Developing an evidence-based guideline for the referral of short stature

Floor K. Grote[1#], Paula van Dommelen[2#], Wilma Oostdijk[1], Sabine M.P.F. de Muinck Keizer- Schrama[3], Paul H. Verkerk[4], Jan M. Wit[1], Stef van Buuren[2,5]

[1] Dept. of Paediatrics, Leiden University Medical Center, Leiden, The Netherlands

[2] Dept. of Statistics, TNO Quality of life, Leiden, The Netherlands

[3] Dept. of Paediatrics, Erasmus MC - Sophia Children's Hospital, Rotterdam, The Netherlands

[4] Dept. of Child Health, TNO Quality of life, Leiden, The Netherlands

[5] Dept. of Methodology & Statistics, University of Utrecht, The Netherlands

[#] These authors contributed equally to this work

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Address for correspondence

Stef van Buuren, Dept. of Statistics, TNO Quality of Life, P.O. Box 2215, 2301 CE Leiden, The Netherlands

Email: Stef.vanBuuren@tno.nl

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Abstract

Objective: To establish an evidence-based guideline for growth monitoring on a population basis.

Study design: Several auxological referral criteria were formulated and applied to longitudinal growth data from four different patient groups and from three samples from the general population.

Results: Almost 30% of pathology can be detected by height standard deviation score (HSDS) below -3 or at least two observations of HSDS below -2.5 at a low false-positive rate (<1%) in 0-3 year old infants. For 3-10 year olds, a rule concerning distance to target height of >2 SD for those with HSDS < -2.0 has the best predictive value. After adding a rule concerning severe short stature (<-2.5 SDS) and a rule on slowed growth, 85.7% of children with Turner's syndrome and 76.5% of short children due to various disorders are detected at a false-positive rate of 1.5-2%.

Conclusion: The proposed guideline for growth monitoring shows a high sensitivity at an acceptably low false-positive rate in 3-10 year old children. Distance to target height is the most important criterion. Below the age of 3 years the sensitivity is considerably lower. The resulting flow chart can help practitioners in industrialized countries, but requires further testing in other populations.

Introduction

Growth monitoring in infancy and childhood has been part of preventive child health programs for more than a century, and short stature or growth retardation is regarded as a relatively early sign of poor health. Despite this longstanding and wide acceptance of growth monitoring, there is little evidence for its effectiveness and efficiency. [1] In developing countries, growth monitoring is primarily aimed at detecting malnutrition. In industrialized countries, the major purpose of growth monitoring is early detection of growth disorders, such as Turner's syndrome (TS), Growth Hormone deficiency (GHD) and celiac disease (CD).

For early identification of children with abnormal growth one needs good growth monitoring systems as part of preventive child health programs; well-defined and accurate referral criteria; and good diagnostic work-up after referral. Although most industrialized countries have a child health program including regular growth monitoring, there is a wide diversity in protocols used for growth monitoring and diagnostic work-up of growth disorders, and a virtual absence of experimental studies on the efficacy of these screening and diagnostic procedures. [2] Few guidelines have been published on referral criteria and diagnostic work-up, and these are generally based on expert consensus rather than on experimental evidence. [3;4] In the few experimental studies on growth monitoring quite different referral criteria have been used. [5-7]

In the Netherlands, a consensus meeting was held in the mid nineteen nineties to establish auxological referral criteria. [3] Three auxological parameters were chosen: height standard deviation score (HSDS), drop in HSDS (HSDS slowed growth), and distance between height and target height SDS. Additional criteria included clinical signs (disproportion or dysmorphism), specific symptoms (such as those associated with emotional deprivation), or previous history of low birth weight and/or length (small for gestational age, SGA). Later, it was shown that applying these auxological criteria would lead to far too many unnecessary referrals. [8]

The aim of this project was to produce evidence-based criteria for growth monitoring. Previously we studied the predictive value of various auxological criteria for the detection of TS, [9] and evaluated the auxological parameters of patients with various causes of growth failure referred to the paediatric clinics.[10] In the present report we describe the performance of the best screening rules in terms of sensitivity and specificity in four groups of patients with growth disorders and in three reference samples. We suggest that these rules can be used in growth monitoring.

Method

Material

Longitudinal height and weight data from four different patient groups and three reference populations were used. Each group was analysed separately. For the patient groups only measurements before or at age of diagnosis or start diet (CD-population) were taken into account.

The first group of patients consisted of 777 girls with TS, collected from three sources and previously described by van Buuren et al [9]. The second group was a group of new patients referred for short stature to the outpatient clinics of the general paediatric departments of two hospitals (Erasmus MC - Sophia Children's Hospital, Rotterdam and Spaarne Hospital, Haarlem) in 1998-2002. Out of 542 children referred to the clinic, 27 children with pathology (mainly GHD (n=7), CD (n=7) and TS (n=3)) were found. Only these 27 children were included in the analyses. The third group consisted of CF patients collected from three major CF clinics in The Netherlands: Erasmus MC - Sophia Children's Hospital in Rotterdam (n=166), University Hospital Maastricht (n=30) and Juliana Children's Hospital in The Hague (n=20). The last group was a group of CD-patients consisting of two separate subgroups: a retrospective study [11], and a prospective study [12].

The first reference sample was obtained from the Social Medical Survey of Children Attending Child Health Clinics (SMOCC) cohort, a nationally representative cohort of 2,151 children born in the Netherlands in 1988-1989, consisting of data of length and

weight up to the age of 2.5 years. [13] The second reference population is a cohort of all children born in the years 1989 and 1990 in Landgraaf and Kerkrade, located in the southern part of The Netherlands ("Limburg", n = 970). [8] The third population is a sample of children born in 1985-1988, attending school doctors between 1998 and 2000 in Leiden and Alphen aan den Rijn, the Netherlands ("ZHN", n = 400) (unpublished data).

Screening rules

Based on evidence from previous studies, we formulated three rules.

The first rule compares, for children with a HSDS below some cut point, the difference between the HSDS and the target height SDS (THSDS). This type of rule performed best for identifying TS.[9] We used a distance between HSDS and THSDS of 2 and varied cut-off points for entry HSDS as -2, –1.5, or –1.0 SDS. This rule is labelled *"short for target height"*.

The second rule concerns HSDS, which is often viewed as the most important growth parameter, especially when parental height is not available. [2;4] In order to keep the percentage of false-positives low, we chose for historical and pragmatic reasons a cut-off of -2.5 (~ 0.6th percentile), as it is the lowest line on several growth charts. This rule is labelled "*very short"*.

The third rule is based on deviation from the expected growth channel, expressed as loss of HSDS during some time interval. A loss in HSDS reflects the deviation from canalisation of the growth curve. Although the usefulness of slowed growth for screening appears limited, [7 14] many clinicians can show examples of cases where slowed growth is the only indication of a growth disorder, e.g. an acquired GH deficiency caused by a brain tumour or primary hypothyroidism by Hashimoto disease. Referring children with a loss in HSDS over 0.25 SDS per year leads to a large number of false-positives.[8] The predictive value can be improved in several ways: demand a continuous drop in HSDS over 3 years (e.g. 0.25 SDS/yr during at least 3 years) [9;14], demand a larger drop over

an arbitrary time interval (e.g. a drop of >1.0 SDS), or apply the rule only to short children with HSDS<-2. Various combinations were tried. The present analysis used cut-off points for HSDS: <-2.0, <-1.5 and <-1.0. This decision rule is labelled "*slowed growth"*. A rule using a drop of 1.0 SDS would probably be most practical as it should be able to detect both a slow and fast bend of the growth curve. Several reference diagrams include lines with a distance of 1 SDS [15].

Analytic procedure

All auxologic measures were expressed as SDS, using up-to-date reference data.[16-19] Sensitivity was calculated as the referral percentage in the patient data. Specificity was defined as the referral percentage in the reference data.

Parental height was frequently (4-58%) missing in the data. We imputed these data under the assumption that data were missing at random using Multivariate Imputation by Chained Equations (MICE). [20 21] The imputation model consisted of the last known HSDS (except for the CF-population where we chose the HSDS closest to the age of 5 years instead because in most children catch-up growth has resulted in a normal height at this age [22]), HSDS, weight SDS, weight for height SDS, BMI SDS, gender (except for the TS group as these are all girls), HSDS of the father and/or HSDS of the mother (if available), ethnicity (except for the TS and Limburg cohort) and for CF and CD age at diagnosis or start diet. The number of iterations was set to 15. Predictive mean matching was used to create parental height imputations.

Target height

Target Height (TH) was calculated by Tanner's method with an additional correction for secular trend: TH(boys) = (Father's Height (FH)+ Mother's Height (MH)+ 13)/2 + 4.5 and TH(girls) = (FH + MH - 13)/2 + 4.5. The Target Height Standard Deviation Score (THSDS) was calculated as THSDS(boys) = (TH(boys)-184)/7.1 and THSDS(girls) = (TH(girls)-170.6)/6.5.

Calculations were based on the assumption that a child is referred if the growth pattern meets the criteria of a given screening rule for the first time. If a child only had one measurement the child can not comply to criteria concerning slowed growth or repetition and is therefore considered as non referred. All rules were analysed separately as well as in combination with the others. A false-positive rate of <1% for the separate rules and < 2% for the combined rules was considered to be acceptable from the perspective of preventive child health care.

Results

Table 1 shows the number of children per age group and the mean number of measurements.

Applying the three auxological criteria separately to all age groups resulted in a high number of referrals in the general population (presumably false positives) (data not shown). This was primarily due to referrals in the 0-3 year group: the *slowed growth* and *short for target height* rules would produce a high false-positive rate. All analyses were therefore performed separately for two age groups: 0-3 years and 3-10 years. Table 2 shows the scenarios that had the best test performance. Table 3 provides estimates of sensitivity (true-positives). Table 4 contains estimates of 1-specificity (false-positives).

For children under the age of three years the true positive rate for pathology is modest. The best rule consists of an HSDS <-2.5 at least twice within 1 year (*very short repeated*) or an HSDS <-3 (*extremely short)* rule, confined to infants born at or after 37 weeks of gestational age (or when information on gestational age is not available) and born with a weight >= 2500 g (if birth weight was not available, the first measurement within 0.1 year (5 weeks) with a weight SDS >= -2 was used). With this rule 14.7% of the children with TS can be detected, at a false positive rate of <1%. This is probably an underestimate, because the percentage of 7.1% for a repeated HSDS <-2.5 increased to 15.8% by assessing only the subgroup of children with more than 2 measurements. The *short for target height* rule did not have in acceptable test characteristics in this age group.

Above the age of 3 years a total of 85.7% of children with TS and 76.5% of the children with mixed pathology can be detected by the combination of the *short for target height* rule, the *very short* rule and the rule for *slowed growth*.

If a stepwise approach is taken for 3-10 year old children, the *very short* rule would add 42 patients (7.7%) to the 76.9% of the girls with TS who complied with the *short for target height* rule. For the group of children with short stature due to mixed pathology 3 cases (17.7 %) would be added to the 58.8% of children who complied with the *short for target height* rule. The addition of this rule would increase the false-positive rate by 0.3 % (1 child) in the ZHN cohort and 0.7% (7 children) in the Limburg cohort. Applying the rule for *slowed growth* after the two other rules would only add few extra patients (4 patients (0.8%) for TS, none for the children with mixed pathology), while the false-positive rate would increase by 0.6% (2 children).

Discussion

We established an evidence-based guideline for growth monitoring on a population basis. In 0-3 year old infants, after exclusion of babies born preterm and with a low birth weight, we found that a HSDS <-3 or at least two observations of a HSDS <-2.5 within 1 year, has the best performance at a low false-positive rate. However, only 14.7% of the children with TS and 26.1% of children with other growth disorders can be detected with these rules. For 3-10 year old children the *short for target height* rule in combination with the *very short* rule and a minor contribution of the rule for *slowed growth* detects 85.7% of children with TS and 76.5% of short children due to various disorders at a low false-positive rate.

The low efficacy and efficiency of rules for *slowed growth* for ages 0-3 years can be attributed to the low correlations among successive length measurements. Crossing centiles in this age period is quite common. The low correlation between midparental height at birth[23] may explain the modest performance for these ages of *short for target height*.

In line with previous research on TS only,[9] we found, for ages 3-10 years, that the *short for target height* rule performed best also for a mixed set of growth disorders. This result contrasts with earlier speculations that parental height might be too inaccurate.[4] For screening, the rule for *slowed growth* does not add much. However, we propose to keep this rule for detecting those rare cases with acquired growth disorders in a timely fashion. In order to keep the false-positive rate low, we combined the rule for slowed growth with entry criterion HSDS<-2.0. However, a severe drop without HSDS<-2.0 should also be considered as an alarm signal.

The best rules have been cast into flow chart in Figure 1. We expect that the practitioner will be able to follow the branches without much effort. The chart includes clinical symptoms and signs. If the medical history reveals that birth weight and/or length was low, and HSDS is <-2.0 at age 3, the diagnosis of persistent short stature after SGA can be made. It is known that approximately 10% of children born SGA do indeed remain short, and do not achieve normal adult height [24]. Referral to a growth clinic is needed for further diagnostic tests and for the decision on growth hormone treatment. As catch-up can emerge within the first 2 years but sometimes between the age of two and three, we set the age limit for catch-up to occur at three years. An important, but fortunately rare issue is to check for symptoms of emotional deprivation (psychosocial short stature).[25-27] Obviously, a thorough physical examination should be carried out, and special attention should be given to body proportions and dysmorphic features. Abnormal body proportions are important signs of skeletal dysplasia and dysmorphic features can direct the attention to various primary growth disorders ("syndromes"). We propose that combining a HSDS<-2.0 with any of these clinical symptoms and signs is sufficient reason for referral.

Concern has been raised about the applicability of target height as the height of the father is often missing. One could either ignore the height of the mother altogether and not correct for parental height, or one may assume that father's height is equal to mother's height with a correction of 13 cm (the mean difference in adult height between

men and women). It is not known which option is better, but we favour the latter one. A similar approach can be taken if one of the parents is known to have a pathological growth disorder.

The UK90 standards use an inter-centile bandwidth of 0.67 SDS, so that the two lower centiles are the 0.4th and 2.3th centiles, equivalent to -2.67 and -2.0 SDS. If the 0.4th centile (-2.67 SDS) would be used instead of -2.5 SDS (0.6th centile), specificity will be slightly higher and sensitivity slightly lower than calculated for a height SDS of -2.5. With respect to the “slowed growth”, crossing an interval of 1 SD is equal to 1.5 times the interval between two reference lines on the UK charts (or 50% of the interval between the P50 and P2.3). For a more accurate estimate, the first SDS and the second SDS can be calculated and then subtracted.

In conclusion, the proposed guideline for growth monitoring shows a high sensitivity at an acceptably low false-positive rate in 3-10 year old children. Distance to target height is the most important criterion. Below the age of 3 years the guideline can only detect a small percentage of pathology at an acceptably low false-positive rate, and is therefore probably only useful for identifying the most extreme pathology. Besides auxological rules, clinical issues taken form the medical history and physical examination can offer important guidance in taking the decision to refer patients for further tests. Finally, no flow chart can replace clinical judgement of the physician. For cases where an unusual growth pattern does not comply with the referral rules, physicians are encouraged to follow their clinical judgement.

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What is already known on this subject:

- Short stature is regarded as a relatively early sign of poor health.
- Early identification of children with abnormal growth needs a good growth monitoring system; well-defined and accurate auxological screening criteria; and a good diagnostic work-up afterwards.

What this study adds:

This is the first large evidence-based investigation on various types of auxological criteria for the assessment of children with short stature, with a new flow diagram as a result.

Reference List

(1) Garner P, Panpanich R, Logan S. Is routine growth monitoring effective? A systematic review of trials. *Arch Dis Child.* 2000; 82(3):197-201.

(2) Grote F.K., Oostdijk W, de Muinck Keizer-Schrama SMPF, Dekker FW, Verkerk PH, Wit JM. Growth monitoring and diagnostic work-up of short stature: an international inventorisation. *J Pediatr Endocrinol Metab.* 2005; 18(11):1031-1038.

(3) Muinck Keizer-Schrama SM. [Consensus 'diagnosis of short stature in children.' National Organization for Quality Assurance in Hospitals]. *Ned Tijdschr Geneeskd.* 1998; 142(46):2519-2525.

(4) Hall DM. Growth monitoring. *Arch Dis Child.* 2000; 82(1):10-15.

(5) Ahmed ML, Allen AD, Sharma A, Macfarlane JA, Dunger DB. Evaluation of a district growth screening programme: the Oxford Growth Study. *Arch Dis Child.* 1993; 69(3):361-365.

(6) Frindik JP, Kemp SF, Kearns FS, Hale B. Growth screening. A positive medical experience. *Clin Pediatr (Phila).* 1992; 31(8):497-500.

(7) Voss LD, Mulligan J, Betts PR, Wilkin TJ. Poor growth in school entrants as an index of organic disease: the Wessex growth study. *BMJ.* 1992; 305(6866):1400-1402.

(8) Van Buuren, S, Bonnemaijer-Kerckhoffs DJ, Grote FK, Wit JM, Verkerk PH. Many referrals under Dutch short stature guidelines. *Arch Dis Child.* 2004; 89(4):351-352.

(9) van Buuren S, van Dommelen P, Zandwijken GR, Grote FK, Wit JM, Verkerk PH. Towards evidence based referral criteria for growth monitoring. *Arch Dis Child.* 2004; 89(4):336-341.

(10) Grote F.K., Oostdijk W, Muinck Keizer-Schrama SM, Dekker FW, van Dommelen P, van Buuren S et al. Referral patterns of children with poor growth in primary health care. *BMC Public Health.* 2007; 7:77.

(11) Damen GM, Boersma B, Wit JM, Heymans HS. Catch-up growth in 60 children with celiac disease. *J Pediatr Gastroenterol Nutr.* 1994; 19(4):394-400.

(12) Boersma B, Houwen RH, Blum WF, van Doorn J, Wit JM. Catch-up growth and endocrine changes in childhood celiac disease. Endocrine changes during catch-up growth. *Horm Res.* 2002; 58 Suppl 1:57-65.

(13) Herngreen WP, Reerink JD, van Noord-Zaadstra B.M., Verloove-Vanhorick SP, Ruys JH. The SMOCC-study: Design of a representative cohort of live-born infants in the Netherlands. *Eur J Public Health.* 1992; 2:117-122.

(14) Van den BJ, Hokken-Koelega A, Wit J. Validity of height velocity as a diagnostic criterion for idiopathic growth hormone deficiency and Turner syndrome. *Horm Res.* 1999; 51(2):68-73.

(15) Use and interpretation of anthropometric indicators of nutritional status. WHO Working Group. *Bull World Health Organ.* 1986; 64(6):929-941.

(16) Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E et al. Continuing positive secular growth change in The Netherlands 1955-1997. *Pediatr Res.* 2000; 47(3):316-323.

(17) Fredriks AM, van Buuren S, Wit JM, Verloove-Vanhorick SP. Body index measurements in 1996-7 compared with 1980. *Arch Dis Child.* 2000; 82(2):107-112.

(18) Fredriks AM, van Buuren S, Jeurissen SE, Dekker FW, Verloove-Vanhorick SP, Wit JM. Height, weight, body mass index and pubertal development reference values for children of Turkish origin in the Netherlands. *Eur J Pediatr.* 2003; 162(11):788-793.

(19) Fredriks AM, van Buuren S, Jeurissen SE, Dekker FW, Verloove-Vanhorick SP, Wit JM. Height, weight, body mass index and pubertal development references for children of Moroccan origin in The Netherlands. *Acta Paediatr.* 2004; 93(6):817-824.

(20) van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. *Stat Med.* 1999; 18(6):681-694.

(21) Van Buuren S, Brand JPL, Groothuis-Oudshoorn CGM, Rubin DB. Fully conditional specification in multivariate imputation. *Journal of Statistical Computation and Simulation.* 2006; 76(12):1049-1064.

(22) Karlberg J, Kjellmer I, Kristiansson B. Linear growth in children with cystic fibrosis. I. Birth to 8 years of age. *Acta Paediatr Scand.* 1991; 80(5):508-514.

(23) Gibson AT, Carney S, Cavazzoni E, Wales JK. Neonatal and post-natal growth. *Horm Res.* 2000; 53 Suppl 1:42-49.

(24) Hokken-Koelega AC, De Ridder MA, Lemmen RJ, Den Hartog H, de Muinck Keizer-Schrama SM, Drop SL. Children born small for gestational age: do they catch up? *Pediatr Res.* 1995; 38(2):267-271.

(25) Doeker B, Simic S, Hauffa BP, Andler W. [Psychosocially stunted growth masked as growth hormone deficiency]. *Klin Padiatr.* 1999; 211(5):394-398.

(26) Gohlke BC, Khadilkar VV, Skuse D, Stanhope R. Recognition of children with psychosocial short stature: a spectrum of presentation. *J Pediatr Endocrinol Metab.* 1998; 11(4):509-517.

(27) Gohlke BC, Frazer FL, Stanhope R. Growth hormone secretion and long-term growth data in children with psychosocial short stature treated by different changes in environment. *J Pediatr Endocrinol Metab.* 2004; 17(4):637-643.

Table 1. Number of children (N) and mean number of measurements (n) per child in each group

		Limburg *N=970*	*ZHN* *N=400*	*SMOCC* *N= 2151*	*Turner's syndrome* *N= 777**	*Short stature due to pathology* *N= 27*	*Cystic Fibrosis* *N=216*	*Celiac disease* *N=120*
Age group	Number of measurements	N (n)	N (n)	N (n)	N (n)	N (n)	N (n)	N (n)
0-3	≥1 AND at least 1 weight measurement before 0.1 years	931 (11)	341 (11)	1942 (8)	353 (4)	23 (6)	89 (5)	86 (7)
	≥2 with 0.5-1 year interval AND at least 1 weight measurement before 0.1 years	810 (12)	321 (14)	1835 (9)	158 (8)	15 (9)	32 (10)	66 (12)
3-10	≥1	958 (3)	361 (4)	0	524 (5)	17 (3)	25 (2)	22 (4)
	≥2	893 (4)	339 (4)	0	472 (6)	13 (3)	14 (3)	16 (5)

* 492 children had measurements under the age of 3 years.

Table 2. Referral criteria with the best test characteristics

A.

0-3 years	*Criteria*	*Rule nr.*
Repeatedly very short: at least twice a length SDS < -2.5	HSDS_1 < -2.5 and HSDS_2 < -2.5 AND 0.5≤Age_2-Age_1<1 year AND [birth weight >=2500 grams or if no birth weight available than first measurement within 0.1 year (5 weeks) with weight SDS≥ -2, and gestational age ≥37 weeks (or not available)]	1.
Extremely short: at least once a length SDS < -3	HSDS < -3 AND [birth weight ≥2500 grams or if no birth weight available than first measurement within 0.1 year (5 weeks) with weight SDS ≥ -2, and gestational age ≥37 weeks (or not available)]	2.
Combination of rule 1+2		3.

B.

3-10 years	*Criteria*	*Rule nr.*
Short for target height	HSDS-THSDS < -2 AND HSDS < -2	1.
Very short: length SDS < -2.5	HSDS < -2.5	2.
Slowed growth	Delta HSDS < -1 AND HSDS < -2	3.
Combination of rule 1+2+3		4.

Table 3. Sensitivity (%) of several auxological rules for four different patient-groups (true-positives)

		Turner's syndrome	*Short stature due to pathology*	*Cystic Fibrosis*	*Celiac disease*
0-3 years	Repeatedly very short*	7.1%	14.8%	0.0%	1.2%
	Extremely short	13.0%	26.1%	6.7%	4.7%
	Combination	14.7%	26.1%	6.7%	4.7%
3-10 years	Short for target height	76.9%	58.8%	8.0%	27.3%
	Very short	74.0%	58.8%	4.0%	18.2%
	Slowed growth**	13.4%	17.6%	0.0%	18.2%
	Combination	85.7%	76.5%	8.0%	27.3%

Note: if a child has only 1 measurement, the child cannot be referred according to the repeatedly very short rule and the rule for slowed growth.

* In the subgroup with ≥2 measurements sensitivity would be 15.8% for Turner's syndrome, 26.7% for mixed pathology, and 1.5% for celiac disease

** In the subgroup with ≥2 measurements sensitivity would be 14.8% for Turner's syndrome, 23.1% for mixed pathology, and 25.0% for celiac disease.

Table 4. Estimated percentages of referrals in three reference populations (%false-positive). The specificity is equal to 100-%false positive.

		Limburg	*ZHN*	*SMOCC*
0-3 years	Repeatedly very short*	0.2%	0.0%	0.4%
	Extremely short	0.2%	0.6%	0.7%
	Combination	0.3%^	0.6%	0.9%^
3-10 years	Short for target height	0.7%	1.1%	NA
	Very short	0.9%	0.8%	NA
	Slowed growth**	0.1%	0.8%	NA
	Combination	1.5%#	1.9%#	NA

NA=not available

Note: if a child has only 1 measurement, the child cannot be referred according to the repeatedly very short rule and the rule for slowed growth.

* Based on subgroup with ≥2 measurements specificity is 100-0.2=99.8% Limburg and 99.6% SMOCC

** Based on subgroup with ≥2 measurements specificity is 100-0.1=99.9% Limburg and 99.1% ZHN

^ No significant difference between Limburg and SMOCC for the combined rule 0-3 years (χ^2 (1)=2.79, p=0.10)

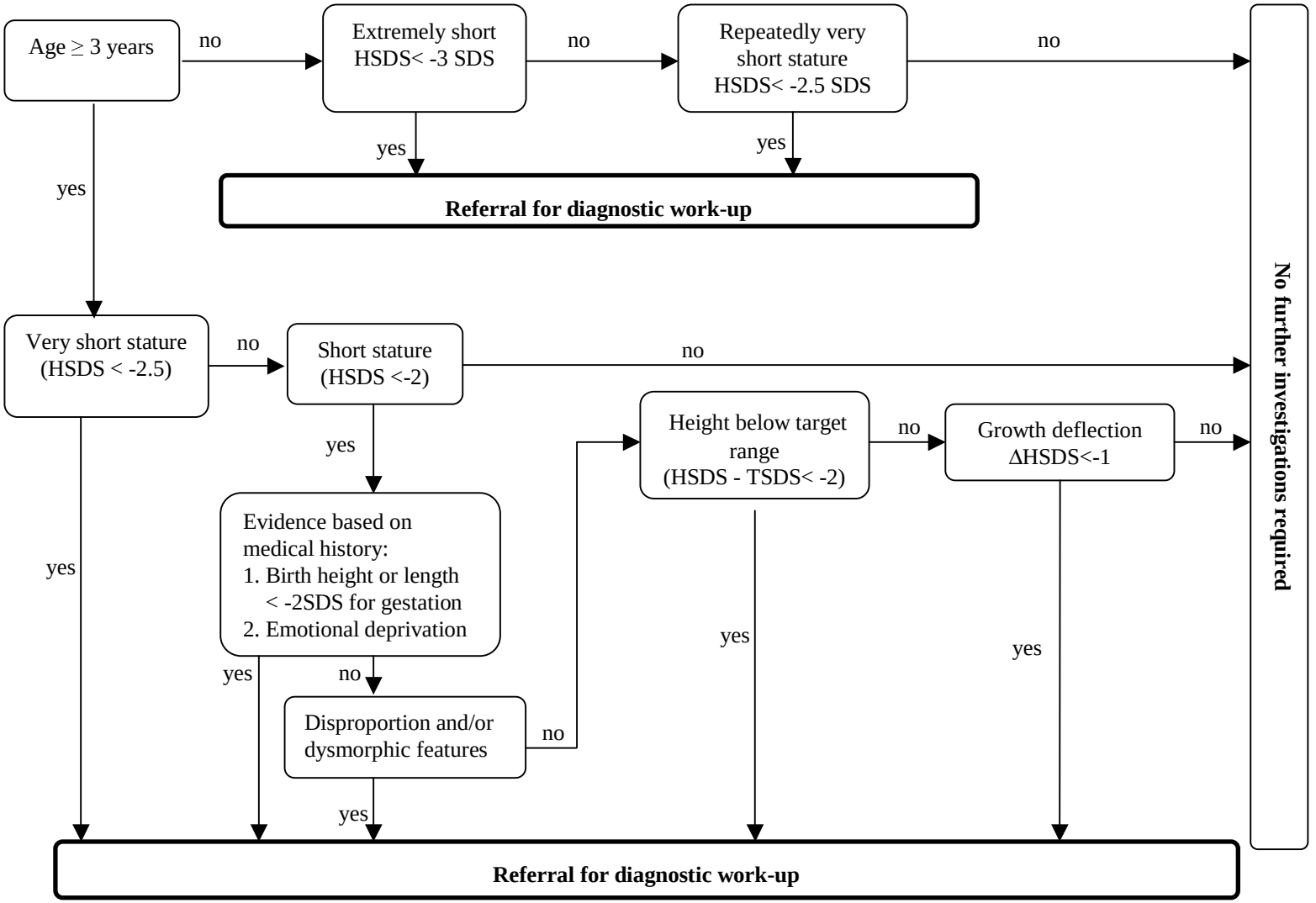
No significant difference between Limburg and ZHN for the combined rule 3-10 years significant (χ^2 (1)=0.38, p=0.54)

Figure captions.

Fig 1. Flow diagram of proposed criteria for referral of children with growth disorders.

HSDS= Height Standard Deviation Score

THSDS= Target Height Standard Deviation Score



This guideline is proposed for screening purposes only. In case of an unusual growth pattern, certainly if associated with clinical symptoms or signs, even if it would not comply with the rules for referral or the recommendations, physicians should still be free to follow their clinical judgment.