity (apparently post hoc grouping) • Lower insulin requirement: Mean ± SD insulin 37±1.5 U/m²/day; HgbA1c 10±1.8% • Higher insulin requirement: Insulin 42±0.5 U/m²/day; HgbA1c 9±2.4%	Peak height velocity (during pubertal growth) cm/year
Wise 1992 92387067	HgbA1c level categories • 6.0-7.9 • 8.0-9.9 • 10.0-11.9 • 12.0-13.9 • 14.0-15.9 • 16.0-21.9	Height velocity Change in SDS, based on National Center for Health Statistics

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Insulin Dependent Diabetes Mellitus – Part III

Author, Year	Associations found	Potential Biases	Comments
Arreola 1991 93191566	Children with diabetes with HgbA1c > 11% (no data on number of subjects) had significantly lower height velocity (0.54 cm/month, from graph) compared to those with HgbA1c < 11% (0.22 cm/month). There was a significant correlation between HbA1c level and height velocity.	True number of subjects included not reported.	No data on funding source
Court 1982 83021090	For children with diabetes that was under poor control (n=57) mean height (–0.96 SDS) was significantly lower than those under good control (n=54, –0.22 SDS). Mean height velocity was significantly lower for children under poor control (–1.22 SDS) than those under good control (–0.61 SDS).	Determination of diabetes control based on glucosuria frequency and 24 hour urine glucose instead of HgbA1c	No data on funding source.
Herber 1988 88180314	In children with diabetes (n=67), "no significant effect on [change in height] was apparent with differing levels of HgbA1c."	Specific data on height SDS in relation to HbA1c levels was not given. Overall good control (mean HbA1c levels at commencement 10.2%; mean HbA1c levels at end 9.9%.	No data on funding source.
Izumi 1995 96105591	Among children with diabetes, mean height of those with HgbA1c < 10% (n=28) was –0.54 SDS, of those with HgbA1c of 10-12.4% (n=53) was –0.76, and of those with HgbA1c ≥ 12% (n=26) was –0.75. Height was not significantly associated to HgbA1c level. No data on height velocity.	Categories of severity of diabetes overlapping. Unclear if statistical analysis based on groups or on individual HgbA1c levels	No data on funding source.
Jivani 1973 73134278	The mean height percentile among girls with diabetes with poor control (n=22) was 38% and among those with good control (n=34) was 40%. There was no significant difference between the two groups. The mean height percentile among boys with diabetes with poor control (n=19) was 35% and among those with good control (n=29) was 29%. There was no significant difference between the two groups. Among both boys and girls with diabetes, height velocity was not associated with level of diabetes control	Eligibility criteria unclear. Age of children at time of follow-up analysis unclear. Statistical analysis unclear. Determination of diabetes control based on factors other than HgbA1c	No data on funding source. The text and table of the criteria for assessment of diabetic control were not concordant.

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease

Insulin Dependent Diabetes Mellitus – Part III

Author, Year	Associations found	Potential Biases	Comments
Pitukcheewanont 1995 96136504	Among children with type I diabetes (n=82), there was no association between mean HgbA1c and mean height SDS in univariate analysis. In multivariate analysis, controlling for age of diabetes onset and initial height, there remained no association between HgbA1c and height. There was no association between mean HgbA1c and mean height velocity at any Tanner stage in univariate analysis.	Retrospective analysis	No data on funding source.
Rosenbloom 1982 83032889	Diabetic children with mild (n=31), moderate (n=19) or severe (n=24) limited joint mobility were significantly more likely to be below the 25th percentile for height (~75%, from graph) than those without limited joint mobility (n=68, ~37%)). However, the correlation between HgbA1c and joint mobility was poor. No data on height velocity	Joint mobility is a poor proxy for severity of diabetes. Only looked at quartiles of height.	Study hospital funded
Salardi 1987 87127000	In children with insulin dependent diabetes (n=79), height SDS and height velocity SDS were not significantly correlated with HgbA1c.	Only summary of results reported.	Study was government funded
Soliman 1996 96412723	Children with diabetes whose HbA1c < 10% (n=30) had significant higher growth velocity (+0.75 SDS) than DM subject HbA1c > 10% (n=15, –1.6 SDS).	None noted	No data on funding source.
Vanelli 1992 93052062	In a subset of girls who became diabetic at onset of puberty (n=42), the 23 treated with greater amounts of insulin (mean 41.5 U/m²/d) and who had lower mean HgbA1c (8.9%) had significantly higher mean peak growth velocity (8.5 cm/y) than the 19 treated with less insulin (37.3 U/m²/d and higher HgbA1c (10.1%), at 6.9 cm/y.	Study poorly defined. Unclear a priori hypotheses Definitions of sample groups poorly defined Single analysis of subgroup only	No data on funding source
Wise 1992 92387067	Among children with diabetes (n=122) a significant linear relationship was seen between HgbA1c and growth velocity. HgbA1c < 8% was associated with growth acceleration (+0.10 SDS); the most severe growth retardation occurred when HgbA1c levels were > 16% (–0.07 SDS).	None noted	No data on funding source

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease

ß-thalassemia – Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Types of Diseases / Conditions	Study Design (Duration)
Constantoulakis 1975 75129833	Location: Greece Setting: Outpatients Mean age: ND Age range: 7 months – 28 y Mean height: ND Male: 58% Race: ND SES: ND Enrolled: 229 Evaluated: 171 Number of sites: 1	Diagnosis of homozygous ß-thalassemia	None reported	ß thalassemia major	Retrospective longitudinal cohort (Range 4-7 y)
Kattamis 1970 71003038	Location: Greece Setting: Clinic Mean age: ND Age range: 1-11 y Mean height: ND Male: 53% Race: ND SES: ND Enrolled: 74 Evaluated: 74 Number of sites: 1	Diagnosis of homozygous β-thalassemia	Clinical picture of thalassemia intermedia and hemoglobin between 7-10 g/dL Age > 11 y	ß thalassemia major	Prospective cross-sectional cohort

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease

ß-thalassemia – Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Types of Diseases / Conditions	Study Design (Duration)
Madeddu 1978 78167848	Location: Italy Setting: Clinic Mean age: ND Age range: 2-13 y Mean height: ND Male: 46% Race: ND SES: ND Enrolled: 50 Evaluated: 50 Number of sites: 1	Homozygous ß thalassemia	None reported	ß thalassemia major	Prospective cross-sectional

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease

ß-thalassemia – Part II

Author, Year	Severity of Illness Groups	Outcomes
Constantoulakis 1975 75129833	Multiple linear regression including • Mean hemoglobin level over previous 2-4 years • Total blood transfused since birth • "Index of severity of disease" based on amount of blood transfused during previous 2 years • (Age)	Height percentiles, based on various Greek sources
Kattamis 1970 71003038	β-thalassaemia severity • Group I: Pre-transfusion hemoglobin > 8 g/dL, frequent transfusions • Group II: Unable to follow regularly, pre-transfusion hemoglobin 6-8 g/dL, either very low SES or had to travel "very long distance" for transfusion • Group III: Transfused only when hemoglobin < 6 g/dL, usually < 5 g/dL	Height percentile, based on Children's Medical Center, Boston growth chart
Madeddu 1978 78167848	Hemoglobin concentration between two transfusions	Height percentile, based on Tanner, 1962

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
ß-thalassemia – Part III

Author, Year	Associations found	Potential Biases	Comments
Constantoulakis 1975 75129833	Among children with ß-thalassemia major (n=171) there was a trend toward lower height percentiles being associated with low hemoglobin levels and severity of disease; however, neither was statistically significant in a linear regression controlling for age. Total blood transfused since birth was not associated with height. No data on height velocity.	No data on hemoglobin levels, total blood transfused since birth, and index of severity of disease. Provides only the regression results. Definition of the severity of the disease unclear. Large numbers of subjects were not included in analyses. No explanation. Model adjusted for non-independent variables.	No data on funding source
Kattamis 1970 71003038	Children with mild ß-thalassemia major (n=38) had significantly higher mean height percentile (56%) than children with moderate (n=14, 22%) and severe (n=22, 7%) disease. No data on height velocity.	Thalassemia severity based on how low hemoglobin allowed to fall before transfusion	No data on funding source
Madeddu 1978 78167848	Children with ß thalassemia major who were < 3rd percentile for height (n=18) had mean hemoglobin of 6.6 g/dL, which was not significantly lower than those whose height was 3rd -25th percentile (n=12, 7.2 g/dL) and whose height was 25th-75th percentile (n=19, 7.0 g/dL) (One child had height above 75th percentile). No data on height velocity.	Cross-sectional study cannot evaluate previous degree of anemia	No data on funding source

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Inflammatory Bowel Disease – Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Types of Diseases / Conditions	Study Design (Duration)
Farmer 1979 80023814	Location: US Setting: Clinic Mean age: ND (41% < 16 y) Age range: < 20 y Mean height: ND Male: ND Race: ND SES: ND Enrolled: 522 Evaluated: 522 Number of sites:1	Crohn's disease established by clinical, radiographic and/or histological means Age < 20 y Diagnosis made form 1955-1974	Unable to obtain follow-up data	Crohn's disease	Retrospective longitudinal case series (Mean 7.7 y)
Griffiths 1993 93345883	Location: Canada Setting: Clinic Mean age: 11±2.3 y Age range: 5 - 17 y Mean height, SDS: –1.1±1.3 Male: 66% Race: ND SES: ND Enrolled: 100 Evaluated: 100 Number of sites: 1	Diagnosis of Crohn's disease Tanner stage 1 or 2	Transferred after initial diagnosis and referred for consultation only	Crohn's disease	Retrospective longitudinal case series (≥ 2 y)

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease

Inflammatory Bowel Disease – Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Types of Diseases / Conditions	Study Design (Duration)
Saha 1998 98182041	Location: Finland Setting: Pediatrics department Mean age: 7 y Age range: ND Mean height: ND Male: 43% Race: ND SES: ND Enrolled: 47 Evaluated: 47 Number of sites: 1	Diagnosis of inflammatory bowel disease	None reported	Inflammatory bowel disease: Ulcerative colitis Crohn's disease	Retrospective longitudinal cohort (13 y)

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Inflammatory Bowel Disease – Part II

Author, Year	Severity of Illness Groups	Outcomes
Farmer 1979 80023814	Location of Crohn's disease • Ileocolic pattern • Colon pattern • Small intestine pattern • Anorectal pattern	Short stature Height < 3rd percentile, based on growth charts
Griffiths 1993 93345883	Severity of gastrointestinal symptoms over given year • Quiescent: No symptoms, normal complete blood count and sedimentation rate • Mild: Some symptoms, no prednisone treatment needed • Moderate: Intermittent exacerbations requiring prednisone or nutritional support • Severe: Chronic unremitting symptoms requiring prednisone or alternate treatment Location of Crohn's disease • Small bowel • Ileocecal • Ileocolic • Colon	Height velocity cm/year Percent with growth retardation < 4 cm/year Height SDS, based on National Center for Health Statistics Change in height SDS
Saha 1998 98182041	Severity of Crohn's disease/ulcerative colitis 12 point scale based on number of relapses, exacerbations, medications and need for surgery (correct scoring mechanism not clear) • Mild: 1-3 points • Moderate: 4-6 points • Severe: ≥ 7 points	Height SDS, based on Finnish population mean Height velocity SDS

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Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Inflammatory Bowel Disease – Part III

Author, Year	Associations found	Potential Biases	Comments
Farmer 1979 80023814	Among children with Crohn's disease likelihood of short (< 3rd height percentile) was not related to location of disease. Of those with ileocolic disease (n=175) 7% were short; of those with colonic disease (n=162) 8% were short; of those with small intestine disease (n=151) 6% were short; of those with anorectal disease (n=34) 9% were short. No data on height velocity	No statistical analyses. "Severity" based on location of disease	No data on funding source
Griffiths 1993 93345883	Among children with Crohn's disease, "severity of gastrointestinal symptoms was the major factor influencing linear growth during the first two years [after diagnosis]. Height velocity significantly decreased with increasing gastrointestinal symptoms during both year and year two, after adjusting for corticosteroid use. During year one, height velocity of children with quiescent disease (n=14) was ~5.7 cm/year (from graph), with mild disease (n=54) was ~4.6 cm/year, with moderate disease (n=23) was ~3 cm/year, and with severe disease (n=9) was ~2.7 cm/year. During year two, height velocity of children with quiescent disease (n=23) was ~7.3 cm/year, with mild disease (n=44) was ~4.5 cm/year, with moderate disease (n=24) was ~4 cm/year, and with severe disease (n=8) was ~4.1 cm/year. Among children with Crohn's disease who were followed to maturity, initial and ultimate height were not associated with disease severity. Initial and ultimate height severity were –0.88 and –0.43 SDS for those with mild disease (n=26), –1.17 and –1.15 SDS for those with moderate disease (n=15), –1.48 and –0.70 SDS for those with moderate or severe disease with sustained remission (n=14), and –1.12 and –1.37 SDS for those with chronically severe disease (n=12). Among children with Crohn's disease who were followed to maturity, change in height was significantly associated with disease severity. Change in height was 0.58 SDS for those with mild disease (n=26), 0.03 SDS for those with moderate disease (n=15), 0.68 SDS for those with moderate or severe disease with sustained remission (n=14), and –0.11 SDS for those with chronic severe disease (n=12). Among children with Crohn's disease, at year two (n=100), disease location was not significantly associated with height velocity (cm/year) or percentage with height velocity < 4 cm/year. Among those with long-term follow-up (n=65), disease location was not associated with initial height SDS, ultimate height SDS, or change in height SDS.	Retrospective	No data on funding source

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Inflammatory Bowel Disease – Part III

Author, Year	Associations found	Potential Biases	Comments
Saha 1998 98182041	Among children with ulcerative colitis (n=29), mean overall change in height over 4 years was –0.16 SDS for those with mild disease, –1.09 SDS for those with moderate disease, and –1.74 SDS for those with severe disease. This trend did not reach statistical significance. The overall change in height velocity was significantly greater in those with mild disease (+1.14 SDS) than those with moderate disease (+0.39 SDS) and those with severe disease (+0.12 SDS). Among children with Crohn's disease (n=18), mean overall change in height over 4 years was +0.51 SDS for those with mild disease, –0.27 SDS for those with moderate disease, and –0.11 SDS for those with severe disease. This trend did not reach statistical significance. The overall change in height velocity was significantly greater in those with mild disease (+0.42 SDS) than those with moderate disease (+0.09 SDS) and those with severe disease (–1.09 SDS).	Height outcomes are difficult to interpret. Numbers of subjects in each category not reported.	Study was hospital and privately funded.

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Juvenile Rheumatoid Arthritis – Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Types of Diseases / Conditions	Study Design (Duration)
Bernstein 1977 87026009	Location: US Setting: Clinic Mean age: ND Initial age range: 1-12 y Mean height: ND Male: 24% Race: ND SES: ND Enrolled: 31 Evaluated: 31 Number of sites: 1	Children with diagnosis of juvenile rheumatoid arthritis	None reported	Juvenile rheumatoid arthritis	Retrospective longitudinal cohort (mean [range] 6.6[2.3-11] y, up to age of 15)
Polito 1997 97283189	Location: Italy Setting: Pediatric clinic Initial mean age: 7 y Follow-up mean age: 12 y Age range: ND Initial mean height, SDS: +0.34 Follow-up mean height, SDS: –0.05 Male: 26% Race: ND SES: ND Enrolled: 58 Evaluated: 58 Number of sites:1	Children with active juvenile rheumatoid arthritis for ≥ 1 y Follow-up for ≥ 1 y	Steroid use Growth hormone therapy	Juvenile rheumatoid arthritis: Pauciarticular onset Systemic onset Polyarticular onset	Retrospective longitudinal case series (≥ 1 y)

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Juvenile Rheumatoid Arthritis – Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Types of Diseases / Conditions	Study Design (Duration)
Saha 1999 99374796	Location: Finland Setting: Hospital based clinic Mean age: 4 y Age range: 0.9-11 y Mean height: ND Male: 36% Race: ND SES: ND Enrolled: 64 Evaluated: 64 Number of sites: 1	Children with mild to moderate juvenile onset chronic arthritis Prepuberty Followed for ≥ 1 y	Ullrich-Turner syndrome	Juvenile rheumatoid arthritis: Pauciarticular onset Systemic onset Polyarticular onset	Retrospective longitudinal case series (1-11 y, until age 12 y)

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Juvenile Rheumatoid Arthritis – Part II

Author, Year	Severity of Illness Groups	Outcomes
Bernstein 1977 87026009	Mode of onset of juvenile rheumatoid arthritis • Systemic • Polyarticular • Pauciarticular	Mean percent change in height per year
Polito 1997 97283189	Type of juvenile rheumatoid arthritis • Systemic • Polyarticular • Pauciarticular Number of joints affected (systemic or polyarticular only) Sum of periods of time with disease flares (systemic or polyarticular only) joint swelling, tenderness, functional impairment, ESR > 25 mm/hr) Functional class, not defined (systemic or polyarticular only)	Change in height SDS, based on Tanner 1976 Change in height SDS per year
Saha 1999 99374796	Severity of juvenile chronic arthritis score 6 point scale based on local anti-inflammatory administrations and number of systemic antirheumatics • Mild: Score 1-3 • Moderate: Score ≥ 4 Type of disease • Pauciarticular • Polyarticular • Systemic • Iridocyclitis	Height velocity SDS, based on Tanner 1966 Height SDS

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Juvenile Rheumatoid Arthritis – Part III

Author, Year	Associations found	Potential Biases	Comments
Bernstein 1977 87026009	Among children with juvenile rheumatoid arthritis, those with systemic disease (n=13) had significantly greater mean change in height per year (–0.85%) than those with polyarticular disease (n=9, +0.04%) and those with pauciarticular disease (n=9, –0.01%).	Definition of outcome measure (percent change in height per year) not well defined	Study was privately funded.
Polito 1997 97283189	Among children with juvenile rheumatoid arthritis, those with pauciarticular disease (n=21) were less likely to lose > 1 height SDS between first and last visits (0%) than those with systemic disease (n=19, 26%) or those with polyarticular disease (n=18, 28%). No statistical analysis was performed. Among children with either systemic or polyarticular disease (n=37), change in height SDS per year was not associated with number of affected joints but was associated with the sum of the periods of disease flares. Children in functional class I (not defined) had significantly smaller change in height SDS per year (–0.01 SDS) than those in functional class II (–0.06 SDS)	Retrospective analysis Inclusion criteria was no steroids, thus children with most severe disease, were excluded. Functional class not defined.	No data on funding source
Saha 1999 99374796	Among children with juvenile rheumatoid arthritis (n=64), by multivariate analysis of covariance "the most obvious decrease in [height] velocity was seen in children with polyarthritis and growth velocity was affected slightly more in children with moderate than mild disease," adjusting for sex and duration of disease. "Heights were more affected in children with polyarthritis and the severity of the disease had an additive effect," adjusting for glucocorticoid use and duration of disease.	Exclusion criteria unclear. No children with severe arthritis. Limited reporting of data. Statistical significance of relevant findings not reported.	Study hospital and privately funded

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease

Chronic Kidney Disease / Kidney Failure – Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Types of Diseases / Conditions	Study Design (Duration)
Claris-Appiani 1989 91002131	Location: Italy Setting: ND Mean age: 1.6-9 y Age range: ND Mean height: ND Male: 65% Race: ND SES: ND Enrolled: 17 Evaluated: 17 Number of sites: ND	Children with chronic kidney disease Pre-dialysis Stable	Acute obstruction Pyelonephritis Hypertension Hyposthenuria Salt wasting Steroid treatment	Chronic kidney disease Stage 3 Stage 4	Prospective longitudinal cohort
Ismaili 2001 21219717	Location: Belgium Setting: Pediatric nephrology Initial mean age: 6 mo Follow-up mean age: 4 y Age range: ND Mean height: ND Male: 55% Race: ND SES: ND Enrolled: 11 Evaluated: 11 Number of sites: 1	Infants with kidney dysplasia and chronic kidney disease	Obstructive renal dysplasia	Chronic kidney disease Kidney dysplasia Stage 4 Stage 5	Retrospective longitudinal cohort (4 y)

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Chronic Kidney Disease / Kidney Failure – Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Types of Diseases / Conditions	Study Design (Duration)
Karlberg 1996 96384503	Location: Europe Setting: Pediatric nephrology clinics Mean age: ND Age range: 0-5 y Mean heights (various ages), SDS: – 1.05 to –3.09 Male: 70% Race: ND SES: ND Enrolled: 73 Evaluated: 61 Number of sites: 22	Onset of chronic kidney disease age < 6 mo GFR < 3 SD below mean for age ≥ 2 height measurements before age 1 y and followed until at least age 3 y	Primary glomerulonephropathy Systemic metabolic disorder	Chronic kidney disease Stage 4 Stage 5	Prospective longitudinal case series (Mean [Range] 7.3 [3-16] y)

Konrad 1995 96162281	Location: Europe
	Setting: Pediatric nephrology clinics
	Initial mean age: 1.7 y
	Initial age range: 1-8 y
	Follow-up man age: 5.6 y
	Follow-up age range: 2-9 y
	Mean height: ND
	Male: 59%
	Race: ND
	SES: ND
	Enrolled: 67
	Evaluated: 58
	Number of sites: 22
		Autosomal recessive polycystic kidney disease
		Prepuberty
		  Girls ≤ 9 y old
		  Boys ≤ 10 y old
		Age ≥ 1 y at first assessment
		≥ 1 y follow-up
		
		Subset of Karlberg, 1996 [#226] and Schaefer, 1996 [#3001]
			Single growth measurement only	Autosomal recessive polycystic kidney disease
				
				Stage 1
				Stage 2
				Stage 3
				Stage 4
					Prospective longitudinal case series
					(≥ 1 y)

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Chronic Kidney Disease / Kidney Failure – Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Types of Diseases / Conditions	Study Design (Duration)
Schaefer 1996 96384504	Location: Europe Setting: Pediatric nephrology clinics Initial median age: 2.6 y Initial age range: 0-8 y Follow-up age: ~ 10 y Height range, SDS: –4.2 to +4.1 Male: ND Race: White 96%, Arab or Asian 4% SES: ND Enrolled: 500 Evaluated:321 Number of sites: 22	Born between 1970 and 1992 Marked reduction in functional kidney mass	Primary glomerulonephropathy Systemic metabolic disorder	Chronic kidney disease Stage 4 Stage 5	Prospective longitudinal case series (Median [Range] 3.3 [0.5-10] y)
Norman 2000 21024968	Location: UK Setting: Clinic Mean age: ND Age range: 2-17 y Mean height: ND Male: 63% Race: ND SES: ND Enrolled: 95 Evaluated: 95 Number of sites: 1	Children scheduled for GFR measurements	Congenital growth abnormalities Receiving dialysis	Chronic kidney disease Stage 1 Stage 2 Stage 3 Stage 4	Prospective cross-sectional cohort

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Chronic Kidney Disease / Kidney Failure – Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Types of Diseases / Conditions	Study Design (Duration)
Rizzoni 1984 85010647	Location: Italy Setting: Pediatric clinic Mean age: 6 y Age range: < 6 mo - 15 y Initial mean height, SDS: –1.6 Follow-up mean height, SDS: –1.5 Male: 69% Race: ND SES: ND Enrolled: 47 Evaluated: 47 Number of sites: 1	Children with GFR < 70 ml/min/1.73 m^2 ≥ 1 bone age determined Follow-up for ≥ 1 y	Proteinuria Nephrotic syndrome Steroid treatment	Chronic kidney disease Stage 2 Stage 3 Stage 4 Stage 5	Retrospective longitudinal case series (Mean [Range] 4.3 [1-12] y)
Schärer 1999 20068988	Location: US Setting: Clinic Mean age: 4.5 y Age range: 1.2-10 y Mean height: ND Male: 67% Race: ND SES: ND Enrolled: 45 Evaluated: 38 Number of sites: ND	Prepubertal children with idiopathic nephrotic syndrome	Chronic kidney failure	Idiopathic nephrotic syndrome	Prospective longitudinal cohort (Mean [Range] 9.0 [2-19] y)

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Chronic Kidney Disease / Kidney Failure – Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Types of Diseases / Conditions	Study Design (Duration)
Tejani 1983 84068349	Location: US Setting: Pediatric nephrology clinic Mean age at onset: Steroid resistant 7.7±3.7 y; Steroid sensitive, 3.5±2.5 y Age range at onset: 10 mo - 15 y Mean height: ND Male: 42% Race: White 16%, Black 50%, Hispanic 33% SES: ND Enrolled: 25 Evaluated: 24 Number of sites: 1	Nephrotic syndrome Biopsy-proven focal segmental sclerosis Biopsy performed because of lack of response to steroids or relapse after treatment with steroids	Diffuse increase in mesangial cells or with mesangial deposition of immunoglobulin	Focal segmental sclerosis	Retrospective longitudinal case series (Steroid resistant: 7±5 y; Steroid sensitive: 13±8 y))
Tsau 1989 90155156	Location: Taiwan Setting: Hospital Mean age of onset: 5 y Age range: ND Mean height: ND Male: 83% Race: Chinese SES: ND Enrolled: 52 Evaluated: 52 Number of sites: 1	Nephrotic syndrome beginning before age 15 y Followed up for at least 2 y	Development of chronic kidney insufficiency	Nephrotic syndrome	Retrospective longitudinal cohort (5.5±2.8 y)

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Chronic Kidney Disease / Kidney Failure – Part II

Author, Year	Severity of Illness Groups	Outcomes
Claris-Appiani 1989 91002131	GFR, Schwartz formula estimate	Height SDS, based on Tanner 1976 Growth velocity per year SDS
Ismaili 2001 21219717	Chronic kidney disease severity, Schwartz formula estimate and direct measurement - GFR < 15 mL/min/1.73 m² - GFR > 15 mL/min/1.73 m²	Height SDS, based on Tanner 1966
Karlberg 1996 96384503	GFR, age-specific Schwartz formulae estimates	Height SDS, based on normal Swedish children
Konrad 1995 96162281	GFR, Schwartz formula estimate Chronic kidney disease severity - GFR < 60 mL/min/1.73 m² - GFR > 260 mL/min/1.73 m²	Height SDS, based on First Zurich Longitudinal Growth Study
Schaefer 1996 96384504	GFR, age-specific Schwartz formulae estimates Chronic kidney disease severity - GFR < 25 mL/min/1.73 m² - GFR > 25 mL/min/1.73 m²	Height SDS Height velocity SDS
Norman 2000 21024968	Chronic kidney disease severity, based on GFR direct measurements - Normal: GFR > 75 mL/min/1.73 m² - Mild: GFR 50-75 mL/min/1.73 m² - Moderate: GFR 25-50 mL/min/1.73 m² - Severe: GFR < 25 mL/min/1.73 m²	Height SDS, based on normal UK population
Rizzoni 1984 85010647	GFR, estimate or direct measurement	Height SDS, based on Tanner 1976 Height velocity, cm/year

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Chronic Kidney Disease / Kidney Failure – Part II

Author, Year	Severity of Illness Groups	Outcomes
Schärer 1999 20068988	Final kidney status • Reached final height in absence of kidney function deterioration or ESRD • Reached final height with serum creatinine > 1.2 mg/dL after age 13.6 years • (Lost to follow-up before kidney function deterioration -- not evaluated in this report) • Developed ESRD before reaching adult height Idiopathic nephrotic syndrome severity (mean serum albumin level and serum protein level)	Height SDS Change in height SDS
Tejani 1983 84068349	Responsiveness (improvement of proteinuria) of focal segmental sclerosis to steroids • Steroid responsive: Complete remission within 8 wk of prednisone, persisting for 2 mo after cessation of treatment • Steroid resistant: No remission after 8 wk of treatment	Growth retardation Height for age < 5th percentile at follow-up
Tsau 1989 90155156	Nephrotic syndrome severity • Less favorable clinical courses, including frequent relapsing, steroid-dependent, and steroid-resistant nephrotic syndromes • Had responded to steroid therapy initially with occasional or no relapse	Change in Height SDS, based on Department of Health, Taiwan Growth velocity index Ratio of actual growth velocity to normal growth velocity for age (% of expected growth)

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Chronic Kidney Disease / Kidney Failure – Part III

Author, Year	Associations found	Potential Biases	Comments
Claris-Appiani 1989 91002131	Among children with pre-dialysis chronic kidney disease (n=17) there was a significant positive correlation between height SDS and creatinine clearance. In multivariate analysis, height velocity was not associated with creatinine clearance, controlling for bone age, BUN, change in BUN, PTH, calcitriol, caloric and protein intake.	Univariate analysis only was performed for height. No univariate analysis for height velocity and creatinine clearance. Creatinine clearance not independent of other variables. Far too few subjects for multivariate analysis	No data on funding source
Ismaili 2001 21219717	Among infants with chronic kidney disease with GFR < 15 mL/min/1.73 m^2 at age 6 months (n=5) mean height did not improve between age 6 months (–2.6 SDS) and 4 years (–2.3 SDS). Among those with GFR > 15 mL/min/1.73 m^2 (n=6) mean height increased from age 6 months (–2.6 SDS) to 4 years (–1.4 SDS).	Small sample size	No data on funding source.
Karlberg 1996 96384503	Among children with chronic kidney disease (n=47) change in height SDS between 9 months and 2 years was not associated with GFR in a multiple linear regression. Among infants with chronic kidney disease (n=14) change in height SDS during the "first postnatal months of life" were not associated with GFR.	No data on variables in model. Many children not included in all analyses	Study was pharmaceutical funded. Same dataset as Schaefer 1996
Konrad 1995 96162281	Among girls with autosomal recessive polycystic kidney disease, those with GFR < 60 mL/min/1.73 m^2 (n=9) had mean height of –2.1 SDS; those with higher GFR (n=15) had mean height of –0.3 SDS. Boys with GFR < 60 mL/min/1.73 m^2 (n=10) had mean height of –1.5 SDS; those with higher GFR (n=24) had mean height of –0.5 SDS. There was a significant correlation between GFR and height SDS among girls but not among boys. No data on height velocity.	None noted	No data on funding source. Subset of Karlberg, 1996 [#226] and Schaefer, 1996 [#3001]

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Chronic Kidney Disease / Kidney Failure – Part III

Author, Year	Associations found	Potential Biases	Comments
Schaefer 1996 96384504	Among children with chronic kidney disease (n=321) height velocity was positively correlated with GFR among 6 year olds and among children of 4 other age groups (of 9 age groups total). Children with GFR > 25 mL/min/1.73 m² had consistently higher annual height velocities than children with lower GFR. Children with GFR > 25 mL/min/1.73 m² were taller (mean height −1.65 SDS) than those with lower GFR (−2.79 SDS).	Numbers of children analyzed with GFR > 25 mL/min/1.73 m² and with lower GFR not reported Results for specific age groups not reported	Study was pharmaceutical funded. Same dataset as Karlberg 1996
Norman 2000 21024968	Among children with chronic kidney disease, those with GFR > 75 mL/min/1.73 m² (n=35) had mean height of +0.40 SDS, those with GFR 50-75 mL/min/1.73 m² (n=23) had mean height of −0.34 SDS, those with GFR 25-50 mL/min/1.73 m² (n=19) had mean height of −0.58 SDS, those with GFR < 25 mL/min/1.73 m² (n=18) had mean height of −1.52. Those with moderate and severe chronic kidney disease had significantly lower height than those with normal GFR. No data on height velocity	None noted	No data on funding source.
Rizzoni 1984 85010647	Among children with chronic kidney disease (n=47) there was no association between GFR and growth velocity. or height SDS.	Limited data reported	No data on funding source
Schärer 1999 20068988	Children with nephrotic syndrome who reached final height without deterioration of kidney function (n=16) had a mean change in height SDS from onset of kidney disease to final height of +0.27 SDS; those who developed serum creatinine > 1.2 mg/dL before reaching final height (n=8) had a mean change in height SDS of −0.08 SDS; those who developed ESRD before reaching final height (n=9) had a mean change in height of −1.35 SDS. Children who developed ESRD had a significant decrease in their height SDS compared to other groups. Among children with steroid resistant nephrotic syndrome in whom steroid therapy was stopped before puberty (n=16) change in prepubertal height SDS and height velocity SDS correlated positively and significantly with total protein and albumin levels.	Analyses performed on only subgroups of subjects Categorization of children by severity of disease is retrospective. Categorized only after reaching final height. Serum albumin and protein are poor markers of disability - related severity of disease	No data on funding source.

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Chronic Kidney Disease / Kidney Failure – Part III

Author, Year	Associations found	Potential Biases	Comments
Tejani 1983 84068349	In children with focal segmental sclerosis, those with steroid responsive disease (n=10) were significantly less likely to have short stature (< 5th percentile) than those with steroid resistant disease (n=14) despite greater steroid doses among the former. No data on growth velocity	Detailed results not reported.	No data on funding source
Tsau 1989 90155156	Among children with nephrotic syndrome, those with relapsing disease (n=29) had significantly lower height velocity (80% of normal) and change in height SDS (–0.63 SDS) than those without relapsing disease (n=23, 104%, +0.19 SDS). This association was true for up to 7 years of follow-up	Cannot distinguish the effect of steroid use from severity of disease. Those with relapsing disease required significantly longer duration of steroid use (8 months) than those without relapsing disease (4 months).	No data on funding source

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Human Immunodeficiency Virus – Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Types of Diseases / Conditions	Study Design (Duration)
Brettler 1990 91011887	Location: US Setting: Hemophilia clinic Median age: 8 y Age range: 2.5-15 y Mean height: ND Male: 100% Race: ND SES: ND Enrolled: 36 Evaluated: 36 Number of sites: 1	Hemophilia HIV infection 2 y of growth data before HIV diagnosis Age ≤ 12.5 y in 1980	None reported	HIV (with hemophilia)	Prospective and retrospective longitudinal cohort (ND)
Matarazzo 1994 95143841	Location: Italy Setting: Pediatric clinic Median age: 2.6 y Age range: 0-8 y Mean height: ND Male: 49% Race: ND SES: ND Enrolled: 24 Evaluated: 24 Number of sites: 1	Perinatal HIV infection	None reported	HIV	Prospective longitudinal cohort (24 mo)

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Human Immunodeficiency Virus – Part II

Author, Year	Severity of Illness Groups	Outcomes
Brettler 1990 91011887	Progression to AIDS or ARC (not defined)	Growth failure Decrease in ≥ 15 percentile points in height or weight for age for 2 consecutive years
Matarazzo 1994 95143841	Clinical condition • Stable: not defined • Clinical deterioration: not defined	Height SDS, based on Tanner 1966 Height velocity SDS

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Human Immunodeficiency Virus – Part III

Author, Year	Associations found	Potential Biases	Comments
Brettler 1990 91011887	Among boys with hemophilia and HIV infection "progression to AIDS or [AIDS related complex]" was more common in those with "growth failure" over 2 years (n=9, 55%) than those with normal growth (n=27, 7%). In multivariate analysis, "growth failure was the strongest prognostic variable" for progression to AIDS or AIDS related complex, adjusted for CD4, p24 antigenemia, and possibly other variables.	Methods, predictors and outcomes poorly defined Variables included in multivariate analysis not reported Definition of growth failure includes weight	No data on funding source
Matarazzo 1994 95143841	Among children with perinatal HIV infection (n=24), those with stable disease courses (n=14) had mean height at 1 year follow-up of –0.7 SDS, mean height at 2 year follow-up of –0.7 SDS, mean height velocity at 1 year follow-up of +1.2 SDS, and mean height at 2 year follow-up of +0.4 SDS. Children with unstable disease courses (n=10) had lower heights and height velocities. Mean height at 1-year follow-up was –2.0 SDS, mean height at 2 year follow-up of –2.6 SDS, mean height velocity at 1 year follow-up of –2.6 SDS, and mean height at 2 year follow-up of –3.0 SDS. "At follow-up [after 2 years], most children with normal growth maintained a stable clinical condition, whereas those with growth reduction showed progression in the severity of the disease….Growth failure was a simple, sensitive predictor of clinical course [stable condition vs clinical deterioration]."	Direct comparison of children with stable and unstable disease had to be calculated from reported raw data. Clinical condition not defined. No statistical analysis.	Study was government and privately funded

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Atopic Dermatitis / Eczema – Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Types of Diseases / Conditions	Study Design (Duration)
Massarano 1993 93312068	Location: UK Setting: Pediatric clinic Mean age: 6 y Age range: 2.3-12 y Mean height: ND Male: 68% Race: ND SES: ND Enrolled: 68 Evaluated: 68 Number of sites: 1	Diagnosis of eczema Prepubertal	Chronic non-atopic disease which would limit growth	Atopic eczema	Prospective cross-sectional cohort
Patel 1988 99014336	Location: UK Setting: Pediatric clinic Mean age: 5.5±0.3 (SEM) Age range: 2-10 y Mean height, initial, SDS: +0.1±0.1 (SEM) Mean height, follow-up, SDS: –0.1±0.2 (SEM) Male: 55% Race: ND SES: ND Enrolled: 80 Evaluated: 80 Number of sites:1	Atopic dermatitis that began before age 1 y Prepubertal, age 2-11 y Referred by pediatrician or dermatologist because of severity of disease	Systemic steroids	Atopic dermatitis	Prospective longitudinal cohort (2 y)

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Atopic Dermatitis / Eczema – Part II

Author, Year	Severity of Illness Groups	Outcomes
Massarano 1993 93312068	Maximum percentage of skin surface area affected by atopic eczema (erythema, vesicle, and crusts) Subgroups by percentage of skin surface area affected • < 50% • > 50%	Height SDS, based on Tanner 1966
Patel 1988 99014336	Percentage body surface area affected by atopic dermatitis • < 50% • > 50% Coexistence of disease • With asthma • Without asthma	Height SDS, based on Tanner 1966 Height velocity SDS

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease

Atopic Dermatitis / Eczema – Part III

Author, Year	Associations found	Potential Biases	Comments
Massarano 1993 93312068	Among children with atopic eczema (n=68), in a multivariate regression analysis, height SDS was correlated with surface area of eczema, controlling for parental height, diet, duration of eczema, treatment and asthma. Those children with < 50% of skin affected (n=41) had mean height of +0.11 SDS; those with 50% of skin affected (n=27) had significantly shorter mean height of – 0.83 SDS. No height velocity data.	None noted	No data on funding source
Patel 1988 99014336	Among children with atopic dermatitis height SDS and height velocity SDS "did not differ between patients with < 50% body surface area (n=43) involvement and those with ≥ 50% body surface area involvement (n=37)…and between patients without asthma (n=36) and those with asthma (n=44)."	Complete results not reported. No statistical analyses reported.	No data on funding

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Miscellaneous Diseases – Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Types of Diseases / Conditions	Study Design (Duration)
Evliyaoglu 1996 97097381	Location: Turkey Setting: Pediatric hematology clinic Mean age: 10 y Age range: 5.5-15 y Mean height, percentile: 20±22% Height range, percentile: 3-75% Male: ND Race: ND SES: ND Enrolled: 24 Evaluated: 24 Number of sites: 1	Homozygote sickle cell anemia	None reported	Homozygous sickle cell anemia	Prospective cross-sectional cohort
Rasat 1995 95372015	Location: New Zealand Setting: ND Median age: 15 y Age range: 2-31 y Mean height: ND Male: 50% Race: ND SES: ND Enrolled: 16 Evaluated: 9 Number of sites: 1	Congenital adrenal hyperplasia diagnosed and treated at one hospital between 1962 and 1993	None reported	Congenital adrenal hyperplasia	Retrospective longitudinal case series (Median [Range] 14 [2-31] y)

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Miscellaneous Diseases – Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Types of Diseases / Conditions	Study Design (Duration)
Samson-Fang 1998 99066563	Location: US Setting: Rehabilitation center Mean age: 4.5 y Age range: 1-12 y Mean height, SDS: -1.2±1.5 Male: 53% Race: White 80%, Black 20% SES: ND Enrolled: 175 Evaluated: 81 Number of sites: 1	Children with cerebral palsy Age < 10 years old at the mid-point of assessing growth interval Minimum time interval of measurements of 0.8 years	Genetic disorders Complicating medical issues	Cerebral Palsy	Retrospective cross-sectional cohort

Evidence Table 3. Association of Decreased Growth Velocity with Severity of Disease
Miscellaneous Diseases – Part II

Author, Year	Severity of Illness Groups	Outcomes
Evliyaoglu 1996 97097381	Severity of sickle cell anemia • Mild: No blood transfusion or crises • Severe: Blood transfusion needed early in life, frequent crises	Height percentile (not defined)
Rasat 1995 95372015	Number of episodes of biochemical escape from congenital adrenal hyperplasia suppression (morning 17-OH Progesterone > 60 nmol/L) • < 3 episodes over at least 2 years • > 3 episodes	Height SDS. based on Tanner 1966
Samson-Fang 1998 99066563	Cerebral palsy cognitive impairment • Cognitive impairment: Learning disability, or delay in problem solving or receptive language skills • No cognitive impairment Type of cerebral palsy • Spastic • Extrapyramidal • Mixed Ambulatory status • Ambulatory: Functionally ambulated with or without aids at home • Non-ambulatory	Growth velocity SDS, based on Rikken 1992

Association of Decreased Growth Velocity with Severity of Disease Abbreviations

Author, Year	Associations found	Potential Biases	Comments
Evliyaoglu 1996 97097381	Among children with sickle cell anemia, those with mild disease (n=12) had significantly greater mean height percentile (22.5%) than those with severe disease (n=12, 17.3%). No data on height velocity	Only mild and severe sickle cell. Height measurement (percentile) not clear. Unclear why all children had low height percentile	No data on funding source
Rasat 1995 95372015	Among children with congenital adrenal hyperplasia there was no significant difference in final height SDS in those with < 3 biochemical escape episodes (n=4) and those with > 3 episodes (n=5). No data on height velocity.	Very small numbers Results shown only graphically.	No data on funding source
Samson-Fang 1998 99066563	Among children with cerebral palsy those with cognitive impairment (n=62) had significantly lower mean growth velocity (–1.25 SDS) than those with no cognitive impairment (n=19, –1.25 SDS)) Those age ≥ 2 years who were non-ambulatory (n=35) had significantly lower mean growth velocity (–1.20 SDS) than those who were ambulatory (n=37, –0.35 SDS). There was no significant difference in mean height velocity among those with spastic disease (n=22, mean height velocity = –0.69 SDS), those with extrapyramidal disease (n=36, –0.86 SDS), and those with mixed disease (n=22, –1.50 SDS)	Exclusion criteria limit most severe impairments due to cerebral palsy	Study was privately funded.

Appendix A. Table 1. Main search performed in MEDLINE®

#	Search History	Results	Summary
1	disab$.af.	66184	Disability
2	Limitation$.af.	45673	
3	Handicap$.af.	13104	
4	Impair$.af.	152795	
5	**1 or 2 or 3 or 4**	**263105**	
6	exp bone diseases, developmental/	36107	Height, growth disorders and short stature
7	exp growth disorders/	16301	
8	exp body height/	18639	
9	short stature.tw.	3374	
10	**6 or 7 or 8 or 9**	**68793**	
11	**5 and 10**	**3203**	Questions 1 & 2
12	exp *bone diseases, developmental/	27528	Linear growth and linear growth delay
13	(short stature or skeletal dysplasia).tw.	3798	
14	Growth velocity.tw.	1257	
15	Growth retardation.tw.	8452	
16	Growth delay.tw.	1306	
17	Growth restriction.tw.	725	
18	Height retardation.tw.	16	
19	(height adj6 restrict$).tw.	54	
20	linear velocity.tw.	160	
21	(height adj6 delay).tw.	89	
22	Length delay.tw.	106	
23	(length adj6 retardation).tw.	145	
24	exp growth disorders/	16301	
25	**12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24**	**51939**	
26	*fetal development/	6938	Excluded diseases/conditions
27	*pregnancy/	21154	
28	*facial bones/	3492	
29	*facies/	103	
30	*failure to thrive/	443	
31	*thanatophoric dysplasia/	122	
32	*fetal growth retardation/	3897	
33	exp basal cell nevus syndrome/	536	
34	exp craniofacial dysostosis/	3267	
35	exp klippel-feil syndrome/	469	
36	exp synostosis/	4073	
37	exp funnel chest/	828	
38	exp gigantism/	823	
39	exp leg length inequality/	1670	
40	exp marfan syndrome/	2697	
41	exp fibrous dysplasia of bone/	2313	
42	exp hyperostosis, cortical, congenital/	353	
43	exp hyperostosis frontalis interna/	241	
44	exp exostoses, multiple hereditary/	601	
45	exp osteopetrosis/	1419	
46	exp osteopoikilosis/	209	
47	exp acquired hyperostosis syndrome/	37	
48	exp platybasia/	278	

49	26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48	**54379**	
50	**25 not 49**	**32177**	Question 3
51	**11 or 50**	**36731**	**Questions 1, 2 & 3**
52	Case Report/	964105	Exclude case reports
53	51 not 52	22559	
54	limit 53 to human	18613	Limit to humans and English language
55	limit 54 to English language	14258	
56	limit 55 to (newborn infant <birth to 1 month> or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)	9857	Limit to children
57	55 not 56	4401	
58	limit 57 to (adult <19 to 44 years> or middle age <45 to 64 years> or "aged <65 and over>" or "aged, <80 and over>")	900	
59	55 not 58	13358	
60	limit 59 to (addresses or bibliography or biography or comment or dictionary or directory or editorial or festschrift or interview or letter or news or periodical index)	714	
61	**59 not 60**	**12644**	

Table 2.   Supplemental searches performed in MEDLINE®

#	Search History	Results	Summary
1	exp growth	203509	Growth / Growth disorders
2	exp growth disorders	16301	
3	1 or 2	215194	
4	exp Heart diseases	445916	Growth & Heart diseases
5	3 and 4	9467	
6	**limit 5 to human, English, and children; Exclude main search results**	**667**	
7	exp Arthritis, rheumatoid	44173	Growth & Arthritis
8	3 and 6	184	
9	**limit 8 to human, English, and children; Exclude main search results**	**47**	
10	exp Asthma	52692	Growth & Asthma
11	2 and 8	618	
12	**limit 11 to human, English, and children; Exclude main search results**	**169**	
13	**6 or 9 or 12**	**883**	Total

Appendix B. Acronyms and Abbreviations

AAP	American Academy of Pediatrics
ACH	Achondroplasia
ADL	Activities of daily living
AHRQ	Agency for Healthcare Research and Quality
AIDS	Acquired immunodeficiency syndrome
ARC	AIDS-related complex
ARPKD	Autosomal recessive polycystic kidney disease
BAER	Brainstem auditory evoked responses
BAS	British Ability Scales
BASC	Behavior Assessment System for Children
BDI	Beck Depression Inventory
BSA	Body surface area
BSID	Bayley Scales of Infant Development
CARA	Chronic aspecific respiratory affection
CAS	Cognitive abilities score
CBCL	Child Behavior Checklist
CBPC	Child Behavior Problem Checklist
CGD	Constitutional growth delay
CHD	Congenital heart disease
CHF	Congestive heart failure
CHIPS	Children's Interpersonal Problem Solving Scale
CKD	Chronic kidney disease
CKF	Chronic kidney failure
CP	Cerebral palsy
CPQ	Children's Personality Questionnaire
DDST	Denver developmental screening test
Dept	Department
DM	Diabetes mellitus
EPC	Evidence-based Practice Center
ESRD	End-stage renal disease
FEV_1/FVC	Forced expiratory volume in 1 second divided by forced vital capacity
FRNS	Focal relapsing nephrotic syndrome
FSGS	Focal segmental glomerular sclerosis
FSS	Familial short stature
FVC	Forced vital capacity
GFR	Glomerular filtration rate
GH	Growth hormone
GHb	Glycohemoglobin
GHD	Growth hormone deficiency

Acronyms and Abbreviations, continued

GVI   Growth velocity index
HANES   Hamburg Neuroticism Extraversion Scale
Hgb   Hemoglobin
Hgb A_{1c} Hemoglobin A_{1c} (Glycosylated hemoglobin)
HIV   Human immunodeficiency virus
HRQOL   Health-related quality of life
IBD   Inflammatory bowel disease
IQ   Intelligence quotient
ISS   Isolated short stature
IUGR   Intrauterine growth retardation
JLO   judgment of line orientation
JRA   Juvenile rheumatoid arthritis
K-BIT   Kaufman-Brief Intelligence Test
KTEA   Kaufman Test of Educational Achievement
LPA   Little People of America
LPS   Structural Intelligence Test, in German
MES   Marburg Scales of Perceived Parental Behavior
MHD   Multiple hormone deficiency
min   Minutes
N&S   Nowicki and Strickland Locus of control scale
NCHS   National Center for Health Statistics
Neale   Neale analysis of reading ability, British edition
NS   Non-significant
OI   Osteogenesis imperfecta
ORNS   Occasional or no relapsing nephrotic syndrome
P CO2   Carbon dioxide partial pressure
P O2   Oxygen partial pressure
PEDI   Pediatric Evaluation of Disability Inventory
PIAT   Peabody Individual Achievement Test
PKD   Polycystic kidney disease
PPVT-R   Peabody Picture Vocabulary Test-Revised
RBQ   Rutter's Behavior Questionnaire
ROM   Range of motion
RR   Relative Risk
RSS   Russell-Silver Syndrome
RV   Residual volume
SB   Stanford-Binet Intelligence Scale
SD   Standard deviation
SDNS   Steroid dependent nephrotic syndrome

Acronyms and Abbreviations, continued

SDS	Standard deviation score
SEP	Somatosensory evoked potentials
SES	Socioeconomic status
SIT	Slosson Intelligence Test
SRNS	Steroid-resistant nephrotic syndrome
SSA	Social Security Administration
SSTAI	Spielberger State-Trait Anxiety Inventory Score
TS	Turner Syndrome
UC	Ulcerative colitis
VMI	Visual motor integration
VSD	Ventricular septal defect
WISC	Wechsler Intelligence Scale for Children
WRAT	Wide Range Achievement Test

Appendix C. Acknowledgments

The Evidence-based Practice Center staff acknowledges the collaboration of the clinical experts who served on the EPC Technical Expert Panel. The EPC also acknowledges the contributions by those who acted as peer reviewers for the evidence report.

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