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?
**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. Further 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. Further 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 a marker for the severity of the underlying disease. The studies 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.

**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. The 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.

**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.

**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.