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Early Detection of Abnormal Growth Associated with Juvenile Acquired Hypothyroidism

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Abbreviations: AUC – area under the curve; BMI – body mass index; BMISDS – body mass index-for-age standard deviation score; fT4 – free thyroxine; HSDS – height-for-age standard deviation score; ΔHSDS – change in height-for-age standard deviation score over time; JHT – juvenile acquired hypothyroidism; ROC – receiver operating characteristic; $TH^{DEV}SDS$ – height-for-age deviation from target height standard deviation score; THL – National Institutes of Health and Welfare; TSH – thyroid stimulating hormone

Abstract

Context: Development of the typical growth phenotype of juvenile acquired hypothyroidism (JHT), the faltering linear growth with increasing weight, has not been thoroughly characterized.
Objective: To describe longitudinal growth pattern in children developing JHT and investigate how their growth differs from the general population in systematic growth monitoring.
Desing: Retrospective case-control study.
Setting: JHT cases from three Finnish University Hospitals and healthy matched controls from primary health care.
Patients: 109 JHT patients aged 1.2–15.6 years (born 1983–2010) with 554 height and weight measurements obtained for 5 years preceding JHT diagnosis. Each patient was paired with 100 healthy controls (born 1983–2008) by sex and age. Longitudinal growth pattern was evaluated in mixed linear models. Growth monitoring parameters were evaluated using receiver operating characteristics analysis.
Results: At diagnosis, JHT patients were heavier (mean adjusted body mass index-for-age [BMISDS] difference, 0.65 [95% CI: 0.46–0.84]) and shorter (mean adjusted height-for-age deviation from the target height [TH^{DEV}SDS] difference, -0.34 [95% CI: -0.57– -0.10]) than healthy controls. However, five years before diagnosis, patients were heavier (mean BMISDS difference, 0.33 [95% CI: 0.12–0.54]) and taller (mean TH^{DEV}SDS difference, 0.29 [95% CI: 0.06–0.52]) than controls. JHT could be detected with good accuracy when several growth parameters were used simultaneously in screening (area under the curve, 0.83 [95% CI: 0.78–0.89]).
Conclusions: Abnormal growth pattern of patients with JHT evolves years before diagnosis. Systematic growth monitoring would detect abnormal growth at an early phase of JHT and facilitate timely diagnosis of JHT.

Key words: child, growth monitoring, hypothyroidism, screening, sensitivity and specificity

Précis

In a retrospective growth assessment of children with juvenile acquired hypothyroidism, the abnormal growth phenotype evolved several years prior to the diagnosis and could have been detected with a good accuracy using systematic growth monitoring.

Introduction

Thyroid hormones are crucial for normal childhood growth and development. They regulate linear growth directly at the growth plate and also enhance growth hormone secretion from the pituitary gland and potentiate its effects on target tissues. In juvenile acquired hypothyroidism (JHT), slow linear growth and excessive weight gain are the pathognomonic auxological signs of the disease. This typical growth pattern with or even without clinical symptoms such as fatigue, cold intolerance, or obstipation warrants thyroid function assessment (1, 2). Despite a general understanding of the roles of thyroid hormones in growth regulation, very little is known about the development of JHT-associated growth failure over time (3). To our knowledge, there is only one small study (13 participants), by Rivkees et al., describing longitudinal growth in JHT patients several years before diagnosis (3).

Childhood growth monitoring aims for early detection of disorders that affect growth, ideally at an early stage before any other signs or symptoms of disease appear. Auxological screening is based on growth reference cut-off values (4-8). Recently, we and others have shown that auxological screening is a highly accurate tool for the early diagnosis of Turner syndrome (4-7), and it may facilitate the earlier detection of celiac disease (6, 8). However, the use of growth screening for the detection of JHT has not been previously assessed.

We hypothesized that in JHT, the typical growth pattern evolves early, potentially years before clinical symptoms of the disease. Therefore, systematic growth monitoring using robust population-specific cut-off values for abnormal growth can aid the diagnosis of JHT. In this study, we characterized longitudinal growth patterns up to 5 years prior to JHT diagnosis and tested the performance of auxological screening for the condition.

Patients and Methods

Permissions for the study were obtained from the Espoo Municipality Institutional Review Board, three Finnish University Hospitals (Helsinki, Kuopio, and Tampere) and the National Institute of Health and Welfare (THL). The study was approved by the Ethics Committee of the Pohjois-Savo Health Care District. No contact was made with study participants; all data were analyzed anonymously.

Participants with Juvenile Autoimmune Hypothyroidism

All patients aged 0 to 20 years with diagnoses of JHT (International Classification for Diseases version 10, codes E03.3 – E03.9) were identified in patient registries of three University Hospitals in Finland (Helsinki, Kuopio, and Tampere). For these patients, clinical and laboratory data were collected retrospectively from patient files. The age at diagnosis, symptoms at JHT onset, and laboratory results (thyroid stimulating hormone [TSH], free thyroxine [fT4], and thyroid peroxidase autoantibodies [TPOAb]) were recorded.

In Finland, all children and adolescents are provided at least 24 routine visits to child welfare clinics and school health-care programs, and measurements are captured in an electronic patient management system. The service has nearly a full coverage of the Finnish population (9). All weight and height data from these regular primary care visits as well as from possible hospital visits and data on parental heights of the JHT patients were collected.

The JHT diagnosis was set at each university hospital outpatient clinic by a pediatrician. It was based on elevated serum TSH concentration (> 10 mIU/L) measured at least twice prior to diagnosis in combination with either clinical symptoms of JHT or reported TPO autoantibodies. In children and adolescents, the TSH cut-off value of 10 mIU/L is generally regarded as the criterion for JHT that warrants levothyroxine treatment regardless of fT4 or TPOAb levels (10). To further verify the constancy of the diagnoses in these children, we confirmed from the Finnish Hospital Discharge Register the continuing regular outpatient visits with JHT with permanent need of medication.

The initial JHT cohort comprised 184 children and adolescents (68% girls) that were born between 1983 and 2010 with 992 height and weight measurements (**Figure 1**). None had congenital hypothyroidism. Patients with any other disease, condition or medication possibly affecting growth were excluded (N = 70). Reasons for exclusion were congenital syndromes (N = 32), type 1 diabetes (N = 12), asthma (N = 11), preterm birth or missing birth data (N = 10), growth hormone deficiency (N = 3), and celiac disease (N = 2). Additionally, patients with subclinical JHT (TSH ≤ 10 mU/L) were excluded (N = 5). The final JHT cohort consisted of 109 patients aged 1.2 to 16.2 years at diagnosis (median age, 10.6 years; 75% girls) **(Figure 1, Table 1)**. All patients were treated with levothyroxine.

Longitudinal growth data were divided into seven annual time slots based on the point of diagnosis (-5, -4, -3, -2, or -1 years [preceding diagnosis], at diagnosis, and +1 year [following diagnosis]). Only one height and weight measurement per child was included per annual time slot, closest to the exact full year, for analyses. Overall, 554 height and weight measurements were included for the 109 patients during the 5 years preceding and 1 year following JHT diagnosis (**Table 1**, **Figure 1**).

Reference Population and Selection of Controls Matched for Age and Sex

The population-based growth data for 32,592 healthy Finnish children and adolescents (16,039 girls) aged 0 to 20 years that were born between 1983 and 2008 with 167,982 measurements comprised the reference population. These healthy controls were measured during routine visits at child welfare clinics or school health programs. Data collection of the reference population is described in detail elsewhere (5).

Because a greater proportion of JHT patients, compared to the reference population, was female (75% vs. 50%), a case-control design was chosen for analyses, matching each of the 109 JHT patients with 100 controls by age and sex. This resulted in a reference population of 10,900 healthy controls (75% girls) with 74,925 measurements (**Table 1**). Potentially false measurements, typing errors, missing values, and duplicated recordings were evaluated using scatter plots and then were either corrected or excluded. They were then divided into 7 annual time slots, and superfluous measurements within each time slot were excluded, amounting to 16,483 exclusions.

Growth Monitoring Parameters and Statistical Analysis

Longitudinal height and weight measurements were transformed into several standard deviation scores (SDS): height-for-age SDS (HSDS), HSDS deviation from target height SDS (TH^{DEV}SDS), body mass index (BMI; calculated as weight in kilograms divided by the squared height in meters)-for-age SDS (BMISDS), and changes in HSDS and BMISDS over time (ΔHSDS and ΔBMISDS, respectively) using contemporary Finnish growth references (4-6). The independent samples *t* test was used for comparing normally distributed continuous parameters, and the Mann-Whitney test was used as a non-parametric test. Categorical variables were compared using the X^2 test. A mixed linear model for

repeated measures was used to compare differences in the growth parameters between JHT patients and healthy controls.

Several perinatal and neonatal factors obtained from the Finnish birth register for the cases and controls were considered as potential covariates (11): maternal parity, maternal smoking during pregnancy, mode of delivery, birth weight, birth length, plurality, maternal age, gestational age at birth, and season at birth (**Table 1**). Birth length and weight were converted into SDS using the Finnish population-based birth size reference (12). The first six of the potentially confounding factors were accounted for because they showed statistically significant differences ($P < .05$) between cases and controls in the mixed linear model.

The accuracy of the five growth monitoring parameters (HSDS, TH^{DEV}SDS, BMISDS, ΔHSDS, and ΔBMISDS) and their combinations in auxological screening for JHT were tested using receiver operating characteristic (ROC) curve analysis. The ROC analyses were based on individual probabilities for abnormal growth, calculated for each child in the JHT cohort and the control population using logistic regression. The results of ROC analyses were classified based on area under the curve (AUC) values, classified as *fail* (AUC, 0.50 to 0.59), *poor* (AUC, 0.60 to 0.69), *moderate* (AUC, 0.70 to 0.79), *good* (AUC, 0.80 to 0.89), or *excellent* (AUC, 0.90 to 1.00).
When *P* was less than .05, statistical significance was recognized. Data were analyzed using SPSS software (version 21; IBM Corporation, Armonk, NY).

Results

Characteristics of the Juvenile Hypothyroidism Cohort

The median age at JHT diagnosis was 10.6 years (range, 1.2 to 15.6 years). In all, 93 (85.3%) JHT patients were measured at diagnosis, 73 (67.0%) 5 years prior to diagnosis, and 83 (76.1%) during the year following diagnosis. At diagnosis, all patients had TSH repeatedly exceeding 10 mIU/L (the diagnostic criteria for JHT). The median was 36.7 mIU/L (range, 10.2 to 1339.0 mIU/L; laboratory reference value, 0.3 to 4.2 mIU/L). In addition, 79 patients (72.5%) had fT4 below the normal range (median, 8.40 pmol/L [range, 0.01 to 18.00 pmol/L]; laboratory reference value, 11 to 22 pmol/L) and 75 patients (68.8%) had positive TPO autoantibodies (median, 460 IU/mL [range, 0 to 10,625 IU/mL]; laboratory reference for abnormal value, > 6 IU/mL) (**Table 1**).

At diagnosis, JHT patients were significantly shorter and heavier than healthy controls prior to adjustment for perinatal confounders (**Table 1**). The most pronounced difference was seen in linear height growth during the one-year period preceding JHT diagnosis (mean unadjusted ΔHSDS difference from healthy controls, -1.06 [95% CI, -1.34 to -0.79]). The growth difference remained significant after adjustments for perinatal confounders. The adjusted TH^{DEV}SDS difference between the groups was -0.35 [95% CI, -0.58 to -0.11]), and the BMISDS difference was 0.65 [95% CI, 0.45 to 0.85)] at diagnosis. In addition, significantly slower linear growth was observed in the JHT patients than in controls 2 years before diagnosis (mean adjusted ΔHSDS difference, -0.53 [95%CI, -0.80 to -0.26]) (**Figure 2**).

In contrast to the shorter stature at diagnosis, children and adolescents with JHT were taller and heavier than healthy controls 5 to 3 years before diagnosis. Mean adjusted differences of TH^{DEV}SDS and BMISDS between JHT patients and controls were 0.32 (95% CI, 0.07 to 0.58) and 0.44 (95% CI, 0.20 to 0.68), respectively, 5 years before diagnosis. After 1 year of levothyroxine therapy, there was

a complete catch-up in linear growth, reaching on average the target height of the population (**Figure 2**). Within the JHT cohort, growth patterns were not statistically significantly different between TPOAb-positive and -negative or between fT4-abnormal and -normal patients (data not shown).

Auxological Screening for Juvenile Hypothyroidism

Screening for abnormal growth in children and adolescents with JHT using any of the growth parameters (HSDS, TH^{DEV}SDS, BMISDS, ΔHSDS, or ΔBMISDS) alone yielded poor to moderate accuracy (**Figure 3**). The accuracies, as evaluated by AUCs, varied from 0.56 (95% CI, 0.49 to 0.62) for HSDS to 0.70 (95% CI, 0.64 to 0.77) for ΔHSDS. However, when all five screening parameters were used in combination, growth failure at diagnosis was detected in JHT patients with good accuracy (AUC, 0.83 [95% CI, 0.78-0.89]) (**Figure 3**).

Performance of auxological screening for JHT is shown in **Table 2**. Simulation of a growth monitoring program was carried out, testing three pre-defined cut-off values for the growth parameters. When the cut-off level was -1.7 SDS for the height parameters (ie, height parameter below –1.7 SD is abnormal) and +1.7 SD for weight parameters at diagnosis, the combination of all five parameters resulted in 58% detection of JHT (sensitivity, 58% [95% CI, 43% to 72%]; specificity, 87% [95% CI, 86% to 87%]). Comparatively, when the cut-off level was +/- 2.7 SD, the sensitivity was 25% (95% CI, 13% to 39%) and specificity, 98% (95% CI, 97% to 98%). The best detection rate (sensitivity) identifying abnormal growth in JHT patients using a single parameter was only 25% (95% CI, 15% to 37%) using a cut-off value of -1.7 SD for change in HSDS (ΔHSDS).

Discussion

In this study, we describe, for the first time, the longitudinal growth pattern in a large cohort of JHT children and adolescents starting at 5 years prior to diagnosis and ending one year after diagnosis. We observed that initially, these patients are heavier and taller than their healthy peers from child welfare clinics and school health-care programs. The pathognomonic growth failure observed at JHT diagnosis (ie, height deviation together with excessive weight gain) evolves over time and could reflect the gradual development of thyroid hormone deficiency. A significant number of children and adolescents diagnosed with JHT could have been detected using longitudinal growth monitoring and auxological screening with pre-established cut-off values, methods that are simple and non-invasive.

The growth patterns among JHT patients are insufficiently explored. The study by Rivkees et al., describing longitudinal growth in JHT patients several years before diagnosis (3) finding that those with JHT were shorter than expected, similar to our results. However, growth in weight was not reported. They further demonstrated incomplete catch-up growth after levothyroxine therapy (3), and this contrasts with our results. The difference might be because of their relatively small study cohort, possible differences in weight gain, certain methodological limitations or timing of diagnosis. A more recent study by Ranke et al. showed a completed catch-up growth after levothyroxine therapy in 20 children with JHT who were short at time of diagnosis (13). However, they did not report longitudinal growth pattern of JHT prior to the diagnosis. Nevertheless, we were not able to combine catch-up growth with data on pubertal status and bone-age, that might have been influenced by JHT and levothyroxine therapy. Thus, impact of JHT on adult height remains to be studied.

We found that children and adolescents with JHT were heavier and taller than healthy controls as many as 5 years before diagnosis and gained additional weight as time of diagnosis neared. Obesity can contribute to the pathogenesis of several autoimmune disorders (14). Thyroid function could have a bidirectional association with childhood weight gain (15, 16): obesity can lead to subclinical elevation of TSH (17), but also vice versa, a higher prevalence of thyroid autoimmunity has been observed in overweight children (18). Furthermore, excess weight gain during childhood has been associated with autoimmune hypothyroidism in late adulthood (15). Thus, excess weight gain years before disease onset, as observed in our cohort, might be an early sign for thyroid autoimmunity. However, the greater stature observed, together with elevated weight, years before JHT diagnosis might reflect, partially, the excess energy balance, given that weight gain in children is typically associated with rapid linear growth (19).

Population-based growth monitoring programs aim for early detection of disorders that affect growth at an early stage. To our knowledge, this is the first study evaluating systematic growth monitoring to detect JHT. We found that the best screening accuracy was accomplished if linear growth change (ΔHSDS) is monitored rather than using one-off measurements and by combining several growth parameters. However, the screening accuracy for JHT was not as good as has been achieved for detecting Turner syndrome (4, 7, 8, 20), but is close to that found for detecting celiac disease (6).

When growth monitoring, cut-offs should ideally detect as many abnormally growing children and adolescents as possible (ie, high sensitivity) without producing numerous referrals or investigations of healthy people (ie, high specificity). The diagnostic accuracy of any screening program always provides a trade-off between sensitivity and specificity. In JHT, the relatively low specificity can be deemed acceptable because cases are investigated further using inexpensive and widely available thyroid function tests. For example, in this study, almost 60% of JHT patients could have been detected (sensitivity) using growth status at diagnosis if abnormalities were defined for the height parameters (HSDS, TH^{DEV}SDS, and ΔHSDS) as less than -1.7 SD and for the weight parameters (BMISDS and ΔBMISDS) as greater than +1.7 SD. With these parameters, 13% of the healthy controls would have been flagged for JHT (specificity 87%). These false-positive and false-negative rates seem acceptable.

A recent review revealed a large gap between the aims of the widespread implementation of growth monitoring and the achieved levels of early detection of growth disorders in children (21). Indeed, the pre-established screening cut-off values have not been implemented in most developed countries (21-25). In growth monitoring and screening, the primary challenges are suboptimal methods (8, 21), resulting in both inappropriate referrals and delayed diagnoses. The cost-benefit ratio of the auxological screening is also insufficiently explored (26, 27). The most intensive growth monitoring programs that include systematic screening for abnormal growth are established in Finland and the Netherlands (23, 25). We and others have recently shown that systematic growth monitoring facilitates the early diagnosis of Turner syndrome (4, 7, 8, 20). Furthermore, in this study, we demonstrated that a significant proportion of JHT patients had grown abnormally before diagnosis. The threshold for conducting thyroid function laboratory tests is very low in the Finnish primary care, and we assume that most cases of JHT are diagnosed considerably early in this population. Thus, growth screening accuracy could be even better in countries with less intensive growth monitoring program and higher thresholds for laboratory exams, and therefore, simplified screening algorithms for height-for-age percentile change and weight status could be developed. For

example, weight gain exceeding cut-off value for overweight simultaneously with the height-for-age falling across ten percentiles over time resulted in 19% sensitivity and 99% specificity for JHT.

The major strength of this study is the carefully examined relatively large cohort of JHT children and adolescents with verified diagnoses from the nationwide registers, and the large number of matched healthy controls. We were able to evaluate the longitudinal growth data starting 5 years prior to JHT diagnosis. Furthermore, data from the national birth register were available so that potential confounding factors for linear growth could be evaluated.

A limitation of this study is its retrospective nature. Thus, a prospective growth monitoring program in a population might provide different results. Furthermore, the observations of excessive weight gain in JHT patients as many as 5 years before diagnosis could be biased because thyroid hormone levels are more likely to be investigated in obese children and adolescents. A prospective population-based study is warranted to evaluate the benefits and costs of a growth monitoring program and to confirm the observations of longitudinal growth in JHT patients.

Conclusions

JHT patients showed distinct longitudinal growth patterns in height and weight as many as 5 years before diagnosis, and this could be an early sign of thyroid autoimmunity; however, its significance should be re-evaluated in further studies in prospective settings. In addition, our findings suggest that children and adolescents with JHT could be distinguished with good screening accuracy using systematic growth monitoring. Thus, an early diagnosis of JHT might be facilitated by systematic growth monitoring combined with thyroid function tests. Early detection of JHT is important not only for neurocognitive development but also for preventing a permanent height deficit resulting from thyroid hormone deficiency (3). A challenge of the growth monitoring proposed here in is related to the mathematical complexity of the screening algorithms. However, this can be overcome through the implementation of screening rules into electronic health records systems, as has already been done in Finnish primary care services (28).

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Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Legends of the Figure

Figure 1. Flow chart of the study population.

Figure 2. Mean (95% confidence interval) HSDS) THDEVSDS and BMISDS (panel A), and changes in HSDS and BMISDS over time (ΔHSDS and ΔBMISDS) (panel B) in 109 patients with juvenile acquired hypothyroidism compared to 10,900 healthy controls (indicated as the zero line).

Figure 3. Screening accuracy of 5 growth monitoring parameters (HSDS, THDEVSDS, ΔHSDS, BMISDS, ΔBMISDS]) and their combination for 109 patients with juvenile acquired hypothyroidism. Areas under the curves and their 95% confidence intervals are shown.

Tables

Table 1. Characteristics of patients with juvenile acquired hypothyroidism (*N* = 109) at diagnosis and of the healthy controls (*N* = 10,900) matched for age and sex.

	JHT (*N*=109)	**Controls (*N*=10,900)**	**P-value**
Female sex, count (%)	82 (75%)	8200 (75%)	>.999
Age (years), median (range)	10.6 (1.2–15.6)	10.6 (0.5–16.5)	.83
Number of measure per individual, median (range)	5 (2–7)	6 (1–7)	<.001
Paternal height (cm) , mean (SD)	178.5 (5.9)	180.0 (6.5)	.04
Maternal height (cm), mean (SD)	165.7 (6.0)	166.1 (5.9)	.61
Target height SDS, mean (SD)[a]	-0.13 (0.64)	0.00 (0.66)	.09
Birth characteristics			
Maternal age (years), median (min–max)	30 (19–41)	30 (16–46)	.49
Maternal smoking, count (%)	17 (17.0)	1,245 (12.5)	.10
Parity, first child, count (%)	35 (35.0)	4,878 (48.8)	.03
Gestational age (weeks+days), median (min–max)	40+1 (37+0–43+0)	40+0 (37+0–43+6)	.09
Vaginal delivery, count (%)	83 (83.0)	8,338 (83.4)	.42
Plurality, singleton, count (%)	95 (95.0)	9,813 (98.1)	.55
Birth length SDS, mean (SD)[c]	-0.07 (1.13)	-0.33 (0.99)	.01
Birth weight SDS, mean (SD)[c]	-0.07 (1.30)	-0.16 (1.03)	.42
Growth[b]			
Height-for-age SDS, mean (SD)[c]	-0.32 (1.33)	-0.02 (1.06)	.01
Height-for-age SDS deviation from target height SDS, mean (SD)[a,c]	-0.29 (1.31)	-0.02 (1.08)	.04
Height-for-age SDS change over time, mean (SD)[d]	-1.00 (1.63)	0.07 (1.10)	<.001
BMI-for-age SDS, mean (SD)[c]	0.72 (1.18)	-0.07 (1.06)	<.001
BMI-for-age SDS change over time, mean (SD)[d]	0.33 (1.05)	-0.03 (1.01)	.01
Laboratory values[e]			
TSH (mIU/L), median (range)	36.7 (10.2–1339.0)	NA	NA
fT4 (pmol/L), median (range)	8.40 (0.01–18.00)	NA	NA
TPOAb (IU/mL), median (range)	460 (0–10,625)	NA	NA
Symptoms at the time of diagnosis[f]			
Asymptomatic/not recorded, number (%)	52 (47.7)	NA	NA
At least one symptom below, number (%)	57 (52.3)	NA	NA
Fatigue or dizziness	34 (31.2)	NA	NA
Skin problems	28 (25.7)	NA	NA
Stomach pain	21 (19.3)	NA	NA
Increased sensitivity to cold	9 (8.3)	NA	NA

Headache	7 (6.4)	NA	NA
Pubertal changes	4 (3.7)	NA	NA
Mood changes	3 (2.8)	NA	NA

[a]Finnish target height formula (4)

[b]Growth data not available for 16 JHT patients at the time of diagnosis

[c]Finnish growth references (5,12)

[d]Finnish reference values for height-for-age SDS change (available from birth to 12 years of age) and BMI-for-age SDS change (available from 2–12 years of age) over time (4, 6)

[e]Laboratory reference values: TSH, 0.3–4.2 mIU/L; fT4, 11–22 pmol/L; and TPOAb, <6 IU/mL.

[f]Data not available for 33 children

Abbrevations: BMI, body mass index; fT4, free thyroxine; JHT, juvenile acquired hypothyroidism; NA, not available; SDS, standard deviation score; TPOAb, thyroid peroxidase antibodies; TSH, thyroid stimulating hormone

Table 2. Performance of auxological screening for juvenile acquired hypothyroidism in children and adolescents using pre-defined cut-off levels I, II, and III for abnormal growth: below -1.7 SD (I), -2.0 SD (II), or -2.7 SD (III) for height parameters and above +1.7 SD (I), +2.0 SD (II), or +2.7 SD (III) for weight parameters among 109 patients and 10,900 healthy controls.

	Cut-off level I (±1.7 SD)		Cut-off level II (±2.0 SD)		Cut-off level III (±2.7 SD)	
Growth monitoring parameter	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
HSDS[a]	16.1 (9.3–25.2)	94.2 (93.7–94.7)	8.6 (3.8–16.3)	97.0 (96.6–97.4)	5.4 (1.8–12.1)	99.5 (99.3–99.6)
$TH^{DEV}SDS$[b]	11.8 (5.2–21.9)	94.1 (93.6–94.6)	8.8 (3.3–18.2)	96.7 (96.4–97.1)	4.4 (0.9–12.4)	99.4 (99.2–99.5)
ΔHSDS[c]	25.0 (15.0–37.4)	95.4 (94.8–95.9)	21.9 (12.5–34.0)	97.5 (97.1–97.9)	14.1 (6.6 -25.0)	99.4 (99.2–99.6)
BMISDS[a]	23.9 (15.6–33.9)	94.1 (93.5–94.6)	15.2 (8.6–24.2)	97.3 (97.0–97.7)	4.3 (1.2–10.8)	99.7 (99.6–99.8)
ΔBMISDS[c]	7.9 (2.6–17.6)	95.4 (94.9–95.9)	4.8 (1.0–13.3)	97.4 (97.0–97.8)	1.6 (0.0–8.5)	99.3 (99.1–99.5)
Combined parameters						
BMISDS and ΔHSDS[a,c]	45.2 (32.5–58.3)	89.7 (88.9–90.4)	30.7 (19.6–43.7)	95.1 (94.5–95.6)	16.1 (8.0–27.7)	99.2 (98.7–99.2)
All five parameters[a,b,c]	58.3 (43.2–72.4)	86.6 (85.7–87.4)	54.2 (27.6–56.8)	88.2 (87.4–89.0)	27.1 (15.3–41.9)	97.8 (97.4–98.2)

[a]Finnish growth references (5)
[b]Finnish target height formula (4)
[c]Finnish reference values for height-for-age SDS change (available from birth to 12 years of age) and BMI-for-age SDS change (available from 2–12 years of age) over time (4, 6)
Abbrevations: BMISDS, body mass index-for-age SDS; ΔBMISDS, body mass index-for-age SDS change over time; CI, confidence interval; HSDS, height-for-age SDS; ΔHSDS, height-for-age SDS change over time; $TH^{DEV}SDS$, height-for-age SDS deviation from target height SDS.

Figures

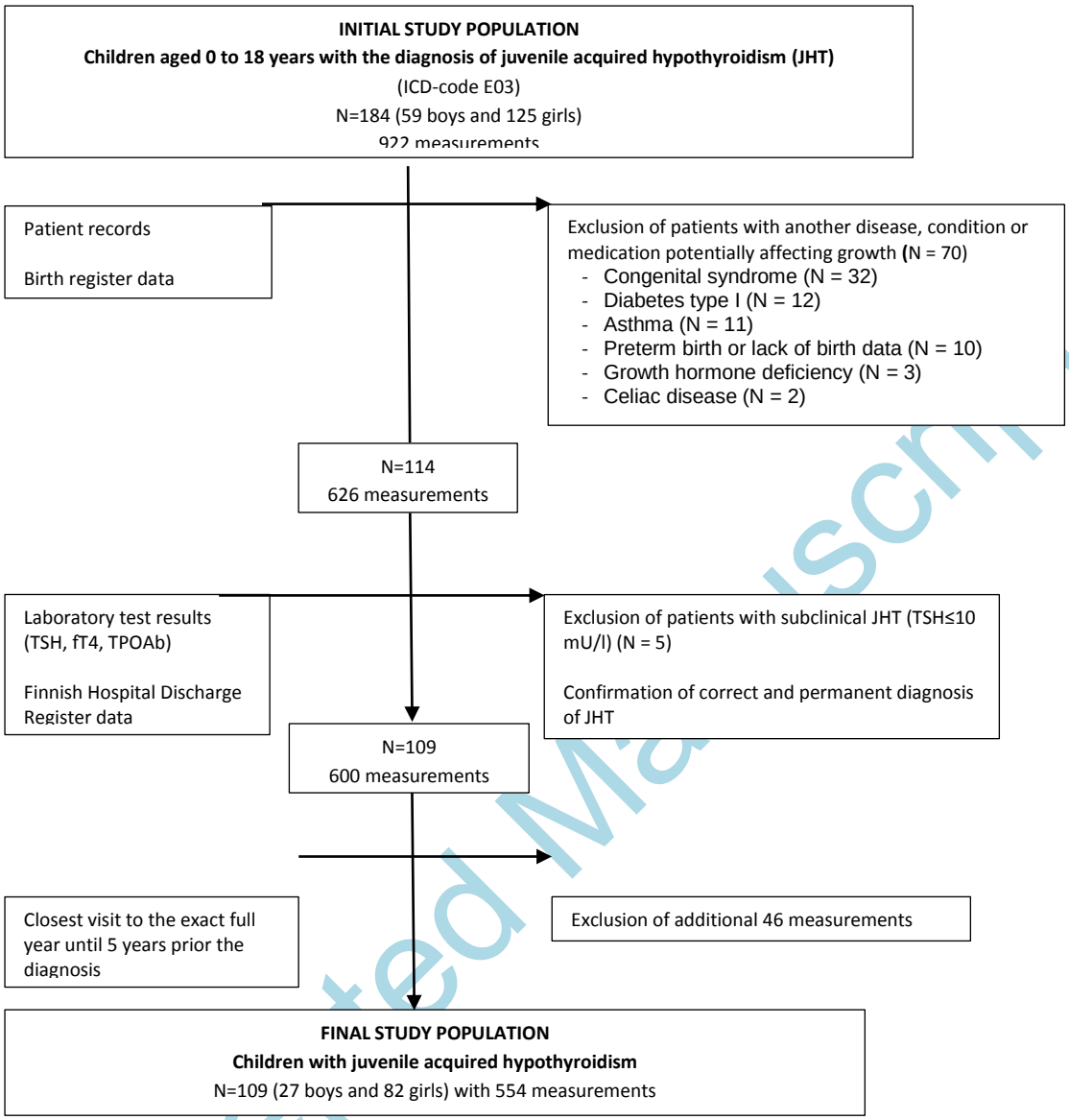

Figure 1. Flow chart of the study population.

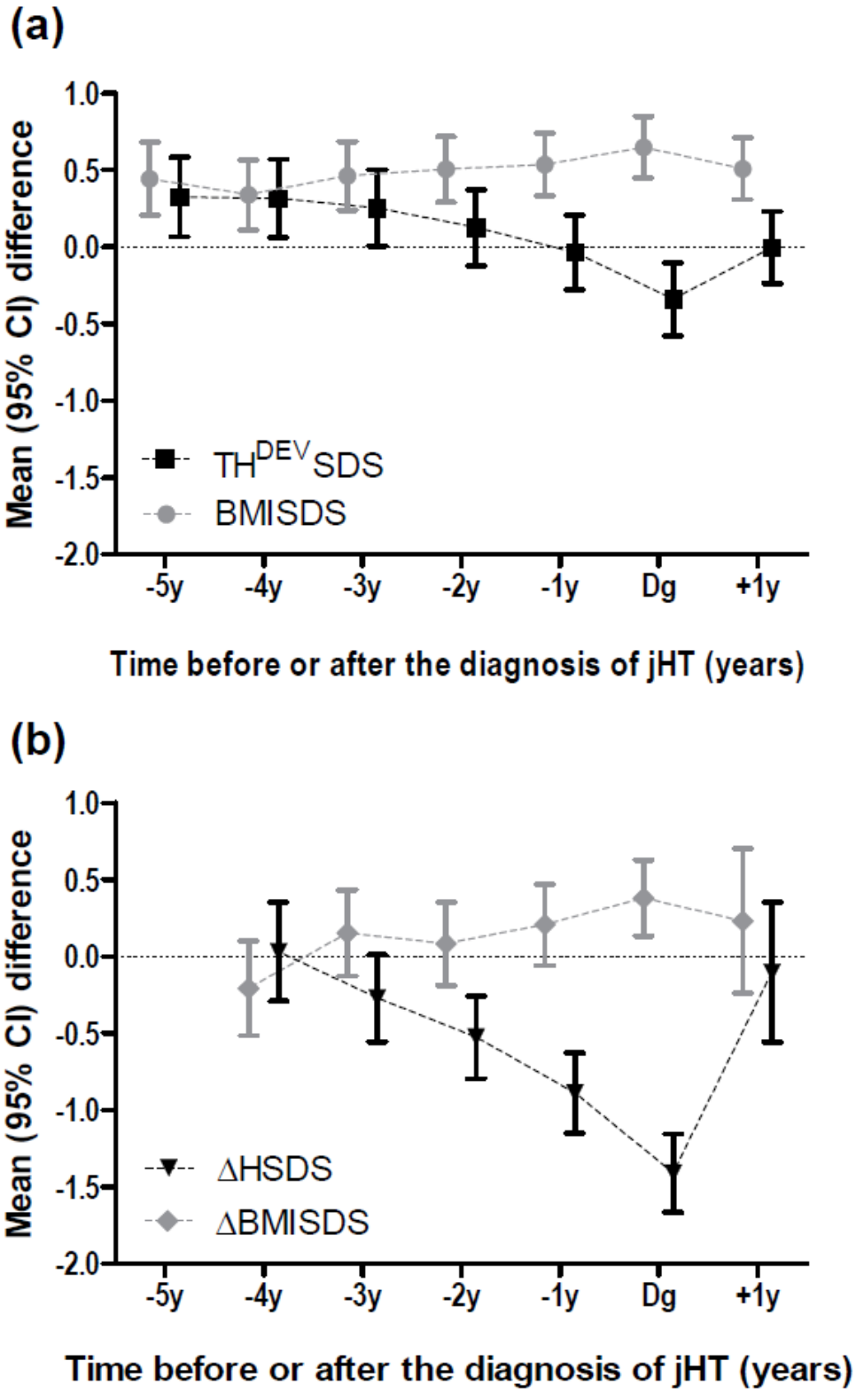

Figure 2. Mean (95% confidence interval) HSDS) TH^{DEV}SDS and BMISDS (panel A), and changes in HSDS and BMISDS over time (ΔHSDS and ΔBMISDS) (panel B) in 109 patients with juvenile acquired hypothyroidism compared to 10,900 healthy controls (indicated as the zero line).

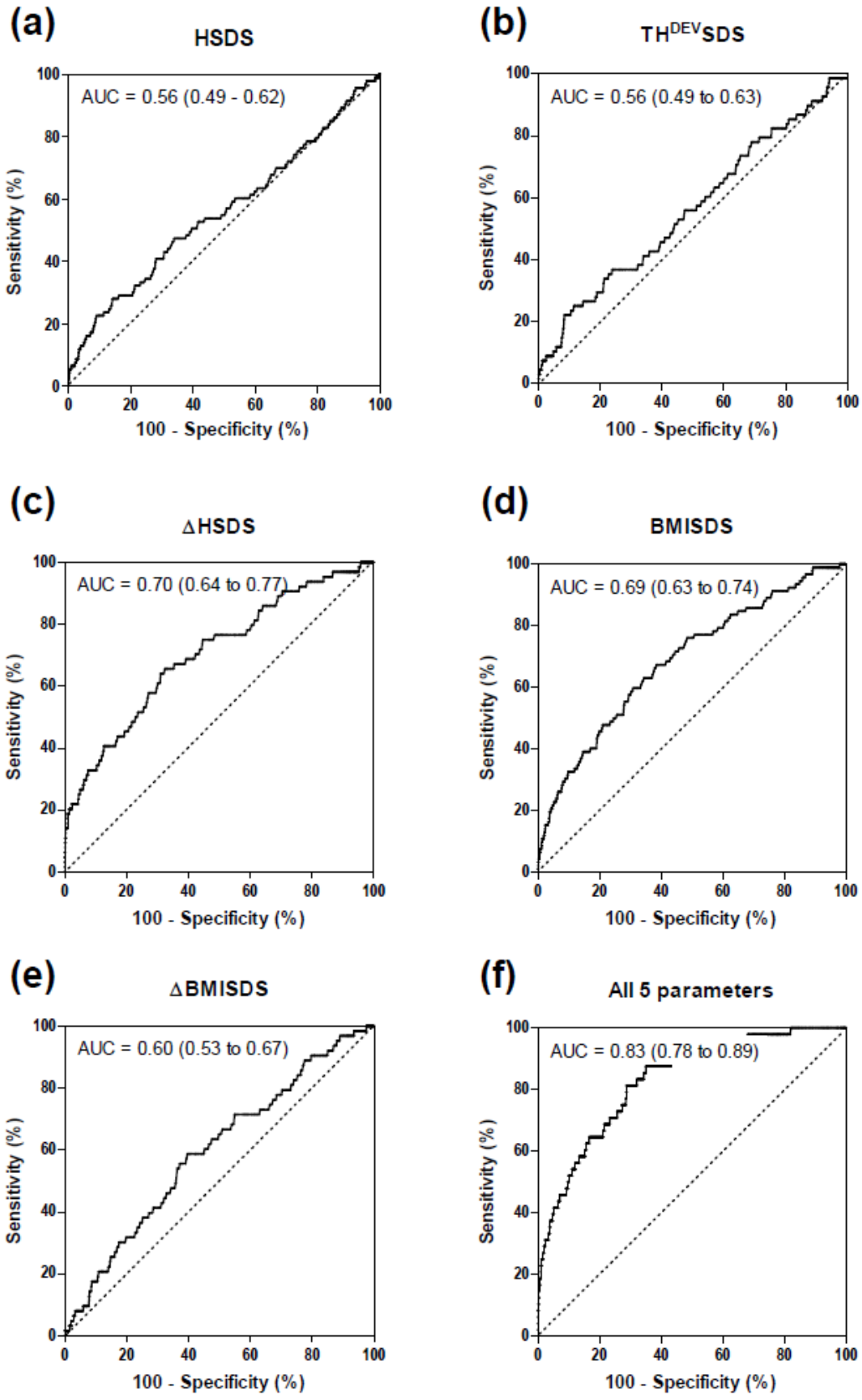

Figure 3. Screening accuracy of 5 growth monitoring parameters (HSDS [a], TH^{DEV}SDS [b], ΔHSDS [c], BMISDS [d], ΔBMISDS [e]]) and their combination (f) for 109 patients with juvenile acquired hypothyroidism. Areas under the curves and their 95% confidence intervals are shown.