Newborn screening TSH values <15 mIU/L are not associated with long-term hypothyroidism or cognitive impairment

Rachel West[*1], Joyce Hong[*1,2], José G B Derraik[1,3,4], Dianne Webster[5], Natasha L Heather[1,5], Paul L Hofman[1]**

[1] Liggins Institute, Faculty of Medical and Health Sciences, University of Auckland, Private Bag 92019, Auckland, New Zealand

[2] Department of Paediatrics, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur

[3] Department of Endocrinology, Children's Hospital, Zhejiang University School of Medicine, Hangzhou, China

[4] Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden

[5] Newborn Metabolic Screening Programme, LabPlus, Auckland District Health Board, Auckland, New Zealand

***RW and JH contributed equally to the study.**

****Corresponding author:**

Dr Natasha Heather, LabPlus, Auckland District Health Board, New Zealand Newborn Metabolic Screening Programme, PO Box 110031, Auckland City Hospital, Auckland 1148, New Zealand; Email: NHeather@adhb.govt.nz

Accepted Manuscript

Downloaded from https://academic.oup.com/jcem/article-abstract/doi/10.1210/clinem/dgaa415/5864811 by Science Library user on 02 July 2020

© Endocrine Society 2020. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com jc.2020-00609 https://academic.oup.com/endocrinesociety/pages/Author_Guidelines for Accepted Manuscript disclaimer and additional information.

Acknowledgements: We thank the staff of the National Screening Unit, in particular Moira McLeod, for ongoing programme support and data access.

Author contributions: NLH, PLH, DW, and RW conceived and designed the study; RW and JH carried out the clinical assessments; RW, JH, and NLH compiled the data; JGBD carried out the statistical analysis; JH, NLH, JGBD, PLH wrote the manuscript with input from DW and RW. All authors have approved the final version of this manuscript.

Funding: This research received funding from the New Zealand Ministry of Health and the Australasian Paediatric Endocrine Group.

Disclosure statement: The authors have nothing to disclose.

Accepted Manuscript

Downloaded from https://academic.oup.com/jcem/article-abstract/doi/10.1210/clinem/dgaa415/5864811 by Science Library user on 02 July 2020

ABSTRACT

Background: It is unclear whether newborns with mild TSH elevation (mTSHe) are at risk of neurocognitive impairment. We assessed whether mTSHe at birth persists during childhood and compared neurocognitive functioning to siblings.

Methods: This study encompassed children born in the Auckland region with a newborn screen TSH level 8–14 mIU/L blood, aged 6.9–12.6 years at assessment, and their siblings. Thyroid function tests (serum TSH and FT4) and neurocognitive assessments were performed, including intelligent quotient (IQ) via Wechsler Intelligence Scale for Children IV.

Results: Ninety-six mTSHe subjects were studied, including 67 children recruited with 75 sibling controls. Mean mTSHe newborn TSH level was 10.1 mIU/L (range 8–14 mIU/L, blood) and 2.4 mIU/L at assessment (range 0.8–7.0 mIU/L, serum). Although higher newborn TSH levels in the mTSHe group correlated with lower full-scale IQ scores (r=0.25; p=0.040), they were not associated with the magnitude of the IQ difference within sibling pairs (p=0.56). Cognitive scores were similar for mTSHe and controls (full-scale IQ 107 vs 109; p=0.36), with a minor isolated difference in motor co-ordination scores.

Conclusions: Our data do not demonstrate long-term negative effects of neonatal mild TSH elevation. TSH elevation below screen threshold appears largely transient and mid-childhood neurocognitive performance of these children was similar to their siblings. We propose that associations between neonatal mild TSH elevation and IQ are due to familial confounders. We caution against the practice of reducing screening CH cutoffs to levels where the diagnosis may not offer long-term benefit for those detected.

Key words: Neonatal screening; mild TSH elevation; congenital hypothyroidism; thyrotropin; intelligence tests; neuropsychological tests.

Accepted Manuscript

Downloaded from https://academic.oup.com/jcem/article-abstract/doi/10.1210/clinem/dgaa415/5864811 by Science Library user on 02 July 2020

INTRODUCTION

Congenital hypothyroidism (CH) is a common preventable cause of mental retardation (1, 2). The current question is not whether the early detection of CH through newborn screening is beneficial, but concerns the additional utility of extending the screening target to include subclinical disease (2-4). There is wide variability in newborn screening TSH cutoffs around the world, which mostly reflects the value placed on detecting subtle changes in thyroid biochemistry (4). Other considerations when comparing cutoffs include the baby's age at sample collection (and distance from the post-natal surge in TSH), the assay used, and whether TSH levels are expressed directly as blood levels or converted to serum (typically using a conversion factor of 2.2 (5)). Please note that all screening TSH values within this manuscript are expressed as whole blood levels unless otherwise specified.

TSH screening cutoffs have greatly decreased from inception (typically 20–50 mIU/l), with some programmes now recalling babies with screening TSH levels as low as 6–10 IU/L (6-9). Programmes that have recently reduced cutoffs report a dramatic increase in the incidence of CH, mostly as a result of increased cases of eutopic and/or transient CH (6-9). In addition, lower TSH cutoffs lead to many more false positive results, which increase potential screening harm through parental anxiety and additional use of health services. For example, a reduction in the Greek screening threshold from TSH 20 mIU/L to 10 mIU/L was accompanied by a ten-fold increase in the recall rate (8). In addition, low TSH screening thresholds can lead to the over-diagnosis and medicalisation of children with clinically inconsequential biochemical abnormalities. Screening follow-up data from Michigan demonstrates the burden a mild or uncertain CH diagnosis places on families, as at least 20% of screen-diagnosed children were found to have discontinued treatment without medical supervision by 3 years of age (10).

Importantly, it is not clear whether newborns with mild TSH elevation are at risk of neuro-cognitive impairment without treatment. In the absence of randomised controlled trials, natural history studies

Accepted Manuscript

Downloaded from https://academic.oup.com/jcem/article-abstract/doi/10.1210/clinem/dgaa415/5864811 by Science Library user on 02 July 2020

can help describe the outcome of untreated neonatal mild TSH elevation (4). A recent epidemiological-linkage study from Australia reported a dose-dependent association between poorer educational outcomes and newborn screening TSH levels above the 90th centile and below screening threshold (11). Possible confounding factors within this population included maternal iodine insufficiency and the inclusion of children with premature birth (11). Conversely, in a Belgian study an inverse association between newborn screening TSH levels and verbal IQ scores was no longer apparent when controlled for confounding factors such as maternal education and income (12, 13). Smaller studies have reported inconsistent associations between high cord blood TSH levels and poorer cognitive development (14-16).

Screening for CH has been performed in New Zealand as part of the Newborn Metabolic Screening Programme using TSH levels since 1978, with a national incidence of approximately 1:2500 (17). Unlike many other screening programmes, the TSH cut-off (≥15 mIU/L) has remained the same for several decades (18), offering the opportunity to observe the natural history of children with mildly raised TSH levels below the newborn screening threshold. Babies with a TSH level <15 mIU/L blood are considered to have had a negative screen for CH and have no further follow up.

The aims of this study therefore were: 1) to determine whether mild TSH elevations at birth persist in later childhood; 2) to compare neurocognitive functioning in children with mild TSH elevation to siblings with normal newborn screening TSH levels.

Accepted Manuscript

Downloaded from https://academic.oup.com/jcem/article-abstract/doi/10.1210/clinem/dgaa415/5864811 by Science Library user on 02 July 2020

METHODOLOGY

Ethics approval

The study was approved by the Southern Health and Disability Ethics Committee, Ministry of Health, New Zealand (14/STH/39). Written consent was obtained from parents or guardians, as well as verbal and/or written consent from each child as was appropriate to their age.

Participants

In New Zealand, screening for CH is based on measurement of whole-blood TSH. Heel-prick samples on specialised collection paper are collected from all newborn babies between 48 and 72 hours of age. These are immediately sent for testing at the centralised screening laboratory, and TSH assessed by immunofluorescence (DELFIA PerkinElmer). The threshold for an abnormal screen (leading to either direct clinical referral or request for collection of a further heel-prick sample) is TSH ≥15 mIU/L and has not changed for several decades. Early samples collected <46 hours were not considered suitable for CH screening, and a further specimen was requested. For the purpose of this study, those samples collected at ≥46 hours with a newborn screening TSH level 8–14 mIU/L were considered to have mild TSH elevation.

The study population was identified from the National Newborn Screening Unit database, and encompassed children aged 6-12 years at the time of testing, living within the Auckland region, and with a newborn screening result consistent with mild TSH elevation. Auckland has a population of approximately 1.5 million and 22,000 births per year. The control cohort consisted of siblings aged 6–16 years with a newborn screening TSH level ≤7 mIU/L. Exclusion criteria for both groups included the presence of a condition that results in impaired intellect independent of thyroid insufficiency (e.g. Down syndrome); premature birth (<37 weeks of gestation) or small for gestational age (≤-2 SDS); a later diagnosis of CH; a chronic medical issue requiring more than two hospitalisations within the past

Accepted Manuscript

Downloaded from https://academic.oup.com/jcem/article-abstract/doi/10.1210/clinem/dgaa415/5864811 by Science Library user on 02 July 2020

year; care and protection issues that were documented within medical records; and if children/parents/guardians were not fluent in English and therefore not able to understand the participant information sheets.

Study parameters

All clinical and neurocognitive assessments were carried out by trained examiners at the Maurice and Agnes Paykel Clinical Research Unit (Liggins Institute, University of Auckland). Assessors were not blinded to group designation. Children with mild TSH elevation (mTSHe) were given blood testing forms, and asked to get their thyroid function tested (serum free T4 and TSH) within 2 weeks of the assessment. Electrochemiluminescence immunoassays of serum TSH and FT4 were performed using Roche Elecsus and Modular Analytics analysers (Roche). The intra- and inter-assay coefficients of variation were, respectively, 8.6% and 8.7% for TSH, and 1.6% and 3.5% for FT4. The childhood reference range (1–18 years) for FT4 is 10.0–20.0 pmol/L, and for TSH is 0.30–4.00 mIU/L. Sibling controls were not required to have thyroid biochemistry assessed.

Ethnicity was identified by self-report using a prioritised system, such that if multiple ethnicities were selected, participants were assigned to a single ethnicity following a hierarchical system of classification (19). Socio-economic status was determined using the New Zealand Index of Deprivation 2013 (NZDep2013), a geocoded deprivation score derived from current residential address (20).

Neurocognitive assessments

All participants underwent the Wechsler Intelligence Scale for Children – fourth edition (WISC-IV) (21). This is an age-standardised test, with a mean of 100 and SD of 15. Core subtests were used to obtain composite scores on verbal comprehension, perceptual reasoning, working memory, and processing speed, which were then combined to calculate full-scale IQ.

Accepted Manuscript

Downloaded from https://academic.oup.com/jcem/article-abstract/doi/10.1210/clinem/dgaa415/5864811 by Science Library user on 02 July 2020

Visual motor integration, visual perception, and motor co-ordination were measured with the Beery Developmental Test of Visual-Motor-Integration, 6th edition (Beery VMI) (22). Motor development was further assessed using the Movement Assessment Battery for Children, second edition (MABC-2) (23). Three subcomponents (manual dexterity, aiming and catching, and balance) were combined to give a total movement score, standardised with a mean of 10 and SD of 3.

Power calculation

Our sample size and power calculation was derived from our paired study design (cases and sibling controls), and a standard deviation of 14 from our previous Auckland CH study (24). Therefore, to detect a difference in full-scale IQ ≥5 points (deemed to be clinically relevant) we needed to recruit 64 cases and 64 sibling controls, with α=0.05 and 80% power.

Statistical analysis

Demographic data for mTSHe and control groups were compared with one-way ANOVA, non-parametric Kruskal-Wallis test, or Chi-square tests, as appropriate. Generalized linear mixed models were used to examine potential differences between groups, including family and assessor as random factors to account for sibling clusters and possible inter-assessor scoring variations, respectively. Models also adjusted for important confounding factors, namely gender, and socioeconomic status (NZDep2013); models examining WISC-IV outcomes also adjusted for having English as their first language (yes vs no).

In addition, linear associations between TSH levels at birth and the WISC-IV components were evaluated, with models constructed as described above. Assuming that newborn TSH would be the primary cause of a possible later decrease in cognition, one would expect that the greater the newborn TSH, the greater would be the gap in full-scale IQ scores between the child with mild TSH elevation

Accepted Manuscript

Downloaded from https://academic.oup.com/jcem/article-abstract/doi/10.1210/clinem/dgaa415/5864811 by Science Library user on 02 July 2020

and their sibling. As a result, models were constructed as above, examining the association between newborn TSH and the difference in IQ between children with mild TSH elevation and their respective siblings.

Two analyses were performed: i) on the whole group including all recruited mTSHe participants with or without sibling controls (n=96); and ii) on the smaller mTSHe group who had one or more sibling control (n=67).

Statistical analyses were carried out in SAS v9.4 (SAS Institute, Cary, NC, USA) and Minitab v16 (Pennsylvania State University, State College, PA, USA). All statistical tests were two-tailed and maintained at a 5% significance level. Figures were created with GraphPad Prism v8.2.1 (GraphPad Software Inc., San Diego, CA, USA).

RESULTS

A total of 1,255 children aged 6-12 years born in Auckland with a newborn screening TSH level 8–14 mIU/l were identified from the National Newborn Screening database. 574 were not registered within the Auckland hospital system and 3 were deceased; 130 were excluded (including a monozygotic twin with missed CH (25)), and 430 were not contactable (Figure 1). From the 118 eligible children who were contacted, 94 agreed to participate, with two additional siblings with mild TSH elevation also included, so that 96 children with mild TSH elevation were studied (Figure 1). Of the 96 children with mild TSH elevation, 67 had one or more sibling control (n=75).

Overall, 172 children (96 mTSHe and 75 sibling controls) underwent neurocognitive assessments at a mean age of 9.8 years (range 5.8 to 15.8 years). Of the 96 mTSHe children, 65 underwent requested blood tests to determine serum TSH, and 52 had both TSH and free T4 levels assessed. The mean newborn screening TSH level amongst the mTSHe group was 10.1 mIU/L (range 8–14 mIU/L, whole blood) and mean TSH level at study assessment was 2.4 mIU/L (range 0.8–7 mIU/L, serum level).

Accepted Manuscript

Downloaded from https://academic.oup.com/jcem/article-abstract/doi/10.1210/clinem/dgaa415/5864811 by Science Library user on 02 July 2020

The mean serum free T4 level at assessment was 15.3 pmol/L (range 10–19 pmol/L), with all results within the normal range. There were 7 children with marginally elevated TSH levels at assessment (4.2–7 mIU/L) but with normal free T4 levels (14-16 pmol/L).

Children with mild TSH elevation and controls were of similar age and sex ratio (Table 1). However, when all mTSHe cases were considered, these children were slightly younger than controls (Table 1). Although no participants had a full-scale IQ score <70, three mTSHe children and one sibling control had IQ scores 70–85 (p=0.34 for the between-group comparison from a Fisher's exact test). The 7 children with mTSHe upon mid-childhood assessment had a median full-scale IQ score of 101 (range 83–129).

Larger group analyses

When all recruited mTSHe children were considered (n=96), for every 1 mIU/L increase in newborn TSH (in the 8–14 mIU/L range) there was a 1.8 point decrease in full-scale IQ scores (95% CI -3.2, -0.3; p=0.021). Similarly, every 1 mIU/L increase in newborn TSH was associated with a 2.0 point decrease in verbal score (95% CI -3.8, -0.2; p=0.033), and a 1.6 point decrease in perceptual reasoning score (95% CI -3.2, -0.4; p=0.045).

When children with mTSHe and controls were compared, there were no observed differences in IQ between the two groups (Table 2). However, children with mild TSH elevation had WISC-IV perceptual reasoning scores 3.8 points lower than controls (95% CI 0.2, 7.3; p=0.037) (Table 2). In addition, BERRY motor co-ordination scores were marginally lower in mTSHe children (Table 2).

Accepted Manuscript

Downloaded from https://academic.oup.com/jcem/article-abstract/doi/10.1210/clinem/dgaa415/5864811 by Science Library user on 02 July 2020

Sibling analyses

In the smaller group of mTSHe children paired with recruited siblings (n=75), higher newborn TSH levels were also correlated with lower full-scale IQ scores (r=0.25; p=0.040) (Figure 2). In adjusted analysis, each 1 mIU/L increase in newborn TSH was associated with a 2.3 point decrease in full-scale IQ score (95% CI -4.1, -0.5; p=0.013). Importantly however, increasing newborn TSH levels were not associated with the magnitude of the difference in full-scale IQ scores between the children with mild TSH elevation and their respective siblings (p=0.56 from the adjusted model; Figure 3).

Further, when we compared children with mTSHe to sibling controls, there were no differences in full-scale IQ, verbal comprehension, working memory, or processing speed between children with mild TSH elevation and their siblings (Table 3). In addition, there were no between-group differences in MABC-2 total or subcomponent scores (Table 3). BEERY scores were also similar between groups, with the exception of slightly higher motor co-ordination scores (+1.1) seen in sibling controls (95% CI 0.2, 1.9; p=0.012), as observed for the larger group (Table 3).

DISCUSSION

This study demonstrates that children with mild TSH elevation have normal thyroid function in mid-childhood and function at a similar level to siblings. We found that the risk of overt hypothyroidism in mid-childhood following mild TSH elevation in the neonatal period was very low. Although each 1 IU/mL increase in TSH (blood) was associated with a 2.3 point decline in WISC full-scale IQ score among children with mild TSH elevation, we did not observe a corresponding difference in IQ between these children and their sibling controls. Furthermore, mTSHe and sibling groups performed similarly across a wide range of neurocognitive parameters. Together, our findings suggest that lower mid-childhood IQ levels are unlikely to be a consequence of untreated mild TSH elevation, but that the apparent correlation occurs due to familial and other environmental confounders.

Accepted Manuscript

Downloaded from https://academic.oup.com/jcem/article-abstract/doi/10.1210/clinem/dgaa415/5864811 by Science Library user on 02 July 2020

This study is consistent with previous reports that mild TSH elevation in term neonates is typically transient and unlikely to progress to overt hypothyroidism (26-28). Pre-assessment blood tests were performed in just over two thirds of the mTSHe group. TSH levels had reduced in all mTSHe children who underwent assessment, approximately 10% had mild persistent mild TSH elevation, and no children had developed overt hypothyroidism. In an Italian longitudinal study of 44 screen positive children with mild TSH elevation (TSH ≥20 mIU/L blood) and followed until mid-childhood, progressive normalisation was observed in the majority (68%) and TSH receptor mutations were observed commonly in those with persistent mild TSH elevation (26, 27). Heterozygous TSH receptor gene mutations are associated stable thyroid hormone production during childhood and an appropriately adjusted set point for pituitary-thyroid feedback (29). Similarly, a German study reported that almost all of 61 newborn screen positive infants with transient CH or mild TSH elevation reassessed at a median age of 10 years had biochemically normal thyroid function, except for 2 children with mild persistent mild TSH elevation (28).

In addition to this and separate to a general discussion of neonatal mild TSH elevation, a monozygotic twin with an ectopic sublingual thyroid and false negative newborn screen (25) was identified within our screened database, but excluded from the study cohort. Multiple births, particularly monozygotic twins, are recognised to be at risk of initial false negative CH screens due to fetal blood mixing (30). The recommended approach to early detection of CH within this special group are either through collection of repeat screens or clinical vigilance, as opposed to the adoption of lower cutoffs (30, 31).

The association that we observed between neonatal TSH levels consistent with mild TSH elevation and lower IQ scores is striking and consistent with data from a large Australian epidemiological record linkage study (11). In that study of nearly 500,000 preschool and school-aged children, high-normal TSH levels between the 90th and 99.95th centile (and below screening cutoff) were associated with poorer developmental assessment scores and educational performance. Conversely, outcomes for those with TSH levels above the 99.95th centile, predominantly children with screen detected CH, were similar to those for infants <75th centile. These data raised concerns that the TSH cutoff was set

Accepted Manuscript

Downloaded from https://academic.oup.com/jcem/article-abstract/doi/10.1210/clinem/dgaa415/5864811 by Science Library user on 02 July 2020

too high to detect all those who would benefit from early thyroxine replacement. However, limitations included the inclusion of participants with conditions where both high newborn TSH levels and neurodevelopmental impairment can occur independently, such as maternal iodine deficiency, prematurity, and syndromic diagnoses. Furthermore, educational achievement and developmental achievement are both indirect measures of cognitive capacity, and likely to be more impacted by motivation and unaccounted environmental factors than standardised neurocognitive assessments.

Within our study, we found that children with mild TSH elevation functioned at a similar level to their siblings. Critically, despite the association between higher TSH levels and lower IQ scores observed amongst the mTSHe group, we did not observe a corresponding correlation between TSH levels and the IQ score difference between mTSHe subjects and their siblings. Overall, this combination of findings suggests that the apparent association between mild TSH elevation and IQ may be due to familial or other environmental confounders. This assessment is consistent with the results of a well-controlled Belgian study of >300 children (12, 13). Although high-normal day 3-5 newborn screening TSH levels below screening cutoff (10-15 mIU/L blood) were associated with lower pre-school verbal IQ scores, this association was no longer significant when confounding factors such as maternal education, income, bilingualism and parity were considered.

In addition, the mTSHe and control groups performed similarly across a wide range of standardised neuro-cognitive parameters. We observed minor differences in motor co-ordination and perceptual reasoning scores that favoured the control group. However, these were both subtle isolated differences seen amongst a number of related measures. Further, only the difference in motor co-ordination remained in the analyses of mTSHe children who had sibling controls. Whilst these may reflect true differences following mild TSH elevation that warrant further investigation, they are likely to be of minimal clinical significance.

Maternal iodine deficiency can lead to both increased neonatal TSH levels and impaired neurodevelopment, and may modify the relationship between neonatal TSH and cognitive outcomes

Accepted Manuscript

Downloaded from https://academic.oup.com/jcem/article-abstract/doi/10.1210/clinem/dgaa415/5864811 by Science Library user on 02 July 2020

(32). The proportion of newborn screening TSH levels >5 mIU/L is proposed to reflect maternal iodine sufficiency within a population, with >3% indicative of iodine deficiency (33, 34). However, the screening assay has limited precision at low levels and TSH levels are not a reliable test of an individual's iodine sufficiency. Variation in assay performance also means that caution should be applied when comparing populations. The proportion of newborn screening TSH levels >5 mIU/L within the neonatal population with mild TSH elevation in the Australian study (6.5%) suggests a population with mild iodine deficiency (11). The prevalence of iodine deficiency is less clear within the New Zealand (3.1%) and Belgian study populations (2.6-3%) (12). Therefore, iodine deficiency is a possible uncorrected modifier within all of these studies (11, 12). Both the New Zealand and Australian birth cohorts preceded national recommendations for routine iodine supplementation of pregnant women, such that maternal iodine deficiency may now be less common in these countries.

It is also important to recognise that neonatal TSH elevation can occur outside of the pituitary-thyroid feedback loop, as TSH can also be released in response to stress. Cord blood TSH levels are influenced by a variety of factors, including maternal parity, mode of delivery, fetal distress, birth weight, and gestational age (35). TSH levels on day 2–3 newborn screening samples are similarly associated with maternal diabetes, parity, male gender, mode of delivery, low Apgar scores, and premature birth/low birth-weight (11, 35-38). Within Australasia, social factors linked to elevated newborn screening TSH levels include socio-economic deprivation, not speaking English as a first language, and belonging to minority ethnic groups such as New Zealand Māori (11, 36). Whilst it is possible that these factors relate to birth factors, maternal dietary patterns, or the prevalence of heterozygous TSH-receptor mutations, there appears to be a common association between environmental adversity and raised neonatal TSH which may confound outcome studies.

The major strengths of this study design include the use of sibling controls and active exclusion of children at risk of developmental delay unrelated to mild TSH elevation. The use of sibling controls is an important consideration, as it allowed for shared genetic and environmental factors to be controlled for within sibling pairs. Twin, family, and adoption studies demonstrate that general intelligence is a

Accepted Manuscript

Downloaded from https://academic.oup.com/jcem/article-abstract/doi/10.1210/clinem/dgaa415/5864811 by Science Library user on 02 July 2020

highly heritable behavioural trait (39), such that siblings offer a more individualised prediction of IQ than age- or gender- matched controls. In addition, the shared sibling environment is likely to be more similar than that of controls matched by socio-economic status. Furthermore, the confounding effect of co-morbidity was minimised as a number of subjects with conditions associated with intellectual impairment independent of thyroid function were excluded from this study, including children diagnosed with Trisomy 21 and Williams syndrome. Premature and low birth-weight infants have higher rates of both CH and developmental issues and are likely to be over-represented within a database of those with high-normal TSH levels, and were also excluded from the study cohort.

The major limitation to this study was sample size. Our study was powered to identify a minimum IQ difference of 5 points between the mTSHe and sibling control groups, with very large participant numbers needed to identify more subtle abnormalities. In particular, our cohort was limited by a relatively small number of subjects with TSH levels close to cut-off (13–14 mIU/L). This reflects both their infrequent occurrence within our population (approximately 5 newborn samples per year within the Auckland region), as well as practical difficulties in recruiting generally healthy subjects who are not already in contact with a paediatric service. Family contact details were only available for children who had either attended an emergency department or been admitted to hospital within the Auckland region, and were frequently out of date. Although uptake was high amongst those contacted, the most frequent reason given for declined participation was lack of concern about their child's development. As a result, the mTSHe group was potentially enriched with children with concurrent health problems and parental concern about their development. We acknowledge that the categorisation of neonatal mild TSH elevation used in this study is based on newborn screening results rather than definitive testing. It is not known whether any infants from the mTSHe group would have been treated for CH if early follow-up investigations had been performed. Similarly, the duration of TSH elevation is unknown, as TSH levels were only checked during the newborn period and mid-childhood. Furthermore, almost a third of participants with mild TSH elevation declined the pre-assessment blood test, and we cannot report on their mid-childhood thyroid biochemistry. Large, well-defined

Accepted Manuscript

Downloaded from https://academic.oup.com/jcem/article-abstract/doi/10.1210/clinem/dgaa415/5864811 by Science Library user on 02 July 2020

cohorts of children with treated and untreated mild TSH elevation are needed in order to characterise subtle differences, and to demonstrate whether there is true benefit from early detection and treatment.

Implications and recommendations

Our data do not demonstrate clinically meaningful long-term negative effects of neonatal mild TSH elevation. Mild TSH elevation below screen threshold appears largely transient, with the majority demonstrating normalisation in TSH by mid-childhood. Critically, we did not find evidence of decreased IQ in subjects with mild TSH elevation as compared with their siblings, and we propose that previously reported associations between neonatal mild TSH elevation and IQ may be due to familial and environmental confounders. This supports the New Zealand newborn screening TSH cutoff ≥15 mIU/L whole blood as being sufficient to detect CH cases requiring treatment. We caution against the practice of reducing screening CH cutoffs to levels where the diagnosis may not offer any long-term benefit for those detected.

Acknowledgements: We thank the many children who volunteered to participate and their families, who have made this study possible. We are grateful to the staff of the National Screening Unit. We acknowledge the Paykel Trust for long-term funding of the Maurice and Agnes Paykel Clinical Research Unit at the Liggins Institute (University of Auckland). This work was supported by unrestricted grants from the New Zealand Ministry of Health, the Auckland District Health Board (A+ Trust), and the Australasian Paediatric Endocrine Group.

Accepted Manuscript

Downloaded from https://academic.oup.com/jcem/article-abstract/doi/10.1210/clinem/dgaa415/5864811 by Science Library user on 02 July 2020

REFERENCES

1. **Ford G, LaFranchi SH** 2014 Screening for congenital hypothyroidism: a worldwide view of strategies. Best Pract Res Clin Endocrinol Metab 28:175-187
2. **Grosse SD, Van Vliet G** 2011 Prevention of intellectual disability through screening for congenital hypothyroidism: how much and at what level? Arch Dis Child 96:374-379
3. **Korada SM, Pearce M, Ward Platt MP, Avis E, Turner S, Wastell H, Cheetham T** 2010 Difficulties in selecting an appropriate neonatal thyroid stimulating hormone (TSH) screening threshold. Arch Dis Child 95:169-173
4. **Lain S, Trumpff C, Grosse SD, Olivieri A, Van Vliet G** 2017 Are lower TSH cutoffs in neonatal screening for congenital hypothyroidism warranted? Eur J Endocrinol 177:D1-D12
5. **Clinical and Laboratory Standards Institute** 2013 Blood collection on filter paper for newborn screening programmes; approved standard - sixth edition. In: Clinical and Laboratory Standards Institute ed. CLSI document NBS01-A6. Wayne, PA
6. **Corbetta C, Weber G, Cortinovis F, Calebiro D, Passoni A, Vigone MC, Beck-Peccoz P, Chiumello G, Persani L** 2009 A 7-year experience with low blood TSH cutoff levels for neonatal screening reveals an unsuspected frequency of congenital hypothyroidism (CH). Clin Endocrinol 71:739-745
7. **Langham S, Hindmarsh P, Krywawych S, Peters C** 2013 Screening for congenital hypothyroidism: comparison of borderline screening cut-off points and the effect on the number of children treated with levothyroxine. Eur Thyroid J 2:180-186
8. **Mengreli C, Kanaka-Gantenbein C, Girginoudis P, Magiakou MA, Christakopoulou I, Giannoulia-Karantana A, Chrousos GP, Dacou-Voutetakis C** 2010 Screening for congenital hypothyroidism: the significance of threshold limit in false-negative results. J Clin Endocrinol Metab 95:4283-4290
9. **Olivieri A, Fazzini C, Medda E** 2015 Multiple factors influencing the incidence of congenital hypothyroidism detected by neonatal screening. Horm Res Paediatr 83:86-93

Accepted Manuscript

Downloaded from https://academic.oup.com/jcem/article-abstract/doi/10.1210/clinem/dgaa415/5864811 by Science Library user on 02 July 2020

10. **Korzeniewski SJ, Grigorescu V, Kleyn M, Young WI, Birbeck G, Todem D, Romero R, Paneth N** 2013 Transient hypothyroidism at 3-year follow-up among cases of congenital hypothyroidism detected by newborn screening. J Pediatr 162:177-182
11. **Lain SJ, Bentley JP, Wiley V, Roberts CL, Jack M, Wilcken B, Nassar N** 2016 Association between borderline neonatal thyroid-stimulating hormone concentrations and educational and developmental outcomes: a population-based record-linkage study. Lancet Diabet Endocrinol 4:756-765
12. **Trumpff C, De Schepper J, Vanderfaeillie J, Vercruysse N, Van Oyen H, Moreno-Reyes R, Tafforeau J, Vandevijvere S** 2016 Neonatal thyroid-stimulating hormone concentration and psychomotor development at preschool age. Arch Dis Child 101:1100-1106
13. **Trumpff C, De Schepper J, Vanderfaeillie J, Vercruysse N, Van Oyen H, Moreno-Reyes R, Tafforeau J, Vanderpas J, Vandevijvere S** 2015 Thyroid-Stimulating Hormone (TSH) concentration at birth in Belgian neonates and cognitive development at preschool age. Nutrients 7:9018-9032
14. **Williams FL, Watson J, Ogston SA, Visser TJ, Hume R, Willatts P** 2013 Maternal and umbilical cord levels of T4, FT4, TSH, TPOAb, and TgAb in term infants and neurodevelopmental outcome at 5.5 years. J Clin Endocrinol Metab 98:829-838
15. **Freire C, Ramos R, Amaya E, Fernandez MF, Santiago-Fernandez P, Lopez-Espinosa MJ, Arrebola JP, Olea N** 2010 Newborn TSH concentration and its association with cognitive development in healthy boys. Eur J Endocrinol 163:901-909
16. **Calaciura F, Mendorla G, Distefano M, Castorina S, Fario T, Motta RM, Sava L, Delange F, Vigneri R** 1995 Childhood IQ measurements in infants with transient congenital hypothyroidism. Clin Endocrinol 43:473-477
17. **Albert BB, Cutfield WS, Webster D, Carll J, Derraik JG, Jefferies C, Gunn AJ, Hofman PL** 2012 Etiology of increasing incidence of congenital hypothyroidism in New Zealand from 1993-2010. J Clin Endocrinol Metab 97:3155-3160
18. **Heather NL, Hofman PL, de Hora M, Carll J, Derraik JG, Webster D** 2017 Evaluation of the revised New Zealand national newborn screening protocol for congenital hypothyroidism. Clin Endocrinol 86:431-437
19. **Ministry of Health** 2004 Ethnicity data protocols for the health and disability sector. Wellington: Ministry of Health
20. **Atkinson J, Salmond C, Crampton C** 2014 NZDep2013 Index of Deprivation. Wellington: University of Otago
21. **Weshler D** 2003 WISC-IV Australian Administration and Scoring Manual. In. Marrickville, New South Wales: Harcourt Assessment
22. **Beery KE, Buktenica N.A., Beery N.A.** 2004 Beery-Buktenica Developmental Test of Visual Moor Integration. Austin, Texas: Pro-Ed

Accepted Manuscript

Downloaded from https://academic.oup.com/jcem/article-abstract/doi/10.1210/clinem/dgaa415/5864811 by Science Library user on 02 July 2020

23. **Henderson S.E. SDA, Barnett A.L.** 2007 The Movement Assessment Battery for Children-2 Examiner's Manual. London: Harcourt Assessment
24. **Albert BB, Heather N, Derraik JG, Cutfield WS, Wouldes T, Tregurtha S, Mathai S, Webster D, Jefferies C, Gunn AJ, Hofman PL** 2013 Neurodevelopmental and body composition outcomes in children with congenital hypothyroidism treated with high-dose initial replacement and close monitoring. J Clin Endocrinol Metab 98:3663-3670
25. **Azam A, Cutfield W, Mouat F, Hofman PL, Jefferies C, Webster D, Gunn AJ** 2012 Missed congenital hypothyroidism in an identical twin. J Paediatr Child Health 48:936-938
26. **Calaciura F, Motta RM, Miscio G, Fichera G, Leonardi D, Carta A, Trischitta V, Tassi V, Sava L, Vigneri R** 2002 Subclinical hypothyroidism in early childhood: a frequent outcome of transient neonatal hyperthyrotropinemia. J Clin Endocrinol Metab 87:3209-3214
27. **Leonardi D, Polizzotti N, Carta A, Gelsomino R, Sava L, Vigneri R, Calaciura F** 2008 Longitudinal study of thyroid function in children with mild hyperthyrotropinemia at neonatal screening for congenital hypothyroidism. J Clin Endocrinol Metab 93:2679-2685
28. **Kohler B, Schnabel D, Biebermann H, Gruters A** 1996 Transient congenital hypothyroidism and hyperthyrotropinemia: normal thyroid function and physical development at the ages of 6-14 years. J Clin Endocrinol Metab 81:1563-1567
29. **Tenenbaum-Rakover Y, Almashanu S, Hess O, Admoni O, Hag-Dahood Mahameed A, Schwartz N, Allon-Shalev S, Bercovich D, Refetoff S** 2015 Long-term outcome of loss-of-function mutations in thyrotropin receptor gene. Thyroid 25:292-299
30. **Perry R, Heinrichs C, Bourdoux P, Khoury K, Szots F, Dussault JH, Vassart G, Van Vliet G** 2002 Discordance of monozygotic twins for thyroid dysgenesis: implications for screening and for molecular pathophysiology. J Clin Endocrinol Metab 87:4072-4077
31. **Leger J, Olivieri A, Donaldson M, Torresani T, Krude H, van Vliet G, Polak M, Butler G, ESPE-PES-SLEP-JSPE-APEG-APPES-ISPAE, Congenital Hypothyroidism Consensus Conference Group** 2014 European Society for Paediatric Endocrinology consensus guidelines on screening, diagnosis, and management of congenital hypothyroidism. J Clin Endocrinol Metab 99:363-384
32. **Bath SC, Steer CD, Golding J, Emmett P, Rayman MP** 2013 Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC). Lancet 382:331-337
33. **Zimmermann MB, Aeberli I, Torresani T, Burgi H** 2005 Increasing the iodine concentration in the Swiss iodized salt program markedly improved iodine status in pregnant women and children: a 5-y prospective national study. Am J Clin Nutr 82:388-392
34. **World Health Organization** 1994 Indicators for Assessing Iodine Deficiency Disorders and their Control troug Salt Iodisation. Geneva, Switzerland: World Health Organization.

Accepted Manuscript

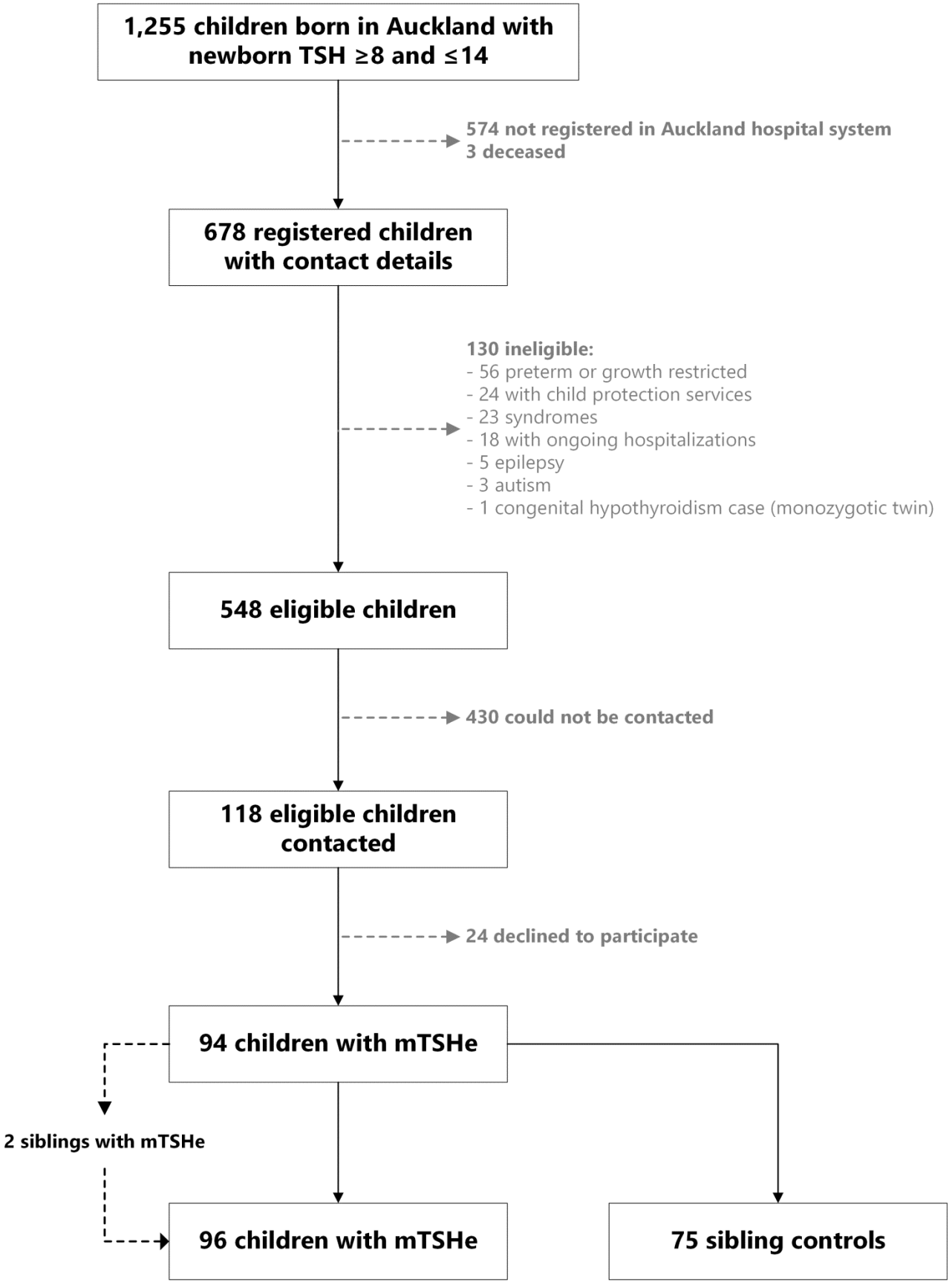
Downloaded from https://academic.oup.com/jcem/article-abstract/doi/10.1210/clinem/dgaa415/5864811 by Science Library user on 02 July 2020

35. **Korevaar TI, Chaker L, Jaddoe VW, Visser TJ, Medici M, Peeters RP** 2016 Maternal and birth characteristics are determinants of offspring thyroid function. J Clin Endocrinol Metab 101:206-213
36. **Heather NL, Derraik JGB, Webster D, Hofman PL** 2019 The impact of demographic factors on newborn TSH levels and congenital hypothyroidism screening. Clin Endocrinol 91:456-463
37. **Tanaka K, Shimizu T, Hosaka A, Tokita A, Shiga S, Yamashiro Y** 2007 Serum free T4 and thyroid stimulating hormone levels in preterm infants and relationship between these levels and respiratory distress syndrome. Pediatr Int 49:447-451
38. **Ryckman KK, Spracklen CN, Dagle JM, Murray JC** 2014 Maternal factors and complications of preterm birth associated with neonatal thyroid stimulating hormone. J Pediatr Endocrinol Metab 27:929-938
39. **Deary IJ, Johnson W, Houlihan LM** 2009 Genetic foundations of human intelligence. Hum Genet 126:215-232

Accepted Manuscript

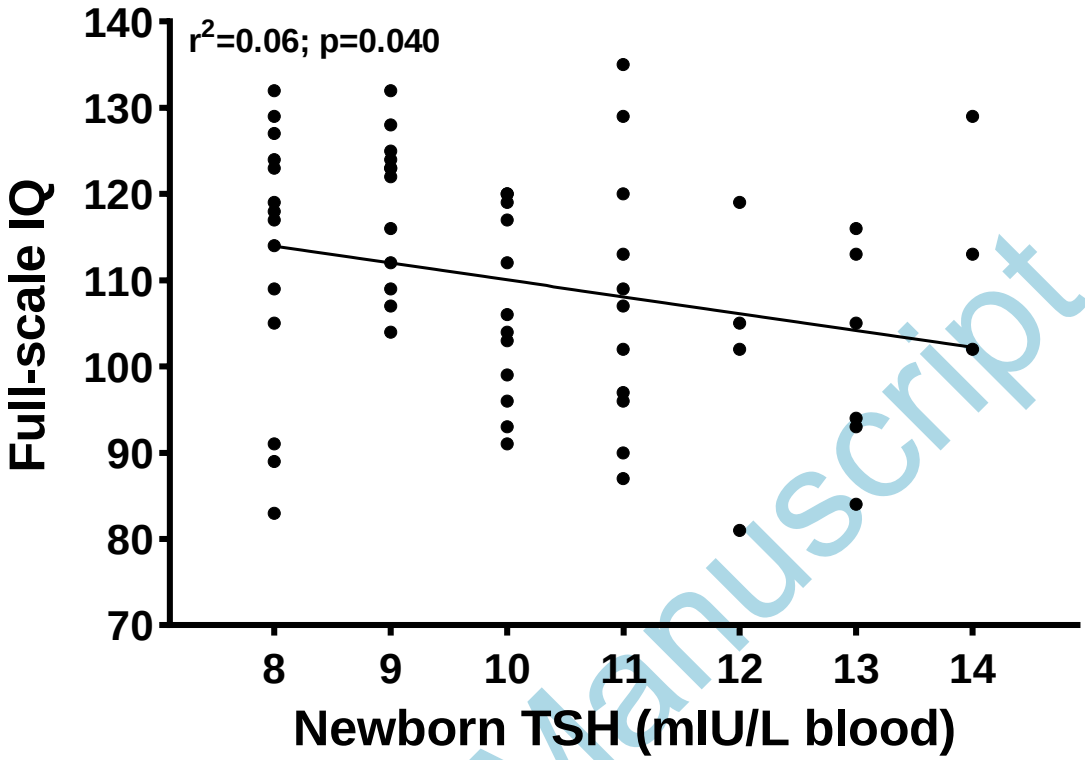
Downloaded from https://academic.oup.com/jcem/article-abstract/doi/10.1210/clinem/dgaa415/5864811 by Science Library user on 02 July 2020

Figure 1. Recruitment of participants with mild TSH elevation (mTSHe).



Downloaded from https://academic.oup.com/jcem/article-abstract/doi/10.1210/clinem/dgaa415/5864811 by Science Library user on 02 July 2020

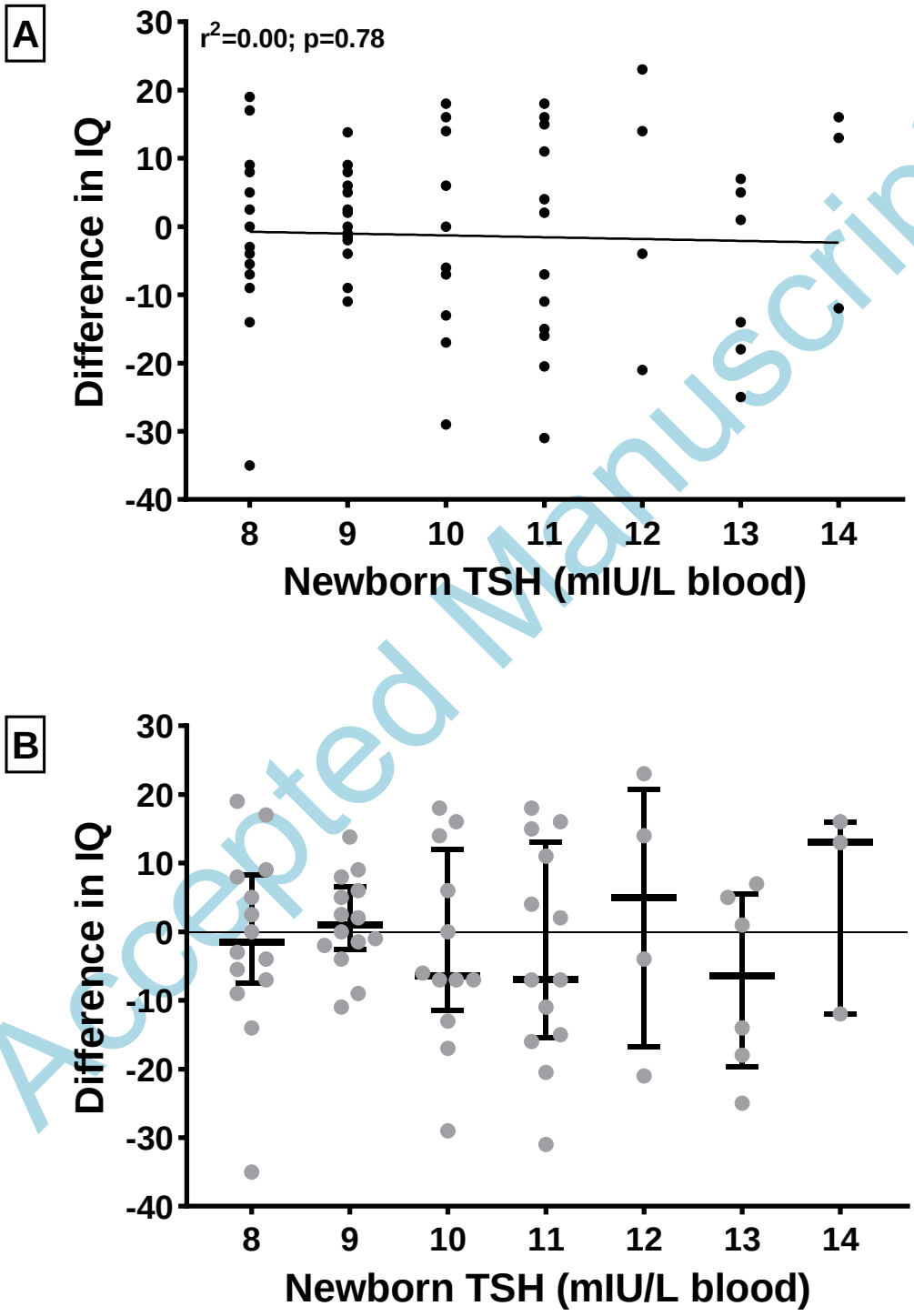
Figure 2. Linear association between full-scale IQ scores and newborn TSH levels.



Accepted Manuscript

Downloaded from https://academic.oup.com/jcem/article-abstract/doi/10.1210/clinem/dgaa415/5864811 by Science Library user on 02 July 2020

Figure 3. Differences in full-scale IQ scores between children with mild TSH elevation and their respective siblings in association with newborn TSH levels. A) Scatter plot showing examining the linear association; B) Horizontal bars represent the medians, quartile 1, and quartile 3 at each TSH level.



Accepted Manuscript

Downloaded from https://academic.oup.com/jcem/article-abstract/doi/10.1210/clinem/dgaa415/5864811 by Science Library user on 02 July 2020

Table 1. Demographics of children with mild TSH elevation (mTSHe) and their sibling controls participating in the study.

		Siblings only			All children		
		Control	mTSHe	p-value	Control	mTSHe	p-value
n		75	67		75	96	
Age (years)		10.2 [7.6, 12.7]	9.7 [8.5, 10.5]	0.30	10.2 [7.6, 12.7]	9.4 [8.3, 10.4]	0.12
Sex	**Males**	41 (55%)	40 (60%)	0.55	41 (55%)	57 (59%)	0.64
	Females	34 (45%)	27 (40%)		34 (45%)	39 (41%)	
Ethnicity	**NZ European**	56 (75%)	47 (70%)	0.94	56 (75%)	68 (71%)	0.96
	Māori	2 (3%)	2 (3%)		2 (3%)	3 (3%)	
	Pacific	9 (12%)	10 (15%)		9 (12%)	13 (14%)	
	Asian	8 (11%)	8 (12%)		8 (11%)	12 (13%)	
NZ deprivation index		3 [2, 6]	4 [2, 6]	0.38	3 [2, 6]	4 [2, 6]	0.28

Data are median [quartile 1, quartile 3] or n (%), as appropriate.

Accepted Manuscript

Downloaded from https://academic.oup.com/jcem/article-abstract/doi/10.1210/clinem/dgaa415/5864811 by Science Library user on 02 July 2020

Table 2. WISC-IV, Movement ABC-2, and BEERY scores in all children with mild TSH elevation (mTSHe) and controls.

		Control	mTSHe	p-value
n		75	96	
WISC-IV	Full-Scale IQ	111 (104, 119)	109 (102, 116)	0.20
	Verbal comprehension	113 (102, 124)	112 (102, 123)	0.68
	Perceptual reasoning	109 (103, 114)	105 (99, 110)	**0.038**
	Working memory	107 (103, 110)	106 (102, 110)	0.75
	Processing speed	104 (100 108)	103 (99, 108)	0.56
Movement ABC-2	Total movement	11.4 (10.7, 12.0)	11.4 (10.8, 12.0)	0.94
	Manual dexterity	10.2 (9.4, 11.1)	11.0 (10.2, 11.7)	0.15
	Aiming and catching	11.3 (10.5, 12.1)	10.6 (9.9, 11.3)	0.16
	Balance	11.9 (11.3, 12.4)	11.5 (11.0, 12.0)	0.27
BEERY	Beery VMI	10.8 (7.3, 14.4)	11.0 (7.5, 14.6)	0.56
	Visual perception	11.3 (10.1, 12.5)	11.4 (10.2, 12.5)	0.90
	Motor coordination	10.7 (5.7, 15.1)	9.4 (4.7, 14.1)	**0.015**

Data are means and 95% confidence intervals, adjusted for gender and level of socioeconomic deprivation. WISC-IV models also adjusted for whether or not English was the child's first language.
Beery VMI, Beery Developmental Test of Visual-Motor-Integration, 6th edition; MABC-2, Movement Assessment Battery for Children, 2nd edition; WISC-IV, Wechsler Intelligence Scale for Children, 4th edition.
P-values for statistically significant differences (at $p<0.05$) are shown in bold.

Accepted Manuscript

Downloaded from https://academic.oup.com/jcem/article-abstract/doi/10.1210/clinem/dgaa415/5864811 by Science Library user on 02 July 2020

Table 3. WISC-IV, Movement ABC-2, and BEERY scores in children with mild TSH elevation (mTSHe) and sibling controls.

		Control	mTSHe	p-value
n		75	67	
WISC-IV	Full-Scale IQ	109 (105, 112)	107 (104, 111)	0.36
	Verbal comprehension	108 (104, 112)	107 (103, 111)	0.53
	Perceptual reasoning	107 (103, 111)	104 (100, 108)	0.13
	Working memory	105 (99, 112)	106 (99, 113)	0.79
	Processing speed	103 (99, 107)	103 (99, 107)	0.88
Movement ABC-2	Total movement	11.5 (10.8, 12.1)	11.9 (11.3, 12.6)	0.26
	Manual dexterity	10.3 (9.5, 11.1)	11.2 (10.4, 12.1)	0.07
	Aiming and catching	11.3 (10.5, 12.1)	11.0 (10.1, 11.8)	0.47
	Balance	12.0 (11.4, 12.5)	12.1 (11.5, 12.6)	0.76
BEERY	Beery VMI	10.8 (7.3, 14.3)	11.0 (7.5, 14.5)	0.49
	Visual perception	11.0 (10.4, 11.6)	11.0 (10.4, 11.6)	0.90
	Motor coordination	9.9 (6.3, 13.4)	8.8 (5.2, 12.3)	**0.012**

Data are means and 95% confidence intervals, adjusted for gender and level of socioeconomic deprivation. WISC-IV models also adjusted for whether or not English was the child's first language.
Beery VMI, Beery Developmental Test of Visual-Motor-Integration, 6th edition; MABC-2, Movement Assessment Battery for Children, 2nd edition; WISC-IV, Wechsler Intelligence Scale for Children, 4th edition.
P-values for statistically significant differences (at $p<0.05$) are shown in bold.

Accepted Manuscript

Downloaded from https://academic.oup.com/jcem/article-abstract/doi/10.1210/clinem/dgaa415/5864811 by Science Library user on 02 July 2020