The Journal of Clinical Endocrinology & Metabolism, 2023, **00**, 1–7
https://doi.org/10.1210/clinem/dgad334
Advance access publication 6 June 2023
Clinical Research Article

Comorbidity in Congenital Hypothyroidism—A Nationwide, Population-based Cohort Study

Emmi Danner,[1] Jarmo Jääskeläinen,[1] Laura Niuro,[2] Hanna Huopio,[1] Harri Niinikoski,[2] Liisa Viikari,[2] Jukka Kero,[2] and Reijo Sund[3]

[1]Department of Pediatrics, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland
[2]Department of Pediatrics, University of Turku and Turku University Hospital, Turku, Finland
[3]School of Medicine, Institute of Clinical Medicine, University of Eastern Finland, Kuopio, Finland

Correspondence: Emmi Danner, MD, Department of Pediatrics, Kuopio University Hospital, PO 100, 70028 KYS, Kuopio, Finland.
Email: emmi.danner@pshyvinvointialue.fi.

Abstract

Context: Patients with congenital hypothyroidism (CH) are affected more often than the general population by other chronic diseases and neurological difficulties.

Objective: The aim of this nationwide population-based register study was to investigate the incidence of congenital malformations, comorbidities, and the use of prescribed drugs in patients with primary CH.

Methods: The study cohort and matched controls were identified from national population-based registers in Finland. All diagnoses from birth until the end of 2018 were collected from the Care Register, and subject-specific prescription drug purchases were identified from The Prescription Register from birth until the end of 2017.

Results: Diagnoses of neonatal and chronic diseases were collected for 438 full-term patients and 835 controls (median follow-up time 11.6 years; range, 0-23 years). Newborns with CH were more often found to have neonatal jaundice (11.2% and 2.0%; $P < .001$), hypoglycemia (8.9% and 2.8%; $P < .001$), metabolic acidemia (3.2% and 1.1%; $P = .007$), and respiratory distress (3.9% and 1.3%; $P < .003$) as compared to their matched controls.

Congenital malformations were diagnosed in 66 of 438 (15.1%) CH patients and in 62 of 835 (7.4%) controls ($P < .001$). The most commonly affected extrathyroidal systems were the circulatory and musculoskeletal systems. The cumulative incidence of hearing loss and specific developmental disorders was higher among CH patients than controls. The use of antidepressant and antipsychotic drugs was similar in CH patients and their controls.

Conclusion: CH patients have more neonatal morbidity and congenital malformations than their matched controls. The cumulative incidence of neurological disorders is higher in CH patients. However, our results do not support the existence of severe psychiatric comorbidity.

Key Words: congenital hypothyroidism, comorbidity, congenital malformations, neurological disorders

Abbreviations: ADHD, attention deficit hyperactivity disorder; CH, congenital hypothyroidism; ICD-10, International Classification of Disease, Tenth Revision.

Congenital hypothyroidism (CH) is the most common congenital endocrine disorder. The global incidence varies between 1:1000 and 1:3000 (1-8). If CH is not treated promptly after birth, it leads to impaired neurocognitive development and growth (9). The etiology of primary CH can be abnormal development or function of the thyroid gland but also impaired thyroid hormone action (10). Thyroid dysgenesis is the most common etiology, representing 75% to 85% of CH cases, while dyshormonogenesis is less common (9, 11). However, the proposed recent increase in the incidence of CH has mainly been caused by an increased incidence of dyshormonogenesis (12).

Since the initiation of newborn screening programs, there have been reports on chromosomal alterations, other congenital anomalies, and comorbidities associated with CH. The most frequently reported extrathyroidal malformations are heart defects (4, 13-18) followed by abnormalities of the urogenital system (4, 16, 19), musculoskeletal system (4, 18, 20), and cleft palate/lip (13, 14, 19). Of chromosomal abnormalities, the association with Down syndrome is most common (21).

If not screened, CH is difficult to recognize clinically during the neonatal period because of its initially mild and nonspecific symptoms and findings. Prolonged jaundice, large tongue, and muscle hypotonia (17, 22) accompanied by a large head circumference (8, 22) are well known findings in CH. Also, a higher prevalence of respiratory distress syndrome has been described (23). Hearing impairment is often found in patients with CH (24-26), but the association of CH with other chronic comorbidities is not well established. The treatment of CH in accordance with current recommendations has been shown to lead to grossly normal cognitive outcomes (27, 28). However, CH patients are affected more often than the general population by other moderate or

Received: 12 March 2023. **Editorial Decision:** 2 June 2023. **Corrected and Typeset:** 14 June 2023
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even severe chronic diseases, most frequently neurologic or mental disorders (29, 30). Furthermore, several studies have reported milder neurological and behavioral difficulties in CH patients (25, 31-33).

The aim of this nationwide population-based register study with cases and controls was to investigate the incidence of congenital malformations, neonatal diagnoses, comorbidities, and the use of prescribed drugs in patients with primary CH.

Materials and Methods

Participants

The study cohort was identified from 4 distinct national population-based registers in Finland: the Prescription Register (established in 1993) maintained by the Social Insurance Institution of Finland, the Care Register for Health Care (established in 1994) (earlier the Hospital Discharge Register, information available since 1969), the Medical Birth Register (established in 1987), and the Register of Congenital Malformations (established in 1963) maintained by the Finnish Institute for Health and Welfare. All permanent residents in Finland have a unique personal identity code, which makes these registers linkable.

The criteria to recognize CH patients from these registers were a diagnosis of primary CH (International Classification of Diseases, Tenth Revision [ICD-10] E03.1 or E03.0/ICD9 243) under the age of two years (the Hospital Discharge Register and the Care Register for Health Care) and/or the purchase of levothyroxine (Anatomical Therapeutic Chemical [ATC] H03AA01/03) under the age of one year (the Prescription Register), and/or the diagnosis of CH in the Medical Birth Register and/or the Register of Congenital Malformations. To verify the diagnosis and thus confirm eligibility for the study, ICD-10 or ICD-9 code of primary CH had to be recorded in one or more of the aforementioned registers at least twice with at least a 2-month interval, if not recorded as a cause of death. The exclusion criteria were a diagnosis of end-stage renal disease (ICD-10 N18/ICD9 585 or 586) or panhypopituitarism (ICD-10 E23.00/ICD9 253.2). The purpose of these criteria was to exclude patients with suspected but unconfirmed CH, patients using levothyroxine for other reasons than primary CH, and clear logging errors. We used data from the establishment of the Medical Birth Register, January 1, 1987, to December 31, 2018, and recognized 584 cases with CH.

A matched control cohort was created using the Medical Birth Register. Two matched controls for each patient were randomly selected, except 2 patients (twin pair) who received only 1 control (number of controls = 1166). The control group was matched for date of birth (± 3 months), sex, mother's age at childbirth (± 2 years), number of fetuses, parity (1, 2, 3, or more), and place of childbirth (hospital district).

To create the final study group, we excluded all premature babies born before 37 weeks of pregnancy, which led to an exclusion of 37 premature newborns with CH and 62 premature controls. Additionally, 2 CH patients and 3 controls lacking information on gestational age were excluded.

From the patients and controls born between 1996 and 2018, we excluded patients with known chromosomal or genetic abnormalities, which led to the exclusion of 13 CH patients and 7 controls (including 5 and 4 patients with Down syndrome, respectively). In addition to trisomies, other specified genetic abnormalities in the CH group were Goldenhar, Aarskog, Prader-Willi, and Klinefelter syndromes.

In total, the final number of full-term patients with CH born between 1987 and 2018 was 531 and the number of controls 1019.

Methods

From the Prescription Register of the Social Insurance Institution of Finland we collected information about all prescribed drugs (ie, all other than over-the-counter drugs and medications used in hospital care) bought from the birth (or from the beginning of the register, January 1, 1993) until December 31, 2017. Purchased peroral drugs available with prescription were recorded by ATC classification codes and the number of packages bought per year. In this study we focused on the use of antibiotics, antipsychotics, antidepressants, and agents used for attention deficit hyperactivity disorder (ADHD). The use of antibiotics was assessed only for individuals born after the Prescription Register reached complete coverage at the beginning of 1995 (number of cases = 441 and number of controls = 841; median follow-up time, 11.8 years, range, 0-23 years). Antipsychotics, antidepressants, and agents used for ADHD are not commonly used for children younger than 5 years, and thus, this analysis was performed for the study population born between 1987 and 2017 (number of cases = 513 and number of controls = 984; median follow-up time: 13.6 years, range, 0-31 years).

From the Care Register for Health Care we collected all diagnoses from the birth to December 31, 2018. We studied the subgroup born after the initiation of ICD-10 coding in 1996 (cases = 438 and controls = 835; median follow-up time 11.6 years, range 0-23 years). In this study we focused on the most common neonatal diagnoses and chronic diseases diagnosed and/or treated mainly in public specialized health care in Finland and on congenital malformations and deformations (ICD-10 codes Q00-Q89). Diseases usually treated in primary health care and diagnoses not systematically made in specialized health care were excluded. Furthermore, if the diagnosis of a chronic disease was registered only once, it was considered as an error and not recorded (except if the diagnosis occurred as a cause of death). Each individual was followed from birth until the occurrence of the event under investigation, death, or the end of the study.

Dates and causes of death were collected from the registers of Statistics Finland. The data were linked and pseudonymized in Statistics Finland and provided for the researchers' use by a remote access system.

The Finnish Institute for Health and Welfare, the Social Insurance Institution of Finland, and Statistics Finland granted permission for this study. The study protocol was approved by the ethics committee of the Northern Savo Hospital District.

Statistical Methods

The prevalence of neonatal diagnoses and congenital malformations between patients with CH and their matched controls was compared using the Pearson chi-square test. We recorded the age when the drug was purchased for the first time and the age when the diagnosis of a chronic disease was made for the first time, and used cumulative incidence function analysis taking into account the competing risks to investigate the incidence of chronic diseases and use of medication for chronic diseases. For antibiotic use, we counted the number of packs

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Table 1. The most common neonatal diagnoses of full-term patients with congenital hypothyroidism born between 1996 and 2018 in Finland and their matched controls

ICD-10 diagnosis	Cases (n = 438)	Controls (n = 835)	*P*[c]
P58-59 Neonatal jaundice[a]	49 (11.2%)	17 (2.0%)	<.001
P70 Neonatal hypoglycemia[b]	39 (8.9%)	23 (2.8%)	<.001
P22 Respiratory distress of newborn	17 (3.9%)	11 (1.3%)	.003
P21 Metabolic acidemia in newborn	14 (3.2%)	9 (1.1%)	.007

Abbreviation: ICD-10, International Classification of Disease, Tenth Revision.
[a]Iatrogenic jaundice (P58.4) excluded.
[b]Diabetes mellitus of newborn (P70.2) and iatrogenic hypoglycemia excluded (P70.3).
[c]Pearson chi-square.

bought per year of age and counted the cumulative use per person.

The data were analyzed using the Statistical Package for Social Sciences (SPSS for Windows, version 27, IBM Corp) and R (R Foundation for Statistical Computing, version 3.6.2). A *P* value of less than .05 was considered statistically significant.

Results

We recognized 531 full-term patients diagnosed with primary CH born between 1987 and 2018 in Finland. The sex ratio was 1:1.9 (181 boys and 350 girls). Four of them (0.8%) were twins. The mean age of mothers at childbirth was 29.6 years (95% CI, 29.2-30.1 years), and 211 (39.7%) of them were primiparas, 190 (35.8%) secundiparas, and 130 (24.5%) multiparas.

Neonatal and chronic diagnoses were studied in full-term CH patients born between 1996 and 2018 without known chromosomal and genetic abnormalities (n = 438, 148 boys and 290 girls).

Neonatal morbidity was more common in CH patients than their controls. Prolonged gestation (>42 weeks) was detected more often among newborns with CH (11.2% of CH patients, 2.8% of controls; $P < .001$). Neonatal jaundice, hypoglycemia, metabolic acidemia, and respiratory distress were diagnosed more often in newborns with CH than in their controls (Table 1).

A congenital malformation or deformation (ICD-10 Q00-Q89) was diagnosed in 66 of 438 CH patients (15.1%), whereas 62 of 835 controls (7.4%) had an accordant diagnosis ($P < .001$). More than 1 diagnosis of congenital abnormalities was found in 14 patients with CH (3.2%) compared to 3 individuals (0.4%; $P < .001$) in the control group. The most commonly affected extrathyroidal organ systems were the circulatory system (6.4% of CH patients and 3.2% of controls) and the musculoskeletal system (5.3% of CH cases, and 2.4% of controls) (Table 2). The most common cardiac defects in both studied groups were ventricular septal defects, patent foramen ovale, and patent ductus arteriosus, while the most common musculoskeletal defects in both groups were congenital deformities of the hip, followed by polydactylies and osteochondrodysplasias in CH patients,

Table 2. Congenital malformations and deformations (Q00-Q89) diagnosed in specialized health care of full-term patients with congenital hypothyroidism born between 1996 and 2018 in Finland and their matched controls

ICD-10 DIAGNOSIS	CASES (N = 438)	CONTROLS (N = 835)	*P*[B]
Q00-Q89 ANY CONGENITAL MALFORMATION OR CHROMOSOMAL ABNORMALITY	66 (15.1%)	62 (7.4%)	<.001
Q20-Q28 CONGENITAL MALFORMATIONS OF THE CIRCULATORY SYSTEM	28 (6.4%)	27 (3.2%)	.008
Q65-Q79 CONGENITAL MALFORMATIONS AND DEFORMATIONS OF THE MUSCULOSKELETAL SYSTEM	23 (5.3%)	20 (2.4%)	.007
Q10-Q18+Q35-Q37 CONGENITAL MALFORMATIONS OF the EYE, EAR, FACE, AND NECK[A] AND CLEFT LIP AND CLEFT PALATE	8 (1.8%)	7 (0.8%)	.121
Q60-Q64 CONGENITAL MALFORMATIONS OF THE URINARY SYSTEM	6 (1.4%)	4 (0.5%)	.087

Abbreviation: ICD-10, International Classification of Disease, Tenth Revision.
[a]Congenital stenosis and stricture of lacrimal duct (Q10.5) and prominent ear (Q17.5) excluded.
[b]Pearson chi-square.

and congenital deformities of the foot in controls. There was no significant difference between cases and controls in the incidence of malformations of the nervous system, facial area, digestive system, genital organs, or urinary system.

Hearing loss was diagnosed significantly more often in the CH group than in the control group (Fig. 1). The cumulative incidence of hearing loss, mostly sensorineural, was 5.0% (95% CI, 2.8%-8.0%) in CH patients and 1.0% (95% CI, 0.4%-2.3%) in controls at 15 years of age. There was no significant difference in the incidence of epilepsy in CH patients and controls during childhood and adolescence. However, at the age 20 years, the cumulative incidence of epilepsy was 6.5% (95% CI, 2.8%-12.5%) in CH patients and 0.4% (95% CI, 0.0%-1.5%) in controls. Furthermore, specific developmental disorders (ie, disorders of motor function, scholastic skills, speech and language) and intellectual disability were significantly more common in the CH group than in the control group. The cumulative incidence of specific developmental disorders was 14.1% (95% CI, 10.6%-18.0%) in CH patients and 5.6% (95% CI, 4.0%-7.6%) in controls at the age 15 years, and the cumulative incidence of intellectual disability was 2.9% (95% CI, 1.4%-5.3%) and 0.5% (95% CI, 0.1%-1.6%), respectively (see Fig. 1). The incidence of developmental disorders and intellectual disability was

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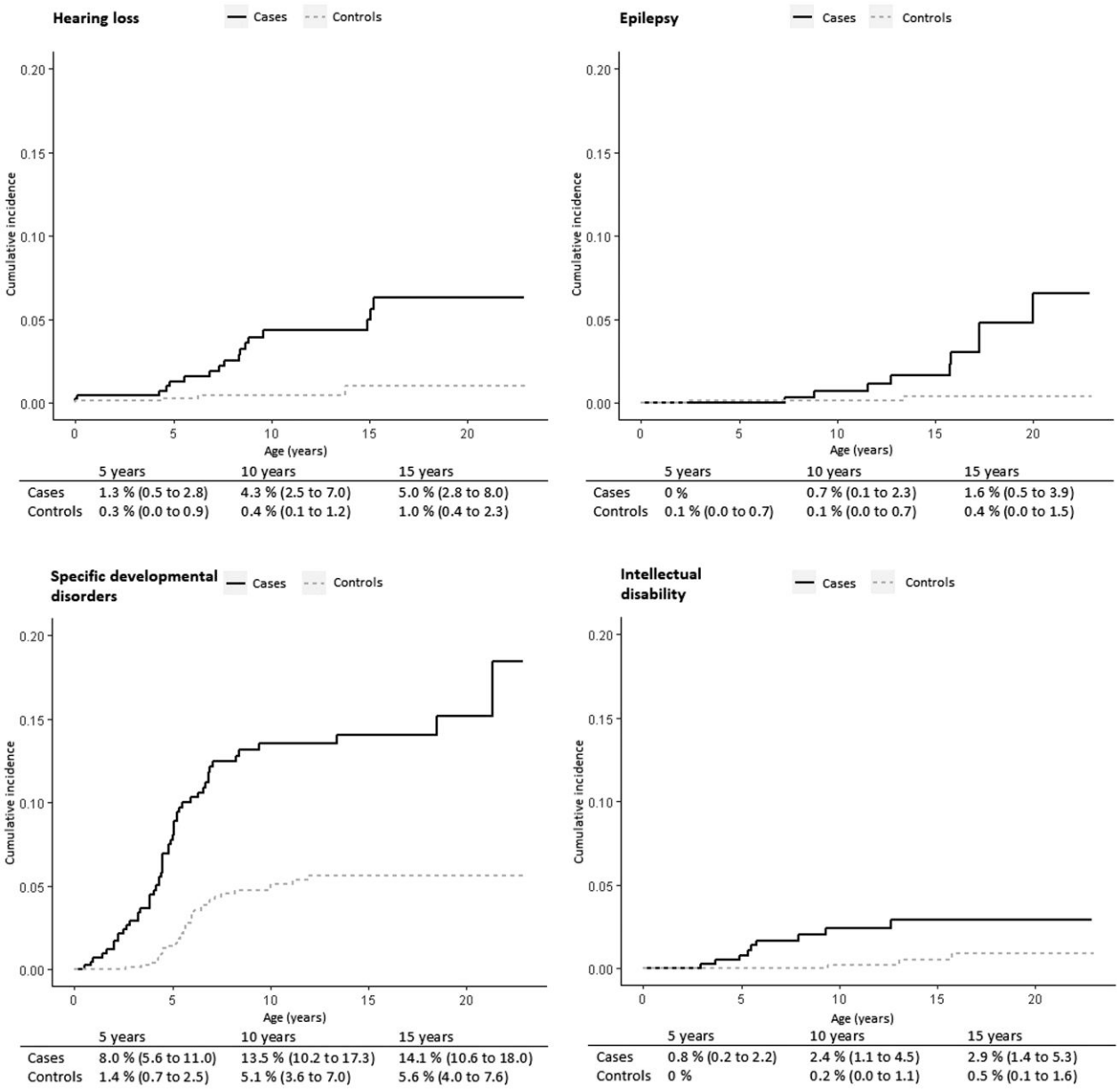

Figure 1. Cumulative incidence of hearing loss, epilepsy, specific developmental disorders, and intellectual disability in full-term congenital hypothyroidism patients and their matched controls born between 1996 and 2018 in Finland. The cumulative incidence at the age of 5, 10, and 15 years and 95% CIs are shown in tables under the curves.

similar in patients born in the first (1996-2007) and the second half (2007-2018) of the study period.

The incidence of neoplasms, juvenile arthritis, type 1 diabetes, inflammatory bowel diseases, and pervasive developmental diseases were recorded but the numbers of cases were too small for reliable comparisons. A trend toward an increased incidence of pervasive developmental diseases was seen in the CH group. The cumulative incidence of death at the age of 15 years was 0.6% (95% CI, 0.2%-1.6%) in CH patients and 0.2% (95% CI, 0.0%-0.7%) in controls.

Use of antidepressants or antipsychotics between CH patients and their controls was similar (Fig. 2). The cumulative incidence of the first purchase of antidepressants at the age of 20 years was 11.8% (95% CI, 7.7%-16.8%) in CH patients and 12.9% (95% CI, 9.7%-16.7%) in controls. At the same age, the cumulative incidence of the first purchase of antipsychotics was 6.5% (95% CI, 3.7%-10.4%) and 6.0% (95% CI, 3.9%-8.5%), respectively. The cumulative incidence of the first purchase of any ADHD medication at the age of 20 years was higher in CH patients (4.3%; 95% CI, 2.4%-7.1%) than in controls (2.7%; 95% CI, 1.6%-4.3%), but this difference was not statistically significant (see Fig. 2).

Moreover, the cumulative use of antibiotics was higher in CH patients, particularly during the first 3 years of life (Fig. 3).

Discussion

Our nationwide study showed that patients with CH have more neonatal morbidity and a higher incidence of congenital malformations than their matched controls. Specific developmental disorders, intellectual disability, and hearing loss were

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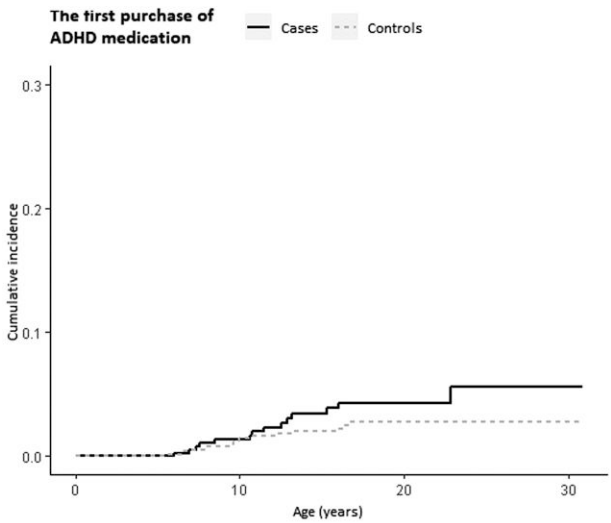
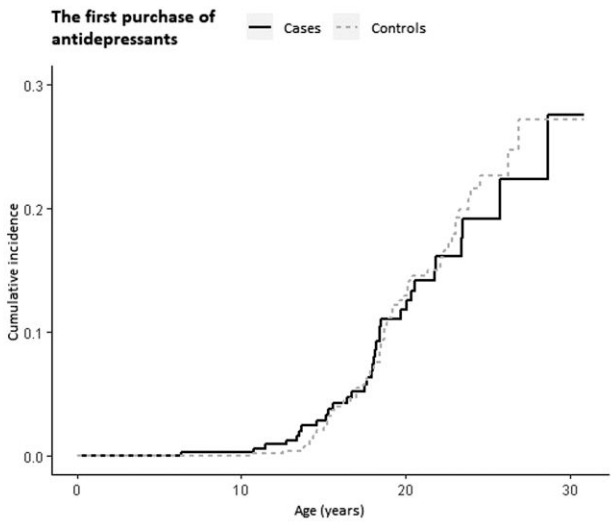
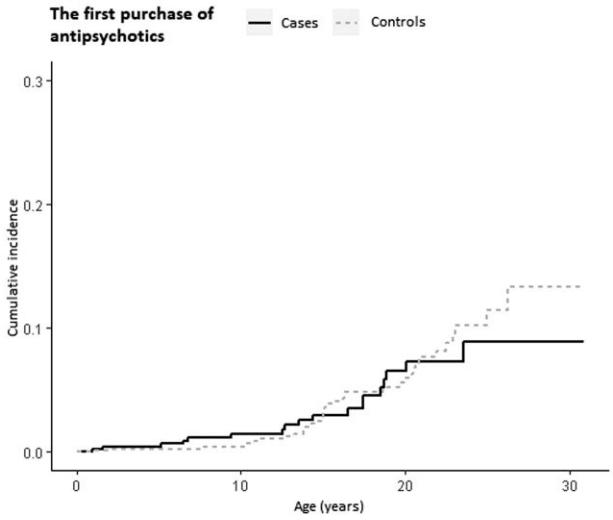




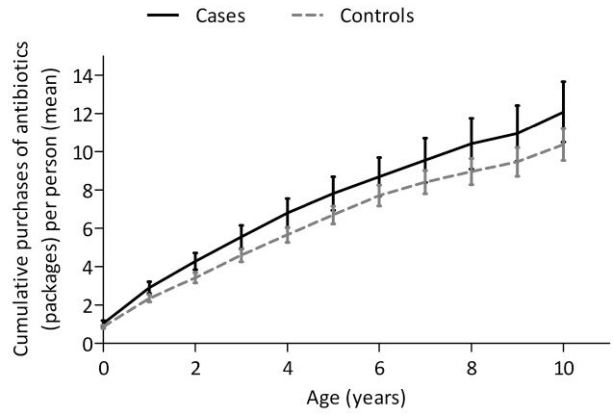


The first purchase of ADHD medication	10 years	15 years	20 years
Cases	1.3 % (0.5 to 2.9)	3.4 % (1.8 to 5.8)	4.3 % (2.4 to 7.1)
Controls	1.4 % (0.7 to 2.5)	2.0 % (1.1 to 3.3)	2.7 % (1.6 to 4.3)

The first purchase of antidepressants	10 years	15 years	20 years
Cases	0.3 % (0.0 to 1.3)	2.9 % (1.3 to 5.4)	11.8 % (7.7 to 16.8)
Controls	0 %	2.3 % (1.2 to 4.0)	12.9 % (9.7 to 16.7)

The first purchase of antipsychotics	10 years	15 years	20 years
Cases	1.4 % (0.6 to 3.0)	3.0 % (1.5 to 5.3)	6.5 % (3.7 to 10.4)
Controls	0.4 % (0.1 to 1.0)	3.1 % (1.9 to 4.9)	6.0 % (3.9 to 8.5)

Figure 2. Cumulative incidence of the first purchase of antidepressants, antipsychotics, and agents used for attention deficit hyperactivity disorder (ADHD) in full-term congenital hypothyroidism patients and their matched controls born between 1987 and 2017 in Finland. The cumulative incidence at the age of 10, 15, and 20 years and 95% CIs are shown in tables.



Age (years)	0	1	2	3	4	5	6	7	8	9	10
Cases	432	418	398	380	360	340	316	294	271	253	236
Controls	825	798	761	724	687	648	601	563	518	482	449

Figure 3. Cumulative purchases of antibiotics (packages) per person during the first 10 years in congenital hypothyroidism patients and their matched controls born between 1995 and 2017. Error bars represent 95% CIs.

also more common in CH patients. The use of antibiotics and ADHD medication was also more frequent in the CH group.

After initializing newborn screening programs, little is reported on neonatal morbidity related to CH. However, prolonged gestation (8, 34), large fontanels, and large head circumference (8, 17, 22, 34) together with prolonged jaundice, muscle hypotonia, and large tongue (17, 22, 34) are well-known features accompanying CH in the neonatal period. Furthermore, respiratory distress is known to occur more often in newborns with CH (23, 34). In line with previous reports, in the present study the most common neonatal condition was jaundice (11.2%). In Finland, the ICD-10 code of neonatal jaundice is used only if treatment is indicated or jaundice is prolonged, which explains the relatively low incidence rate in the control group (2.0%) being in line with other Nordic countries; for example, in Norway 3.5% of babies born at week 40 of pregnancy develop jaundice (35).

In the present study, 8.9% of CH patients had neonatal hypoglycemia. To our knowledge, an association between neonatal hypoglycemia and CH has not been previously described. However, many of the known neonatal problems

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occurring in CH are simultaneous risk factors for neonatal hypoglycemia.

The embryonic thyroid development is closely associated with the developing heart. Hence, cardiac defects are the most common extrathyroidal anomalies in CH patients. In the present study, the incidence of congenital malformations in the circulatory system was 6.4% in CH patients. In line with this finding, the incidence of cardiac malformations in CH patients has been reported to vary between 4% and 16% in previous studies (4, 14-18, 23). The incidence of other congenital malformations has varied more in earlier reports, but similar to our study, increased incidence of musculoskeletal anomalies (4, 18, 20) has been reported in CH patients.

In our study, there was no significant difference in the incidence of congenital malformations of the urogenital organs, gastrointestinal system, eye, ear, face, neck, and the nervous system or in the incidence of cleft lip and palate between the CH and control groups. In earlier studies, an increased prevalence of urogenital (13, 19, 20) and gastrointestinal (15, 17) malformations and cleft lip and/or palate (14) has been described. We excluded undescended testicles and testis saltans (ie, retractile testis), ankyloglossia, prominent ear, and stricture of the lacrimal duct from our study because of a potential reporting bias related to the nature of the applied registers. These conditions are often followed-up in primary health care in Finland and are therefore not recorded in the Care Register for Health Care used in this study. Furthermore, central, instead of primary, CH is more often associated with malformations of the nervous system. These limitations of the study and the small number of detected malformations in these organ systems could explain the difference from previous literature.

Several studies have reported subnormal cognitive and motor development in some CH patients (25, 31-33). In a French study, the incidence of major mental or neurological diseases was remarkably higher in the CH population than in the general population (odds ratio = 4.36) (30). Our data reveal a striking increase in the cumulative incidence of specific developmental disorders in CH. In addition, it should be noted that milder disorders are diagnosed and treated in primary health care and are therefore not even recognized in this study. The effect of these disorders on everyday life in childhood and adulthood remains unclear.

In Finland, ADHD and most psychiatric conditions can be diagnosed both in primary and secondary health care. Therefore, we examined the use of ADHD medications, antipsychotics, and antidepressants instead of recorded diagnoses. In earlier quality-of-life studies, anxiety and depressive mood have been more common in CH patients than in the general population (36, 37). Our results, however, do not support increased existence of severe psychiatric comorbidity since the use of antidepressants and antipsychotics was similar among CH patients and controls.

In ADHD, the role of CH per se along with overtreatment and undertreatment with levothyroxine has been debated. Overtreatment during the first months of life has been suggested to lead to an increase in ADHD-associated symptoms (38, 39). In Australia, children with mildly elevated thyrotropin levels (under the cutoff limit) in the newborn screening test were prescribed stimulant medication for the treatment of ADHD more likely than their siblings (40). On the contrary, in a Norwegian study, the ADHD risk appeared to be elevated among newborns with low thyrotropin levels (41). On the other hand, in a study from Washington, DC, neonatal thyroxine levels of ADHD patients did not differ from controls (42). In the present study, we found a nonsignificant trend toward an increased use of ADHD medication in CH patients.

To our knowledge, the use of antibiotics in CH patients has not been studied previously. The observed increase in the use of antibiotics particularly during the first 3 years of life is likely to reflect the medical burden caused by the higher prevalence of congenital malformations and chronic diseases among CH patients.

Our study is a large, population-based register study covering all CH patients born in Finland during the study period and their matched controls. We were able to retrieve similar reliable (43) data from nationwide registers both for CH cases and their controls. Unfortunately, we were not able to link patient records with register data and therefore could not compare the cases with thyroid dysgenesis and dyshormonogenesis. Neither did we have data on possible overtreatment and undertreatment or mothers' thyroid status.

The results of this study help to understand the overall burden associated with CH and remind us to pay attention in follow-up not only to the CH but also to development and comorbidities.

In conclusion, CH patients have more neonatal morbidity and more congenital malformations than their matched controls. The cumulative incidence of hearing loss and specific developmental disorders is increased in CH patients. However, our results do not support the existence of severe psychiatric comorbidity.

Funding

This work was supported by grants from the Foundation for Pediatric Research (Helsinki, Finland) and Kuopio University Hospital (Kuopio, Finland).

Disclosures

The authors have nothing to disclose.

Data Availability

Restrictions apply to the availability of all data generated and analyzed during this study to preserve patient confidentiality. The corresponding author will on request detail the restrictions in data sharing.

References

1. Kurinczuk JJ, Bower C, Lewis B, Byrne G. Congenital hypothyroidism in Western Australia 1981-1998. *J Paediatr Child Health*. 2002;38(2):187-191.
2. Waller DK, Anderson JL, Lorey F, Cunningham GC. Risk factors for congenital hypothyroidism: an investigation of infant's birth weight, ethnicity, and gender in California, 1990-1998. *Teratology*. 2000;62(1):36-41.
3. Albert BB, Cutfield WS, Webster D, *et al*. Etiology of increasing incidence of congenital hypothyroidism in New Zealand from 1993-2010. *J Clin Endocrinol Metab*. 2012;97(9):3155-3160.
4. Tuli G, Munarin J, Tessaris D, Matarazzo P, Einaudi S, de Sanctis L. Incidence of primary congenital hypothyroidism and relationship between diagnostic categories and associated malformations. *Endocrine*. 2021;71(1):122-129.
5. Hinton CF, Harris KB, Borgfeld L, *et al*. Trends in incidence rates of congenital hypothyroidism related to select demographic factors:

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data from the United States, California, Massachusetts, New York, and Texas. *Pediatrics*. 2010;125(Suppl 2):S37-S47.
6. McGrath N, Hawkes CP, McDonnell CM, *et al.* Incidence of congenital hypothyroidism over 37 years in Ireland. *Pediatrics*. 2018;142(4):e20181199.
7. Deladoëy J, Ruel J, Giguère Y, Van Vliet G. Is the incidence of congenital hypothyroidism really increasing? A 20-year retrospective population-based study in Québec. *J Clin Endocrinol Metab*. 2011;96(8):2422-2429.
8. Danner E, Niuro L, Huopio H, *et al.* Incidence of primary congenital hypothyroidism over 24 years in Finland. *Pediatr Res*. 2023;93(3):649-653.
9. Wassner AJ. Congenital hypothyroidism. *Clin Perinatol*. 2018;45(1):1-18.
10. Van Trotsenburg P, Stoupa A, Léger J, *et al.* Congenital hypothyroidism: a 2020-2021 consensus guidelines update—an ENDO-European Reference Network initiative endorsed by the European Society for Pediatric Endocrinology and the European Society for Endocrinology. *Thyroid*. 2021;31(3):387-419.
11. Peters C, van Trotsenburg ASP, Schoenmakers N. Congenital hypothyroidism: update and perspectives. *Eur J Endocrinol*. 2018;179(6):R297-R317.
12. Wassner AJ, Brown RS. Congenital hypothyroidism: recent advances. *Curr Opin Endocrinol Diabetes Obes*. 2015;22(5):407-412.
13. Gu YH, Harada S, Kato T, Inomata H, Aoki K, Hirahara F. Increased incidence of extrathyroidal congenital malformations in Japanese patients with congenital hypothyroidism and their relationship with down syndrome and other factors. *Thyroid*. 2009;19(8):869-879.
14. Kreisner E, Neto EG, Gross JL. High prevalence of extrathyroid malformations in a cohort of Brazilian patients with permanent primary congenital hypothyroidism. *Thyroid*. 2005;15(2):165-169.
15. Chao T, Wang JR, Hwang B. Congenital hypothyroidism and concomitant anomalies. *J Pediatr Endocrinol Metab*. 1997;10(2):217-221.
16. Mazahir FA, Khadora MM. A retrospective analysis of congenital anomalies in congenital hypothyroidism. *J Pediatr Endocrinol Metab*. 2020;33(9):1147-1153.
17. Baş VN, Özgelen Ş, Çetinkaya S, Aycan Z. Diseases accompanying congenital hypothyroidism. *J Pediatr Endocrinol Metab*. 2014;27(5-6):485-489.
18. Olivieri A, Stazi MA, Mastroiacovo P, *et al;* Study Group for Congenital Hypothyroidism. A population-based study on the frequency of additional congenital malformations in infants with congenital hypothyroidism: data from the Italian Registry for Congenital Hypothyroidism (1991-1998). *J Clin Endocrinol Metab*. 2002;87(2):557-562.
19. Kumar J, Gordillo R, Kaskel FJ, Druschel CM, Woroniecki RP. Increased prevalence of renal and urinary tract anomalies in children with congenital hypothyroidism. *J Pediatr*. 2009;154(2):263-266.
20. Kholy ME, Fahmi ME, Nassar AE, Selim S, Elsedfy HH. Prevalence of minor musculoskeletal anomalies in children with congenital hypothyroidism. *Horm Res*. 2007;68(6):272-275.
21. Fort P, Lifshitz F, Bellisario R, *et al.* Abnormalities of thyroid function in infants with Down syndrome. *J Pediatr*. 1984;104(4):545-549.
22. Virtanen M. Manifestations of congenital hypothyroidism during the 1st week of life. *Eur J Pediatr*. 1988;147(3):270-274.
23. Fernhoff PM, Brown AL, Elsas LJ. Congenital hypothyroidism: increased risk of neonatal morbidity results in delayed treatment. *Lancet*. 1987;329(8531):490-491.
24. Rovet J, Walker W, Bliss B, Buchanan L, Ehrlich R. Long-term sequelae of hearing impairment in congenital hypothyroidism. *J Pediatr*. 1996;128(6):776-783.
25. Léger J. Congenital hypothyroidism: a clinical update of long-term outcome in young adults. *Eur J Endocrinol*. 2015;172(2):R67-R77.
26. Vanderschueren-Lodeweyckx M, Debruyne F, Dooms L, Eggermont E, Eeckels R. Sensorineural hearing loss in sporadic congenital hypothyroidism. *Arch Dis Child*. 1983;58(6):419-422.
27. Aleksander PE, Brückner-Spieler M, Stoehr AM, *et al.* Mean high-dose l-thyroxine treatment is efficient and safe to achieve a normal IQ in young adult patients with congenital hypothyroidism. *J Clin Endocrinol Metab*. 2018;103(4):1459-1469.
28. Cherella CE, Wassner AJ. Update on congenital hypothyroidism. *Curr Opin Endocrinol Diabetes Obes*. 2020;27(1):63-69.
29. Léger J, Ecosse E, Roussey M, Lanoë JL, Larroque B*;* French Congenital Hypothyroidism Study Group. Subtle health impairment and socioeducational attainment in young adult patients with congenital hypothyroidism diagnosed by neonatal screening: a longitudinal population-based cohort study. *J Clin Endocrinol Metab*. 2011;96(6):1771-1782.
30. Azar-Kolakez A, Ecosse E, Dos Santos S, Léger J. All-cause and disease-specific mortality and morbidity in patients with congenital hypothyroidism treated since the neonatal period: a national population-based study. *J Clin Endocrinol Metab*. 2013;98(2):785-793.
31. Bongers-Schokking JJ, De Muinck Keizer-Schrama SMPF. Influence of timing and dose of thyroid hormone replacement on mental, psychomotor, and behavioral development in children with congenital hypothyroidism. *J Pediatr*. 2005;147(6):768-774.
32. Rovet JF. Children with congenital hypothyroidism and their siblings: do they really differ? *Pediatrics*. 2005;115(1):e52-e57.
33. Buluş AD, Tiftik E. Evaluation of neurodevelopment of children with congenital hypothyroidism by the Denver Developmental Screening Test. *J Pediatr Endocrinol Metab*. 2017;30(10):1061-1066.
34. Smith DW, Klein AM, Henderson JR, Myrianthopoulos NC. Congenital hypothyroidism—signs and symptoms in the newborn period. *J Pediatr*. 1975;87(6):958-962.
35. Murzakanova G, Räisänen S, Jacobsen AF, Sole KB, Bjarkø L, Laine K. Adverse perinatal outcomes in 665,244 term and post-term deliveries—a Norwegian population-based study. *Eur J Obstet Gynecol Reprod Biol*. 2020;247:212-218.
36. Van Der Sluijs Veer L, Kempers MJE, Last BF, Vulsma T, Grootenhuis MA. Quality of life, developmental milestones, and self-esteem of young adults with congenital hypothyroidism diagnosed by neonatal screening. *J Clin Endocrinol Metab*. 2008;93(7):2654-2661.
37. Sato H, Nakamura N, Harada S, Kakee N, Sasaki N. Quality of life of young adults with congenital hypothyroidism. *Pediatr Int*. 2009;51(1):126-131.
38. Álvarez M, Iglesias Fernández C, Rodríguez Sánchez A, Dulín Íñiguez E, Rodríguez Arnao MD. Episodes of overtreatment during the first six months in children with congenital hypothyroidism and their relationships with sustained attention and inhibitory control at school age. *Horm Res Paediatr*. 2010;74(2):114-120.
39. Bongers-Schokking JJ, Resing WCM, Oostdijk W, De Rijke YB, De Muinck Keizer-Schrama SMPF. Relation between early over- and undertreatment and behavioural problems in preadolescent children with congenital hypothyroidism. *Horm Res Paediatr*. 2019;90(4):247-256.
40. Lain SJ, Wiley V, Jack M, Martin AJ, Wilcken B, Nassar N. Association of elevated neonatal thyroid-stimulating hormone levels with school performance and stimulant prescription for attention deficit hyperactivity disorder in childhood. *Eur J Pediatr*. 2021;180(4):1073-1080.
41. Villanger GD, Ystrom E, Engel SM, *et al.* Neonatal thyroid-stimulating hormone and association with attention-deficit/hyperactivity disorder. *Paediatr Perinat Epidemiol*. 2020;34(5):590-596.
42. Soldin OP, Nandedkar AKN, Japal KM, *et al.* Newborn thyroxine levels and childhood ADHD. *Clin Biochem*. 2002;35(2):131-136.
43. Sund R. Quality of the Finnish Hospital Discharge Register: a systematic review. *Scand J Public Health*. 2012;40(6):505-515.

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