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2020-11

Kärkinen , J , Miettinen , P J , Raivio , T & Hero , M 2020 , ' Etiology of severe short stature below-3 SDS in a screened Finnish population ' , European Journal of Endocrinology , vol. 183 , no. 5 , pp. 481-488 . https://doi.org/10.1530/EJE-20-0313

http://hdl.handle.net/10138/340888
https://doi.org/10.1530/EJE-20-0313

unspecified
acceptedVersion

Etiology of Severe Short Stature below minus three SDS in a Screened Finnish Population

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A short title: **Etiology of Severe Short Stature**

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Short title: Etiology of Severe short stature

Keywords: Short stature, idiopathic short stature, syndrome, growth hormone deficiency, skeletal dysplasia

Wordcount Abstract - Acknowledgments, 3889, 19 pages.

Abstract

Objective

To describe the etiology of severe short stature in the Helsinki University Hospital district covering a population of 1.2 million that is subject to frequent growth monitoring and screening rules during childhood.

Design

Retrospective cohort study.

Methods

We identified all subjects born 1990 or later with a height SD score <-3, after the age of three years, from the Helsinki University Hospital district growth database. 785 subjects (376 females and 409 males) fulfilled our inclusion criteria; we reviewed their medical records, growth data, and report their underlying diagnoses.

Results

A pathological cause for short stature was diagnosed in 76% of the girls and 71% of the boys (P=NS). Syndromes were the most numerous pathological cause (n=160; 20%), followed by organ disorders (n=127; 16%), growth hormone deficiency (GHD, n=94; 12%), SGA without catch-up growth (n=73; 9%), and skeletal dysplasias (n=57; 7%). Idiopathic short stature (ISS) was diagnosed in 210 (27%) subjects. The probability of growth-related pathology, particularly of a syndrome or skeletal dysplasia, increased with the shorter height SD score and the greater deviation from the target height. Sitting height to height SDS was increased in subjects with ISS, GHD, and SGA (all $P < 0.01$).

Conclusions

Height <-3 SDS after three years of age usually results from a pathological cause and should be thoroughly investigated in specialized health care. The chance of finding a specific etiology increased with the severity of short stature, and the mismatch with target height.

INTRODUCTION

Short stature is one of the most common reasons for referring children to tertiary care pediatric endocrinologist services. Growth monitoring is widely considered important as it aims to detect serious underlying pathological conditions early which may improve prognosis. Based on recent guidelines, short stature with height standard deviation score (SDS) of less than -3 (i.e. below the 0.1st centile) is considered a condition with a high likelihood of underlying acquired or genetic pathology, which requires diagnostic evaluation, including targeted and eventually untargeted (exome sequencing) genetic studies in those with an unexplained underlying cause (1-4). The etiology of short stature has been studied extensively, in cohorts of patients that have been referred to pediatric outpatient clinics for evaluation of short stature or growth failure (5-7), in few (pre-next generation sequencing era) population-level studies (8-11), and in studies evaluating the performance of growth monitoring screening rules (12-14). However, these studies have included a very limited number of patients with severe short stature or the cohorts have been influenced by apparent selection bias. Moreover, the percentage of subjects with a pathological condition has varied widely in relevant studies (5-7, 14) while the benefit and cost-effectiveness of short stature screening have been questioned, based on low rate of detected pathology in routine screening of asymptomatic subjects with a mean height of -2.5 SDS (5). However, the etiology of short stature at the severe end of the spectrum is poorly characterized. Filling this knowledge gap is of importance for refining growth screening at the population level and diagnostic practices in specialized health care.

In Finland, growth monitoring at the population level is an important part of pediatric preventive health care. Each child is measured more than 20 times, including 10 measurements during the first year of life and at least annual measurements thereafter, and subjected to screening rules before reaching adult height (15). Over 99% of children in Finland participate in well-child services (16). Thus, Finnish growth monitoring and referral practices in preventive health care produce a rich vein of population-level auxological data and the growth measurements can be used in diagnostic decision-making (13,1722).

Our objective was to describe the underlying etiology of severe short stature (height less than -3 SDS (i.e. below the 0.1st centile)) in children aged more than 3 years in a large tertiary center that serves as the primary referral center for the region's well-child and school primary health care. Considering the high percentage of children participating in the population height screening, we estimate that our study represents the etiology of severe short stature at the population level.

PATIENTS AND METHODS

Centers

This retrospective study was conducted at the Children's Hospital, Helsinki University Hospital during the years 2015-2020.

Patients and methods

The study population and auxological data were gathered from the growth surveillance database Pediator®. At the time of data retrieval (2015), the database included measurements from more than 123 600 children. The growth database has been used systematically since 1999 to store and evaluate growth measurements in secondary care in Helsinki and Uusimaa Hospital (HUH) catchment area, including the municipalities of Helsinki, Espoo, Vantaa, Kirkkonummi, Kerava, and Kauniainen which covered a population of 1.22 million in 2017 (23), and thus, more than 23% of the Finnish population. The birth rate in this area is approximately 13500 (2017) per year. The growth database includes measurements performed in primary care child welfare and school healthcare clinics, as these data are routinely transferred and saved to the growth database by HUH trained secretaries before the first evaluation in pediatric specialized health care**.** The inclusion criteria of the study were i) height in two or more occasions at least 3 SD below the age and sex-specific population mean (corresponding to below the 0.1st centile) at the age of 3 years or more, ii) the year of birth 1990 or more recently to only include patients with adequate history in electronic medical records, and iii) municipality of residence residing in the HUH catchment area. The most recent reference material, obtained from the same district, was used (17). The Population Register Center was used to determine the place of residence. We reviewed all obtained auxological, clinical, and laboratory data from electronic medical records (Uranus by CGI in addition to Pediator) and excluded subjects with no medical records or diagnostic evaluation for short stature. Auxological data were assessed and erroneous measurements excluded. A total of 21600 height measurements were available for the study cohort, with a mean of 27 per subject. Over 90% of the subjects had 10 or more height measurements available.

The patients were classified into diagnostic groups based on the review of medical records (Supplementary Table 1). In those with unambiguous diagnoses set by pediatricians or, in the majority of cases, by pediatric subspecialists based on sufficient workup, the classification was recorded by the first author (J.K.). In other patients, the diagnostic classification was based on a joint decision by the last author M.H., an experienced pediatric endocrinologist, and J.K. after the review of all available data. The classification is based on the *International Classification of Pediatric Endocrine Diagnoses* for short stature (24) combined with nosology and classification of genetic skeletal disorders (25). In brief, the disorders were classified into primary and secondary growth disorders. The former included: ***syndromes, small for gestational age (SGA) without catch-up growth (CUG)*** defined as birth height and/or weight less than -2 SDS, with failure to catch up by the age of 3 years, and no other specific cause for the growth failure, and ***skeletal dysplasias***. The latter was comprised of ***malnutrition, disorders in organ systems, growth hormone deficiency*** (GHD confirmed with two GH stimulation tests with a subnormal response, defined as <6.7 ug/L or 20 mU/L (1). GHD included neurosecretory dysfunction; see Supplementary Table 1), ***other disorders of growth hormone-IGF1 axis, other endocrine disorders, metabolic disorders, psychosocial causes, and iatrogenic causes,*** including adoption which was diagnosed if no other condition was found and growth rate accelerated after adoption. Subjects were classified as having ***ISS*** ~~if~~ when no specific cause for short stature was detected, the birth size for gestational age was normal, and there was no evidence of chronic organic, psychiatric, or endocrine disease, or undernutrition (26). ISS subjects were classified as familial (including familial CDGP) using criteria: parental height below -2 SDS in either parent, target height below -1.6 SDS or short stature was considered familial by the physician (28% of cases). If puberty and pubertal growth acceleration were delayed, and hypogonadism was not diagnosed, the subjects were classified as having constitutional delay of growth and puberty (CDGP), a subclass of ISS. Subjects with unclear classification after the first review of all clinical data by JK, the classification was determined by an experienced pediatric endocrinologist MH.

Auxology

Formulas used by the growth database to calculate the target height used in the diagnostic evaluation and data availability are shown in Supplementary Figure 1. Distance to target height was calculated by comparing the target height and the lowest height SDS after the age of three years. For calculating sitting height to height (SH/H) SDS, the most recent sitting height measurement was used. Mean ages were 11.1, 12.3, 12.4, and 12.0 years and data were available in 97, 85, 37, and 50 subjects with ISS, GHD, SGA without CUG, and skeletal dysplasia, respectively. Finnish reference data (27) were used in those aged at least 8 years (n=208), and Dutch reference data (28) for those with measurements at a younger age (n=61).

Statistical analyses

We used Fisher's exact test and chi-square test, as appropriate, for statistical analyses of between-sex differences in distributions of underlying diagnoses. Between-sex difference regarding the shortest measured height in etiological groups was analyzed using Mann-Whitney U test. The study cohort was divided into four groups based on the severity of short stature and into four quartiles based on the degree of deviation from the target height. Statistical testing regarding the proportion of pathology was done by comparing groups/quartiles 1 and 4 using Fisher's exact test and chi-square test, as appropriate. For comparison of normally and non-normally (skeletal dysplasias) distributed SH/H values against the population mean, single sample T-test and Wilcoxon sign rank test were used. Between-group differences in SH/H values were analyzed with Welch's ANOVA and Games-Howell posthoc test.

P-value < 0.05 was considered to denote statistical significance. The results are presented as mean (SD) unless otherwise stated. We performed all statistical analyses with SPSS® statistical software for Windows, version 25.0 (SPSS®, Chicago, IL, USA).

Ethical Considerations

The study was approved by the Ethics Committee of Helsinki University Hospital.

RESULTS

Overview on the etiology of severe short stature

A total of 2550 subjects in the growth database fulfilled the auxological inclusion criteria of the study. After removing subjects with erroneous personal information, identification due to spurious height data, no medical records or no diagnostic evaluation for short stature, born before the year 1990, or place of residence not residing in the HUH catchment area we identified 785 subjects with severe short stature after the age of three years (376 girls, 409 boys)(Figure 1). Overview of the study cohort and the diagnostic classification is presented in Supplementary Table 1. The prevalence of severe short stature according to the year of birth showed no apparent sex difference (Supplementary Figure 2). A pathological cause for short stature (*i.e.* condition other than ISS) was diagnosed in 286 (76%) girls and 289 (71%) boys (P=NS, Figure 2). A primary growth disorder was diagnosed in (37%) and a secondary growth disorder in (36%) of the patients. The five most frequent pathological causes were syndromes, disorders in organ systems, growth hormone deficiency (GHD), SGA without catch-up growth (CUG), and skeletal dysplasias, whicin aggregate accounted for 89% of all detected pathology. Sex differences were evident in favor of girls in the frequency of syndromes ($P < 0.0001$) and favor of boys in the frequency of GHD ($P < 0.001$).

Primary growth disorders

A primary growth disorder was diagnosed in 290 patients (163 girls, 127 boys; [$P < 0.001$]). ***Syndromes*** were the most numerous primary growth disorder and more frequent in girls ($P < 0.0001$) (Supplementary Table 1). 36% of syndromic patients received growth hormone (rhGH) treatment. The most frequent single syndrome (27%) was Down syndrome. No other single syndrome was particularly prevalent in boys, whereas Turner syndrome explained 16% of the syndromic cases in girls. Other syndromes with at least three patients were Mulibray nanism (n=8; 5% of syndromic patients), Noonan syndrome (n=6; 4%), Silver-Russell syndrome (n=4; 3%), DiGeorge syndrome (n=4; 3%), Cornelia de Lange syndrome (n=4; 3%), and CHARGE syndrome (n=3; 2%). An unspecified

syndrome was diagnosed in 14% of the syndromic patients. ***SGA without CUG*** was idiopathic in most of the patients and 31% were treated with rhGH. Nearly half (48%) of the SGA without CUG patients had a short-statured (height ≤-2 SDS) parent. ***Skeletal dysplasia*** was the least common primary growth disorder and altogether 24 different skeletal dysplasia diagnoses affected the patients. The most frequent skeletal dysplasias were those related to *FGFR3* (n=16; 28% of the skeletal dysplasia patients), followed by *skeletal dysplasias with abnormal mineralization* (n=9; 16%)*, metaphyseal dysplasias* (n=6; 11%), *and type 2 collagenopathies* (n=6; 11%). Other skeletal dysplasias with at least three subjects were Sulphation disorder group (n=3; 5%), Acromelic dysplasia (incl. Tricho-rhino-phalangeal dysplasia, Acrodysostosis, Albright hereditary osteodystrophy) (n=3; 5%), Mesomelic and rhizo-mesomelic dysplasia (incl. SHOX deficiency) (n=3; 5%), and Cleidocranial dysplasia and related disorders (n=3; 5%). Skeletal dysplasias related to the Finnish disease heritage, *i.e.* ~~c~~Cartilage-hair dysplasia and ~~d~~Diastrophic dysplasia were rare (14%) (Supplementary Table 1).

Secondary growth disorders

A secondary growth disorder was diagnosed in 285 patients (123 girls, 162 boys) (Supplementary Table 1). ***Organ system disorders*** were the most numerous secondary causes and the most common organ system disorder for both sexes was muscular and neurological disorders (n=71; 56% of the organ system disorders), followed by cardiac (n=21; 17%; 6 patients had cyanotic and 15 non-cyanotic), renal (n=13; 10%; 10 patients with chronic renal failure) and intestinal causes (n=7; 6%; 3 patients with celiac disease and 2 with Crohn's disease). ***GHD*** (n=94) was more prevalent in boys ($P < 0.001$) and all patients were treated with rhGH. Isolated GHD was diagnosed in 76 patients, of whom 60 had idiopathic GHD and 16 GHD associated with malformations. GHD as a part of multiple pituitary hormone deficiency was diagnosed in 6 patients: neurosecretory dysfunction in 12. Brain MRI was performed in 83% of the GHD patients. In isolated GHD, brain MRI abnormalities were relatively rare (26%; 16/62 with data available), whereas in those with multiple deficiencies they were always present (100%).

One-third of GHD patients had a short parent. Other secondary causes were significantly fewer in number (Supplementary Table 1).

Idiopathic short stature

In 210 (27%) subjects (120 boys, 90 girls; [P=NS]), no pathological cause for severe short stature was detected. Eight percent of them received rhGH treatment. Familial ISS as well as CDGP were more frequent in boys, whereas non-familial ISS was equally common in both sexes. Familial ISS was the most common ISS subgroup (65%) and 98 ISS subjects had a parent with short stature (height ≤-2 SDS). Turner syndrome was excluded in 82% of the girls diagnosed with ISS. Other genetic studies included microarray-based comparative genomic hybridization (5), Fragile X analysis (4), FISH studies (2), and TRIM37 gene sequencing (1). The number of severely short children decreased after the year 2000, which was explained by the decreased number of ISS subjects; the percentage of ISS decreased from 32% in those born in 1990-1999 to 26% and 14% in those born 2000-2004 and 2005-2011, respectively. No such decrease was evident in other diagnostic groups (data not shown).

Predictors of the underlying pathology

The severity of short stature did not differ between sexes in any of the six most numerous etiological groups (P=0.17-0.67) (Figure 3). The study cohort divided into four groups according to the lowest measured height SDS is shown in Figure 4. With increasing severity of short stature, the proportion of patients with skeletal dysplasias and syndromes increased, whereas the proportion of GHD and ISS decreased (all $P < 0.01$). In the 1st group (height -3.0 to -3.5 SDS), a pathological condition was detected in 55% of the boys and 65% of the girls. The proportion of patients with pathological underlying disease increased with increasing severity of short stature and correspondingly the frequency of ISS decreased, being 29, 10, and 0% in those with the shortest height in the range of -3.5 to -4.0 SDS, -4.0 to -5.0 SD, and less than -5 SDS, respectively. In patients with shortest measured height < -4 SDS, a syndromic cause or skeletal dysplasia was identified in half of the cases, whereas ISS was rare (< 7%). Similarly, the distribution of underlying diagnoses was closely associated with

the distance to target height (Supplementary Figure 1). With increasing distance to target height, the frequency of syndromes, skeletal dysplasias, and organ system disorder increased, whereas ISS decreased (all $P < 0.05$). SGA without CUG and GHD showed no significant differences across distance to target height quartiles.

Sitting height to height ratio

We analyzed age and sex-specific SH/H SDS values of the following diagnostic groups with sufficient data available: ISS, GHD, SGA without CUG, and skeletal dysplasias (Figure 5). SH/H was increased in all groups: ISS (0.5 SDS), GHD (0.9 SDS), SGA without CUG (1.2 SDS), and skeletal dysplasia (3.6 SDS median) (all $P < 0.01$). Skeletal dysplasia patients had the highest SH/H, whereas ISS subjects had a lower mean SH/H score than GHD or SGA without CUG patients. No statistically significant difference in SH/H was evident between SGA without CUG and GHD groups. SH/H was above +2 SDS in 8, 11, 30, and 68% of the ISS, GHD, SGA without CUG, and skeletal dysplasia patients, respectively.

DISCUSSION

We show that severe short stature, *i.e.* height less than -3 SDS after three years of age, is associated with a high likelihood of detecting an underlying pathological condition. This was the case for both sexes in more than 70% of cases, a finding which supports thorough diagnostic evaluation in all children with short stature of this severity. Underlying etiology correlated with the severity of the short stature, with increased frequency of syndromes and skeletal dysplasias and decreased frequency of GHD and particularly ISS in the shortest patients. Idiopathic short stature was virtually absent in those with height less than -4 SDS. Our findings are based on a cohort that represents the general population and is exceptionally large, including 785 patients and more than 21600 height measurements. No such large, systematic population-based study on the etiology of severe short stature has been reported before, with previous population-based reports comprising fewer than 50 patients with severe short stature (8, 11). In line with our findings, the percentage of detected pathology in these population-based studies ranged from 50 to 58% (8, 11). However, the rate of pathology in cohorts of children referred to specialized health care for evaluation of short stature has ranged from only 1 to ~ 40% (5-7, 12, 14). In asymptomatic children with normal growth velocity and a mean height SDS of -2.5, the diagnostic yield of standard workup may be as low as 1.3% and based on the low frequency of pathology the value of short staturescreening has been questioned (5). This difference in the rate of observed pathology between unselected population-based and referral studies is likely explained by a low number of symptomatic and severely short-statured patients in the latter. In support of this, a pathological condition was detected in over half of the patients with heights below -3 SDS in a large Korean referral study (7). Taken together, accumulated evidence supports a thorough workup for children with a height below -3 SDS after the age of 3 years.

Our study included a similar number of girls and boys and no significant sex difference either in the shortest measured height after the age of three years within the main etiological groups or in the yearly prevalence of severely short-statured patients were evident. In previous studies boys have almost universally outnumbered girls (5, 6, 10), a phenomenon which may be accounted for by referral bias. Such bias is unlikely in our cohort due to comprehensive growth monitoring and application of screening rules. However,

syndromes were more frequently diagnosed in girls, whereas boys more frequently had GHD. The former was largely explained by Turner syndrome. The reason for the higher prevalence of GHD in boys is unclear, yet it corresponds with findings in previous population-level studies (10, 29).

Almost half of the subjects with ISS and SGA without CUG, and over a third of the patients with GHD, had a parent with short stature. This finding supports the view that genetic factors may have an important role in explaining the growth disturbance in these patients. Several lines of evidence suggest that frequently these are monogenic defects in genes that regulate growth plate function, particularly in short children with a short parent (30-33). Increased sitting height to height ratio supports the view that this may be the case in some of our patients with ISS, GHD, and SGA without CUG. In a recent whole-exome sequencing study, single-gene pathogenic or likely pathogenic variants, that mostly affected the growth plate, were found in 43% of GH-treated short children with GHD or SGA and a short parent (30). The low detection rate of patients with mild skeletal dysplasia phenotypes is further supported by the distribution of these patients to the severe end of the height spectrum in our cohort. Thus, the true rate of pathology in our cohort may be even higher than reported, as gene panels or WES were seldom used in our patients.

Our study has several strengths and limitations. Although the cohort comprised of subjects that had been referred to secondary care, we estimate that the study population is a truly representative one, for several reasons. First, over 99% of the child population in Finland participate in well-child services (15, 16). Second, these children are routinely admitted to secondary or tertiary care based on national Finnish screening criteria (13, 17, 19-21) which are well adhered to. Third, in the HUH district, auxological data are routinely stored using exclusively the Pediator® software.

Incomplete data are an inherent feature of any retrospective study of this nature~~a~~. Target height and thus distance to target height could not be calculated for 3% and 30% of subjects with ISS or a pathological condition, respectively. Furthermore, SH/H data were representative only in those with GHD, skeletal dysplasia, SGA without CUG, and ISS, of whom 90, 88, 51, and 46% had these data available. Moreover, due to the study design, the incidence of severe short stature declined for both sexes from the year 2000

onwards, probably reflects the lack of subjects presenting at an older age, particularly those with ISS.

In conclusion, we found that severe short stature, i.e. height less than -3 SDS, was associated with a high frequency of pathology in both sexes. Primary and secondary underlying causes were equally frequent in severely short children, and the frequency of pathology depended heavily on the degree of short stature and distance to target height. Increased sitting height to height ratio in those with ISS, GHD, and SGA without CUG supports the view that undiagnosed monogenic growth plate defects may explain the height disturbance in a proportion of these patients. Our results lend support to in-depth diagnostic workup for children with height less than -3 SDS at age 3 years or older.

FUNDING

This work was supported by the Finnish foundation for Pediatric Research (grant number 170067) and the Academy of Finland (298949).

CONFLICT OF INTEREST

The authors declare that no conflict of interest could be perceived as prejudicing the impartiality of the research reported. Taneli Raivio is on the Editorial Board of European Journal of Endocrinology. Taneli Raivio was not involved in the review or editorial process for this paper, on which he is listed as an author.

Acknowledgments

We thank Dr.Harri Markkula for sharing his expertise with the database Pediator® and Annika Tarkkanen, MSc, for review of the English language.

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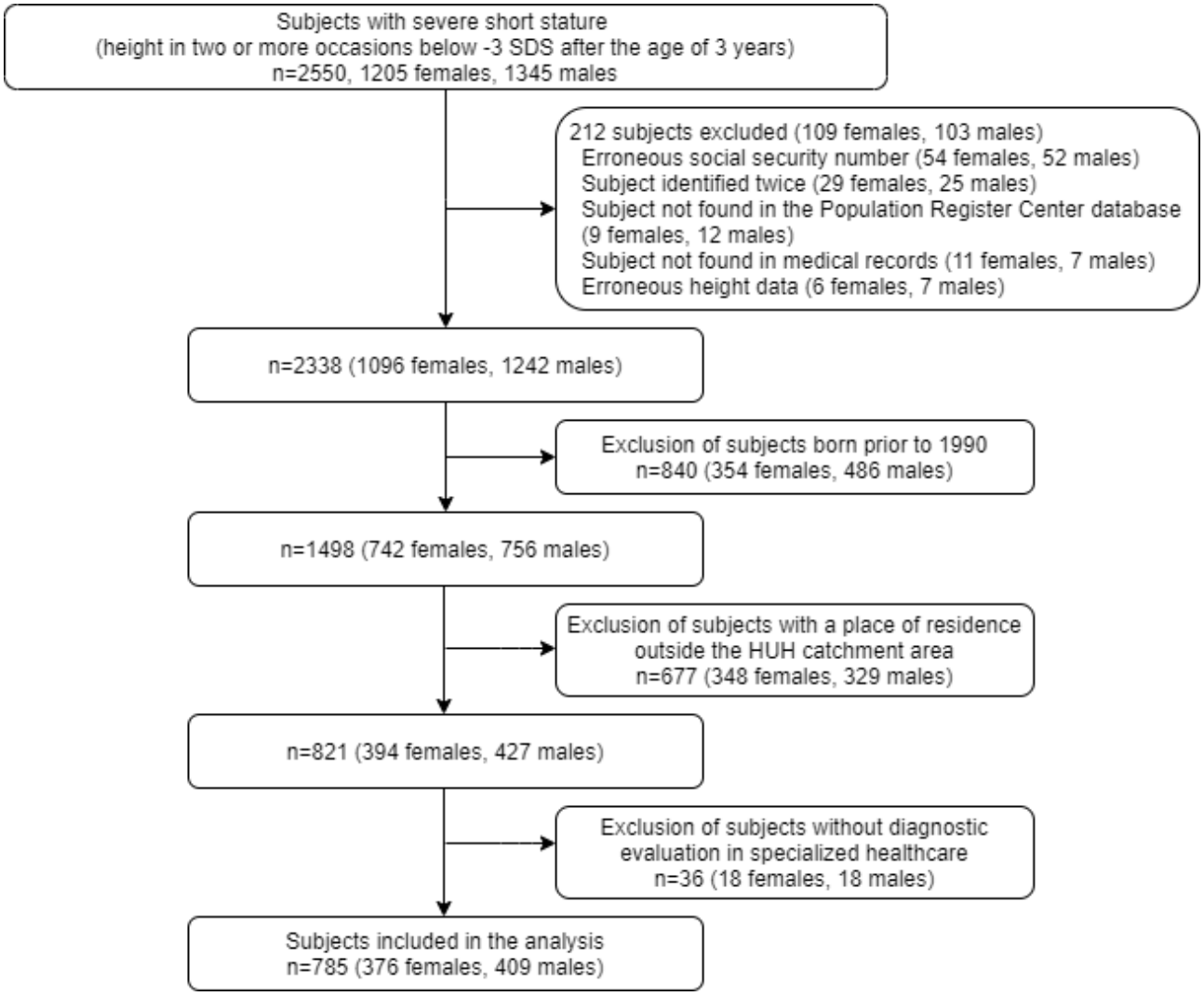


Figure 1. *Flowchart depicting the selection of patients with severe short stature. Patients were identified from the growth monitoring software Pediator® based on our inclusion criteria of at least two height-measurements below -3 SDS after the age of three years. Subjects with* erroneous personal information, no medical records, identified based on erroneous height data, born prior to the year 1990, place of residence outside HUH district, and not investigated for severe short stature were excluded.

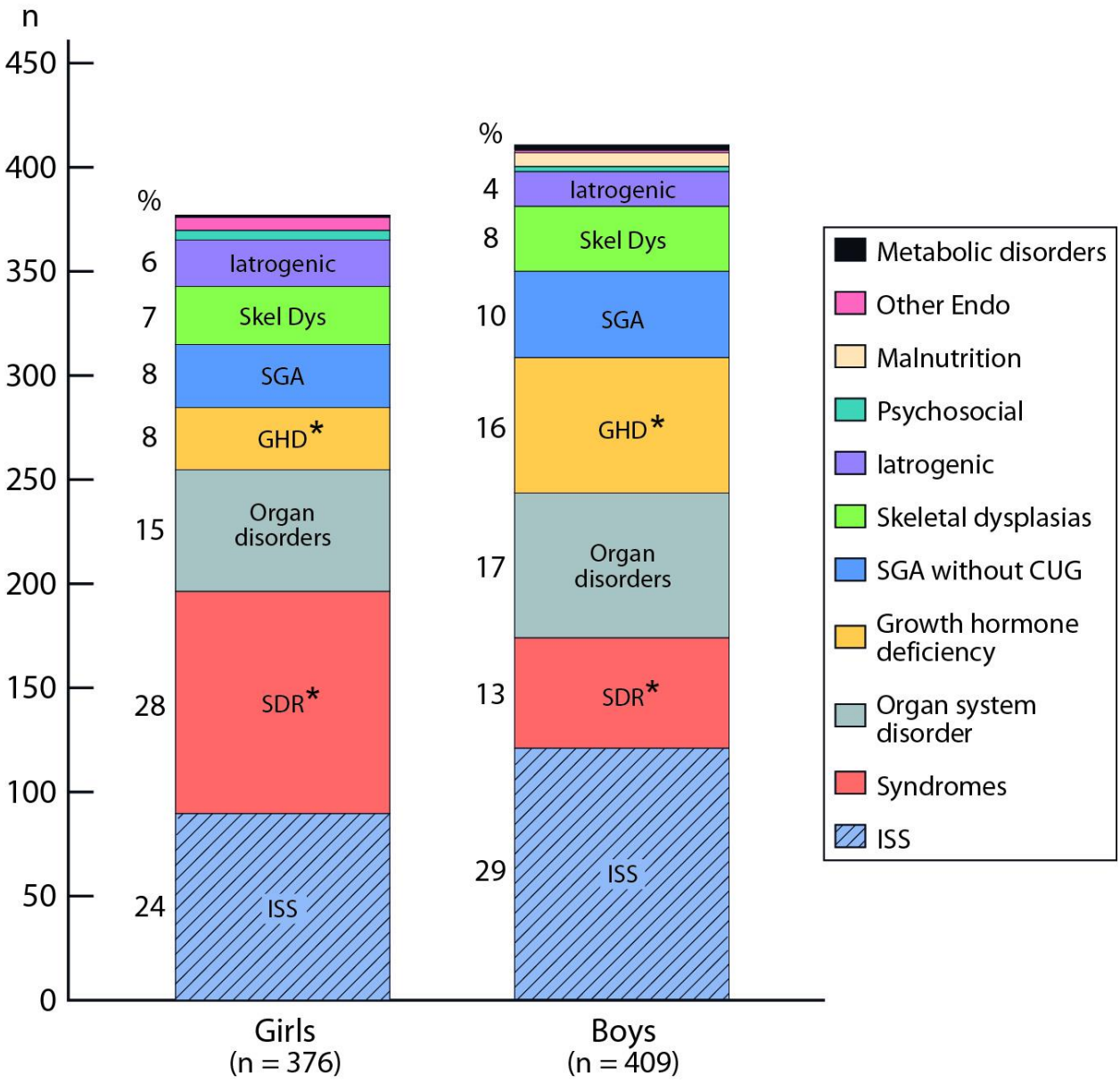


Figure 2. *Etiology of severe short stature, determined as height less than -3 SDS at the age of more than 3 years, in children born 1990 or later in the Helsinki University Hospital catchment area. *P <0.001 between sexes.*

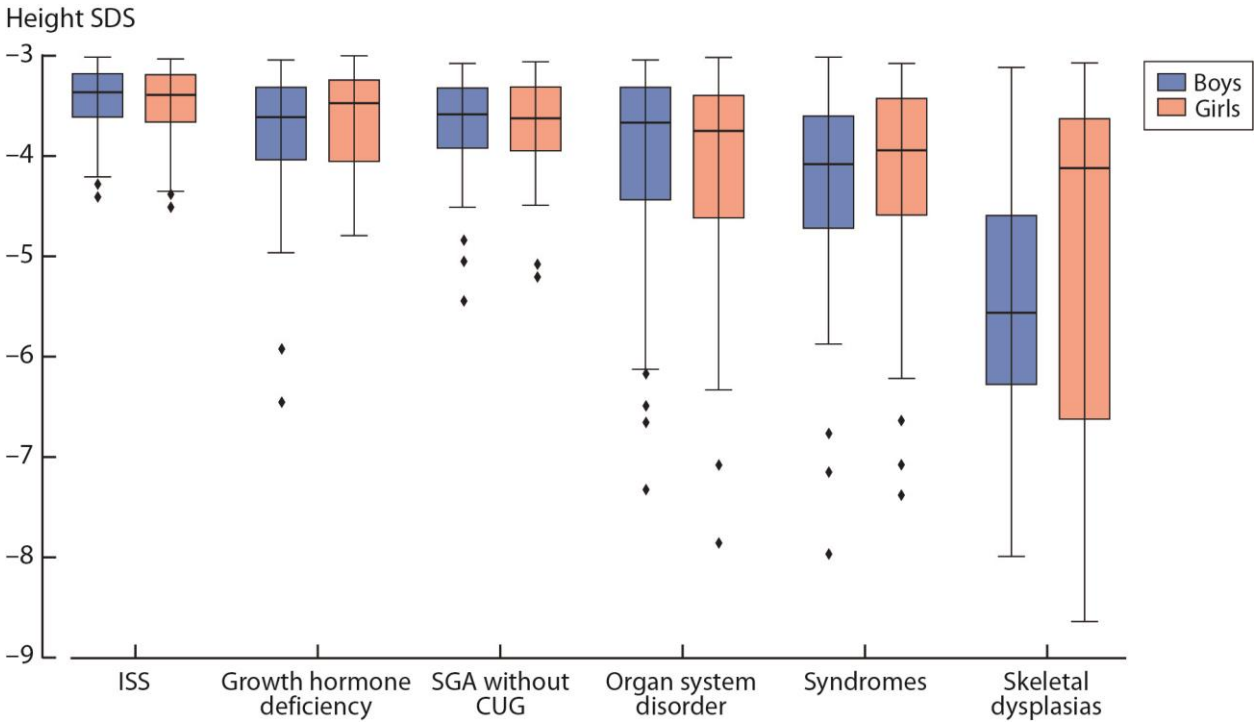


Figure 3. *Median and distribution of the shortest measured height SDS after the age of three years in subjects of the six most numerous etiological categories of severe short stature.*

Footnote: Two patients with skeletal dysplasia and extremely short stature (a boy with height -11 SDS and a girl with height -15 SDS) are not shown in the Figure but their data were used in the analyses.

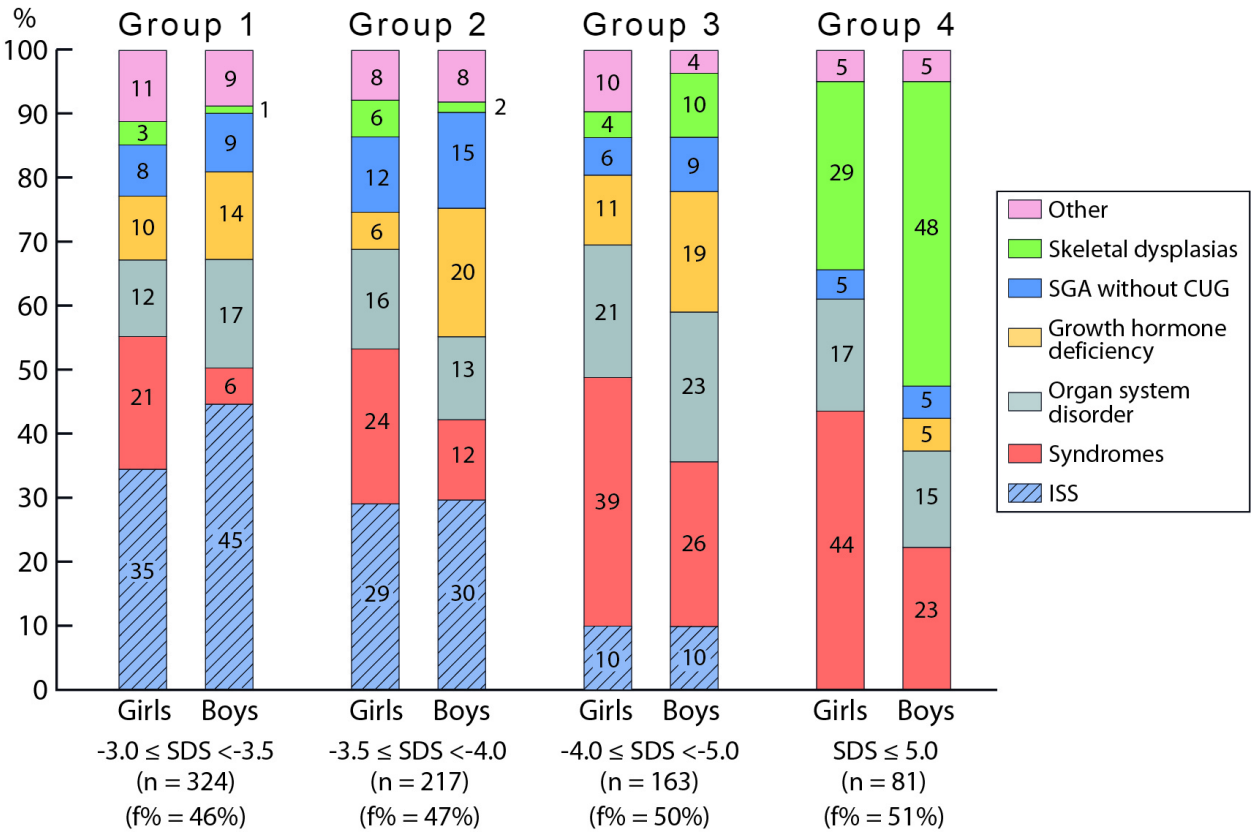
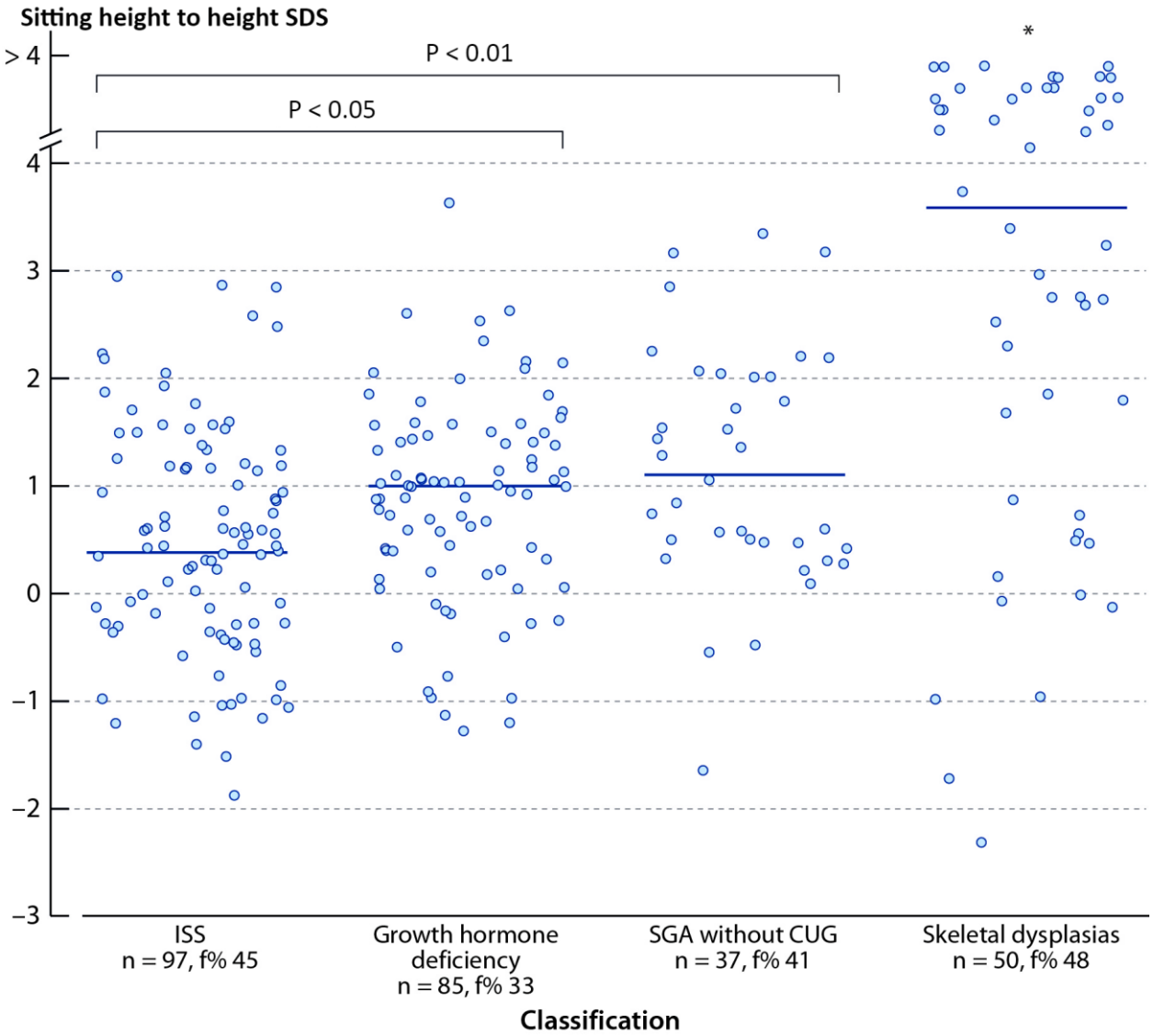


Figure 4. *Distribution of the underlying causes of short stature according to the severity of short stature. Classification is based on the lowest measured height SDS after the age of 3 years.*

Footnote: Other-group consisted of malnutrition, other disorders of the growth hormone-IGF-1 axis, other endocrine disorders, metabolic disorders, psychosocial, and iatrogenic causes. The female proportion is displayed as f%.

Figure 5. *SD scores of age and sex-specific sitting height to height ratio in subjects with ISS, GHD, SGA without CUG and skeletal dysplasia.*



*Footnote: Skeletal dysplasia group had a statistically higher sitting height to height SDS; ** (P<0.001). *The most recent sitting height to height, measured at the mean age of 11, 12, 12, and 12 years in ISS, GHD, SGA without CUG and skeletal dysplasia patients, respectively, was used. The female proportion is displayed as f%.*