Trends in Incidence Rates of Congenital Hypothyroidism Related to Select Demographic Factors: Data From the United States, California, Massachusetts, New York, and Texas

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abstract

Primary congenital hypothyroidism (CH) is a common and preventable cause of intellectual disability. The incidence rate of CH has been reported to be increasing in the United States, but the factors behind the observed rate increase are not known. We summarize here the data presented at a workshop on CH, at which factors potentially related to the CH-incidence-rate increase (namely, race, ethnicity, sex, and birth outcomes) were evaluated. Data sources for the analyses included a national data set of newborn-screening results and state-specific data from newborn-screening programs in California, Massachusetts, New York, and Texas. The incidence rate of CH increased in the United States by 3% per year; however, an increase did not occur in all states, at a constant rate, or even at the same rate. Analysis of US data (1991–2000) showed a CH-incidence-rate increase only among white newborns. More recently, in California (2000–2007), the rate was constant in non-Hispanic newborns, but it increased among Hispanic newborns. In the national data, the CH-incidence rate increased similarly among boys and girls, whereas in Texas (1992–2006), the rate among boys increased significantly more than among girls and varied according to race and ethnicity. In Massachusetts (1995–2007), low birth weight newborns or newborns who had a delayed rise in thyrotropin concentration accounted for the majority of the recent rate increase. Race, ethnicity, sex, and pregnancy outcomes have affected the observed increasing incidence rate of CH, although there have been some inconsistencies and regional differences. The association with preterm birth or low birth weight could reflect the misclassification of some cases of transient hypothyroxinemia as true CH. Future studies of risk factors should focus on correct initial identification and reporting of demographic characteristics and pregnancy outcomes for cases of CH. In addition, long-term follow-up data of presumed cases of CH should be ascertained to differentiate true cases of CH from cases of transient hypothyroidism. *Pediatrics* 2010;125:S37–S47

Primary congenital hypothyroidism (CH) is a common and preventable cause of intellectual disability (mental retardation). Treatment for life with carefully monitored thyroxine (T4) supplementation has all but eliminated intellectual disabilities caused by untreated CH, although some educational and psychological impairments still exist.[1–3] Failure of the thyroid gland to develop during gestation (aplasia) and maldevelopment of the gland (hypoplasia or ectopia) account for 80% to 85% of cases of CH; most other newborns with CH have an inherited molecular defect in the synthesis of thyroid hormone or a thyrotropin receptor defect. Causes of most congenital defects of thyroid location or structure are not known, but multiple epidemiologic studies have revealed several consistent trends in associated factors, particularly the newborn's race, ethnicity, sex, birth weight, and gestational age. CH has been reported as more common among Hispanic[4–6] and Asian and Native Hawaiian or other Pacific Islander (ANHOPI)[4,5,7] newborns and less common among non-Hispanic black newborns than among non-Hispanic white newborns.[4,5,8] CH occurs more often in girls than in boys, generally with a ratio of 2.[4,5] An elevated risk for CH has also been reported for newborns with birth weights of <2000 or >4500 g[5,9] and with a gestational age of <37 or >40 weeks.[9]

The incidence rate of CH has been reported to be increasing in the United States, from ~1 in 4100 live births in 1987 to 1 in 2350 live births in 2002, an increase of 73%.[7] Although definitive cause(s) of this increase have not been identified, it has been suggested, on the basis of data from New York State (NYS), that 36% to 38% of the increase nationally could be accounted for by changes in demographic characteristics among live births, including race, ethnicity, sex, birth plurality, birth weight, and mother's age. Given public health concerns posed by a possible increase in the incidence rate of CH in the United States, a workshop of invited experts convened February 27 through 28, 2008, to consider possible factors behind the rate increase. For an overview of the workshop, see the article by Olney et al.[10]

During the workshop, presentations were provided on the CH-incidence rate relative to a number of demographic factors in the United States overall, in other countries, and in 4 states (California, Massachusetts, New York, and Texas). These 4 states were chosen because of large birth cohorts and availability of data that had been evaluated for the CH-incidence rate in relation to demographics or birth outcomes. Here, we summarize the data presented at the workshop, specifically the relationship of race, ethnicity, sex, and birth outcomes to the increasing incidence rate of CH, by using a national data set of newborn-screening (NBS) results and state-specific data from the 4 representative state NBS programs. We evaluated the following questions: (1) Is the incidence rate of CH increasing in the United States? (2) Is the incidence rate uniform across the country and, specifically, in the 4 states evaluated here? (3) Are changes in the CH-incidence rate related to changing demographics among live births? and (4) Are increasing rates of preterm births or low birth weight (LBW) newborns associated with a changing incidence rate of CH?

INCIDENCE RATES OF CH: UNITED STATES, CALIFORNIA, MASSACHUSETTS, NEW YORK, AND TEXAS

Each of the 4 state NBS programs reported the results of analyses conducted on its own data. Analysis of data on the incidence rate of CH in the United States overall was conducted by using NBS data on CH for 1991–2000 (obtained from the National Newborn Screening and Genetics Resource Center [NNSGRC]), which were from previously confirmed and validated cases of CH by the reporting programs. Cases were confirmed as having CH through individual state NBS-program protocols. Live-birth data for each state were obtained from the National Center for Health Statistics (NCHS). For the purpose of our analyses, we assumed that all newborns were screened. The odds of being diagnosed with CH were determined by using a negative binomial distribution to account for extra-Poisson variation using SAS 9.2 (SAS Institute, Inc, Cary, NC). The analysis was performed on data from all reporting states and the District of Columbia, except for NYS. Data from NYS were excluded because of major differences between the number of validated cases of CH reported annually to the NNSGRC and the number of cases of CH reported from the published NYS study, which showed an increasing incidence of CH over time.[7]

On the basis of the reported data in the national data set, the incidence rate of CH increased in the United States from 2.9 cases per 10 000 births in 1991 to nearly 4.0 cases per 10 000 in 2000 (Fig 1). The odds of a newborn having CH increased each year by a factor of 1.03 (or 3%) for a total increase of 30.4% over the decade. The increase in incidence rate was not uniform across the United States. In 11 states (Arkansas, California, Idaho, Iowa, Kansas, Missouri, New Jersey, Ohio, Oklahoma, Oregon, and Tennessee), the odds of reporting a case of CH increased by an average of 11%, varying from 5% in California to 25% in Tennessee over this 10-year period. The odds of a reported case of CH decreased in 2 states (by 5% in Virginia and by 6% in Minnesota).
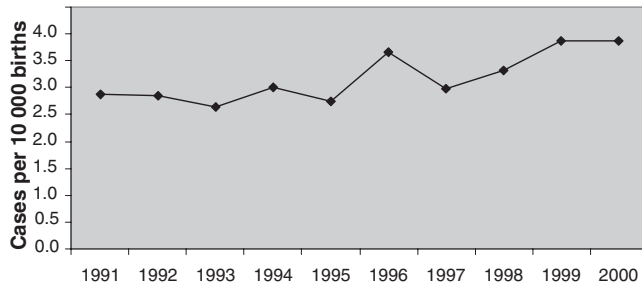
FIGURE 1
Incidence rate of CH in the United States, 1991–2000, based on a national data set provided by the NNSGRC (odds: 1.03 [95% CI: 1.02–1.04]; $P < .0001$).

Data from other states showed an upward but insignificant change.

State-specific data from California revealed a rise in the incidence rate of CH from 1983 to 2006 but relatively little increase from 1991 to 1998 or after 2000 (Fig 2). The overall increase in the CH-incidence rate between 1998 and 1999 did not coincide with a 1997 change in testing technology in which the primary screening analyte changed from both T4 and thyrotropin (TSH) for all screened samples to TSH alone (see the article by Hertzberg et al[11] for a discussion of the effect of laboratory methods on the CH-incidence rate).

Data from Massachusetts revealed an increasing incidence rate of CH from 1976 to 2007 (Fig 3). However, the majority of the incidence-rate increase seems to have occurred after 1990.

The previously reported analyses of NYS data for 1978 (when NBS for CH began in the state) to 2005 revealed an increased CH incidence of 138%.[7] Fig 4 shows the incidence rate of CH over time in NYS for data that have been expanded from the original report[7] to include NYS data from 1978–2007. Figure 4 also shows the US data, minus NYS, which have also been expanded through 2006 using state NBS data reported to the National Newborn Screening Information System (NNSIS) at the NNSGRC. The NYS trend line from the original data[7] shows a slope of 1.5746; with the inclusion of 2 additional years of data, the slope is steeper at 1.6193, a 2.8% increase in 2 years. Similarly, the trend line for the US data had an original slope of 1.1708, but with 4 additional years of data, the slope is steeper at 1.3183, a 12.6% increase. Therefore, in both NYS and the United States, the reported incidence rate of CH continued to increase with each additional year of included data.

In Texas, although the number of cases of CH fluctuated from year to year, there was a positive trend in the frequency of diagnosed cases from 1992 to 2006 (Fig 5), similar to what was observed in the other individual states. Figure 5 also shows that from 1992 to 1995, the birth rate in Texas remained constant; however, since 1995, the birth rate rose steadily.

RACE, ETHNICITY, AND CH-INCIDENCE RATE: UNITED STATES, CALIFORNIA, AND TEXAS

Racial and ethnic designations for the analyses reported here differed between data sets. In the US data (1991–2000) reported to the NNSIS, white and black were not mutually exclusive from Hispanic; therefore, within the categories used here, individuals with Hispanic ethnicity were included in the
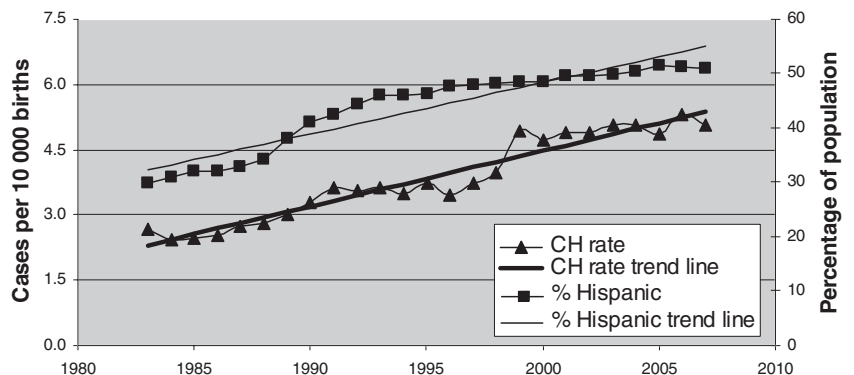

FIGURE 2
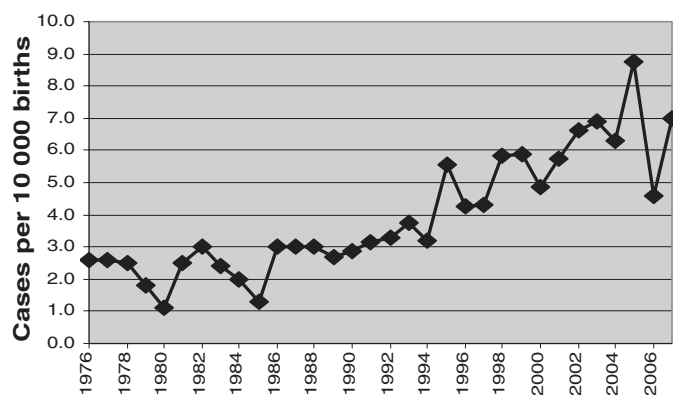Incidence rate of CH and percentage of Hispanic births in California, 1983–2007.

FIGURE 3
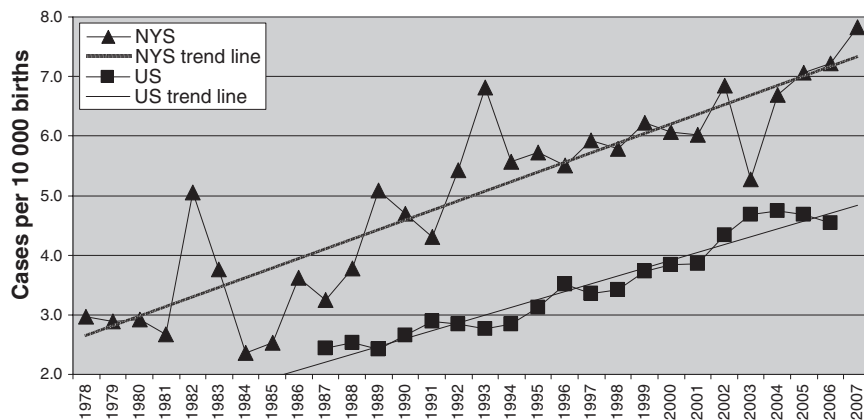Incidence rate of CH in Massachusetts, 1976–2007.

FIGURE 4
Incidence rate of CH in NYS, 1987–2007, and in the United States (excluding NYS), 1987–2006. These data were expanded to include additional years from those reported in 2007.[7]
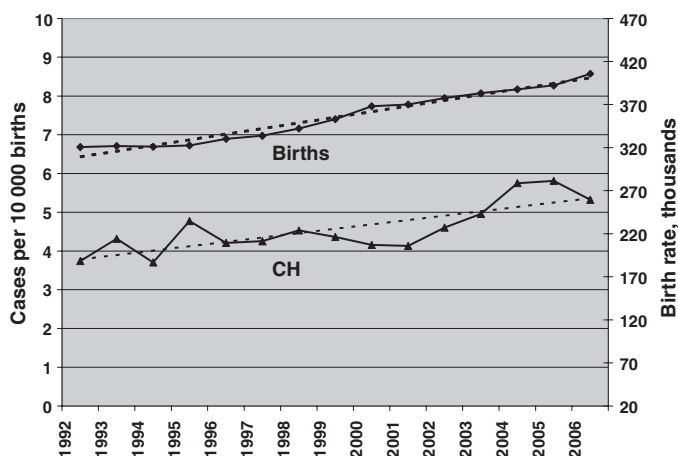

FIGURE 5
Incidence rate of CH and birth rate in Texas, 1992–2006. The dashed lines represent trend lines.

TABLE 1 Odds Ratios of CH According to Demographic Characteristic, United States, 1991–2000

Demographic	Odds Ratio (95% CI)	P
Race or ethnicity		
White[a]	Reference	
Black[a]	0.70 (0.60–0.83)	<.0001
Hispanic	2.01 (1.77–2.28)	<.0001
ANHOPI	1.44 (1.20–1.72)	<.0001
Sex		
Male	Reference	
Female	1.56 (1.35–1.64)	<.0001

[a] White and black include Hispanic ethnicity.

TABLE 2 Odds Ratios of CH According to Year and Demographic Characteristic in the United States, 1991–2000 for Race or Ethnicity, 1993–2000 for Sex

Demographic	Odds Ratio (95% CI) According to Year	P
All	1.03 (1.02–1.04)	<.0001
White[a]	1.03 (1.00–1.07)	.0385
Black[a]	1.04 (0.98–1.08)	.1824
Hispanic	1.01 (0.99–1.03)	.1776
ANHOPI	1.00 (0.95–1.05)	.9971
Male	1.04 (1.02–1.07)[b]	.0006
Female	1.05 (1.03–1.07)[b]	<.0001

[a] White and black include Hispanic ethnicity.
[b] These rates are not comparable with the overall incidence rate increase according to year of 3% from 1991 through 2000, because data for cases of CH stratified according to sex were not available for 1991 and 1992.

white and black racial categories. However, in the California (2000–2007) and Texas (1992–2006) data, Hispanic ethnicity was mutually exclusive from white or black race, so the designations used for these analyses are non-Hispanic white, non-Hispanic black, and Hispanic.

Evaluations of the CH-incidence rate in the United States from 1991 to 2000 were conducted by using NBS data on race and ethnicity reported to the NNSIS. Live births that occurred in each state, subdivided by race or ethnicity, were obtained from the NCHS. The odds of being diagnosed with CH was determined for each race or ethnicity by using a negative binomial distribution to account for extra-Poisson variation using SAS 9.2.

In analyses of data for the United States overall, the incidence rate of CH was 100% higher in Hispanic newborns and 44% higher in ANHOPI newborns compared with that of white newborns; it was 30% lower in black newborns than in white newborns (Table 1). Although the incidence rates of CH varied widely according to race or ethnicity during the 1991–2000 decade, there was a statistically significant increase (3% per year) among white newborns only (Table 2).

Race and ethnicity data from California revealed that CH-incidence rates were significantly higher among Hispanic and some Asian newborns than among non-Hispanic white newborns (Table 3). Ethnicity data, updated from data from Waller et al,[5] revealed CH-incidence rates of 1 in 1600 for Hispanic newborns, 1 in 1757 for Asian

TABLE 3 Incidence Rates of CH According to Race or Ethnicity, California, 2001–2007

Race or Ethnicity	CH Rate/10 000	CH Rate, 1 per
Non-Hispanic white	3.6	3533
Hispanic	6.1	1600
Asian Indian	8.2 (Waller et al[5] [2000])	1200
	5.7 (2001–2007)[a]	1757
Asian (Chinese and Vietnamese)	4.2	2380
Non-Hispanic black	0.9	11 000

[a] Note that the CH incidence rate has actually declined in Asian Indian newborns since an earlier report.[5]

Indian newborns, 1 in 2380 for Chinese and Vietnamese newborns, 1 in 3533 for non-Hispanic white newborns, and 1 in 11 000 for non-Hispanic black newborns. From 2000 to 2007, the CH-incidence rate varied little for non-Hispanic newborns: 1 in 2738 in 2000 and 1 in 2885 in 2007. However, among Hispanic newborns, the CH-incidence rate increased from 1 in 1680 in 2000 to 1 in 1512 in 2007. The overall CH-incidence rate increased steadily in the past 25 years, and the trend line mirrors the percentage increase in Hispanic births in the state (Fig 2).

Analysis of the demographic characteristics of all births in Texas from 1980 through 2006 revealed that the percentage of Hispanic births climbed from ~30% of the Texas birth cohort to ~50%, whereas there was a subsequent decline (~55% down to ~35%) in the percentage of non-Hispanic white births (Fig 6). The percentages of births for non-Hispanic black and other race categories each changed by <5 percentage points between 1980 and 2006. The other race category, primarily Native American and Asian, made up <4% of the total Texas births during these years. The ratio of male to female births in each of the 4 race or ethnicity categories remained constant from 1992 to 2006. Specifically, across this time period there averaged 1.01% more male than female non-Hispanic white births and 0.92% more male than female Hispanic births (data not shown).

CH case data obtained in Texas as part of the NBS follow-up program from 1992 through 2006 were used for this analysis (note that the 2006 birth data used in this analysis are provisional and subject to change). Race and ethnicity information for cases of CH was obtained from the NBS specimen-collection form and may not be the same as that reported from birth certificates to the NCHS. Mean differences
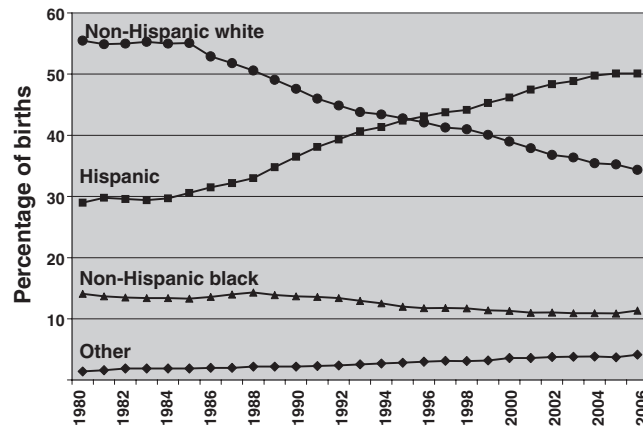
due to race or ethnicity were evaluated by using a 2-way between-subjects analysis of variance to evaluate the effects of race or ethnicity on the increasing incidence rate of CH. Evaluation of mean differences for the main effect of race or ethnicity ($F_{3,119} = 267.20$; $P < .01$) indicated significant differences between the categories (Fig 7). Irrespective of infant sex, Hispanic newborns had a significantly higher CH-incidence rate than those in all other categories, and non-Hispanic white newborns had a higher CH-incidence rate than did non-Hispanic black newborns or those of other races or ethnicities.

FIGURE 6
Percentage of births according to race or ethnicity in Texas, 1980–2006. These changes occurred on the background of a rising overall birth rate and a large shift in the number of Hispanic births.
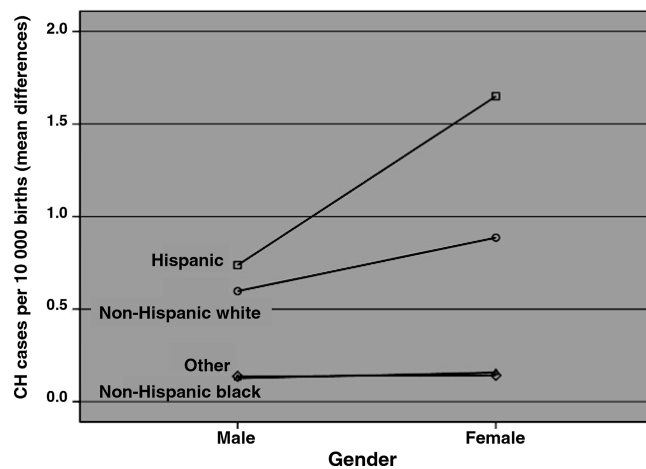

FIGURE 7
Mean differences between male and female CH-incidence rates in Texas, 1992–2006, stratified according to race and ethnicity.

SEX AND CH-INCIDENCE RATE: UNITED STATES, CALIFORNIA, AND TEXAS

Evaluations of the CH-incidence rate in the United States from 1993 to 2000 were conducted by using NBS data on sex reported to the NNSIS; data for cases of CH stratified according to sex were not available for 1991 and 1992. Data on live births that occurred in each state, subdivided according to sex, were obtained from the NCHS. The odds of being diagnosed with CH according to sex were determined by using a negative binomial distribution to account for extra-Poisson variation using SAS 9.2.

The female-to-male CH-incidence ratio was 1.56 (Table 1), somewhat lower than the expected ratio of 2. As shown in Table 2, the CH-incidence rate increased significantly according to year from 1993 through 2000 for both boys and girls by 4% and 5%, respectively. These rates are not comparable to the overall incidence-rate increase according to year of 3% from 1991 through 2000, because data for the first 2 years on sex were not available.

In California the female-to-male ratio during 2005–2007 for cases of CH was 2.2 (95% confidence interval [CI]: 2.0–2.4). The ratio varied according to racial or ethnic group: 2.6 (95% CI: 2.3–2.9) among Hispanic newborns, 2.0 (95% CI: 1.6–2.4) among non-Hispanic white newborns, 1.4 (95% CI: 1.3–1.5) among Asian newborns (Chinese and Vietnamese), and 1.0 (95% CI: 0.8–1.2) among non-Hispanic black newborns.

Cases of CH in Texas historically had a female-to-male ratio of 2; however, since 2001, the ratio has changed to 1.5 (Fig 8). This change in the ratio is attributed to boys having a greater increase in CH-incidence rate than girls from 1992 to 2006 for all racial and ethnic groups. The rate of CH incidence among boys in the other, non-Hispanic black, Hispanic, and non-Hispanic white categories increased by 300.0%, 266.7%, 158.5%, and 145.2%, respectively. Although non-Hispanic black and Hispanic girls showed increases in CH-incidence rates (56.3% and 47.5%, respectively), girls in the non-Hispanic white and other categories had a decrease in CH-incidence rates by 28.2% and 16.7%, respectively.

Using a 2-way, between-subjects analysis of variance, mean differences in CH-incidence rate due to sex in Texas were evaluated. A significant main effect was found for sex ($F_{1,119} = 97.70$; $P < .01$): girls had significantly higher incidence rates of CH than boys. The interaction effect of sex and race or
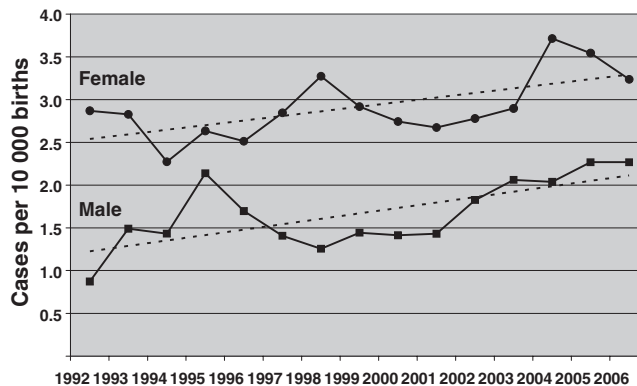

FIGURE 8

Incidence rate of CH according to sex in Texas, 1992–2006. From 2001 to 2006 there was a significant increase in the number of cases of CH in boys relative to that in girls.

ethnicity was also significant ($F_{3,119} = 45.35$; $P < .01$), indicating that both sex and race or ethnicity had a strong effect on CH-incidence rates; that is, Hispanic girls had a significantly higher CH-incidence rate than any other racial or ethnic group when stratified according to sex (Fig 7). When evaluating boys and girls separately, we found similar significant differences between racial or ethnic categories ($F_{3,59} = 76.91$; $P < .01$ and $F_{3,59} = 195.03$; $P < .01$, respectively). Hispanic newborns of both sexes had significantly higher CH-incidence rates than corresponding sexes in all other racial or ethnic categories. Non-Hispanic white newborns of both sexes had higher CH-incidence rates than corresponding sexes of non-Hispanic black newborns and those in the other category.

LBW AND CH-INCIDENCE RATE: MASSACHUSETTS

In Massachusetts, evaluations of the CH-incidence rate were performed relative to birth weight. From 1990 (when the NBS program began tracking these data) to 2007, the proportion of newborns who weighed <1500 g in the screened population increased from ~0.8% to 1.1% (data not shown). In 1995, responding to the observation that a significant number of LBW new-

borns with CH had low or normal T4 and normal TSH concentrations on the initial screen but a decreased T4 and increased TSH concentration, typical of CH, on subsequent screens,[12] the NBS program implemented a repeat-specimen policy for newborns in NICUs, particularly for those who weighed <1500 g. The policy requires all newborns in the NICU to have a second specimen collected at 2 weeks of age or at discharge, whichever is earlier. However, if a newborn's birth weight is <1500 g, specimens are required at 2, 4, 6, and 10 weeks of age or until the infant reaches a weight of 1500 g.

Given the increasing number of LBW newborns in Massachusetts and the changes in the specimen-collection process for these infants, there was concern whether these factors may have contributed to an increasing CH-incidence rate. As shown in Fig 9, the number of cases per 1000 newborns was highest for the <1500-g newborns, although this category had fewer newborns than other categories (only 1% of the total population). The incidence rate of CH cases increased from 1990 to 2007 for each birth weight category (7% per each 3-year interval for <1500 g, 18% per each 3-year interval for 1500–2500 g, and
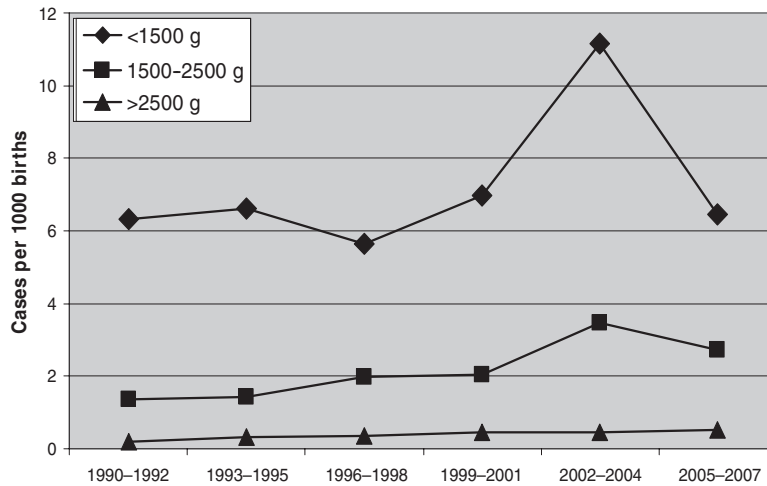
FIGURE 9

Incidence rate of CH in Massachusetts, 1990–2007, for 3-year intervals, stratified according to birth weight category. The scale does not show the 2.5-fold increase in the incidence rate that occurred for newborns born at >2500 g.

(ie, the TSH concentration on the initial screening test was >25 mIU/L). Most of the increase in CH-incidence rate, particularly since 1995, seems to be for newborns who weighed <2500 g or for newborns with a delayed TSH increase (the difference between the upper and lower curves). In contrast, a residual rate increase seems to be occurring among normal weight newborns whose TSH concentration was elevated on the initial screen (lower curve), although the increase seems to have attenuated since the mid-1990s. Therefore, from 1976 to 2007, the CH-incidence rate in Massachusetts increased, but the majority of the incidence-rate increase seems to have resulted from LBW newborns or newborns with a delayed TSH increase.

16% per each 3-year interval for >2500 g), although statistical significance was achieved only for the latter 2 categories ($P = .2672$ for <1500 g, $P = .0002$ for 1500–2500 g, and $P < .0001$ for >2500 g). The total increases in CH-incidence rate for <1500-, 1500- to 2500-, and >2500-g infants between 1990 and 2007 were 40%, 130% and 110%, respectively. Figure 10 shows the incidence rate of cases of CH for all newborns and for those who weighed >2500 g. Comparison of the difference between the 2 groups revealed that since 1995, a growing number of cases of CH in Massachusetts have occurred in newborns who weigh <2500 g at birth.

A significant number of newborns with CH have a delayed TSH increase, reflected by a normal TSH concentration (<25 mIU/L) on the initial screen but a subsequent elevated concentration.[12] Although more common in LBW newborns, delayed TSH increase can also occur in normal birth weight newborns.[12] Fig 11 shows the effects of LBW or delayed TSH increase to the incidence rate of CH. The upper curve includes all newborns diagnosed with CH, whereas the lower curve includes

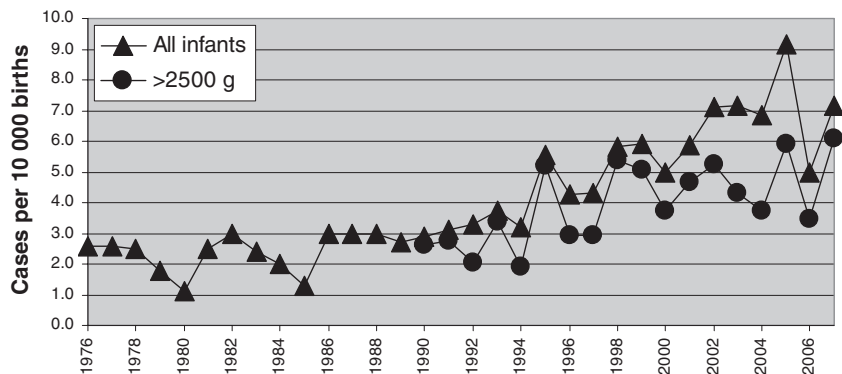only those who weighed >2500 g and did not have a delayed TSH increase

FIGURE 10

Incidence rate of CH in Massachusetts for all newborns and for those born at >2500 g, 1976–2007.
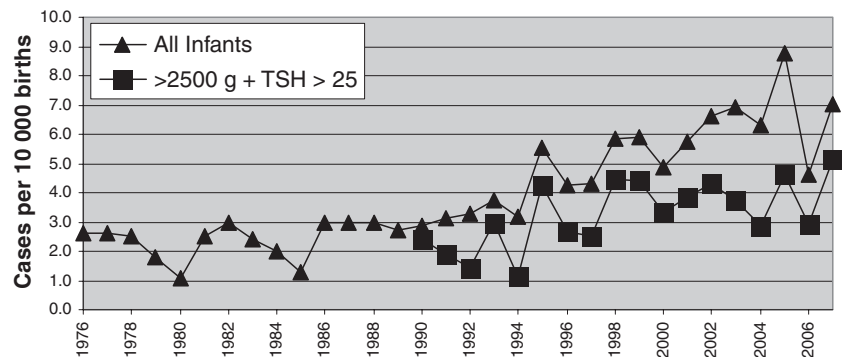

FIGURE 11

Incidence rate of CH in Massachusetts for all newborns and for those born at >2500 g with an initial screening thyrotropin concentration of >25 mIU/L, 1976–2007.

DISCUSSION

We found that the incidence rate of CH increased in the United States during the years 1991–2000, which is consistent with results given in the NYS report.[7] The odds of a newborn being reported with a diagnosis of CH increased by 3% per year for a total 30.4% increase over the decade, but the odds did not increase uniformly across all states. Only 11 states showed a significant increase in the incidence rate of CH, whereas 2 states showed a decrease in the incidence rate; the remaining states had upward but nonsignificant trends in the CH-incidence rate. The NYS report similarly showed that the incidence rate of CH varied across the United States, with states in western, southwestern, Great Lakes, and New England regions more likely to have a higher incidence rate of CH.[7] Moreover, in NYS the CH-incidence rate varied among counties of the state. Among the 4 states with CH-incidence data presented here (California, Massachusetts, New York, and Texas), each showed an increased CH-incidence rate, although the rate increases were neither constant nor the same between states. For example, both California and Massachusetts reported ranges of years in which CH-incidence rates were essentially unchanged.

Clues about the cause(s) of the increasing CH-incidence rate arise from evaluating differences in the CH-incidence rate among newborns with various demographic factors or birth characteristics. The increase in incidence rate of CH differed significantly between racial and ethnic groups. At the national level (1991–2000), only white newborns showed a significant increase in the odds of being reported with CH. However, a significant limitation with the national-level data reported during this time period is that an unknown proportion of Hispanic in-fants with CH were included in the white racial category. Some states included the same cases of CH within both white and Hispanic categories, whereas other states did not provide separate counts of Hispanic infants with CH. Therefore, the fact that Hispanic newborns in the national data set did not show a significant increase in the odds of CH over time is not surprising, whereas the observed increase in the CH-incidence rate among white newborns could be the result, in part, of an increase among those of Hispanic ethnicity. This theory is borne out by data from Texas and California, in which the newborn classifications as Hispanic, non-Hispanic white, or non-Hispanic black were mutually exclusive. In Texas, although the proportion of births attributed to Hispanic newborns increased from 30% to 50% of the birth cohort from 1980 through 2006, the incidence rate of CH increased by 158.5% in Hispanic boys and 47.5% in Hispanic girls from 1992 through 2006. Therefore, Hispanic newborns in Texas, whether male or female, were significantly more likely to be diagnosed with CH than were members of the other racial or ethnic groups. Over the same time period, the proportion of non-Hispanic white births in Texas decreased significantly, and although the rate of CH increased in non-Hispanic white boys (the lowest percentage increase for all racial or ethnic groups), it actually decreased in non-Hispanic white girls, so that the overall incidence rate of CH in non-Hispanic white newborns was essentially unchanged. Similar results were seen in California; CH-incidence rates were significantly higher among Hispanic and some Asian newborns compared with non-Hispanic white newborns, and although the CH-incidence rate was constant for non-Hispanic newborns from 2000 to 2007, the incidence rate for Hispanic newborns increased by 11%. These data suggest that the increasing Hispanic birth rate, in conjunction with the increasing incidence rate of CH among Hispanic newborns, at least partially accounts for the overall increase in the CH-incidence rate that has been observed in the United States.

Questions remain as to why Hispanic newborns have a higher incidence rate of CH than newborns of other racial or ethnic groups and why the incidence rate has been increasing to a greater extent in Hispanic newborns. One clue may come from the study of Schoen et al,[6] who evaluated the role of thyroid scintigraphy in diagnosing and managing CH in the newborn period. In a population of >700 000 newborns in California, there were 249 newborns with a confirmed case of CH, of which 210 received neonatal thyroid scintigraphy to determine the presence, absence, or abnormal location of the thyroid gland. In this population, the incidence rate of CH was highest among Hispanic newborns (1 in 1750) compared with an incidence rate of 1 in 4648 for non-Hispanic newborns. Similar to previous reports, the CH-incidence rate among Hispanic girls was approximately twice that of Hispanic boys. Of newborns with CH evaluated by scintigraphy, female Hispanic newborns (the group with the highest incidence rate of CH) had dysplastic thyroid glands (includes absent and ectopic thyroid) more often than did non-Hispanic girls ($P = .02$). This finding suggests that genetic or environmental factors that contribute to thyroid dysplasia are more common in the Hispanic population. Future studies that focus on elucidating and evaluating potential genetic and environmental factors might reveal a subset of factors that are specifically related to the increasing CH-incidence rate, particularly among Hispanic newborns.

In the national data set, the newborn's sex was not associated with the in-

creasing CH-incidence rate; boys and girls each had similar 4% to 5% increases according to year from 1993 to 2000. In contrast, in Texas, the increase in the CH-incidence rate was greater for boys than for girls from 1992 through 2006, which indicates that the factors that affect the CH-incidence rate related to infant sex need further evaluation. It is interesting to note that in the national data set the female-to-male ratio for CH for all races and ethnicities combined was 1.56, a deviation from the expected ratio of 2. In Texas, the sex ratio for cases of CH for all races and ethnicities combined was 2 until 2001; this ratio changed gradually to 1.5 because of a higher CH-incidence-rate increase among male newborns than among female newborns. In California, the sex ratio for infants with CH of all races and ethnicities combined was 2.2, but the ratio varied significantly according to race or ethnicity. Because the national data set presents aggregate cases of CH for each state according to race and ethnicity or sex, and not by both, it was not possible to assess differences in the sex ratio according to race or ethnicity nationally. However, it is unlikely that the deviation of the sex ratio in the national data set from the expected ratio of 2 is attributable to cases of CH among black and ANHOPI newborns (with a lower female-to-male ratio) given that white and Hispanic newborns make up the overwhelming majority of infants with CH in the United States. Another possible explanation for the deviation from the expected sex ratio is the misclassification of an increasing number of newborns with transient hypothyroidism as having true CH (discussed in the article by Parks et al[13]). Future studies should address the deviation from the expected sex ratio for potential clues regarding the observed increasing incidence rate of CH.

Evaluations of the impact of LBW newborns on the CH-incidence rate in Massachusetts also provide clues about the increasing incidence rate of CH in the United States. According to the 2009 National Vital Statistics report on births from 1980 through 2006,[14] there were increases in the rates of both preterm and LBW births in the United States, although nearly all of the increase in the preterm birth rate for singleton pregnancies was among late-preterm births (34–36 weeks' gestation). Specifically, from 1990 through 2006, rates of singleton preterm births and LBW newborns increased by 14% and 10%, respectively; taking into account all pregnancies, the preterm and LBW birth rates increased by 20% and 19%, respectively. The preterm birth rate from 1990 to 2006 varied according to race or ethnicity, as did changes in that rate. In 1990, the percentage of preterm births was 8.5% in white newborns, 18.9% in black newborns, and 11.0% in Hispanic newborns. Among white and Hispanic newborns, this rate increased by 38% and 11%, respectively, until 2006; among black newborns, there was an 8% decrease until 2000, at which time the rate steadily increased until 2006. In addition to variations according to race or ethnicity, LBW rates varied markedly across regions of neonatal health services; the observed variation could not be explained by known individual and community risk factors or by differing racial composition of the areas.[15] This variation is in line with our findings that the incidence rate of CH has not increased uniformly across the country, suggesting that LBW or preterm birth could have greater or lesser effects on the CH-incidence rates in different geographic regions.

Evaluations of NBS data in Massachusetts showed that the increasing rate of LBW newborns or a delayed rise in TSH concentration after birth (the latter is associated with the former) accounted for a significant portion of the CH-incidence-rate increase that occurred in the state. The observed link between the rate of preterm birth or LBW and the increasing CH-incidence rate is plausible, because preterm or LBW newborns are more likely to require neonatal intensive care and, therefore, may be exposed to agents that affect thyroid function, including topical iodine-containing solutions, dopamine, and amiodarone.[16,17] In addition, in the preterm neonate there are postnatal adaptations in thyroid function that occur related to an immature hypothalamic-pituitary axis, as well as an interruption of exposure to thyroid-releasing hormone (from the placenta) and to maternal thyroid hormone.[18,19] Therefore, preterm newborns have significant risks for the endocrine manifestations of hypothyroidism (including lower cord blood concentrations of T4-binding globulin, total T4, and free T4 and blunting of the neonatal surge in TSH), which result in thyroid hormone concentrations declining to a nadir ~1 week after birth.[20–23] These manifestations have been characterized as transient hypothyroxinemia of prematurity. The increasing preterm birth rate in the United States has likely resulted in an increasing incidence rate of transient hypothyroxinemia of prematurity. The potential misclassification or misreporting of these transient cases as true cases of CH could be reflected in an apparently increasing CH-incidence rate.

Another consideration is the improved survival rate of preterm and LBW infants[24,25] that results from changes in high-risk obstetric and NICU care, particularly the use of antenatal steroids and exogenous surfactant.[26,27] With improved survival rates there was the potential for more infants in the LBW categories who previously would have

died in the newborn period to have been tested and confirmed to have CH, thus contributing to the observed increasing CH-incidence rate in these groups. Although this is potentially a contributory factor, it is not the primary factor in Massachusetts, because the observed 40%, 130%, and 110% increases between 1990 and 2007 in the CH-incidence rates for newborns who weighed <1500, 1500 to 2500, or >2500 g, respectively, far exceed the improvements in survival for newborns during this time period, particularly in the 1500- to 2500- and >2500-g categories.

It is not possible to extrapolate data on the association between LBW and CH-incidence rates in Massachusetts to the entire United States. In addition, LBW is only a rough proxy for preterm birth, so analyses of gestational age are still warranted, although somewhat difficult because many NBS filter-paper cards do not include this information. Furthermore, CH-incidence rates in relation to LBW or preterm births among different racial and ethnic groups could not be examined, but such analyses might be a fruitful next step, because there are significant racial and ethnic differences in rates of

preterm birth and LBW. In addition, twin pregnancy has been associated with an increased incidence rate of CH,[9,28] and because an appreciable number of multiple-plurality pregnancies result in LBW or preterm birth, the effects of singleton versus multiple plurality on the relationship between LBW and the CH-incidence rate should be examined. Finally, examining CH-incidence rates among high birth weight and postterm newborns should be included in an analysis, because these factors have been associated with a higher incidence rate for CH.[5,9] Therefore, studies of data from multiple geographic locations on gestational age and race or ethnicity for confirmed cases of CH that do not include transient hypothyroidism should be performed to evaluate the issue.

A limitation of the analyses we report is that because the US data (1991–2000) provided to the NNSIS were in aggregate form, analyses on each individual demographic factor (race, ethnicity, sex, and birth weight) could not control for the other factors. Thus, confounding is a potential issue, which could only be addressed by analyses of individual-level data in which all demo-

graphic factors are identified for each case. Analyses of individual state NBS-program data are unlikely to be sufficient because of comparably small numbers of cases. To address these issues using multivariate analyses, individual-level data from multiple NBS programs would need to be combined, which will require collaboration between programs.

CONCLUSIONS

We have reported provocative findings regarding race, ethnicity, sex, and pregnancy outcomes related to the incidence rate of CH and the impact of these factors on the observed increasing incidence rate. Future studies to test these observations and hypotheses should focus on initial correct identification of demographic and pregnancy-outcome characteristics of the cases of CH (ie, race, ethnicity, sex, gestational age, birth weight) and long-term follow-up of presumed cases to differentiate true cases of CH from cases of transient hypothyroidism. With consistent case definitions and correct final classifications, robust risk-factor assessments could be performed to evaluate the effect of these factors on the incidence rate of CH.

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Trends in Incidence Rates of Congenital Hypothyroidism Related to Select Demographic Factors: Data From the United States, California, Massachusetts, New York, and Texas

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