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## Are lower TSH cutoffs in neonatal screening for congenital hypothyroidism warranted?

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### Abstract

When newborn screening (NBS) for congenital hypothyroidism (CH) using thyroid-stimulating hormone (TSH) as a primary screening test was introduced, typical TSH screening cutoffs were 20–50 U/L of whole blood. Over the years, lowering of TSH cutoffs has contributed to an increased prevalence of detected CH. However, a consensus on the benefit deriving from lowering TSH cutoffs at screening is lacking. The present paper outlines arguments both for and against the lowering of TSH cutoffs at NBS. It includes a review of recently published evidence from Australia, Belgium and Italy. A section focused on economic implications of lowering TSH cutoffs is also provided. One issue that bears further examination is the extent to which mild iodine deficiency at the population level might affect the association of neonatal TSH values with cognitive and developmental outcomes. A debate on TSH cutoffs provides the opportunity to reflect on how to make NBS for CH more effective and to guarantee optimum neurocognitive development and a good quality of life to babies with mild as well as with severe CH. All authors of this debate article agree on the need to establish optimal TSH cutoffs for screening programs in various settings and to ensure the benefits of screening and access to care for newborns worldwide.

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#### Supplementary data

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#### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

#### Author contribution statement

Introduction: all; Section on FOR: S L, S G, A O; Section on AGAINST: C T, S G, G V V; Section on ECONOMIC IMPLICATIONS: S L, S G; Section on GENERAL CONCLUSIONS: all.

## Introduction

Newborn screening (NBS) for congenital hypothyroidism (CH), which allows the identification and treatment of CH before clinical recognition, has led to the virtual disappearance of the intellectual disability (defined as an intelligence quotient (IQ) of roughly 70 or less, along with functional impairment) that was observed in up to 28% of affected individuals in the pre-NBS era (1). As such, it is one of the NBS programs with the greatest benefits, and it has been adopted progressively and continuously since 1973, and by now, universally in high-income countries (2).

When NBS for CH using thyroid-stimulating hormone (TSH) as primary screening test was introduced, typically with TSH cutoffs of 20–50 U/L of whole blood (all TSH values at screening reported here are on whole blood unless otherwise specified), the prevalence of cases detected through NBS was 1:3000–1:4000 infants. Over the years, lowering of TSH cutoffs in NBS programs has contributed to an increased prevalence of detected CH to roughly 1:2000 infants, although prevalence rates of CH have increased over time even in programs using the same cutoff. For example, in Greece during 2000–2002, the prevalence of primary CH was 1:1758 with a cutoff of 10 U/L and 1:2441 with a cutoff of 20 U/L (3). The latter is substantially greater than the rate of 1:3384 reported by Mengreli *et al.* (2010) for an earlier period using the same reagents and the same cutoff. In Italy, the overall prevalence of CH increased from 1:3000 during 1987–1998 to 1:1940 during 1999–2008, and the prevalence of permanent CH increased from 1:3200 to 1:2320 (4). Olivieri *et al.* report that if the cutoff had remained at 20 U/L, the final prevalence of CH would have been 1:2700 and that of permanent CH would have been 1:3150. When comparing regions and changes over time, it is important to be mindful of different laboratory methods, assays used and postnatal age at collection.

Although lower NBS TSH cutoffs result in the detection of additional cases of CH, (3, 5, 6, 7, 8), no consensus exists on the benefit in terms of developmental outcomes. The purpose of this paper is to present arguments both for and against the lowering of TSH cutoffs at NBS, with the aim of improving the health care and developmental outcomes of affected babies. First, arguments in support of lowering the TSH cutoffs will be presented. Those include evidence of missed cases of CH and potential detrimental effects on cognitive functioning. Second, arguments against the lowering of NBS thresholds will be presented. They include the lack of high-quality evidence concerning the cognitive/psychomotor impairments of children with mild elevation of TSH at NBS and the benefit of treatment of children with mildly elevated TSH values on those developmental outcomes.

### FOR: THE CASE FOR LOWERING TSH CUTOFFS AT NBS

We make two arguments in support of lowering TSH cutoffs: (1) it increases the number of infants treated for CH and (2) it likely improves health and developmental outcomes. First, many infants with a mild increase of TSH subsequently are diagnosed with overt, permanent CH, many with normally located and shaped thyroid glands (3, 9, 10, 11, 12, 13, 14). It is indisputable that infants with permanent CH benefit from treatment. We discuss evidence for three mechanisms underlying that association. Second, even mild abnormalities in thyroid function at birth (serum TSH 6–20 U/L with borderline low FT<sub>4</sub>) may pose a risk to

neurocognitive development. CH is a condition that is considerably more complex than was previously thought.

A proportion of babies with a mild increase of TSH at birth have thyroid dysgenesis. Mengreli *et al.* (2010) observed structural abnormalities of the thyroid (orthotopic hypoplasia or ectopy) in 20% of infants with TSH above screening cutoffs but <20 U/L (3). Similarly, an Italian study showed that 19.6% of babies with permanent CH and TSH between normal values and 15 U/L (considering also those detected at 2–4 weeks of life by repeat sampling strategy; defined hereafter as above screening cutoffs) had defects of thyroid development (orthotopic hypoplasia, hemiagenesis or ectopy) (14). A study conducted in Quebec assessed the impact of a new screening algorithm adopted in 2001; following an initial TSH between 15 and 30 U/L, the cutoff on a second test was decreased from 15 to 5 U/L. The new screening algorithm identified 49 additional cases of CH, and among these, 10 had an ectopic thyroid (12). Taken together, these findings suggest that orthotopic thyroid hypoplasia and ectopic thyroid may show heterogeneous phenotypes, including forms with a mild increase of TSH at birth. The detection by NBS of these forms can lead to an early treatment. Moreover, as thyroid dysgenesis may be familial, the detection of these milder forms of thyroid dysgenesis may allow genetic counseling of affected families (15, 16).

A mild TSH increase at screening does not always translate into mild hypothyroidism at confirmation of the diagnosis. In the above mentioned Italian study, Olivieri *et al.* found that >50% of babies with permanent CH and TSH above screening cutoffs but <15 U/L had serum TSH concentrations >20.0 U/L at confirmation of the diagnosis (Supplementary Fig. 1, see section on supplementary data given at the end of this article) (14). The median age at which the diagnosis was confirmed was 21 days in the group with TSH above screening cutoffs but <10 U/L, and 15 days in the group with TSH 10–15 U/L and in the group >15 U/L.

Recent European guidelines and other authors from the United States (US) recommend to start replacement therapy when serum TSH is >20 U/L even if FT<sub>4</sub> concentration is normal, carefully monitoring thyroid function to avoid overtreatment and retesting after 3 years if the thyroid is normally located (17, 18). Again, in the same Italian study, 19 of the 46 babies with thyroid dysgenesis and TSH above screening cutoffs but <15 U/L were severely hypothyroid at confirmation of the diagnosis with serum TSH concentrations ranging between 40 and 708 U/L. All 19 had orthotopic hypoplasia on ultrasound. In a recent study of the Scottish CH database between 2004 and 2014, among 26 infants with a confirmed diagnosis of CH and TSH at screening between 8.0 and 9.9 U/L, 8 infants (31%) had permanent CH (3 dyshormonogenesis, 2 ectopy, 3 unknown). Seven of these babies were at term and showed a serum TSH at confirmation ranging between 13.7 and >100 U/L. Among these babies, only two had normal serum FT<sub>4</sub> values (>15.0 pM/L), the remaining 4 had serum FT<sub>4</sub> ranging between 14.0 and 3.5 pM/L (19). Therefore, use of lower cutoffs identifies additional infants who need prompt treatment as well as infants with mild hypothyroidism or isolated hyperthyrotropinemia. Moreover, a delay in the increase of TSH among CH babies may occur more frequently than thought and not only in very low-birth weight, ill and preterm neonates as previously described (20, 21).

Another area where lower cutoffs can be helpful is identifying CH cases in preterm and low-birth-weight babies. Although premature infants with immaturity of the hypothalamic–pituitary–thyroid axis most frequently have transient CH, the frequency of preterm birth or low birth weight is also reported to be elevated among children diagnosed with permanent CH. For example, in Italy, 14.4% of all children with permanent CH in a national registry born during 2000–2006 had gestational age <37 weeks (all ages reported here are chronological ages), as did 23.9% of children with transient CH (14). In comparison, 6.5% of Italian infants were born preterm during the same period. In Massachusetts (US), infants with mild or delayed permanent CH was more likely to have birth weight <2500 g (13). In both populations, the increase over time in CH diagnoses occurred largely among infants born preterm or very low birth weight, as a result of lowered cutoff and in particular the practice of repeat testing of infants born preterm or low birth weight.

In particular, preterm infants frequently show a mild increase of TSH at screening and many are diagnosed with permanent CH. In Massachusetts, 30% of infants born during 2001–2004 with delayed CH (initial TSH above screening cutoffs but <20 U/L followed by higher TSH on a repeat screen) who were followed up were classified as having permanent CH, most of whom had birth weight <1500 g (13). In screening programs adopting a lower TSH cutoff at first test in Greece and Italy, (3, 14) the frequency of preterm infants is higher among babies with permanent CH and mildly elevated TSH at screening (Greece 37.5%; Italy 23.4%) than among babies with higher TSH (Greece 8.5%; Italy 12.1%). To avoid missing cases of CH among preterm babies, European guidelines (17) recommend repeat sampling at 2–4 weeks of life. However, this strategy is not adopted by all screening programs. A lower TSH cutoff at screening may help to detect preterm babies with mildly elevated TSH at birth or possibly reduce screening burden because preterm infants might no longer need repeat testing (22).

Infants with mild increase in TSH at birth may have poorer neurodevelopmental outcomes for a number of reasons (23). Information about the long-term cognitive outcomes for neonates with mildly elevated TSH at birth is critical for any debate regarding the lowering of NBS cutoffs. Long-term follow-up studies examining neurodevelopmental outcomes of infants with TSH above or thyroxine below NBS cutoffs have shown contradictory results and have been limited by small sample sizes (24, 25, 26). Recently, two studies with very different study designs have been published examining this topic, again with what appear to be contradictory results (27, 28, 29).

The first study, by Trumpff *et al.*, included children born at term in Belgium (28, 29). This cohort study retrospectively sampled children aged 4–6 years from the total list of infants screened in 2008, 2009 and 2010, stratified by sex and TSH interval (Supplementary Table). Psychologists prospectively performed cognitive testing and motor testing on 311 and 284 children, respectively. Although newborn TSH concentrations were not significantly correlated with any cognitive outcome, when categorized into three TSH groups (<5, 5–9, >10 U/L), there was a significant association between TSH concentrations of  $\geq 10$  U/L and a lower verbal IQ ( $P = 0.006$ ). This difference was no longer significant after adjustment for household income, maternal education and child bilingualism, although the adjusted coefficients for TSH were not reported. There was no association between TSH concentrations and motor development.

The second study, by Lain *et al.*, used NBS data from New South Wales, Australia linked to national education assessments administered to all Australian students in government schools each year and developmental census data routinely collected by teachers in all schools (27). This study found likely benefit to lowering cutoffs. The study consisted of two separate cohorts examining two outcomes; roughly 350,000 children born during 1994–2002 linked to an educational outcome and approximately 150,000 children born during 2002–2008 linked to a developmental outcome. The results of the study showed that, as newborn TSH values increased beyond approximately the 75th centile, the proportions of children with poor education or developmental outcomes increased (Supplementary Table). In particular, school-age children whose screening TSH values were between the 99.5th and 99.90th percentile (<screening cutoff, with absolute values ranging from 9 to 14 U/L depending on the year of birth) had roughly 60% higher adjusted odds of falling below the minimum national score on numeracy.

These apparently conflicting results may be explained in part by differences in study design and population. The designs of both studies have strengths and weaknesses. Trumpff *et al.* conducted a cohort study that collected detailed data about cognitive and motor outcomes and confounding variables, while Lain *et al.* used routinely collected data for outcome measurements and possible confounders, limited by the variables already collected in the population datasets. The greatest strength of the study by Lain *et al.* is the large sample size, particularly the number of infants with mildly elevated TSH concentrations just below the NBS threshold. Trumpff *et al.* had calculated a necessary sample size of 315 children to detect a correlation factor between TSH and IQ of 0.2. This equates to approximately 15 girls and 15 boys recruited in each TSH stratum. However, in the top three TSH strata (8, 9 and 10–15 U/L), less than half of the necessary number were recruited. As a consequence, this study is not powered to detect a difference between these top groups and the children with a lower newborn TSH result. The authors have not discussed the reason that these top TSH strata did not recruit the required sample size, whether infants were not available or refused to be part of the study; however, this is a source of bias that will influence the results.

The large population-based study by Lain *et al.* includes outcome data for approximately 500,000 children, with over 100 children in the top TSH centile groups. This large sample size can detect small differences between groups for mild cognitive outcomes of statistical significance; however, not all of these effects have clinical significance. In terms of absolute numbers, compared to children with newborn TSH concentrations <75th centile, 3.4%–5.6% more children had a poor education or developmental outcome with a neonatal TSH between the 99.5th and 99.90th centile (a neonatal TSH of approximately 8/9–13/14 U/L using recent laboratory methods).

The population of infants included in each study may also impact the results. A number of factors are known to cause a short-term increase in neonatal TSH concentrations, including prematurity, low birth weight and perinatal iodine exposure (30). Preterm infants have a higher risk of both transient and permanent CH, as discussed earlier, and are also more likely to have poorer cognitive and developmental outcomes compared to term infants. Trumpff *et al.* excluded preterm infants and those with birth weight <2500 g while Lain *et al.* only

excluded very low birth weight infants (<1500 g). However, Lain *et al.* performed a sensitivity analysis excluding preterm infants and infants with a 5 min Apgar score less than 7 and found very similar results as the main study findings.

Iodine is crucial for the production of thyroid hormone, and maternal iodine deficiency can lead to increased concentrations of neonatal TSH. Furthermore, severe and mild maternal iodine deficiency during critical windows of fetal neurodevelopment has serious consequences and has been associated with poor childhood cognitive outcomes (31). The proportion of neonates with a TSH >5 U/L at NBS (on day 3–4) has been recommended to be used as a marker for population iodine deficiency by the World Health Organization (WHO), with a proportion higher than 3% indicative of iodine deficiency (32). The study population of Lain *et al.* was mildly iodine deficient with 6.5% of the population with a TSH greater than 5 U/L, as per WHO criteria (33). In Belgium during 2009–2010, only 2.6–3.0% of newborns had TSH >5 U/L (34). As neonatal TSH is on the causal pathway between maternal iodine deficiency and infant cognitive outcomes, (35) maternal iodine deficiency is presumably an effect modifier of the relationship between neonatal TSH and cognitive outcomes. That could contribute to the difference in findings between the Australian and Belgian studies. In any case, a larger sample size than that of Trumpff *et al.* would likely be required to detect an association between maternal iodine deficiency and poor cognitive outcomes in an iodine-sufficient population (31).

Another difference between the study populations of Trumpff *et al.* and Lain *et al.* that may impact the results and generalizability of each study is the socioeconomic status (SES) of the study samples. Trumpff *et al.* included a cohort of mothers with relatively high educational attainment, income and use of childhood dietary supplements, which could limit generalizability to the whole population. Lain *et al.* conducted a population-based study with NBS data on all infants born in New South Wales, Australia. However, for educational outcomes, only assessments from government schools were available for linkage to NBS results. Government schools represent approximately 70% of the population and over-represent children of lower SES. Developmental outcomes, however, were examined across the whole population and exhibited similar results to those of the educational outcomes. This complete population-based cohort is therefore generalizable to the NBS population.

## Conclusions

TSH is the most accessible marker of central nervous system thyroid hormone status and even mild modifications of its serum concentrations should be taken seriously. Despite a lack of blood spot TSH assay standardization, (36) a NBS program with a TSH cutoff <15 U/L can be expected to identify some infants who have overt hypothyroidism at confirmation of diagnosis as well as infants with mild hypothyroidism or transient elevations in TSH. Delay in identification and commencement of treatment of infants who have overt hypothyroidism puts those infants at risk of poorer long-term outcomes (6). Furthermore, diagnosis by NBS is associated with less parental stress than later identification clinically (37). Importantly for this debate, infants with less-severe cognitive outcomes associated with mildly elevated TSH at NBS may not be identified clinically and will miss out on the possible benefits of further clinical testing and treatment if not identified by NBS.

## AGAINST: THE CASE AGAINST LOWERING TSH CUTOFFS AT NBS

The TSH cutoff used for NBS has decreased in many jurisdictions and varies considerably between programs, with some using a cutoff as low as 6 U/L, albeit on day 5, which corresponds to a higher cutoff at day 2 (6). Predictably, a lower TSH cutoff leads to a larger number of newborns being recalled (3) or having confirmed CH, with prevalence estimates ranging from 1:2500 (12) to 1:1000 (5). Importantly, these prevalence estimates are all considerably higher than that of 1:6900 children diagnosed clinically with CH in the pre-NBS era (38).

In addition, not all children who are diagnosed with confirmed CH necessarily require treatment. In some cases, elevated TSH level at NBS results from other factors than CH – such as preterm birth – that are also associated with poor developmental outcomes (23). Providing thyroxine treatment to preterm infant is not associated with improvement of their developmental outcomes (39). Overtreatment with thyroxine of subclinical CH may have harmful health consequences such as iatrogenic hyperthyroidism (40). A retrospective study of administrative data in the United States found that 38% of children who were labeled as having CH at NBS no longer refilled their thyroxine prescriptions by 4 years of age (41). Medically supervised re-evaluation of the need for treatment, which is recommended at age 3 years, often shows transient thyroid dysfunction, (41) the impact of which on development is not established, as discussed below.

Children with normal results on the first NBS sample may have a high TSH at a subsequent sample a few weeks later. This phenomenon, dubbed ‘delayed TSH rise’, has been mostly reported in neonates born with a very low birth weight (13, 21, 42). Two follow-up studies of such children, although based on small samples with relatively short follow-up, suggest that for most children the phenomenon is transient, although many are diagnosed with CH and treated (13, 21). One study evaluated developmental outcomes at age 18 months in nine children, two of whom received thyroxine treatment for 1–3 months (treatment was decided by physicians and not administered in a randomized fashion) (21). Developmental outcomes at 18 months did not differ significantly from children without CH, despite a significant difference in head circumference.

Nevertheless, the occurrence of delayed TSH rise has led to guidelines suggesting that NBS has to be repeated in neonates born preterm or with a low birth weight (17). While the birth weight distribution of CH babies is U-shaped overall, (43) in severe CH due to dysgenesis or dyshormonogenesis, the distributions of birth weight and gestational age are skewed to the right not to the left, (44) which indicates that premature/low birth weight infants are not overrepresented in that subset of children with CH (45, 46). In some programs in the United States, infants are routinely retested at around 2 weeks, and states that do such testing report that on average 11% of infants detected with CH are identified only through the second screen. However, it was suggested by researchers that with an appropriate algorithm, the two-screen states could revert to a single screen without loss of performance (47).

Indeed, another layer of complexity underpinning the present debate arises from the fact that confirmed CH can be either permanent or transient. Contemporary practice is to routinely treat even transient cases during the first 3 years of life, the period during which irreversible

brain damage can result from CH. However, the evidence that transient CH, if untreated, leads to such brain damage is contradictory. Indeed, Alm *et al.* reported on six children whose TSH on the sample collected to detect phenylketonuria (for which NBS was established about 10 years before NBS for CH) ranged from 42 to >100 U/L, but who were euthyroid when evaluated at age 5 years and had IQs comparable to that of controls (48).

To argue against the lowering of the cutoff, we first briefly review outcome studies on both permanent and transient thyroid dysfunction in children born term and preterm. However, because in this section, we have cited evidence that overt CH is not more prevalent in babies born preterm, we focus on term, otherwise normal infants with screening TSH in the 5–15 U/L range. If mild hyperthyrotropinemia is causally linked to disadvantages in neurocognitive development, possibly due to specific etiologies (see below), infants with screening TSH values in that range might benefit from further testing and possible treatment. However, whether they do experience a worse long-term developmental outcome in the absence of treatment is uncertain.

As described in the previous section, recent publications have reported contradictory results on the relationship between TSH concentrations at NBS that are considered normal by most programs and cognitive, psychomotor, behavioral or educational outcomes (27, 29). Here, we contrast and review these recent findings and propose strategies to establish whether the relationship is causal and the implications for optimal screening cutoffs.

Because overdiagnosis is an inherent side effect of population screening, (49) one should also assess the possible harms and economic burden of lowering TSH cutoffs (50). The impacts on the family must also be considered, particularly for infants who need ongoing diagnostic testing to monitor if treatment is necessary (50). A retrospective study of administrative data in the United States found that 38% of children who were labeled as having CH at NBS no longer refilled their thyroxine prescriptions by 4 years of age (51). The study was unable to distinguish between cases where parents chose to stop treatment on their own and children classified as having transient CH and no longer needing treatment, but most discontinuation occurred long before the age of 3 years. A subsequent study from one state followed up families of 3 year-old children with mild elevations of TSH who had been diagnosed with CH and found that one-quarter of families that responded had chosen to discontinue treatment, almost all without medical supervision, because of the perceived burden of frequent monitoring and treatment (41).

Research on the cognitive and psychomotor development of children with mild neonatal thyroid dysfunction is scarce and mostly based on small samples without adjustment for potential confounding. For example, a case–control study was conducted on a small cohort ( $n = 18$ ) of 6–9-year-old children in Italy born with transient CH (elevated TSH and low  $T_4$  at birth and a return to normal values at 1–3 months after birth) or hyperthyrotropinemia (elevated TSH at birth and a return to normal value at 1–3 months after birth) measured in cord blood in comparison with a control group of nine euthyroid children. Lower full scale ( $90.9 \pm 14.2$  and  $78.3 \pm 11.1$ ,  $P < 0.05$ ) and performance scores ( $89.2 \pm 12.5$  and  $75 \pm 8.5$ ,  $P < 0.05$ ) were found in children with thyroid dysfunction at birth using the Wechsler Intelligence Scale Children-Revised compared with euthyroid children (52).



Another retrospective cohort study conducted in Italy on 61 three-year-old children found that elevated TSH concentrations measured three days after birth (between 5 and 10 U/L) were associated with lower McCarthy Scales of Children's Abilities (MSCA) scores in the Perceptual Performance Skills (5.5 points loss), Memory Development (6.5 points loss) and General Cognitive Index (9.8 points loss) ( $n = 13$ ) in comparison with control group ( $n = 48$ ) ( $P < 0.005$ ) (53). These two studies were limited by a small sample size and a lack of adjustment for confounding factors. Because those studies have been conducted in areas of mild-to-moderate iodine deficiency it may be postulated that mild elevation of TSH in these samples may be due to iodine deficiency, and that the solution to avoid developmental impairments could have been to ensure iodine sufficiency in their mothers.

A larger Spanish retrospective cohort study was conducted in 2010 on 178 boys from the general population when aged three years (24). TSH in cord blood (TSH range 0.24–17.00 U/L) was negatively correlated with general cognitive scores and executive function scores at MSCA (24). However, the results of this study are limited by the fact that only boys were studied.

With regards to psychomotor development, an Italian cohort of 102 infants born preterm (between 26 and 32 weeks gestational age) found that children with a neonatal TSH value above 4.3 U/L had a higher risk of suboptimal developmental quotient motor score assessed with the Griffiths Scales of Mental development at 18 months (OR = 14.6; 95% confidence interval (CI): 2.49–86.2) (54). Preterm birth is related to increased TSH concentrations (55) and risk of psychomotor delay; thus, the results of this study are not generalizable to children born full term.

As outlined in the previous section, two recent studies conducted with different designs have found discordant results. The Belgian study conducted by Trumpff *et al.* found no association between TSH concentration (0.1–15 U/L) and cognitive, psychomotor and behavioral development at preschool age when adjusting for confounding factors using multivariate analysis (28, 29, 56). Cognitive and psychomotor assessment was performed by psychologists using age-appropriate clinical diagnostic tools, respectively, the Wechsler Preschool and Primary Scale of Intelligence (third edition) and Charlop-Atwell Scale of Motor Coordination (28, 30). Psychosocial development was assessed using the Child Behavior Check List for age 1½–5 years standardized and validated questionnaire completed by the mothers, a widely used measure for evaluating maladaptive behavioral and emotional problems (56). Of note, the sample size had the statistical power to detect an IQ score difference as small as 4.3 points. However, despite having a larger sample size than previous studies using clinically based tools to assess development, this study has several limitations including its retrospective recruitment, self-reported data and the higher level of education of the population included in the sample (73% of the mothers reported a university degree).

These findings that mild thyroid dysfunction at birth is not associated with neurodevelopmental problems are supported by other studies using different but comparable indicators. A study conducted in Scotland in 2013 assessing thyroid cord blood parameters of 97 children born at term and their neurodevelopment (measured with the MSCA) at age 5 years found unexpected significant positive associations of low concentration of cord blood

T<sub>4</sub> with neurodevelopmental scores (26). Another study conducted in Massachusetts, US, included 500 three-year-old children, and similarly found a significant inverse association between newborn T<sub>4</sub> concentration and cognitive scores (assessed with recognition memory paradigm) at 6 months and no association with vocabulary (assessed with the Peabody Picture Vocabulary Test) and visual motor scores (assessed with the Visual Wide Range Assessment of Visual Motor Ability) (25).

The other recent study conducted by Lain *et al.* in Australia, an epidemiological record linkage study, found higher risk of delayed attainment of educational milestones evaluated with National Assessment Program Literacy and Numeracy test scores for school children and Australian Early Development Census (AEDC) teacher reports for preschool children (27). These results should be interpreted with caution and confirmed by further studies using clinic-based diagnostic tools since educational outcomes are not a direct measure of cognitive capacities and the AEDC is not a diagnostic tool, but is based on teacher reports of developmental problems.

The study by Lain *et al.* included children screened before the introduction of mandatory iodized salt in bread manufacturing and before the implementation of a systematic recommendation of iodine supplementation intake by pregnant women. This means that the increased TSH of the newborns may have been secondary to mild iodine deficiency in their mothers. In that case, the public health implication would have been to implement action to ensure iodine sufficiency of women of childbearing age. The findings of Lain *et al.* should be replicated in iodine-sufficient areas and with clinically based diagnostic tools. Also, an analysis by absolute TSH concentration, rather than percentile, is necessary to translate the Australian study in policy decisions on screening cutoffs.

## Conclusions

The evidence reviewed above does not appear strong enough to justify a lowering in TSH cutoffs at NBS at the present time. Aside from confounding by iodine insufficiency, a high TSH at NBS may reflect a genetic abnormality that is associated with developmental delay regardless of thyroid function. Examples of such genetic abnormalities include mutations in *NKX2.1* (57) or in *GNAS* (58). By contrast, 10–20% of individuals with mild persistent hyperthyrotropinemia have a heterozygous mutation in the TSH receptor gene, (59) a genetic variant that is not associated with developmental delay (60). Thus, persistent mild hyperthyrotropinemia is a biochemical phenotype with various possible mechanisms but for which the evidence that treatment is required is lacking (61).

To prove that the relationship between mildly elevated TSH at NBS and a poorer developmental outcome is causal, a randomized, placebo-controlled, double-blind trial would be needed, although such a study could be considered unethical. The only existing randomized placebo-controlled trial (RCT) of the long-term effect of thyroxine treatment on children with mildly elevated TSH at NBS was completed in children with Down syndrome, not a generalizable population (62, 63). In that study, children were evaluated at 6 months, 1 year and 2 years with the Bayley Scale of Infant Development II administered by a psychologist. Subtle difference in cognitive (–0.8 months; 95% CI: –1.5 to –0.1) and motor

scores (−0.8 months; 95% CI: −1.5 to −0.2) were found at 2 years. However, when children were assessed at 10 years for cognitive and motor development along with communication and fine motor coordination skills, no significant long-term developmental advantage of thyroxine treatment was found (62). In the absence of such high-quality evidence for treating healthy children with mildly elevated TSH at NBS, lower quality evidence could be derived from comparing the developmental outcome of children born in neighboring jurisdictions that apply different TSH cutoffs.

## ECONOMIC IMPLICATIONS

As NBS programs are publicly funded, any decision to change NBS algorithms can potentially benefit from an economic evaluation of the associated costs and health benefits. In deciding whether to change screening cutoffs or testing methods, programs should consider both the cost of healthy children being recalled and retested and the benefits of treatment of children identified as a result of NBS. Such analyses are rarely conducted; instead, people have extrapolated from previous economic analyses of introducing NBS in the first place, which is not valid (64, 65).

At the time NBS for CH was first introduced, it was asserted that avoided costs would be a multiple of 7.8 times the costs of screening and treatment (66). Another analysis which used more realistic estimates about the frequency of residential care for severe intellectual disability estimated a more modest benefit-cost ratio of 1.4–1 (67). In the pre-NBS era, as many as one-fourth of children with clinically diagnosed, overt CH developed mild-to-moderate intellectual disability and received special schooling (1). With NBS and timely and appropriate treatment, children with CH no longer require special education services, (68) although behavioral problems are sometimes reported (69).

The benefits of treating CH include improved cognitive and behavioral development, school performance, and, eventually, economic productivity. In the pre-NBS era, children with untreated subclinical permanent CH often experienced losses in cognitive ability within the normal range (1). The gain in productivity for each 1 IQ point gain can exceed 1% of lifetime earnings, and the aggregate economic value of modest per-person gains may be quite substantial (70). However, there is no evidence that children with CH detected through lower screening cutoffs or repeat screening experience gain in IQ scores, (1) which are not the same as the developmental scores used in other studies cited earlier in this paper.

Lowering screening TSH cutoffs or conducting repeat screens may result in the diagnosis of infants with phenotypes for whom the benefits of early detection are either less marked or unproven (64). Long-term follow-up studies suggest that children with low T<sub>4</sub> and/or delayed bone maturation at diagnosis of CH are at risk for lower cognitive test scores (1). Grosse and Van Vliet noted the lack of ‘evidence that the additional children who are picked up through the use of lower cutoffs or repeat screens would have otherwise experienced cognitive impairment’ (1). Indeed, a study in Rhode Island (US) did not find worse outcomes for children detected through repeat screening who either were not treated or discontinued treatment at <3 months of age (21).

Reducing TSH thresholds will raise the costs of NBS, which include the costs of recalling and retesting infants who do not pass the initial screen, confirmatory and diagnostic testing and treatment of those who are diagnosed. Although the costs associated with collecting repeat samples are not insignificant, (71) particularly when the cost to a family of a clinic visit or the cost of a midwife's home visit are included, the vast majority of those recalled receive one additional blood test with normal results and no further testing or treatment is needed. In Greece, for example, lowering the screening cutoff from 20 U/L to 10 U/L increased the percentage of children recalled for secondary testing ten-fold, from 0.12% to 1.2%, but the rate of diagnosed CH increased by just 39%, from 1:2162 to 1:1557 (3). Of 3408 infants with an initial TSH between 10 and 20 U/L who were recalled, just 56 (1.6%) infants were diagnosed with CH and treated.

Quantifying the benefits of decreased TSH cutoffs is challenging. The first challenge is to establish robust evidence of improved outcomes for those children who would be detected using lower cutoffs. The finding that Australian children with mildly elevated TSH screening values below the upper 0.05th percentile, roughly equivalent to screening cutoffs, had significantly elevated developmental and educational problems, unlike those with TSH values in the upper 0.05% percentile, (27) is suggestive that lowering the screening cutoff could have avoided those problems. For example, 11.3% of children with TSH in the 99.90th to <99.95th percentile had below the national minimum of numeracy, compared with 5.5% of children with TSH <75th percentile. That finding would be more compelling if the analysis had used absolute TSH values and compared children just below and just above the actual screening cutoff values for each birth cohort. Also, it is not known whether the same finding would be found in Australian children born in a state of iodine sufficiency.

The second challenge, which is to model the economic impact of outcomes, such as educational test scores, is relatively straightforward. Published estimates from population-based cohort studies of the association of test scores with earnings exist. For example, a UK study demonstrated that, controlling for family background, higher numeracy and reading test scores at age 10 years predict higher earnings as adults, most of which is mediated by the association of test scores with additional years of schooling (72). However, the association of test scores with earnings appears to vary across countries. A cross-sectional study conducted in 22 high-income countries found that adult numeracy and literacy test scores predicted adult earnings to varying degrees across countries and to a similar magnitude of the IQ-earnings association (73). If the Australian findings hold up, and are not accounted for by mild iodine deficiency, it is plausible that the economic benefit of lowering the TSH cutoff could well exceed the added costs.

## GENERAL CONCLUSIONS

A debate on TSH cutoffs provides the opportunity to reflect on how to make NBS for CH more effective and to guarantee optimum neurocognitive development and a good quality of life to babies with mild as well as with severe CH. Tradeoffs between avoiding false negatives and false positives are inherent to screening programs, and reasonable people may disagree on how to set cutoffs to achieve balance and maximize NBS program efficiency. This exchange is intended to clarify the issues and the current state of the evidence rather

than to resolve differences of opinion. It is unclear to what extent mild iodine deficiency accounts for findings of worse developmental outcomes for children with mildly elevated screening TSH in some populations. There is also uncertainty about long-term outcomes in children with delayed rise in TSH, with or without treatment. Some of us are of the opinion that there is sufficient evidence at present to justify the lowering of TSH NBS cutoffs, while others believe that more research is still needed. All of us agree, though, on the need to continue research to establish the optimal TSH cutoffs for screening programs in various settings.

More importantly, we are all in agreement regarding the overwhelming benefit and importance of NBS for CH. Most critical of all, about 70% of the world's newborns do not benefit from any NBS at all (74). Although much progress has been made in the diagnosis and treatment of CH since NBS was introduced, work still needs to be done to detect and treat all forms of CH and to ensure the benefits of screening and access to care for all newborns worldwide. Furthermore, it is of public health importance to use trends in TSH NBS data to monitor and correct iodine deficiency at the population level.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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