



Epidemiology of Disorders Associated with Short Stature in Childhood: A 20-Year Birth Cohort Study in Finland

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Background: Many primary and secondary disorders disturb growth and cause short stature (height below -2 SDS) in childhood. Growth monitoring programs aim at their early detection but are not evidence-based: epidemiology of childhood growth disorders is poorly characterized, and no consensus exists on priority target conditions. Herein, we describe population-based epidemiological data on several primary and secondary growth disorders associated with short stature in childhood.

Materials and Methods: This retrospective population-based 20-year birth cohort study examined 1 144 503 children (51% boys) born in Finland between 1998 and 2017, with 16.5 million care notifications including medical diagnoses. The first occurrences of key primary or secondary growth disorders were identified in multiple registers. Median ages at diagnosis (MAD), and age- and sex-specific cumulative incidences (CMI) from birth until 16 years of age were determined.

Results: Turner syndrome was the most common primary growth disorder (CMI 52 per 100 000 at 16 years, MAD 4.0 years). Most primary growth disorders were diagnosed before the age of 4 years, and thereafter, secondary growth disorders increased in number. MAD of growth hormone deficiency (GHD) was 8.7 (boys) and 7.2 years (girls). At 16 years, the CMI of GHD was higher in boys than in girls (127 versus 93 per 100 000, respectively), whereas the CMI of hypothyroidism was higher in girls (569 versus 306 per 100 000). Celiac disease was the most common secondary growth disorder and more common in girls than in boys (988 versus 546 per 100 000 at 16 years, respectively).

Conclusion: These population-based epidemiological data indicate that childhood growth monitoring should be age- and sex-specific. In the early childhood, the focus should be on primary growth disorders, and from preschool age also on secondary growth disorders. These results provide evidence for improving growth monitoring programs and diagnostic practices targeting on Turner syndrome, GHD, hypothyroidism, and celiac disease.

Keywords: short stature, childhood, growth disorder, epidemiology, cumulative incidence

Introduction

Short stature is defined as a height standard deviation score (SDS) below -2 (ie, below 2.3rd percentile) for a given age and sex.¹ Growth retardation and poor growth velocity are also frequently used terms in the same context, and if left untreated, these may finally lead to short stature. A wide range of disorders may disturb growth: for example, the European Society of Paediatric Endocrinology has proposed a list of over 100 primary, secondary, and idiopathic diseases that might manifest with short stature.¹ However, basic epidemiological data are scarce even regarding the most common disorders that lead to short stature.²

Primary growth disorders include a number of clinically defined syndromes, in which abnormal growth is observed among other features.^{1,3} With the exception of idiopathic short stature, Turner syndrome (TS) is the most common cause of short stature in otherwise healthy girls.⁴ Early diagnosis of TS is important to identify other comorbidities, as well as to enable timely treatment with growth hormone (GH) and thus to optimize adult height.⁴ Other short stature syndromes

(SSS), such as Noonan, Prader-Willi and Russel-Silver syndrome, are rare congenital syndromes in both sexes, but were the most numerous causes of severe pathological short stature (below -3 SDS) in a recent Finnish study.⁵

Secondary causes for short stature comprise several common childhood disorders. They include endocrine conditions, such as growth hormone deficiency (GHD) and hypothyroidism (HT), in which hormonal treatments are essential to optimise final adult height.^{6,7} There are also systemic disorders that may manifest with growth failure before other symptoms, such as celiac disease (CD) and Crohn's disease.¹ Growth retardation is often evident years before the actual diagnosis of CD,^{8,9} but growth may be optimised with appropriate diet.^{10,11}

Growth monitoring practices have become a universal part of preventive pediatric health care especially in developed countries.¹² However, these practices are not evidence-based and there are remarkable variations among developed countries, as recently demonstrated in a systematic review by Scherdel et al.² Although TS, GHD, HT, and CD are known to be common causes of short stature, and often considered in the evaluation of children with short stature, there is no consensus on priority target conditions. Depending on the growth screening program and population, the target conditions for growth screening vary or remain undetermined.²

In Finland, recently updated growth curves and screening rules are integrated into children's electronic health records which enables an automated growth monitoring program.¹³ Since 1972, virtually whole Finnish child population has been covered with an extensive monitoring program with over 20 scheduled visits focusing on the early diagnostics of growth disorders.^{14,15} Referral from primary health-care system to the outpatient clinic of general paediatric department is made if there is a suspicion of underlying disease. Diagnosis is set at specialized health care and all diagnoses are registered for the Care Register of Health Care (CRHC) as ICD-10 codes.¹⁶

The aim of the present study was to characterize the epidemiology of several primary and secondary growth disorders in a population-based 20-year birth cohort, and thereby obtain a better consensus on a few priority target conditions for growth screening. These data are needed for planning and developing growth screening at the population level and diagnostic practices in specialized health care. We hypothesized that there is age- and sex-specific variation in the epidemiological measures of growth disorders and that the best estimates could be obtained in a population covered with a longitudinal, extensive growth monitoring program, well-functioning health care, and multiple registers gathering data on the population.

Materials and Methods

Study Design, Population and Data Collection

This was a retrospective register study, in which the initial study population consisted of all children ($n = 1\,151\,821$) born in Finland between 1 January 1998 and 31 December 2017 registered in the Medical Birth Register (MBR) containing data on all births¹⁷ (Figure 1). More than 92% of these children in the study population were of Finnish background.¹⁸ Data on medical diagnoses made in hospital care were obtained from the MBR and the Care Register of Health care (CRHC).¹⁶ Both MBR and CRHC are maintained by the Finnish Institute of Health and Welfare (THL). Data on deaths ($n = 4414$) were collected from Statistics Finland¹⁹ and the purchases of prescription medicines from the prescription register maintained by the Social Insurance Institution of Finland (SII).²⁰ People with incorrect personal ID codes or incomplete register notifications ($n = 7318$) were excluded. The final study population included 1 144 503 children (51% boys) with more than 16.5 million register notifications during the follow-up. The first date of an ICD-10 diagnosis given for an individual was considered as the diagnostic date. Data on growth measurements were not available.

Six conditions or groups of conditions were selected for further analysis: Turner syndrome (TS: ICD-10 code Q96), other short-stature syndromes (SSS: Q87.1, Q87.27, Q87.06/D82.1), growth hormone deficiency (GHD: E23.00, E23.01, E23.02), hypothyroidism (HT: E03.2–E03.9, E23.05), celiac disease (CD: K90.0), and Crohn's disease (K50). The selected disorders represent the potential key target conditions for growth screening: they are known to be common childhood diseases, but the detailed epidemiological data are scarce.² Growth failure may be the earliest and only symptom of these disorders; and their early diagnosis and treatment is important to optimize the final adult height. Other SSS are, however, rare, but are included in the analyses because they are the most common cause of severe short stature according to a recent study.⁵

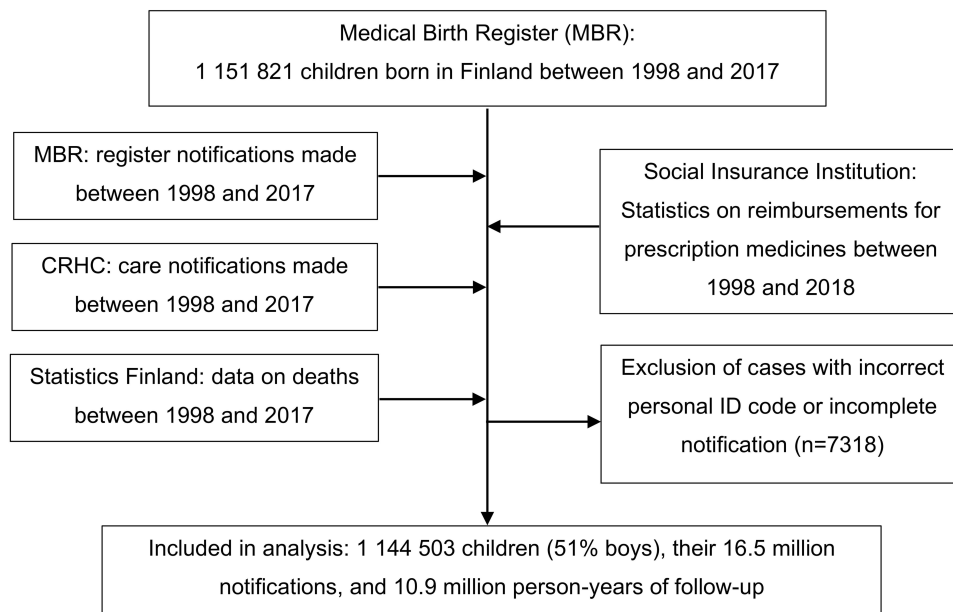


Figure 1 Flowchart of the study population and register data.
Abbreviation: CRCH, Care Register of Health Care.

GHD was subdivided into isolated GHD (E23.01 and E23.02) and panhypopituitarism (E23.00). The diagnosis of GHD in Finland is confirmed with two separately performed GH simulation tests with subnormal responses.²¹ To crosscheck the accuracy of diagnoses, we also verified the dates of the first purchases and reimbursements of growth hormone (ATC code H01AC) and thyroxine (H03AA01) from the drug purchase register of SII between 1998 and 2018.

Statistical Analyses

The variables needed for the analyses were the following: date of birth, diagnosis (ICD-10 code), date of diagnosis, date of death, and sex. The cumulative incidence (CMI) of the disorders was estimated from birth until the maximum of 16 years of age. Estimation was conducted using the Cumulative Incidence Function (CIF, Aalen-Johansen estimator), which estimates the probability of occurrence of the event of interest (the first diagnosis) in the presence of other (competing) events (ie, some children had more than one disease affecting growth, but only one disease can be diagnosed first). Death before the end of the follow-up time was considered as a competing risk, and follow-up was censored at the final day of 2017. Median ages at diagnosis were estimated using the CMI. Incidence rate ratios were calculated between two age groups (children under 4 years of age versus children 4–16 years). Data were processed in SPSS version 25, and R statistical software version 3.6.1 (R Foundation) was used to calculate CIFs.

Research Ethics

Data were pseudonymised. There was no contact between researchers and the study population. According to Finnish legislation, consent was not needed. The study was approved by the Research Ethics Committee of the Northern Savo Hospital District, and permissions to use data were obtained from the data maintainers (THL, Statistics Finland, SII).

Results

The study population resulted in 10.9 million person-years of follow-up (an average of 9.6 years per child). In total, 9987 children (41% boys) had at least one, 288 children had two, and 7 children had three of the selected disorders observed before the age of 16 years during the follow-up.

Primary Growth Disorders

Turner Syndrome

The study population included 223 girls with TS diagnosed during the follow-up. The median age at diagnosis was 4.0 years (range 0–15.2 years) (Table 1). The CMI of TS was 52 per 100 000 (1/1911) at 16 years. Altogether, 67% of the girls (150/223) with TS had reimbursement for growth hormone (GH) and at least one purchase of GH during the follow-up. Of the TS diagnoses, 38%, 50%, 66%, and 82% were made by 1, 4, 8, and 12 years of age, respectively (Figure 2, Table 1).

Table 1 Cumulative Incidences and Median Ages at Diagnosis of Disorders Associated with Short Stature

Growth Disorders (n)	Cumulative Incidence Per 100 000 (Rescaled CIF in %) ^a at Different Ages											Cumulative Incidence (1/Whole Number) at 16 Years of Age	Median Age at Diagnosis, Years
	Years												
	0	1	2	3	4	6	8	10	12	14	16		
Turner syndrome (223)	6.6 (12.6)	20.0 (38.3)	22.3 (42.7)	25.0 (47.7)	26.3 (50.2)	31.0 (59.2)	34.5 (65.9)	40.0 (76.4)	43.0 (82.1)	47.6 (90.9)	52.3 (100.0)	1/1911	4.0
Other SSS Girls (295)	3.8 (6.1)	25.4 (41.5)	33.2 (54.2)	38.3 (62.4)	41.9 (68.4)	50.3 (82.2)	52.5 (85.7)	55.1 (89.9)	55.5 (90.5)	58.0 (94.6)	61.3 (100.0)	1/1632	1.5
Boys (355)	3.8 (5.4)	29.0 (41.8)	36.6 (52.8)	42.6 (61.4)	49.7 (71.8)	56.0 (80.8)	62.3 (89.9)	64.8 (93.6)	67.1 (96.9)	68.1 (98.3)	69.3 (100.0)	1/1443	1.7
GHD ^b Girls (314)	0.4 (0.4)	2.5 (2.7)	4.1 (4.4)	6.3 (6.8)	9.5 (10.2)	28.0 (30.0)	42.7 (45.8)	55.4 (59.4)	73.9 (79.3)	87.2 (93.5)	93.2 (100.0)	1/1073	8.7
Boys (476)	0.3 (0.3)	2.1 (1.6)	3.7 (2.9)	7.6 (6.0)	15.6 (12.3)	44.8 (35.3)	68.4 (54.0)	92.0 (72.6)	110.6 (87.3)	117.3 (92.5)	126.8 (100.0)	1/789	7.2
Hypo-thyroidism Girls (1562)	1.8 (0.3)	14.7 (2.6)	24.3 (4.3)	33.5 (5.9)	45.6 (8.0)	76.6 (13.5)	127.1 (22.4)	206.3 (36.3)	311.6 (54.8)	414.3 (72.9)	568.6 (100.0)	1/176	11.6
Boys (886)	1.2 (0.4)	11.3 (3.7)	19.0 (6.2)	28.3 (9.3)	37.5 (12.3)	54.7 (17.9)	81.8 (26.8)	111.7 (36.5)	160.2 (52.4)	224.7 (73.5)	305.8 (100.0)	1/327	11.8
Celiac disease Girls (3221)	0 (0)	3.1 (0.3)	31.1 (3.1)	73.1 (7.4)	144.2 (14.6)	329.7 (33.4)	494.5 (50.0)	613.2 (62.1)	738.4 (74.7)	849.3 (86.0)	988.1 (100.0)	1/101	8.0
Boys (1862)	0 (0)	2.5 (0.5)	21.1 (3.9)	47.5 (8.7)	90.4 (16.6)	183.2 (33.6)	265.9 (48.7)	340.4 (62.4)	409.2 (75.0)	470.6 (86.2)	545.8 (100.0)	1/183	8.2
Crohn's disease Girls (464)	0 (0)	7.3 (4.8)	12.1 (7.9)	19.8 (12.8)	26.8 (17.4)	37.0 (24.1)	50.7 (33.0)	69.8 (45.4)	93.9 (61.0)	123.5 (80.3)	153.8 (100.0)	1/650	10.9
Boys (624)	0 (0)	6.3 (2.8)	11.0 (5.0)	18.7 (8.4)	26.5 (11.9)	38.9 (17.5)	56.0 (25.2)	75.5 (34.0)	114.5 (51.6)	164.7 (74.2)	222.0 (100.0)	1/450	11.9

Notes: ^a100 x [(cumulative incidence at the indicated age) / (cumulative incidence at 16 years of age)]. ^bIncludes the isolated GHD and panhypopituitarism with GHD.

Abbreviations: GHD, growth hormone deficiency; SSS, short-stature syndrome; CIF, cumulative incidence function.

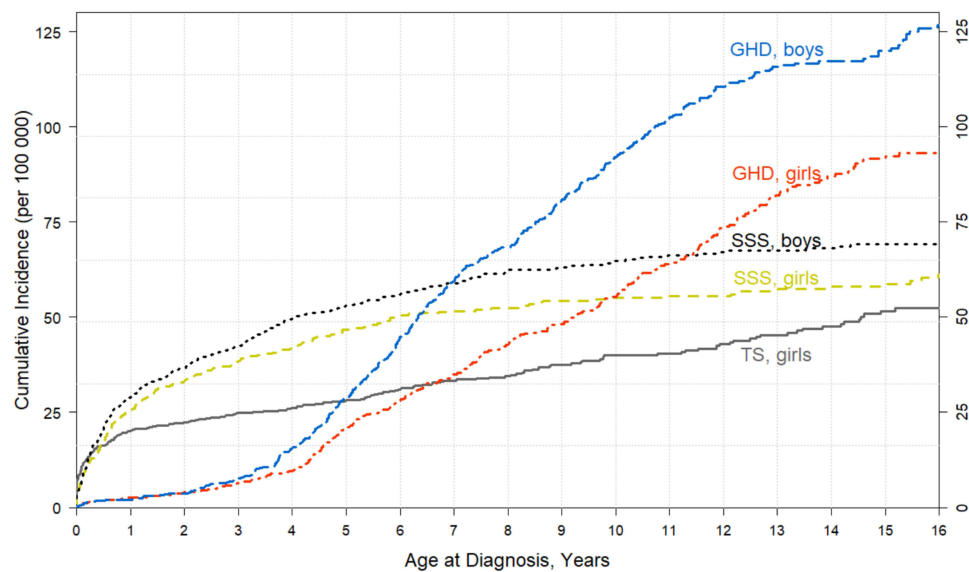


Figure 2 Cumulative incidence of Turner syndrome (TS), other short-stature syndromes (SSS), and growth hormone deficiency (GHD) from birth to 16 years of age. Cumulative incidence of GHD increases steeply from 4 years onwards both in boys and girls, whereas before 4 years of age, the primary growth disorders are more common.

Other Short-Stature Syndromes

A total of 650 children (55% boys) had a diagnosis of other SSS during the follow-up (see [Supplementary Table 1](#) for detailed information). The median age at diagnosis was 1.5 years among girls (range 0–16.0 years) and 1.7 years among boys (range 0–14.3 years) ([Table 1](#)). The CMI of other SSSs at 16 years did not differ between girls (61 per 100 000; 95% CI 54.0–69.4) and boys (69 per 100 000; 95% CI 62.1–77.2). Most SSS diagnoses (68% among girls and 72% among boys) were made before the age of 4 years ([Figure 2](#)).

Before the age of 4 years, the incidence rate of diagnoses of any SSS was 4.8-times higher than later at 4 years or above (95% CI 4.11–5.57, $p < 0.001$).

Secondary Growth Disorders

Growth Hormone Deficiency

Study population included 1002 children diagnosed with GHD during the follow-up. Of these, 212 children also had an underlying syndromic disorder (either TS or other SSS) and were included in these categories a priori. Consequently, there were 790 non-syndromic children with GHD (60% boys). They all had reimbursement for GH and 775 (98%) had at least one purchase of GH.

The median age at GHD diagnosis was 8.7 years among girls (range 0–15.3 years) and 7.2 years among boys (range 0–16.0 years) ([Table 1](#)). At 16 years, the CMI of GHD was higher among boys (127 per 100 000; 95% CI 114.9–139.8) than among girls (93 per 100 000; 95% CI 82.6–105.0) ([Figure 2](#)). Isolated GHD ($n = 719$; 61% boys) was more common than panhypopituitarism ($n = 71$; 56% boys). The CMI of GHD increased from the age of 4 years onwards: 10% and 79% of the GHD diagnoses among girls and 12% and 87% of the GHD diagnoses among boys were made by 4 and 12 years of age, respectively.

Of the children with GHD, 133 (of which 35 panhypopituitarism; 26%) were diagnosed before the age of 4 years, and 657 (of which 36 panhypopituitarism; 5%) were diagnosed between 4 and 16 years of age. The incidence rate of the GHD was 3.0-times higher at 4–16 years of age in comparison to those under 4 years (95% CI 2.5–3.6, $p < 0.001$).

Celiac Disease

The study population included 5083 children (37% boys) with a diagnosis of CD during the follow-up. At 16 years, the CMI of CD was higher among girls (988 per 100 000; 95% CI 951.3–1026.1) than among boys (546 per 100 000; 95% CI 519.1–573.5) ([Table 1](#)). The median age at diagnosis was 8.0 years among girls and 8.2 years among boys (range 0–16.0 years).

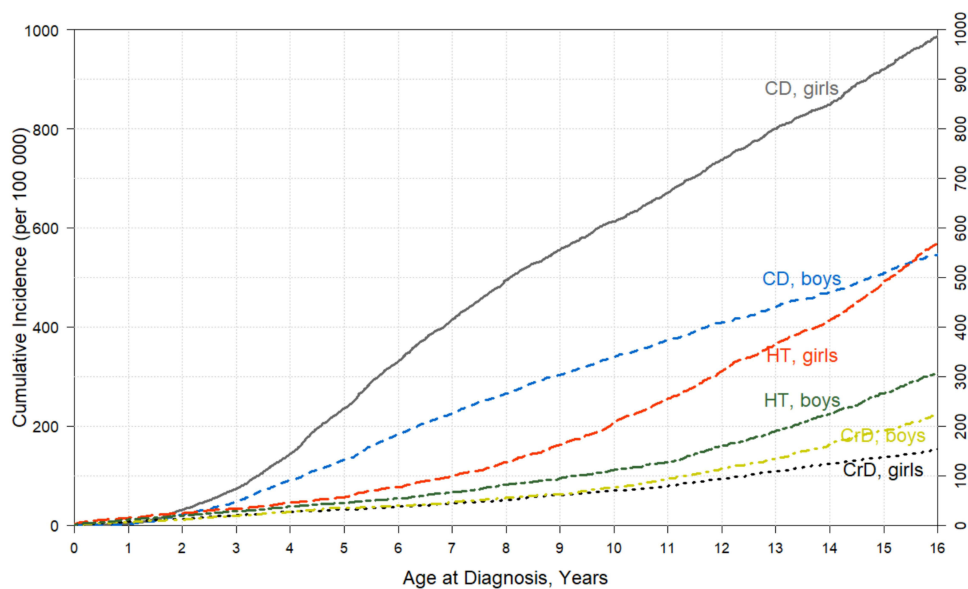


Figure 3 Cumulative incidence of celiac disease (CD), hypothyroidism (HT), and Crohn's disease (CrD) from birth to 16 years of age.

years for both). The CMI of CD began to rise in early childhood, and thereafter, CD was the most common condition in the study (Figure 3).

Hypothyroidism

In total, 2448 children (36% boys) had a diagnosis of HT during the follow-up, of which 2188 (89%) had at least one purchase of thyroxine. The median age at the diagnosis was 11.6 years among girls and 11.8 years among boys (range 0–16.0 years for both sexes) (Table 1). At 16 years, the CMI of HT was higher in girls (569 per 100 000; 95% CI 537.4–601.2) than in boys (306 per 100 000; 95% CI 283.7–329.3) (Figure 3).

Crohn's Disease

A total of 1088 children (57% boys) had Crohn's disease during the follow-up. The median age at diagnosis was 10.9 years among girls (range 0.1–16.0 years) and 11.9 years in boys (range 0–16.0) (Table 1). The CMI of Crohn's disease increased faster from 10 years onwards, and at 16 years, it was higher among boys (222 per 100 000; 95% CI 203.2–242.3) than among girls (154 per 100 000; 95% CI 138.6–170.4) (Figure 3).

The incidence rate of the secondary growth disorders (GHD, CD, TS, or Crohn's disease) was 2.2-times higher at 4 years of age or older in comparison to those under 4 years (95% CI 2.1–2.3, $p < 0.001$).

Discussion

This nationwide 20-year birth cohort study provides the first comparative age- and sex-specific epidemiological data on common childhood disorders that, if left untreated, lead to growth failure and short stature as part of the clinical spectrum. We show that among the selected growth disorders there are remarkable differences in age- and sex-specific epidemiology. These data are important for planning and developing growth screening at the population level and diagnostic practices in specialized health care.

We found only a few previous studies on epidemiology of disorders affecting childhood growth. In a Danish study by Nielsen and Wohler²² the incidence of TS was 1 per 2130 girls which is in line with our result (CMI 1 per 1911 at 16 years). TS is often diagnosed late, resulting in short adult height or other health consequences.^{23–25} The median age of TS diagnosis in our population was 4.0 years, whereas in the study by Massa et al,²⁵ which included 242 Belgian girls, the median age at diagnosis was 6.6 years.

Furthermore, in a study by Gravholt et al,²⁶ 90% of TS diagnoses among Danish girls were made within the first 15 years, compared to 99% in the present study. These observations support our hypothesis that epidemiological measures obtained from our extensively screened population are reliable. Since the incidence of TS is virtually same in different populations, it seems warranted that TS would be made a priority target condition for growth monitoring.

Short stature is a typical feature in many rare congenital syndromes. In infancy, only subtle dysmorphic features may be present even though growth is already compromised. Other studies reporting age at diagnosis of SSSs were not found. Some reviews suggest that the incidence of Noonan syndrome varies between 1/1000 and 1/2500,^{27,28} that of Prader-Willi syndrome varies between 1/10 000–1/30 000,²⁹ and that of Russell-Silver syndrome varies from 1/30 000 to 1/100 000,³⁰ which is in line with our results. The majority (68% among girls and 72% among boys) of the other SSSs were diagnosed before the age of 4 years.

Syndromes were the most numerous primary growth disorder and more frequent in girls in the recent Finnish study that investigated the causes of severe (height below -3 SDS) short stature after the age of three years.⁵ Down syndrome, which was the most frequent ($n = 43$) single syndrome in their study, was not included in our analysis. Other syndromes with severe short stature in their study were, for example, Turner syndrome ($n = 17$), Mulibrey nanism ($n = 8$), Noonan syndrome ($n = 6$), Silver-Russell syndrome ($n = 4$), and DiGeorge syndrome ($n = 4$).⁵ Since the differences in study design, the number of corresponding disorders in our study are bigger and cannot be compared with the study of Kärkinen et al.⁵

After the early childhood, the focus of growth screening should be widened from primary disorders to acquired conditions that become more common from 3–4 years of age. One of the most commonly accepted target conditions for growth screening is GHD. A few studies have focused on the epidemiology of GHD with prevalence estimates varying from 1:3480 to 1:8646.^{31,32} Stochholm et al reported that the average annual incidence rate of childhood onset GHD (ie, diagnoses before 18 years of age) was 2.58 in boys and 1.70 in girls, both per 100 000.³³ The CMI estimates obtained in the present study (93 per 100 000 among girls and 127 per 100 000 among boys at 16 years) are high, but they are not directly comparable with other studies. These diverse results may reflect the intensity of growth monitoring and the full availability of diagnostic tools, such as IGF-I and IGFBP-3 measurements, provocative GH testing, genetic testing, and neuroimaging.³⁴

In their study of etiology of severe short stature, Kärkinen et al identified 94 patients with GHD of which 76 patients had isolated GHD.⁵ GHD was also more prevalent in boys.⁵ Similar observations of boys having higher incidence of GHD have been made in Denmark.³³ The median age at disease onset among boys was higher in a Danish cohort (9.1 years) than in our data (7.2 years), whilst it was almost the same among girls (8.6 versus 8.7 years, respectively).³³ In general, the age at GHD diagnosis differs greatly between countries, ranging from 4.6 years in Germany to 7.0 years in the UK and 9.4 years in the US.³⁵ Overall, most of the GHD diagnoses were made between 5 and 10 years of age in the present population, indicating that the index of suspicion of GHD should be high in prepubertal years when the opportunity to improve adult height is available.

Another endocrine condition that is classically associated with growth failure is acquired hypothyroidism. It is carefully studied among adolescents and adults, but its epidemiology in childhood remains obscure. Rivkees et al report that despite thyroxine treatment, acquired HT may result in a permanent height deficit.⁶ In the present study, the CMI estimates of acquired HT (1 per 176 in girls and 1 per 327 in boys at 16 years) confirm that HT is already more common among girls during childhood. The steepest rise in the CMI of HT was seen between 10 and 16 years of age, warranting a high index of suspicion during late childhood and puberty.

Celiac disease was the most common disorder in the study, and by 4 years of age, the CMI of CD was greater than that of other acquired growth disorders together. At the age of 16 years, the CMI of CD was 0.99% for girls and 0.55% for boys. These results are consistent with the prevalence of CD among Finnish adults (0.70% for women and 0.38% for men).³⁶ Even higher figures were reported in North America, where the CMI of CD is 3.1% at the age of 15 years.³⁷ However, this high incidence of CD could be an isolated cohort effect, as the study discussed.

The observation that CD is significantly more common among girls from the early age onwards is novel. We have previously demonstrated that growth is already abnormal 2 years before the CD diagnosis in the majority of children.⁸ In a recent study, 944 new-borns at risk of CD were examined periodically, and by 6 years, 12% had developed CD. However, the growth failure started before the serology result turned positive for CD.³⁸ We propose that due to the high

incidence and its unfavourable effect of growth, CD should be included among the priority target conditions for growth screening in childhood.

The CMI of Crohn's disease (1 per 650 in girls and 1 per 450 in boys at 16 years) was lower than the CMIs of CD and HT in this study. The biggest rise in the CMI of Crohn's disease diagnoses was seen between 10 and 16 years of age, as observed in other studies.³⁹ Previous studies indicate that growth impairment is one of the most significant complications of pediatric-onset Crohn's disease. In fact, growth failure was observed in 15–40% of patients upon the diagnosis of Crohn's disease.^{40,41} Combined with the diagnostic delays and increasing incidence over the past decades,^{39,42} these findings make Crohn's disease a potential target condition for growth screening.

Strengths

This study has several strengths. First, the study population is large, over 1.1 million individuals representing the whole child population born in a 20-year period. Second, the population was carefully monitored by one of the world's most extensive growth- and health monitoring programs with over 20 check-ups.^{14,15} If growth screening was abnormal, further examinations were programmed systematically to diagnose the potential cause.^{43,44} Therefore, it is probable that the diagnoses of growth disorders are obtained in a timely manner. Third, the nationwide registers are shown to be good data sources.⁴⁵ Additionally, we were able to confirm the accuracy of TS, GHD, and hypothyroidism diagnoses using medication data.

Limitations

Even though the Finnish well-child program is among the most extensive growth monitoring programs worldwide, the diagnostic accuracy of any program is never 100%. Despite careful growth monitoring, there is always a delay of variable length from the onset of a disorder to the diagnosis. Therefore, the CMI figures are always underestimates of true figures. Further, there can be differences in the genetic predisposition to various growth disorders between populations, and thus our data may not be generalizable to all populations. However, based on the previous literature discussed above, this does not seem probable. Migration was not taken into account when calculating the CMI due to a lack of data. However, the number of emigrants/immigrants is known to be small, and disregarding migration is unlikely to have a significant influence on the results. Since we did not have access to the actual growth measurements, we can only speculate about how the yield of growth monitoring would mirror these data. Nevertheless, we can now postulate about how a growth monitoring program should perform in a child population.

Conclusion

This study provides for the first population-based epidemiological data on several primary and secondary growth disorders associated with short stature in childhood. Median age at TS diagnosis was 4.0 years, and it was the most common primary growth disorder. Median age at GHD diagnosis was 8.7 years among girls and 7.2 years among boys. The CMI of GHD was lower in girls than boys, whereas CD and HT were more common in girls than boys. In conclusion, growth monitoring should be age- and sex-specific, and the main focus should be widened from primary also to secondary growth disorders from preschool age and onwards. This study further confirms our understanding that principal target conditions for growth screening are at least TS, GHD, HT, and CD. Further studies evaluating the accuracy and cost-effectiveness of growth monitoring are warranted, focusing on the key target conditions whose age- and sex-specific epidemiological patterns are now elucidated.

Abbreviations

SDS, standard deviation score; TS, Turner syndrome; SSS, short stature syndrome; GHD, growth hormone deficiency; HT, hypothyroidism; CD, celiac disease; CRHC, the Care Register of Health Care; MBR, the Medical Birth Register; SII, the Social Insurance Institution; THL, the Finnish Institute of Health and Welfare; MAD, median age at diagnosis; CMI, cumulative incidence; CIF, Cumulative Incidence Function; CI, confidence interval.

Data Sharing Statements

The health data used in the study arise from the nationwide registers. The individual-level health data that support the findings of this study are neither publicly available nor to be shared. However, other researchers fulfilling the requirements from the data providers could obtain similar data.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Wit JM, Ranke MB, Kelnar C. ESPE classification of paediatric endocrine diagnoses. *Horm Res*. 2007;68(2):1–20.
2. Scherdel P, Dunkel L, van Dommelen P, et al. Growth monitoring as an early detection tool: a systematic review. *Lancet Diabetes Endocrinol*. 2016;4(5):447–456. doi:10.1016/S2213-8587(15)00392-7
3. Oostdijk W, Grote FK, de Muinck Keizer-Schrama SM, Wit JM. Diagnostic approach in children with short stature. *Horm Res*. 2009;72(4):206–217. doi:10.1159/000236082
4. Sybert VP, McCauley E. Turner's Syndrome. *N Engl J Med*. 2004;351(12):1227–1238. doi:10.1056/NEJMra030360
5. Kärkinen J, Miettinen PJ, Raivio T, Hero M. Etiology of severe short stature below -3 SDS in a screened Finnish population. *Eur J Endocrinol*. 2020;183(5):481–488. doi:10.1530/EJE-20-0313
6. Rivkees SA, Bode HH, Crawford JD. Long-term growth in juvenile acquired hypothyroidism: the failure to achieve normal adult stature. *N Engl J Med*. 1988;318(10):599–602. doi:10.1056/NEJM198803103181003
7. Harris M, Hoffman PL, Cutfield WS. Growth hormone treatment in children: review of safety and efficacy. *Pediatr-Drugs*. 2004;6(2):93–106. doi:10.2165/00148581-200406020-00003
8. Saari A, Harju S, Mäkitie O, Saha M, Dunkel L, Sankilampi U. Systematic growth monitoring for the early detection of celiac disease in children. *JAMA Pediatr*. 2015;169(3):e1525. doi:10.1001/jamapediatrics.2015.25
9. Haymond M, Kappelgaard A, Czernichow P, Biller BM, Takano K, Kiess W. Early recognition of growth abnormalities permitting early intervention. *Acta Paediatr*. 2013;102(8):787–796. doi:10.1111/apa.12266
10. 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. doi:10.1097/00005176-199411000-00005
11. Assa A, Frenkel-Nir Y, Leibovici-Weissman Y, et al. Anthropometric measures and prevalence trends in adolescents with coeliac disease: a population based study. *Arch Dis Child*. 2017;102(2):139–144. doi:10.1136/archdischild-2016-311376
12. de Onis M, Wijnhoven TMA, Onyango AW. Worldwide practices in child growth monitoring. *J Pediatr*. 2004;144(4):461–465. doi:10.1016/j.jpeds.2003.12.034
13. Saari A, Sankilampi U. Finland is a pioneer in childhood growth monitoring--Is it evidence-based? *Duodecim*. 2016;132(6):505–513.
14. The Parliament of Finland. Terveystieteidenlaki (Health Care Act); 2010.
15. The Parliament of Finland. Kansanterveyslaki (Public Health Act); 1972.
16. Finnish Institute for Health and Welfare, (THL). Care register for health care; 2018. Available from: <https://thl.fi/en/web/thlfi-en/statistics-and-data/data-and-services/register-descriptions/care-register-for-health-care>. Accessed December 1, 2018.
17. Finnish Institute for Health and Welfare, (THL). Medical birth register; 2019. Available from: <https://thl.fi/en/web/thlfi-en/statistics-and-data/data-and-services/register-descriptions/newborns>. Accessed September 1, 2019.
18. Official Statistics of Finland. Live births by sex and mother's age (5-year) and origin and background country, 1990–2020. Available from: https://statfin.stat.fi/PxWeb/pjweb/en/StatFin_synt/statfin_synt_pxt_12dp.px/. Accessed September 12, 2022.
19. Official Statistics of Finland, (OSF). Deaths. Available from: http://www.stat.fi/til/kuol/index_en.html. Accessed August 17, 2020.
20. The Social Insurance Institution of Finland. Statistics on reimbursements for prescription medicines; 2019. Available from: <https://www.kela.fi/web/en/statistics-by-topic/reimbursements-for-prescription-medicines>. Accessed August 17, 2020.
21. Collett-Solberg P, Ambler G, Backeljauw P, et al. Diagnosis, genetics, and therapy of short stature in children: a growth hormone research society international perspective. *Horm Res Paediatr*. 2019;92(1):1–14. doi:10.1159/000502231
22. Nielsen J, Wohlert M. Sex chromosome abnormalities found among 34,910 newborn children: results from a 13-year incidence study in Arhus, Denmark. *Birth Defects Orig Artic Ser*. 1990;26(4):209–223.

23. Ahn J, Suh J, Kwon A, Chae H, Kim H. Final adult height after growth hormone treatment in patients with turner syndrome. *Horm Res Paediatr.* 2019;91(6):373–379. doi:10.1159/000500780
24. Bramswig J H. Long-Term Results of Growth Hormone Therapy in Turner Syndrome. *Endocr.* 2001;15(1):5–13. doi:10.1385/ENDO:15:1:005
25. Massa G, Verlinde F, De Schepper J, et al. Trends in age at diagnosis of Turner syndrome. *Arch Dis Child.* 2005;90(3):267–268. doi:10.1136/ad.2004.049817
26. Gravholt CH, Juul S, Naeraa RW, Hansen J. Prenatal and postnatal prevalence of Turner's syndrome: a registry study. *BMJ.* 1996;312(7022):16–56. doi:10.1136/bmj.312.7022.16
27. Mendez HMM, Opitz JM, Reynolds JF. Noonan syndrome: a review. *Am J Med Genet.* 1985;21(3):493–506. doi:10.1002/ajmg.1320210312
28. Allanson JE. Noonan syndrome. *J Med Genet.* 1987;24(1):9–13. doi:10.1136/jmg.24.1.9
29. Miller JL. Approach to the child with Prader-Willi syndrome. *J Clin Endocrinol Metab.* 2012;97(11):3837–3844. doi:10.1210/jc.2012-2543
30. Marsaud C, Rossignol S, Tounian P, Netchine I, Dubern B. Prevalence and management of gastrointestinal manifestations in Silver–Russell syndrome. *Arch Dis Child.* 2015;100(4):353–358. doi:10.1136/archdischild-2013-305864
31. Vimpani GV, Vimpani AF, Lidgard GP, Cameron EH, Farquhar JW. Prevalence of severe growth hormone deficiency. *Br Med J.* 1977;2(6084):427–430. doi:10.1136/bmj.2.6084.427
32. Thomas M, Massa G, Craen M, et al. Prevalence and demographic features of childhood growth hormone deficiency in Belgium during the period 1986–2001. *Eur J Endocrinol.* 2004;151(1):67–72. doi:10.1530/eje.0.1510067
33. Stochholm K, Gravholt CH, Laursen T, et al. Incidence of GH deficiency – a nationwide study. *Eur J Endocrinol.* 2006;155(1):61–71. doi:10.1530/eje.1.02191
34. Stanley T. Diagnosis of growth hormone deficiency in childhood. *Curr Opin Endocrinol Diabetes Obes.* 2012;19(1):47–52. doi:10.1097/MED.0b013e32834ec952
35. Brod M, Alolga SL, Beck JF, Wilkinson L, Højbjørre L, Rasmussen MH. Understanding burden of illness for child growth hormone deficiency. *Qual Life Res.* 2017;26(7):1673–1686. doi:10.1007/s11136-017-1529-1
36. Virta LJ, Kaukinen K, Collin P. Incidence and prevalence of diagnosed coeliac disease in Finland: results of effective case finding in adults. *Scand J Gastroenterol.* 2009;44(8):933–938. doi:10.1080/00365520903030795
37. Liu E, Dong F, Barón AE, et al. High incidence of celiac disease in a long-term study of adolescents with susceptibility genotypes. *Gastroenterology.* 2017;152(6):1329–1336.e1. doi:10.1053/j.gastro.2017.02.002
38. Auricchio R, Stellato P, Bruzzese D, et al. Growth rate of coeliac children is compromised before the onset of the disease. *Arch Dis Child.* 2020;105(10):964–968. doi:10.1136/archdischild-2019-317976
39. Benchimol EI, Bernstein CN, Bitton A, et al. Trends in epidemiology of pediatric inflammatory bowel disease in Canada: distributed network analysis of multiple population-based provincial health administrative databases. *Am J Gastroenterol.* 2017;112(7):1120–1134. doi:10.1038/ajg.2017.97
40. Gasparetto M, Guariso G. Crohn's disease and growth deficiency in children and adolescents. *World J Gastroenterol.* 2014;20(37):13219–13233. doi:10.3748/wjg.v20.i37.13219
41. Ishige T. Growth failure in pediatric onset inflammatory bowel disease: mechanisms, epidemiology, and management. *Transl Pediatr.* 2019;8(1):16–22. doi:10.21037/tp.2018.12.04
42. Timmer A, Behrens R, Buderus S, et al. Childhood onset inflammatory bowel disease: predictors of delayed diagnosis from the CEDATA German-Language Pediatric Inflammatory Bowel Disease Registry. *J Pediatr.* 2011;158(3):467–473. doi:10.1016/j.jpeds.2010.09.014
43. Rova M. Historia. Lastenneuvolakäsikirja (History. Handbook for child welfare clinics); 2018. Available from: <https://thl.fi/fi/web/lastenneuvola/kasikirja/lastenneuvolatyon-perusteet/lastenneuolajarjestelma/historia>. Accessed September 1, 2019.
44. The Ministry of Social Affairs and Health, (STM). Government Decree on maternity and child health clinic services, school and student health services and preventive oral health services for children and youth; 2011.
45. Sund R. Quality of the Finnish Hospital Discharge Register: a systematic review. *Scand J Public Health.* 2012;40(6):505–515. doi:10.1177/1403494812456637

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