Congenital hypothyroidism and thyroid function in a Japanese birth cohort: data from The Japan Environment and Children's Study

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Highlights

- The study identified a prevalence of CH in 170.5 per 100,000 children in Japan, noting a higher risk for additional congenital diseases among those diagnosed.
- At age 2, the median TSH and fT4 levels were 2.13 µIU/mL and 1.2 ng/dL, with boys exhibiting slightly elevated levels compared to girls.

Abstract. The most common hormonal and metabolic disease in early childhood is congenital hypothyroidism (CH). This study aimed to describe CH in large-scale birth cohort data and summarize the results of serum thyroid-stimulating hormone (TSH) and free thyroxine (fT4) levels in 2-yr-old children. Data were obtained from the Japan Environment and Children's Study (JECS), and we identified 171 children with CH detected in newborn screenings or medical records (170.5 per 100,000 population). Infants with CH are at higher risk of developing congenital diseases than those without CH. Of 171 children with CH, 20 (11.7%) were diagnosed with congenital heart defects, 33 (19.3%) had chromosomal or other congenital abnormalities, and 23 (13.5%) had Down syndrome. At the age of 2 yr old, the median and 95% reference range values for TSH and fT4 were 2.13 (0.78–5.52) µIU/mL and 1.2 (1.0–1.5) ng/dL, respectively. Moreover, boys had slightly higher TSH and fT4 levels than did girls. Data on the distribution of TSH and fT4 in 2-yr-old children should be useful for decreasing the misclassification of thyroid disorders in the pediatric population. Trial-off treatment and re-evaluation of thyroid function are needed to classify permanent congenital hypothyroidism and transient congenital hypothyroidism after 3 yr of age.

Key words: congenital hypothyroidism, children, birth cohort, thyroid-stimulating hormone, free thyroxine

Introduction

The most common hormonal and metabolic disease in young children is congenital hypothyroidism (CH), in which insufficient thyroid hormones are in the body owing to thyroid dysgenesis or dyshormonogenesis (1). Notably, thyroid hormones are necessary for myelin sheath formation during early life. A lack of thyroid hormones during the fetal and infant periods results in irreversible neurodevelopmental impairments (1). Furthermore, thyroid hormones are associated with growth hormone secretion and bone maturation, and thyroid dysfunction causes failure in childhood and adolescence and early osteoporosis in adulthood (1).

Due to the lack of clinical signs at birth, most infants with CH are identified using newborn screening (NBS). CH is also the most common condition found in NBS, with an incidence of 1 in 2000 ~ 4000 births, according to their data (2). Recent studies have shown that the incidence of CH is increasing in some areas (3). Most NBS programs in Japan measure infant thyroid-stimulating hormone (TSH) levels at 4–6 d of age as an initial screening test. Moreover, children with abnormal TSH levels are retested or undergo detailed thyroid function tests and medical examinations. This approach can screen for primary CH but is useless for central CH. Although CH can be identified in most infants through NBS, some cases still go undetected. This study aimed to describe CH in the Japan Environment and Children's Study (JECS), a large-scale birth cohort study that collects information on CH diagnosed by NBS or clinicians. Other birth cohort studies have shown that major pituitary–thyroid axis changes occur in early life (4). Notably, the JECS monitors children's serum TSH and free thyroxine (fT4) levels every two years after birth. Therefore, the other aim of this study was to summarize the results of serum TSH and fT4 levels in 2-yr-old children.

Methods

Study design

Data were obtained from the JECS, a large-scale birth cohort with 104062 records (5). Pregnant women were recruited between January 2011 and March 2014. The JECS is an ongoing multicenter study aimed at evaluating the relationship between environmental factors and children's health and development. A detailed description of the study design is provided elsewhere (5–7).

The JECS collects information about NBS from medical records at the one-month check-up, known as the Dr1m survey. The JECS also gathers data on developing serious childhood illnesses, including birth defects, Kawasaki disease, epilepsy, hormonal and metabolic diseases, childhood cancers, and mental disorders by questionnaire surveys. Additionally, by reviewing medical record transcripts, the JECS conducts

a more detailed survey to investigate the diagnoses and treatments of children with serious diseases, as identified from the questionnaire surveys. This is referred to as the Serious Disease Survey (SDS). In the SDS, information on the presence of CH is obtained from medical records of children with caregiver-reported hormonal and metabolic diseases. The SDS also includes a question on whether the patient was detected using NBS. We defined CH based on the above 2 surveys. Specifically, CH in this study included 1) those diagnosed through NBS according to information from Dr1m or SDS, 2) central CH in SDS, and 3) those with primary CH who were only identified through medical records in SDS, which included patients who were not identified by NBS or for whom this information was missing. To exclude the possible presence of acquired hypothyroidism, we excluded 11 patients whose initial visit was more than 3 mo old and three cases whose initial visit was unknown.

In addition to questionnaire surveys, the JECS designed a subcohort study (SCS) that included approximately 5000 participants to collect data that could not be obtained from the questionnaire survey, such as allergic sensitization, thyroid function, and 25-hydroxyvitamin D levels (8, 9). The protocols for these studies are available on the website of the Japanese Ministry of Environment (8, 10).

Blood tests were done in 4695 2-yr-old children who were recruited for SCS. After excluding 27 children with missing TSH or fT4 values, 885 children who were reported to be ill at the time of medical examination, 25 children with unknown physical conditions, and six children with CH, 3753 records were used to evaluate the distribution of TSH and fT4 in 2-yr-old children (**Fig. 1**).

The blood samples were measured at the LSI Medicine Corporation (Tokyo, Japan). The chemiluminescence immunoassay (CLIA kit) was used to measure TSH (normal range: 0.350–4.940 µIU/mL) and fT4 (normal range: 0.70–1.48 ng/dL), and the intra- and inter-assay coefficients of variation for TSH and fT4 levels are presented in Supplementary Table 1.

Due to the lack of reference values for TSH/fT4 in children, we used adult reference ranges to define hyper and hypothyroidism as TSH < 0.35 µIU/mL and TSH > 4.94 µIU/mL, respectively. Both were further classified as overt (TSH < 0.35 µIU/mL and fT4 ≥ 1.48 ng/dL for overt hyperthyroidism; TSH > 4.94 µIU/mL and fT4 ≤ 0.7 ng/dL for overt hypothyroidism) and mild (TSH < 0.35 µIU/mL and fT4 < 1.48 ng/dL for mild hyperthyroidism; TSH > 4.94 µIU/mL and fT4 > 0.7 ng/dL for mild hypothyroidism) according to fT4 levels.

The main study and SCS were conducted in accordance with the guidelines specified in the Declaration of Helsinki. The JECS protocol was reviewed and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies and the Ethics Committees of all participating institutions (No.100910001). All JECS participants signed informed consent forms to participate in the main study or the SCS (8).
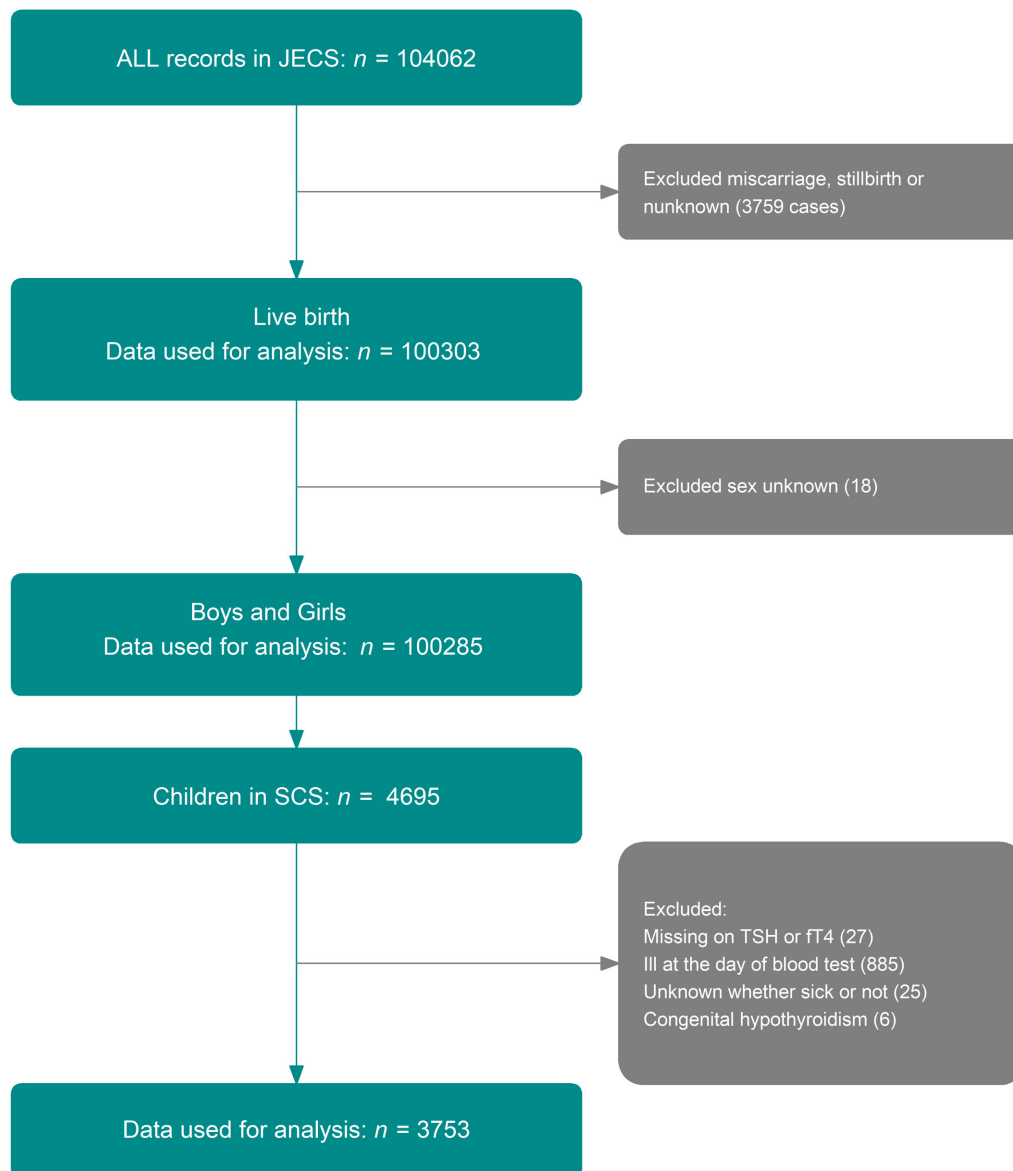
Fig. 1. Flow chart. SCS, Sub-Cohort Study; TSH, thyroid-stimulating hormone; fT4, free thyroxine.

The data used for our analyses were obtained from jecs-ta-20190930-qsn and jecs-ta-20200424-ddr, released by the Program Office (last updated on 2022/10/03).

Statistical analysis

Distributions of TSH and fT4 levels are shown in the 2.5^{th}, 25th, 50th, 75th, and 97.5^{th} percentiles. The two-tailed Pearson chi-square test or Fisher's exact test was used to compare differences in categorical variables between groups. The Mann–Whitney rank sum test was used to compare the TSH and fT4 levels distribution between boys and girls. Furthermore, the relationship between TSH and fT4 levels in 2-yr-old children was evaluated using linear regression analysis. The TSH levels were log-transformed into a model. A restricted cubic spline with three knots was used for continuous variables in the model to relax the linear assumption.

The missing values were excluded from the model. All analyses were performed using the R version 4.3.0 software (Institute for Statistics and Mathematics, Vienna, Austria; www.r-project.org).

Results

CH in the JECS cohort

Based on data from the Dr1m and SDS, 171 cases of CH (170.5 per 100,000 children) were detected. Moreover, we found two cases of central CH (two per 100,000 children) using the SDS. Of the 171 CH, 83 were girls, and 88 were boys, with a sex ratio (female-to-male ratio) of approximately 0.94:1.

No significant difference in developing CH was found between boys and girls. The incidence of CH was significantly higher in preterm and low-birth weight

infants than in healthy children. Furthermore, the incidence was higher in winter and spring; however, there was no statistically significant difference compared to that of other seasons (**Table 1**).

The cases of CH complicated by congenital anomalies are presented in **Tables 1 and 2**. Of the 171 patients with CH, 20 (11.7%), 33 (19.3%), and 23 (13.5%) were diagnosed with congenital heart defects (CHD),

Table 1. Congenital hypothyroidism in the JECS cohort

	n	N	Per 100,000 children	p-value
CH at birth	171	100,303	170.5	
Central CH	2	100,303	2.0	
Sex				0.96
Boys	88	51396	171.2	
Girls	83	48889	169.8	
Gestational weeks				0.005
≥ 37	153	94426	162.0	
< 37	18	5584	322.4	
Birth weight (g)				< 0.001
≥ 2500 g	137	90663	151.1	
< 2500 g	34	9275	366.6	
Twin				0.39
No	170	98412	172.7	
Yes	1	1891	52.9	
Seasons				0.05
Spring	48	23414	205.0	
Summer	35	26849	130.4	
Autumn	40	27594	145.0	
Winter	48	22442	213.9	
Congenital heart defects				< 0.001
No	151	99297	152.1	
Yes	20	1006	1988.1	
Chromosomal abnormality or other congenital abnormality				< 0.001
No	138	98642	139.9	
Yes	33	1661	1986.8	

CH, congenital hypothyroidism; JECS, The Japan Environment and Children's Study.

Table 2. Congenital anomalies in 171 congenital hypothyroidism cases found in JECS

Congenital anomalies	n	%
Congenital heart defect	20	11.7
Ventricular septal defect	10	5.8
Atrial septal defect	7	4.1
Patent ductus arteriosus	9	5.3
Atrioventricular septal defect	3	1.8
Chromosomal abnormality or other congenital abnormality	33	19.3
Down syndrome	23	13.5
Central nervous system	0	0.0
Ear anomalies	7	4.1
Congenital hearing loss	4	2.3
Low-set ear	3	1.8
Cleft palate & lip	0	0.0
Digestive system	6	3.5
Congenital duodenal atresia	2	1.2
Inguinal hernia	3	1.8
Urogenital malformations	4	2.3
Hydronephrosis	3	1.8
Hypospadias	1	1.0
Musculoskeletal anomalies	2	1.2
Achondroplasia	1	1.0
Floppy infant	1	1.0

JECS, The Japan Environment and Children's Study.

chromosomal or other congenital abnormalities, and Down syndrome, respectively (**Table 2**). Furthermore, infants with CH had a higher risk of developing congenital diseases than did those without CH. (**Table 1**).

Thyroid function at 2 yr

The distributions of TSH and fT4 levels are presented in **Table 3**. Histograms of the TSH and fT4 levels at 2 yr of age are shown in **Figs. 2** and **Fig. 3**. At

Table 3. Thyroid-stimulating hormone and free thyroxine among children aged 2 yr

	N	2.5th	25th	50th	75th	97.5th	Mean	SD	*p*-value
TSH									< 0.001
ALL	3753	0.78	1.54	2.13	2.93	5.52	2.39	1.25	
Boys	1891	0.78	1.61	2.21	3.06	5.89	2.49	1.28	
Girls	1862	0.78	1.49	2.04	2.79	5.09	2.28	1.21	
fT4									< 0.001
ALL	3753	1.0	1.1	1.2	1.3	1.5	1.21	0.13	
Boys	1891	1.0	1.1	1.2	1.3	1.5	1.22	0.13	
Girls	1862	1.0	1.1	1.2	1.3	1.5	1.21	0.13	

TSH, thyroid-stimulating hormone; fT4, free thyroxine.
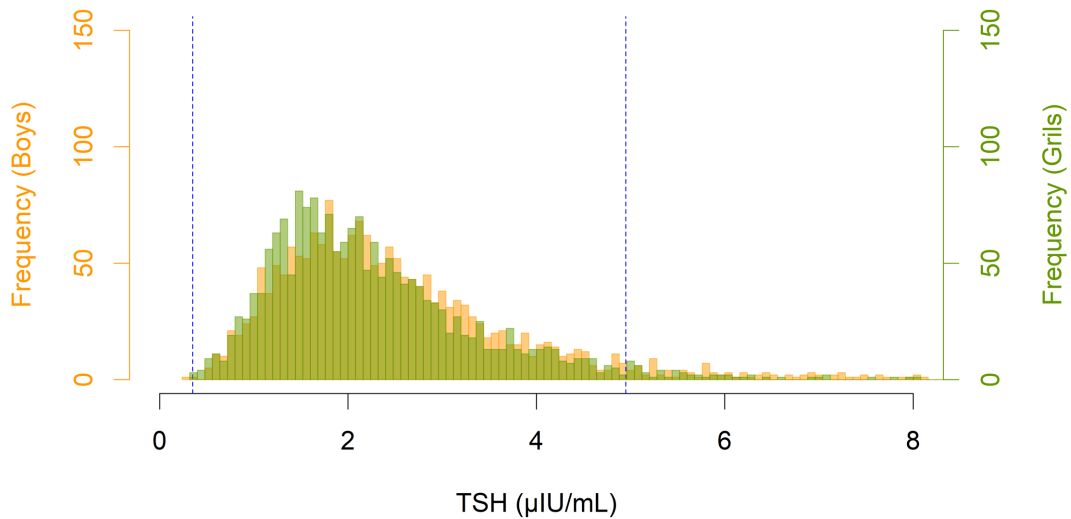
Fig. 2. Histograms of thyroid-stimulating hormone for children aged 2 yr. Break lines are reference ranges for adults. TSH, thyroid-stimulating hormone.
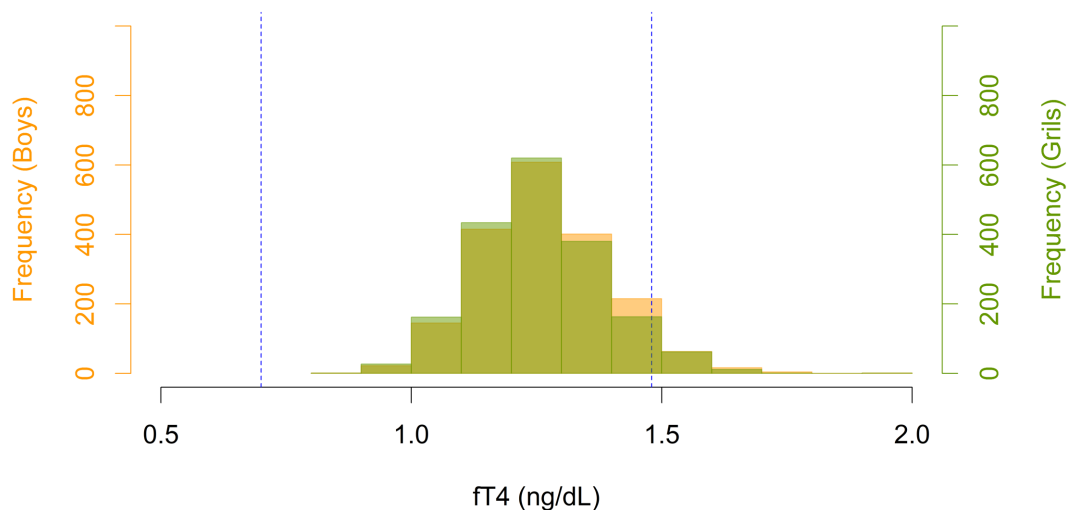
Fig. 3. Histograms of free thyroxine for children aged 2 yr. Break lines are reference ranges for adults. fT4, free thyroxine.

2 yr of age, the median and 95% reference range values for TSH and fT4 were 2.13 (0.78–5.52) μIU/mL and 1.2 (1.0–1.5) ng/dL, respectively. Boys had slightly higher TSH and fT4 levels than did girls.

Table 4 shows hypothyroidism and hyperthyroidism prevalence rates at 2 yr. Among 3753 records, TSH > 4.94 μIU/mL was found in 152 children (4.1%). Only 3 patients were found to have hyperthyroidism, which explained approximately 0.08% of the 2-yr-old population in the SCS. Furthermore, the hypothyroidism rates at 2 yr by sex, preterm status, and birthweight are presented in Supplementary Table 2. Girls had a lower risk for hypothyroidism. There was no significant association of abnormal thyroid function with preterm status and birth weight.

The association between fT4 and TSH levels at 2 yr of age was evaluated using linear regression analysis. After adjusting for sex, preterm birth, weight, and height at 2 yr, fT4 was not associated with TSH ($p > 0.05$) for either the linear or nonlinear parts of fT4, according to Wald statistics. The partial effects of serum fT4 levels in the model are shown in Supplementary Fig. 1.

Discussion

We identified 171 cases of CH within the JECS, which comprises approximately 100,000 participants. Caution should be exercised when comparing this incidence with other countries, as the cases of CH reported in this study include not only permanent CH (PCH) but also a subset of transient congenital hypothyroidism (TCH) cases, which necessitate re-evaluation after 3 yr.

In the JECS, the female-to-male distribution among children with CH was 0.94:1. Notably, this demographic characteristic has been extensively investigated. Reports from Western countries indicate that the ratio for true CH is approximately 2:1 [3]. Moreover, the study found that the female-to-male ratio was 2:1 for thyroid dysgenesis, 1:1 for eutopic thyroid glands, and 0.5:1 to 1:1 for TCH [11–13]; therefore, a deviation from a sex ratio of 2 indicates that TCH may have been misclassified as true CH. However, the sex ratio in CH varies by region and race; specifically, that of children with CH in the JECS was similar to that in other Asian populations, which was 0.65:1 for PCH and 0.89:1 for TCH in Xiamen, China [14], and 1.09:1 in Taiwan [15].

We found that among infants with primary CH detected by NBS according to the Dr1m survey or SDS, approximately 20% of caregivers did not report that their children had hormonal or metabolic conditions in subsequent questionnaire surveys. We speculate that most of these patients were infants with TCH with abnormal fT4 or TSH levels during the first month of life, which normalized thereafter. Notably, the incidence of TCH varies according to the different definitions. Some studies have indicated that approximately 10–15% of CH are TCH. Furthermore, TCH has four causes: transplacental passage of thyrotropin receptor-blocking antibodies, drugs used to manage maternal hyperthyroidism, iodine deficiency, and iodine excess [3]. A previous study in Japan found that approximately 50% of the infants with abnormal screening results recalled for further examination had a history of exposure to excessive maternal iodine intake [3, 16]. Thus, it is difficult to distinguish TCH from CH within 1 month of life because some of the causes of TCH mentioned above cannot be resolved early. Nonetheless, the proportion of TCH and its causes in Japan are beyond the scope of the current report and require further study.

A study of the seasonality of CH may reveal the influence of environmental factors on its pathogenesis. Regarding the seasonality of CH, an English study showed a high incidence from October to March [17], a result which is consistent with our findings. Our data also suggest a high incidence in winter and spring, although there was no significant difference compared with that of the other seasons. In a study by Gu *et al.* on the seasonality of primary CH in Japan, it was suggested that there is temperature-related seasonality in primary CH [18]. Therefore, the lack of significance in our study may be due to the presence of some TCH among CH cases.

There were 20 (11.7%) patients with CH who also had CHD. CH is linked to elevated odds of developing congenital anomalies, particularly CHD. For instance, Gu *et al.* examined 1520 Japanese CH cases and found that 8.9% had CHD [19]. An Italian study reported 17 cardiac malformations in 105 patients (16.1%) [20]. Research in Taiwan similarly indicated that infants with CH had a higher prevalence of CHDs compared to the general infant population [21]. Additionally, a study focusing on young children with CHD reported a

Table 4. Hypothyroidism and hyperthyroidism among children aged 2 yr

	All (n = 3753)		Boys (n = 1891)		Girls (n = 1862)	
	n	%	n	%	n	%
Hypothyroidism	152	4.05	94	4.97	58	3.11
Mild	152	4.05	94	4.97	58	3.11
Overt	0	0	0	0	0	0
Hyperthyroidism	3	0.08	2	0.11	1	0.05
Mild	3	0.08	2	0.11	1	0.05
Overt	0	0	0	0	0	0

higher risk of concurrent CH than in the broader child population (22). The high risk of congenital diseases suggests the importance of monitoring children with CH.

Preterm birth and low birth weight were not associated with hypothyroidism during early childhood, which is consistent with the findings of a previous study. A report from the Generation R study stated that no pregnancy factors were associated with childhood TSH or fT4 (23). In our study, sex differences were observed in TSH and fT4 levels at 2 yr of age. In addition, using the adult reference range for TSH appears to have led to an overestimation of hypothyroidism and an underestimation of hyperthyroidism in children. These findings suggest that it is important to establish reference ranges for childhood thyroid function based on sex and age.

Further, there was no relationship between TSH and fT4 in the 2-yr-old population, suggesting that the hypothalamus–pituitary–thyroid axis was unaffected by the thyroid at an early age. Notably, the Avon Longitudinal Study of Parents and Children reported a negative relationship between TSH and fT4 levels at 7 yr of age (4). Further evaluation is required to determine whether the same pattern exists in the JECS of school-aged children.

The data were obtained from a large-scale birth cohort study. Therefore, the distributions of TSH and fT4 shown in this study can be regarded as reliable. Moreover, better than the estimated incidence based on NBS, our study identified two cases of central CH through medical records. However, this study had some limitations. As mentioned previously, TCH was included in the 171 patients with CH. The most reliable way to distinguish TCH from true CH is to discontinue treatment at 3 yr of age, followed by re-evaluation of thyroid function (3).

In conclusion, we identified 171 cases of CH among approximately 100,000 participants in the JECS. Infants with CH exhibited a higher risk of developing congenital diseases than did those without CH. Moreover, the distribution data for TSH and fT4 in 2-yr-old children are valuable for minimizing the misclassification of thyroid disorders within the pediatric population. Trail-off treatment and subsequent re-evaluation of thyroid function are essential for distinguishing between PCH and TCH after age 3. Further studies focusing on genetics and environmental factors are needed to elucidate the mechanisms underlying CH.

Conflicts of interests: The authors declare no conflict of interest.

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