

## Etiology of Increasing Incidence of Congenital Hypothyroidism in New Zealand from 1993–2010

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**Background:** Recent reports suggest that the incidence of congenital hypothyroidism (CHT) is increasing in some countries. The etiology of this change is unclear, and it may relate to changes in screening thresholds. We aimed to determine whether the incidence of CHT in New Zealand has changed and whether ethnic-specific rates and the rates of CHT subtypes have also changed.

**Methods:** The New Zealand neonatal TSH-based screening program has prospectively identified cases of CHT using the same assay and screening thresholds since 1993. Thyroid scintiscans are routinely recommended. We retrospectively identified all cases of CHT requiring levothyroxine treatment from 1993–2010 recorded by the national newborn screening program (>99.5% coverage). Among other parameters, ethnic and CHT subtype-specific incidence rates were calculated.

**Results:** There were 330 new cases of CHT and 1,053,457 live births registered in New Zealand in the 18-yr period, and 86% of cases had a scintiscan, 67% of which had thyroid dysgenesis (female to male ratio 5.0:1.0) and 33% dyshormonogenesis (0.9:1.0). The overall incidence of CHT rose from 2.6 to 3.6 per 10,000 live births ( $P < 0.01$ ). The incidence of dyshormonogenesis ( $P = 0.01$ ) increased but not of dysgenesis ( $P = 0.13$ ). This was mediated by a 2-fold increase in Asian births and 40% increase in Pacific Island births. Both ethnic groups displayed higher rates of dyshormonogenesis compared with New Zealand Europeans (odds ratio 3.3 and 2.6, respectively). There was no change in the ethnic-specific incidences of CHT.

**Conclusion:** Although the incidence of congenital hypothyroidism in New Zealand has increased, this is due to changes in the country's ethnic composition. (*J Clin Endocrinol Metab* 97: 3155–3160, 2012)

Recent reports suggest that the incidence of congenital hypothyroidism (CHT) is increasing in areas around the world, including the United States (1, 2), Israel (3), and Western Australia (4). Potential causes include changes in population ethnic composition, where ethnic groups have unequal risk (2), environmental changes such as perchlorate exposure (5) and iodine deficiency (6), and diagnostic changes, such as changing screening program methodology and cutoff levels that could result in greater identification of transient or milder cases (7–9).

The data supporting environmental factors are conflicting. The time course of the increased incidence does

not match changes in iodine intake in the United States (7), and regional perchlorate exposure in Nevada and California is not correlated with CHT rates (5). However, in Israel, a higher rate of CHT was recorded among Asian children whose parents were born in Asia compared with those with parents born in Israel, which is consistent with an environmental effect (10). An apparently cyclical annual incidence of CHT has been reported in Japan, suggesting seasonal environmental effects. However, these reports conflict with regards to the peak season (11–13), and the seasonal effects have not been observed in other regions (3, 14, 15). Changes in screening programs practices

leading to identification of more mild cases have been shown to cause large apparent increases in CHT rates in Massachusetts and Quebec (9, 16).

The use of thyroid scintiscan to define etiology may help to better understand the causes of changing rates (7). Thyroid dysgenesis is sporadic in the majority of cases, and therefore an increased rate could potentially reflect contributing environmental factors. In contrast, dyshormonogenesis, including disorders of iodide trapping and T<sub>4</sub> production and release, has autosomal recessive inheritance. Thus, a change in the rate of dyshormonogenesis would imply changes in population genetics, such as migration or differential fertility in high-risk ethnic groups.

There are currently no comprehensive data on the incidence of CHT in New Zealand. Thus, we aimed to determine whether this incidence has changed over the period 1993–2010. We also aimed to assess whether there were any changes in the ethnic-specific rates and etiology of CHT.

## Subjects and Methods

### Ethics

Ethics approval for this study was given by the Northern X Regional Ethics Committee (New Zealand Ministry of Health), Ref. NTY/11/EXP/087.

### Study population

The New Zealand newborn screening program has provided a population-based, prospective record of all newborns with elevated TSH levels, based on consistent screening thresholds and a single assay since 1993. Thyroid scintiscans have been routinely recommended as part of the diagnostic protocol. This national neonatal screening program covers more than 99.5% of New Zealand's population of approximately 4.5 million. We retrospectively identified all cases of CHT recorded in New Zealand between 1993 and 2010.

### Diagnosis

Whole-blood heel-prick samples were collected on filter paper from all newborn babies 48–72 h after birth and immediately sent for testing by immunofluorescence (Delfia PerkinElmer Inc., Waltham, MA). Infants with TSH values over 50 mIU/liter were directly referred to a pediatric endocrinologist or primary pediatrician and midwife. For borderline abnormal TSH values of 15–49 mIU/liter, repeat samples were collected within 2 weeks. If the TSH values were persistently >15 mIU/liter, the infant was referred to the service for definitive evaluation. Congenital hypothyroidism was defined as a positive screen, followed by a confirmatory serum TSH of at least 15 mIU/liter or a subsequent report of a missed CHT case. There has been no change to the assay or cutoff values for repeating tests or case referral over the study period.

The etiology was classified based on thyroid scintiscan as either thyroid dysgenesis (absent, ectopic, or hypoplastic thyroid *in situ*) or dyshormonogenesis (normally sited gland with normal

or increased size and technetium uptake). Cases with no scintiscan were included in the total CHT group but excluded from analysis of etiology. Transient cases where T<sub>4</sub> replacement was not started or was stopped within 2 months of age were excluded.

### Study parameters

A number of neonatal parameters were recorded, including gender, gestational age, birth weight, and ethnicity. Missing information was obtained through the subjects' general practitioner and/or pediatrician as well as hospital notes. Preterm birth was defined as having fewer than 37 completed weeks gestation, and postterm birth as 42 or more completed weeks. Where appropriate, infants were classified as small for gestational age (birth weight <10th percentile) or large for gestational age (>90th percentile).

Ethnicity was recorded using a prioritized system, such that if multiple ethnicities were selected, the patient was assigned to a single category following a hierarchical system of classification (17). Thus, patients were classified as New Zealand European, Maori, Pacific People, or Asian (Chinese, South-East Asian, Indian). To assess a possible geographical environmental effect on hypothyroidism incidence, each subject was allocated to a rural or urban setting. Where known, address at the time of birth was used; otherwise, the earliest known address was adopted as a surrogate. A rural setting was defined as having a rural postal address or living in a town with fewer than 10,000 people.

### Data analyses

Primary outcomes were the rates of total CHT, thyroid dysgenesis, and thyroid dyshormonogenesis over the periods 1993–2001 and 2002–2010. Secondary outcomes included ethnic-specific rates of CHT and differences in birth weight and urban *vs.* rural earliest recorded address for thyroid dysgenesis and dyshormonogenesis.

Hypothyroidism incidence was calculated using New Zealand Ministry of Health data from live birth registration (<http://www.stats.govt.nz/infoshare/> and [http://www.stats.govt.nz/browse\\_for\\_stats/population/estimates\\_and\\_projections/pop-indicators.aspx](http://www.stats.govt.nz/browse_for_stats/population/estimates_and_projections/pop-indicators.aspx)). Ethnic-specific incidence rates were also calculated for each group. Incidences for 1993–2001 and 2002–2010 were compared by two-sample Poisson rate test. Possible changes in the ethnic-specific incidences were assessed with general linear regression models over the period 1996–2010, due to availability of ethnic-specific birth rates. The overall ethnic rates were compared using binary-logistic regressions over the period 2001–2010 because of low numbers of Asian births between 1996 and 2000.

Possible differences in birth weight between subjects with dyshormonogenesis and thyroid dysgenesis were analyzed using general linear regression models, with sex and group as factors and gestational age as a covariate. Differences in gestational age were assessed using nonparametric Kruskal-Wallis. Binary logistic regressions were used to assess differences in frequencies of preterm (<37 wk gestation), term (37–42 wk), and postterm (≥42 wk) birth, in comparison with the published rates among the general population (20, 21). Two-tailed Fisher's exact tests were used to examine differences in sex and rates of abnormal gestation and weight for gestational age between groups. Fisher's tests were also used to compare the proportion of CHT cases due to thyroid dysgenesis in rural and urban settings. All analyses were performed in Minitab (version 15; The Pennsylvania State

**TABLE 1.** The incidence of congenital hypothyroidism, both total and CHT subtype (thyroid dysmorphogenesis or dysgenesis) among ethnic groups, 2001–2010

Ethnicity	Congenital hypothyroidism		Dyshormonogenesis		Dysgenesis	
	Incidence (n)	OR	Incidence (n)	OR	Incidence (n)	OR
NZ European	2.6 (108)		0.6 (26)		1.6 (66)	
Maori	2.1 (36)	0.8 (0.6–1.2)	0.4 (6)	0.6 (0.2–1.4)	1.3 (23)	0.9 (0.5–1.4)
Pacific People	3.5 (32)	1.4 (0.9–2.0)	1.6 (15)	2.6 <sup>b</sup> (1.4–5.0)	1.6 (15)	1.0 (0.6–1.8)
Asian	3.9 (25)	1.5 <sup>a</sup> (1.0–2.3)	2.0 (13)	3.3 <sup>c</sup> (1.7–6.4)	1.6 (10)	1.0 (0.5–1.9)

Incidence data are the rates per 10,000 ethnically matched live births over the study period. OR refer to New Zealand (NZ) Europeans as the reference rate, and values in parentheses represent 95% CI.

<sup>a</sup>  $P = 0.06$  vs. New Zealand Europeans.

<sup>b</sup>  $P < 0.01$  vs. New Zealand Europeans.

<sup>c</sup>  $P < 0.001$  vs. New Zealand Europeans.

University, University Park, PA), with Johnson transformation carried out as required to stabilize the variance.

## Results

A total of 330 cases of CHT were identified in New Zealand over the 18-yr period covered in our study. A total of 281 cases (85%) had screening whole-blood TSH over 50 mIU/liter, and 46 (14%) had TSH of 15–50 mIU/liter. All but two cases were identified by the national screening program; both had normal screening TSH but were later diagnosed with CHT after clinical suspicion and biochemical verification. One case of ectopic thyroid was identified at a late screen (3 months of age) with a whole-blood TSH of 12 mIU/liter; this case was included because the TSH was above upper limits for this age and the scintiscan was abnormal.

Diagnostic thyroid scintiscans were obtained in 86% of cases (282), of whom 33% (92 of 282) had dyshormonogenesis. The remaining 190 newborns (67%) had thyroid dysgenesis: 116 with ectopic or hypoplastic thyroid *in situ* and 74 with athyreosis.

### Incidence of congenital hypothyroidism

There were 1,053,457 live births recorded in New Zealand between 1993 and 2010, so that the 330 cases of CHT represented an overall incidence of 3.1 per 10,000 live births (1:3192). During this period, the incidence of CHT increased from 2.65 per 10,000 in 1993–2001 to 3.60 per 10,000 in 2002–2010 [95% confidence interval (CI) for difference = 0.27–1.62 per 10,000;  $P = 0.007$ ]. The incidence of dyshormonogenesis also increased from 0.64 to 1.11 per 10,000 (95% CI for difference = 0.11–0.82 per 10,000;  $P = 0.014$ ). In contrast, the incidence of thyroid dysgenesis did not change significantly: 1.60 vs. 2.02 per 10,000 (95% CI for difference = –0.09 to +0.93 per 10,000;  $P = 0.13$ ).

### Ethnicity

There were substantial demographic changes in New Zealand during the study period. Between 1996 and 2010, the increase in live birth rates was 9% for New Zealand Europeans, 17% for Maori, 40% for Pacific People, and 116% for Asians (<http://www.stats.govt.nz/infoshare/>). The large increase in the number of Asian births was due to immigration, whereas for Pacific People, it was a combination of increased immigration and fertility rates.

There was no change in the specific incidences of CHT, thyroid dysgenesis, or dyshormonogenesis within any ethnic groups between 1993 and 2010. There were also no differences in the overall incidence of thyroid dysgenesis between ethnic groups (Table 1). However, the incidence of dyshormonogenesis was considerably higher in Asians ( $P < 0.001$ ) and Pacific Islanders ( $P < 0.01$ ) than in New Zealand Europeans and Maori (Table 1).

### Other factors

There was no gender bias in the incidence of dyshormonogenesis (male to female ratio 0.94:1.00; Table 3). However, we observed a female predominance in cases with thyroid dysgenesis, which was 5.0 times more common in girls than boys ( $P < 0.0001$ ; Table 3). Thus, overall females were more likely to be diagnosed with CHT ( $P < 0.0001$ ; Table 2).

The incidence of term birth among both thyroid dysgenesis (80%) and dyshormonogenesis (82%) newborns was significantly lower than that observed in the NZ population (88%,  $P < 0.01$ ). Dyshormonogenesis cases were more likely to be born preterm than subjects with thyroid dysgenesis [odds ratio (OR) = 2.6, 95% CI = 1.5–4.5,  $P < 0.01$ ; Table 3]. In contrast, subjects in the latter group were more likely to be born postterm than those with dyshormonogenesis (OR = 5.6, 95% CI = 3.7–8.6,  $P < 0.0001$ ; Table 3). As a result, cases with dyshormonogenesis were born 1.4 wk earlier than those with thyroid dys-

**TABLE 2.** Birth parameters of subjects with congenital hypothyroidism (CHT) who underwent a thyroid scintiscan vs. those who did not

	Total CHT	Diagnostic thyroid scintiscans		
		Scan	No scan	P value
n	330	284 (86)	46 (14)	
Female	234 (71) <sup>a</sup>	204 (72)	30 (65)	0.38
Gestation (wk)	39.0 (38.7–39.4)	39.2 (38.8–39.6)	37.6 (36.3–38.9)	0.10
Preterm birth	37 (12)	25 (9)	12 (29)	<0.01
Postterm birth	30 (9)	28 (10)	2 (5)	0.40
Birth weight (g)	3377 (3282–3471)	3401 (3499–3303)	3226 (2918–3534)	0.38
SGA	34 (11)	30 (11)	4 (10)	1.0
LGA	22 (7)	19 (7)	3 (7)	1.0

Where appropriate, values in parentheses represent percentages or 95% CI. LGA, Large for gestational age; SGA, small for gestational age.

<sup>a</sup>  $P < 0.0001$  for sex ratio different from 1:1.

genesis (38.3 vs. 39.7 wk gestation;  $P < 0.0001$ ), although with similar birth weight (3285 vs. 3456 g, respectively; Table 3). There was no difference in the proportion of cases born into rural environments between the thyroid dysgenesis and dyshormonogenesis groups (18 vs. 21%,  $P = 0.62$ ).

## Discussion

The present study demonstrates that the rate of CHT has increased over an 18-yr period in New Zealand, primarily due to a large increase in the incidence of dyshormonogenesis. Reassuringly, there was no change in ethnic-specific incidences of CHT or its subtypes.

The proportion of CHT cases due to dyshormonogenesis of 33% is high compared with previous general estimates of 15–20% (22) but similar to the reported incidence of CHT with thyroid gland *in situ* in France (23) and Canada (9) (34 and 30%, respectively). In the French cohort, over a third of the cases were eventually shown to be transient, so that 21% had permanent dyshormonogenesis. The proportion of dyshormonogenesis we identified for New Zealand is therefore not surprising, probably as a result of two primary factors. First, New Zealand has a

relatively large Asian and Pacific population, which was shown here to have an increased rate of dyshormonogenesis as well as proportionately greater fertility rates. Second, the limited follow-up of only 2 months might have failed to exclude cases of transient dyshormonogenesis.

It is unlikely that these patients with dyshormonogenesis in our study have subclinical hypothyroidism (mildly elevated TSH in the absence of disease and with a normal  $T_4$ ) for a number of reasons. First, 84% of cases had a whole-blood TSH higher than 50 mIU/liter on filter paper at the time of presentation, which equates to a very high serum TSH of approximately 100 mIU/liter. In addition, the cutoff of 15 mIU/liter on filter paper (*i.e.* a serum TSH of approximately 30 mIU/liter) is conservative compared with other screening programs internationally (24). Moreover, neither the assay nor the cutoff value has changed over the study period.

Our data do not suggest any changes in environmental risk. Rather, our findings indicate that the apparent overall increase in CHT incidence was a result of demographic changes. This pattern was mostly the result of a large increase in the number of births among Asians and Pacific Islanders (increased immigration and greater fertility rates), both of which had higher CHT rates than New

**TABLE 3.** Birth parameters among subjects with congenital hypothyroidism who underwent a thyroid scintiscan

	Congenital hypothyroidism type			Thyroid dysgenesis type		
	Thyroid dysgenesis	Dyshormonogenesis	P value	Athyreosis	Ectopic thyroid	P value
n	191	93		74	117	
Female	159 (83)	45 (48)	<0.0001	60 (81)	99 (85)	0.55
Gestation (wk)	39.7 (39.4–40.0)	38.3 (37.5–39.1)	<0.001	39.6 (39.0–40.2)	39.7 (39.0–40.1)	0.69
Preterm birth	11 (6)	14 (15)	<0.01	5 (7)	6 (5)	0.75
Postterm birth	25 (14)	3 (3)	<0.01	9 (12)	16 (15)	0.83
Birth weight (g)	3456 (3357–3554)	3285 (3065–3504)	0.38	3452 (2371–3632)	3459 (3345–3572)	0.87
SGA	19 (10)	11 (12)	0.68	10 (14)	9 (8)	0.22
LGA	9 (5)	10 (11)	0.08	3 (4)	6 (5)	1.0

P values refer to thyroid dysgenesis vs. dyshormonogenesis and to athyreosis vs. ectopic thyroid. Where appropriate, values in parentheses represent percentages or 95% CI. LGA, Large for gestational age; SGA, small for gestational age.

Zealand Europeans. Changes in population composition may be an important cause of increasing CHT incidence in other parts of the world, for example Australia where there has also been substantial Asian and Pacific migration (4) and the United States where the Hispanic population is known to have greater risk (2, 25).

The CHT incidence of 3.9 per 10,000 observed in the Asian population in this study is consistent with the relatively high rates reported in India (26) and China (27), countries that have contributed the majority of the Asian migration to New Zealand. The rate of CHT of 3.5 per 10,000 in Pacific Island infants was also relatively high and comparable with that observed among Asians in New Zealand. There are no previous reports of CHT rates among Pacific People, but the comparable rates may reflect the postulated Asian origin of Polynesian populations (28) or, alternatively, genetic founder effects because these islands were historically colonized by small groups.

High rates of CHT among Asians and Pacific Islanders imply increased allele frequencies of genes involved in dysmorphogenesis. Consanguinity could further increase the frequency of homozygous recessive genotypes. There is no evidence to support this in New Zealand, and consanguinity is now infrequent in China (29), although it may be important in India (30) and the Middle East (31, 32).

Two findings suggest the absence of environmental factors associated with the increasing CHT rates in New Zealand. First, there was no change in the rate of thyroid dysgenesis over the study period. Second, there was no difference in the proportion of dysgenesis cases between rural and urban births, suggesting that a geographically delineated environmental exposure is unlikely to be a factor in New Zealand.

Defining the etiology of the congenital hypothyroidism is essential in identifying why changes in incidence are occurring. Although it is not always possible to perform thyroid scintiscans, this study illustrates the importance of appropriately classifying congenital hypothyroidism in the context of large neonatal screening programs.

The apparent marked increase in the risk of postterm birth in children with thyroid dysgenesis compared with those with dysmorphogenesis is intriguing. Older gestational age has previously been associated with congenital hypothyroidism (33). Fetal hypothyroidism seems an unlikely contributor to postterm birth because the fetus is protected *in utero* by significant maternal transfer of T<sub>4</sub>, and thyroid hormone is not known to regulate parturition. Potentially, genes involved in the predisposition to thyroid dysgenesis might have pleiotropic effects on gestational length. Evidence for genetic involvement in the etiology of thyroid dysgenesis exists in the increased rates associated

with consanguinity (34) and family history (35). A pleiotropic effect might also explain the apparent mild association of preterm birth with dysmorphogenesis in the present study. Alternatively, it may be transient thyroid dysfunction due to prematurity of the hypothalamic-pituitary-thyroid axis. However, these observations must be regarded as preliminary. There were only a small number of infants born prematurely with dysmorphogenesis, and potential bias exists; the 14% of cases who were not scanned had an increased rate of prematurity, so were not representative of the total congenital hypothyroidism group.

In this study, athyreosis and ectopic thyroid cases were considered together as thyroid dysgenesis, as is often done in the literature (36, 37). Both thyroid disorders are considered sporadic, result from disrupted embryological development, and may be part of a spectrum of disease. We observed no differences between athyreotic and ectopic cases in any of the parameters examined, further justifying their inclusion in the dysgenesis group.

We observed an increased rate of thyroid dysgenesis among females. This finding is consistent with previous studies using scintiscan (18, 19, 35), but the magnitude of the effect was considerably larger in this study.

In summary, there has been a significant increase in the rate of congenital hypothyroidism in New Zealand over the past 18 yr, which primarily reflects an increase in the rate of dysmorphogenesis associated with increased birth rates among Pacific Island and Asian populations. Our findings are reassuring that there has been no appreciable change in the ethnic-specific rates of CHT over nearly two decades in New Zealand.

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