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THYROID FUNCTION IN PRETERM INFANTS AND NEURODEVELOPMENT AT TWO YEARS

Fiona Williams PhD [1], Alice Lindgren MB ChB[2], Jennifer Watson MPH[2], Anita Boelen PhD[3], Tim Cheetham MB ChB [4]

f.l.r.williams@dundee.ac.uk, a.lindgren@live.se, j.z.watson@dundee.ac.uk, a.boelen@amc.uva.nl, Tim.Cheetham@nuth.nhs.uk

[1] Division of Population Health & Genomics, Ninewells Hospital and Medical School, University of Dundee, Dundee DD2 4BF, UK
[2] Division of Population Health & Genomics, Ninewells Hospital and Medical School, University of Dundee, Dundee DD2 4BF, UK. (This work was undertaken while a medical student, current address: Maidstone and Tunbridge Wells NHS Trust, Hermitage Lane, Maidstone, Kent ME16 9QQ)
[3] Neonatal Screening Laboratory, Laboratory of Endocrinology, Academic Medical Centre, Meibergdreef 9, 1105 AZ Amsterdam, Netherlands
[4] Institute of Human Genetics, Newcastle University, c/o Department of Paediatric Endocrinology, Office block 1, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne, NE1 4LP

Corresponding author: Fiona Williams, Division of Population Health & Genomics, Ninewells Hospital and Medical School, University of Dundee, Dundee DD2 4BF, UK f.l.r.williams@dundee.ac.uk
+44 (0)1382 383727

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Abbreviations: Thyroid stimulating hormone (TSH), thyroid binding globulin (TBG), total thyroxine (T4)

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ABSTRACT

Objectives Postnatal thyroid dysfunction is common in preterm infants but the relationship between mild dysfunction and neurodevelopment is unclear. Our aim is to describe the relationship between thyroid function and neurodevelopment.

Design Cohort analysis

Patients 1275 infants born under 31 weeks' gestation; there were no exclusion criteria

Setting The infants were part of a UK daily iodine supplementation trial.

Main outcomes Thyroid stimulating hormone, thyroid binding globulin and total thyroxine levels were measured in dried blood-spots on postnatal days 7, 14, 28 and the equivalent of 34 weeks' gestation. Neurodevelopment was measured using the Bayley-III scales of infant development at 2 years of age.

Results No infant was identified as hypothyroid through routine screening. The 3% of infants consistently in the top decile of gestationally age-adjusted thyroid stimulating hormone levels had a reduction in cognitive score of 7 Bayley units when compared to those not in the top decile (95%CI -13,-1). A reduction in motor composite score of 6 units (95%CI -12,<-0.1) and fine motor score of 1 unit (95%CI -2,-0.1) was also identified. The 0.7% of infants consistently in the bottom decile of age-adjusted thyroxine levels had a reduction in motor composite score of 14 units (95%CI -25,-2) and its two subset scores, fine and gross motor, of 2 units (95%CI respectively -4.5,<-0.1, and -4.3,-0.3)

Conclusions Preterm infants with consistent 'mild' thyroid dysfunction score less well on neurodevelopmental tests at 2 years of age. Many of these infants will not be detected by current clinical protocols or screening programs.

250 words

INTRODUCTION

The natural history of transiently raised levels of thyroid stimulating hormone (TSH), with or without associated low thyroxine (T4) levels, in preterm infants is complex and affected by factors such as maternal iodine status,[1] developmental immaturity of endocrine systems,[2-5] critical illness,[6] and drug exposure.[7] The incidence of mildly raised TSH levels depends upon the definition, denominator and age-group studied, but in population studies it has been reported as 3.3%[8] and 6%,[9] and in selected clinical studies, as high as 22.3%.[10] There is no consensus on whether subtle thyroid dysfunction should be treated[11,12] and its long-term consequences are unclear, as studies are typically methodologically restricted. It has been suggested that infants with transiently raised TSH levels may have a high risk of sub-clinical hypothyroidism in childhood[4,13] and possibly developmental delay,[9] although this is not a consistent observation.[5,14] The most common neonatal thyroid dysfunction in preterm infants is hypothyroxinaemia (low T4 with normal TSH levels), with an incidence of between 7-100%[15] in infants less than 28 weeks gestation; the wide range of reported incidence reflects varying definitions and methodologies.

A recently completed trial of daily iodide supplementation in infants born <31 weeks gestation with neurodevelopmental outcome measured at 2 years of age[16] provided us the opportunity to describe T4, TSH, and thyroid binding globulin (TBG) distributions in a preterm neonatal cohort. We also examined whether abnormal postnatal thyroid function, characterised by a subtle increase in TSH and/or a reduction T4, or by a pattern of hypothyroxinaemia, was related to neurodevelopmental outcome.

METHODS

Infants <31 weeks' gestation were recruited to a UK trial of iodine supplementation (30µg/kg/day from birth to equivalent of 34 weeks' gestation) with neurodevelopment assessment at 2 years. There were no significant differences in neurodevelopmental outcome, or levels of TSH, TBG and T4 between the arms of the trial[16] and so the data were combined. The trial was approved by Tayside

Committee on Medical Research Ethics (08/S0501/31), all other regulatory bodies (18), and all families provided informed consent. The trial protocol is available at https://www.npeu.ox.ac.uk/downloads/files/i2s2/protocol/I2S2-Protocol.pdf

Data collected

Infant blood was collected on dried bloodspot cards at postnatal days 7, 14, 28, and 34 weeks' gestational age (had the fetus remained *in-utero,* referred to hereafter as equivalent gestational age), ± 1 day. Cards were sent to the Amsterdam Neonatal Screening Laboratory for measurement of TSH, T4 and TBG[17] (for details see Appendix). T4 is expressed as absolute levels and as a standard deviation (SD) of the daily mean, which is calculated from the results of approximately 150 cards of term and preterm infants; levels ≤-3.0SD are considered abnormal (in term infants). TBG concentrations <40 nmol/L is indicative of TBG deficiency.

TSH, TBG and T4 whole-blood levels reported in this paper were taken specifically for the trial. TSH levels were considered raised if ≥6mU/L because many UK laboratories at the time of the trial used 6mU/L as their cut-off for recall. (0.2% of all UK infants screened have a bloodspot TSH >6mU/L.) (A whole-blood TSH level of 6mU/l is approximately 15mU/l when measured in a serum sample.) We recorded the outcome of thyroid function tests, whether or not Levothyroxine therapy was started, and type of thyroid dysfunction.

Definitions

Two approaches were used when evaluating the hypothalamo-pituitary-thyroid axis and subsequent neurodevelopmental outcome. First, we used deciles, corrected to gestational age subgroup (i.e. ≤25, 26-27, 28-30 weeks), to investigate the relationships between TSH, TBG and T4, (top TSH decile and bottom deciles for T4, TBG and T4/TBG ratio versus the remaining deciles) with neurodevelopmental outcome. Secondly, we categorized infants into mutually exclusive groups as: new born screening diagnosis of hypothyroidism, or to study definition of hypothyroid (TSH ≥6 and

T4 ≤-3SD), hyperthyrotropinaemic (TSH ≥6mU/L and T4>-3 SD), hypothyroxinaemic (TSH<6mU/L and T4≤-3 SD) or euthyroid (TSH<6mU/L and T4>-3 SD). This strategy addresses the function of the hypothalamo-pituitary axis in its entirety rather than TSH or thyroid hormone secretion in isolation.

Detailed clinical data were collected[18] from birth until discharge home or until the equivalent of 36 weeks' gestational age. In a previous study investigating thyroid hormones and neurodevelopment we identified 26 factors encompassing maternal, intrapartum, neonatal, lifestyle and the assessor, which contributed to the variation in neurodevelopment.[19,20] The factors with the strongest statistical associations and for which we had data in this study were gender, gestation at birth, the assessor performing the neurodevelopmental test, the hospital of birth, and the level of nursing care reported on the day of blood sampling. The level of nursing care was categorised as high (level 1), medium (level 2) or low (level 3) and was used as a proxy for illness severity.[6] To this list of factors potentially associated with neurodevelopment we included whether or not the infant received iodine supplementation (i.e. trial intervention or placebo) in case it had some unexpected subtle impact, whether or not the infant received Levothyroxine therapy, and T4/TBG ratio as clinically these were also relevant confounders of neurodevelopment in this group of infants. (The T4/TBG ratio is used as a proxy for FT4 concentrations[22]).

Outcome measures

Infants were assessed using the Bayley-III Scales[21] at two years of age corrected for prematurity (±1 month). The Bayley-III Scales provide cognitive, motor composite and language composite scores, each with a population mean=100 and SD=15. The latter two scores have two subtests with mean=10 and SD=3. Infants were assessed using trial personnel specifically trained to use Bayley-III; random performances were video-recorded and audited.

Statistics

Infants were included in the analyses for this paper if they had at least one study blood recorded Data were imputed for the primary outcome of the trial (i.e. Bayley-III score) following a five point protocol.[16]

General linear models, specifically univariate analysis of variance were constructed to evaluate the adjusted association of thyroid function, reported on days 7, 14, 28 and at 34 weeks' equivalent gestational age, on Bayley-III scores. The indices of thyroid function were classified as described earlier in the method section and the outcomes were adjusted for the seven cofactors described previously. Significance was specified at $p<0.05$.

We predicted that some infants would switch between thyroid categories over the sampling period, whilst others would not. We therefore constructed general linear models for the main and subset domains of the Bayley-III, which classified thyroid status over the sampling period as consistently within the bottom (T4, T4/TBG ratio) or top (TSH) deciles, or consistently as: euthyroid, hypothyroid, hyperthyrotropinaemic, hypothyroxinaemic, or as mixed thyroid function where the infant moves between categories. All bloods recorded for an infant (at day 7, 14, 28 and equivalent of 34 weeks' gestation) had to meet the definition for either hypothyroid, hyperthyrotropinaemia, hypothyroxinaemia, or euthyroid to be classified as 'consistent'. To be included in these analyses infants had to have two or more study bloods recorded. The Bayley-III outcomes were adjusted for the seven variables described in the methods and, if appropriate, the T4/TBG ratio. All analyses were undertaken on SPSS version 22.

RESULTS

1275 infants were recruited to the trial (Supplementary Figure 1). One or more bloods were recorded for 1222/1259 (97%) infants, 94% (1185/1259) had ≥2 bloods recorded, and 89% (1126/1259) had ≥3 bloods recorded. Bayley-III assessments were available for 997 infants. No infant was identified as hypothyroid as a part of the routine neonatal blood spot screening programme,

either at 5 days post-delivery or as part of repeat screening conducted at 36 weeks'/time of discharge. Thus all references to hypothyroid in this paper from this point refer to the study definition of hypothyroid (i.e. TSH=>6 and T4=<-3SD)

Sixty-two percent of infants had one or more TSH or T4 values outwith the reference range during the study. T4 and TBG levels and T4/TBG ratios increase as gestation rises and also over time (Table 1). TSH levels also increase as gestation rises, but peak and flatten at day 14 for infants born ≤25 weeks, and peak and then fall for infants born ≥26 weeks (Table 1). None of the infants had TBG concentrations <40nmol/L.

Classification of thyroid function that was consistent over ≥2 bloods showed that 3% (27 infants) were consistently in the top decile of TSH levels (Table 2); 0.7% were consistently in the bottom decile for T4 levels (7 infants) (Table 3); and, 0.2% were consistently in the bottom decile for T4/TBG ratio (2 infants) (Supplementary Table 1). Sixty-nine infants (69/1222) had a TSH level ≥6mU/L (irrespective of T4 levels). The majority (49/69) of infants had one isolated elevated TSH level, and 25% (17/69) had two elevated levels (Table 4). Six infants (4.9 per 1000, 6/1222) had elevated TSH levels noted for the first time when they were measured at the equivalent of 34 weeks' gestation (see Appendix).

Classification of thyroid function that was consistent over ≥2 study bloods by thyroid category showed that the majority (670/1185) of infants switch categories (which represents 4 to 11 weeks in this cohort of infants). No infant was consistently hypothyroid or hyperthyrotropinaemic, 5% (65/1185) were consistently hypothyroxinaemic, and 38% (450/1185) were consistently euthyroid (Supplementary Fig 1); 0.3% (4/1185) were consistently in the bottom decile for T4/TBG ratio.

Bayley-III outcomes

The cognitive score for infants consistently in the top decile for TSH levels was 7 Bayley units lower (95%CI -13, -1) compared to those who were never in the top decile. There was also a reduction in

the motor composite score of 6 units (95%CI -12,-0.012) and the fine motor subset score of 1 unit (95%CI -2,-0.1) (Table 2). For infants consistently in the bottom decile of T4, the motor composite score was reduced by 13 units (95%CI -25,-2) compared to those who were never in the bottom decile. This deficit was contributed by both the fine (2 units 95%CI -4.5,-0.04) and gross (2 units 95%CI -4.3,-0.3) motor subset scores (Table 3).

Infants in the top decile for TSH on day 14 (compared to those not in that decile) had lower cognitive scores, lower expressive language scores on day 7 and day 14, and lower fine motor scores on day 14 (Supplementary Tables 2-8). Infants in the bottom decile for T4 (compared to those not in that decile) had significantly lower cognitive, motor composite and gross motor scores on day 14, (Supplementary Tables 2-8).

Using adjusted regression models, no infants were consistently hypothyroid or hyperthyrotropinaemic. Infants classified as consistently hypothyroxinaemic, compared to those who were consistently euthyroid, scored 8 units lower on the cognitive score (95%CI -14,-3), 9 units lower on the motor composite score (95%CI -15,-4), 11 units lower on the language composite score (95%CI -17,-4) and lower on all subtest domains (Table 5).

Infants classified as hypothyroid on day 7 scored significantly lower on all Bayley-III main, and three of the four subtest domains compared with infants classified as euthyroid. There were two strong significant associations: the classification of hypothyroid on day 7 with the Bayley-III cognitive score (a reduction of 21 units compared with the euthyroid group), and the fine motor subtest score (a reduction of 3 units compared with the euthyroid group) (Supplementary Tables 9-11). Of the seven infants categorized as hypothyroid on day 7, five had TSH levels <11.0 mU/l, one infant's TSH was 11.0 mU/l and one infant's TSH was 22.0 mU/l.

For more clinical characteristics of the infants, see Appendix.

DISCUSSION

This analysis has highlighted two important observations. First, when compared to a euthyroid state, consistent hypothyroxinaemia (i.e. measured on at least two occasions), but not isolated episodes of low T4, is associated with significantly lower (8-11 points) Bayley-III scores in all the domains: cognitive, motor and language. Secondly, isolated mildly raised TSH levels (≥6mU/L) are associated with significantly lower Bayley-III scores when compared to euthyroid.

Several studies[19,24-26] have reported adverse associations between neurodevelopment and low postnatal T4 levels but it has also been queried whether hypothyroxinaemia is simply an epiphenomenon of prematurity and illness.[29] Observational studies cannot provide the definitive answers of a randomised controlled trial, but designing a trial to answer this question is very challenging. Our data suggest that trials in this field should target only those infants who are consistently hypothyroxinaemic. Pragmatically, such infants are difficult to identify as they represent a small proportion of preterm infants (5% in our cohort) and agreeing a definition for hypothyroxinaemia/low T4 is not straightforward. There is an appreciable gestational-age gradient in levels of T4[23] and T4 levels also vary according to the postnatal age at sampling and the media used (whole blood, plasma, serum).[15, 23] Furthermore, to preserve neurodevelopment hypothyroxinaemia needs to be treated quickly as evidence from managing congenital hypothyroidism[33] shows that replacement therapy must start within two weeks in order to optimise neurodevelopment. Use of blood-spot cards may provide a rapid way to identify hypothyroxinaemia and to facilitate trials and management. (It is important to highlight that hypothyroxinaemia is separate from the congenital hypothyroidism due to dysgenesis or dyshormonogenesis that screening programmes were designed to detect.)

We optimised the strength of our observational design by adjusting for many of the key contributors to neurodevelopment in a preterm population. It is relevant therefore that the association between low T4 levels and Bayley-III scores remained significant following adjustment for gender, gestation at birth and level of sickness. The inclusion of gestation in the regression model was important as it

counteracts the impact of using T4 levels derived from term and preterm infants in the definition of hypothyroxinaemia. The data were also adjusted for study relevant factors such as treatment with Levothyroxine and daily iodine supplementation, as well as methodological factors such as assessor variability.[20]

In this large preterm cohort, 5.7% of infants had mildly raised (≥6mU/L) TSH levels. This proportion seems low when compared, for example, to the 6% found by Cuestas[9] in an exclusively term cohort, but is likely due to differences in the day of testing, and the use of whole-blood rather than serum. Mildly raised TSH levels seem to be important as we found associations with neurodevelopment whether the TSH levels were defined by categories of thyroid function or by deciles. An association between borderline bloodspot TSH concentrations and poorer neurodevelopmental outcome has similarly been reported in a large population of primarily term infants.[30] Evidence of poorer cognitive development and motor development, and in particular fine motor development, with mildly raised levels of postnatal TSH now need to be confirmed in other cohorts with intervention trials a logical next step.

This study has limitations. The use of 6mU/L as a cut-off to categorise hypothyroidism is lower than many national screening programmes which more typically use 10mU/L or higher. We chose 6mU/L because several UK laboratories at the time of the trial used 6mU/L as their cut-off for recall. This cut-off corresponded to the 97.3%ile of TSH levels at the Amsterdam Screening Laboratory during the time of the trial and lies around the 99.8th centile on a UK TSH screening program.[31] Fluctuations in TSH levels in response to iodine (the trial intervention) are well recognized and may be more pronounced in our cohort if the mothers were mildly iodide deficient, which is likely.[32]

The definitions of thyroid function used in this paper are those generally applied to term infants, who do not have the biochemical patterns characteristic of preterm infants. Preterm infants are often critically ill, which may alter thyroid function and thyroid binding proteins. We included a measure of illness level in the regression models, which we showed previously to be a good

summary indicator,[6] and also the T4/TBG ratios in an attempt to control for the preterm infants' thyroid function. Several other important confounding measures of neurodevelopment were controlled for, which adds weight to our observations.

In summary, for the majority of infants in this study cohort, postnatal thyroid dysfunction was restricted to an isolated episode. No infants were consistently hypothyroid or hyperthyrotropinaemic; 38% were euthyroid throughout the sampling period and 5% were consistently hypothyroxinaemic. Infants with TSH levels consistently in the top decile or categorised as hypothyroid specifically on postnatal day 7 performed worse on the Bayley scores than those categorised with mixed dysfunction or euthyroid. A small cohort of infants was consistently hypothyroxinaemic and this was associated with appreciably worse outcomes than euthyroid infants on all Bayley-III domains. Hypothyroxinaemia in preterm infants does not appear to be a benign disorder on the basis of the associations that we have identified, and the potential role of thyroxine supplementation in this group of infants requires further investigation.[28]

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CONTRIBUTORSHIP STATEMENT

Fiona Williams: conceptualized and designed the study, designed and contributed to the data analysis, drafted the initial manuscript and approved the final manuscript as submitted.
Alice Lindgren: contributed to the study design, critically reviewed the manuscript and approved the final manuscript as submitted.
Jennifer Watson: contributed to the data analysis, reviewed and revised the manuscript, and approved the final manuscript as submitted.
Anita Boelen: coordinated and supervised the analysis of blood spot cards, critically reviewed the manuscript and approved the final manuscript as submitted.
Tim Cheetham: contributed to the design of the data analysis, reviewed and revised the manuscript, and approved the final manuscript as submitted.

WHAT'S KNOWN ON THIS SUBJECT

- The natural history of transiently raised levels of thyroid stimulating hormone, with or without associated low total thyroxine levels, in preterm infants is complex
- Fluctuations in postnatal thyroid function are common in preterm infants, but the associated patterns and their relationship to longer term neurodevelopment is unclear
- There is no consensus on whether hypothyroxinaemia is an independent clinical entity

WHAT THIS STUDY ADDS

- Preterm infants with higher TSH concentrations at one end of the continuum have poorer neurodevelopment at two years.
- Consistent hypothyroxinaemia is associated with poor neurodevelopment at two years of age. Isolated postnatal hypothyroxinaemia in preterm infants is not associated with adverse neurodevelopment.
- Many of these infants will not be detected by current clinical protocols or screening programs for congenital hypothyroidism.

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TABLE 1: Distributions of T4, TSH, TBG and T4/TBG ratio by day of sampling and gestational age-group; mean (standard deviation) number

Gestational weeks	Day 7 blood	Day 14 blood	Day 28 blood	≡Week 34 blood
T4 nmol/l				
≤25 weeks	18.0 (8.6) 241	22.4 (11.6) 208	31.9 (13.3) 196	45.1 (14.0) 180
26-27 weeks	26.4 (10.2) 311	32.8 (12.7) 309	39.9 (14.6) 297	44.0 (14.8) 290
28-30 weeks	36.5 (13.6) 617	43.2 (14.2) 625	47.3 (15.8) 585	49.3 (14.7) 541
TSH mU/l				
≤25 weeks	1.3 (0.8) 241	1.6 (1.2) 208	1.6 (1.3) 196	1.6 (1.1) 180
26-27 weeks	1.4 (1.4) 311	1.9 (2.5) 309	1.7 (1.4) 296	1.5 (1.1) 290
28-30 weeks	1.8 (1.4) 613	1.9 (1.8) 625	1.6 (1.3) 584	1.6 (1.2) 541
TBG nmol/l				
≤25 weeks	115.6 (40.1) 239	144.0 (46.6) 208	169.7 (54.0) 195	198.0 (58.4) 179
26-27 weeks	131.9 (40.8) 311	155.1 (47.6) 307	170.1 (51.2) 297	179.3 (59.9) 290
28-30 weeks	146.5 (45.7) 610	162.9 (48.9) 624	174.0 (53.2) 584	176.2 (52.5) 541
T4/TBG ratio				
≤25 weeks	14.5 (5.5) 239	13.2 (4.6) 208	14.7 (8.2) 195	16.2 (4.5) 179
26-27 weeks	16.1 (5.3) 311	16.0 (5.3) 307	17.0 (4.9) 297	17.7 (5.7) 290
28-30 weeks	18.3 (5.1) 610	18.9 (6.6) 624	18.9 (5.0) 584	19.4 (5.1) 541

TABLE 2: Adjusted[1] linear regression models of TSH levels which were consistent over at least two study bloods and the Bayley-III main and subtest domains

Bayley-III main domains	N	Effect estimate	T statistic	p value	95% confidence interval Lower	higher
Cognitive Score						
Consistently top decile TSH	27	-6.9	-2.266	0.024	-12.9	-0.9
Mixed dysfunction	474	-1.5	-1.521	0.129	-3.5	0.4
Never in top decile	489	reference				
Motor Composite Score						
Consistently top decile TSH	27	-5.8	-1.967	0.050	-11.7	<-0.1*
Mixed dysfunction	474	-0.6	-0.583	0.560	-2.5	1.3
Never in top decile	488	reference				
Language Composite Score						
Consistently top decile TSH	27	-5.3	-1.528	0.127	-12.0	1.5
Mixed dysfunction	473	-2.1	-1.912	0.056	-4.3	0.1
Never in top decile	488	reference				
Receptive Language Subtest						
Consistently top decile TSH	27	-0.7	-1.179	0.239	-1.9	0.5
Mixed dysfunction	473	-0.2	-1.143	0.253	-0.6	0.2
Never in top decile	488	reference				
Expressive Language Subtest						
Consistently top decile TSH	27	-1.1	-1.719	0.086	-2.3	0.2
Mixed dysfunction	473	-0.5	-2.606	0.009	-0.9	-0.1
Never in top decile	487					
Fine Motor Subtest						
Consistently top decile TSH	27	-1.3	-2.165	0.031	-2.4	-0.1
Mixed dysfunction	474	-0.3	-1.436	0.151	-0.6	0.1
Never in top decile	487	reference				
Gross Motor Subtest						
Consistently top decile TSH	27	-0.7	-1.215	0.224	-1.7	0.4
Mixed dysfunction	473	0.1	0.554	0.580	-0.2	0.4
Never in top decile	489	reference				

[1] adjusted for gender, gestational age, level of nursing care required on day 14, whether or not in receipt of iodine supplement, whether or not treated with L-Thyroxine during the neonatal period or at 2 years of age, assessor and hospital of birth

*Actual figure -0.012

TABLE 3: Adjusted[1] linear regression models of T4 levels which were consistent over at least two study bloods and the Bayley-III main and subtest domains

Bayley-III main domains	N	Effect estimate	T statistic	p value	95% confidence interval Lower	higher
Cognitive Score						
Consistently bottom decile T4	7	-9.2	-1.556	0.120	-20.8	2.4
Mixed dysfunction	239	-1.8	-1.495	0.135	-4.1	0.6
Never in bottom decile	744	reference				
Motor Composite Score						
Consistently bottom decile T4	7	-13.4	-2.336	0.020	-24.6	-2.1
Mixed dysfunction	239	-0.8	-0.675	0.500	-3.0	1.5
Never in bottom decile	743	reference				
Language Composite Score						
Consistently bottom decile T4	7	-10.6	-1.599	0.110	-23.7	2.4
Mixed dysfunction	238	-1.1	-0.814	0.416	-3.7	1.5
Never in bottom decile	743	reference				
Receptive Language Subtest						
Consistently bottom decile T4	7	-1.9	-1.585	0.113	-4.2	0.5
Mixed dysfunction	238	-0.4	-1.512	0.131	-0.8	0.1
Never in bottom decile	743	reference				
Expressive Language Subtest						
Consistently bottom decile T4	7	-1.8	-1.445	0.149	-4.1	0.6
Mixed dysfunction	238	<-0.1	-0.135	0.893	-0.5	0.5
Never in bottom decile	742	reference				
Fine Motor Subtest						
Consistently bottom decile T4	7	-2.2	-1.988	0.046	-4.5	<-0.1*
Mixed dysfunction	239	<0.1	0.178	0.859	-0.4	0.5
Never in bottom decile	742	reference				
Gross Motor Subtest						
Consistently bottom decile T4	7	-2.3	-2.229	0.026	-4.3	-0.3
Mixed dysfunction	238	-0.3	-1.482	0.139	-0.7	0.1
Never in bottom decile	744	reference				

[1] adjusted for gender, gestational age, level of nursing care required on day 14, whether or not in receipt of iodine supplement, whether or not treated with L-Thyroxine during the neonatal period or at 2 years of age, assessor and hospital of birth

*Actual figure -0.04

TABLE 4: Number of infants with a raised TSH (≥6mu/l) levels by day of blood sampling and subsequent raised TSH levels*.

Blood sampling day	1 isolated raised TSH level	2 raised TSH levels	3 raised TSH levels	4 raised TSH levels	Total number of infants with a first raised TSH level per day: incidence data
Day 7	13	5	2	0	20
Day 14	19	8	1	n/a[A]	28
Day 28	11	4	n/a[A]	n/a[A]	15
34 weeks' gestation	6	n/a[A]	n/a[A]	n/a[A]	6
Total	49	17	3	0	**69**

[A] n/a not applicable as it is not possible to obtain this many tests

* for example on Day 7 there were 20 infants with raised TSH levels of whom 13 had an isolated raised level on day 7, 5 infants had two raised levels (on day 7 and either day 14/28/or 34 wks), and 2 infants had three raised levels (on day 7, and two others from days 14/28/or 34 wks)

TABLE 5: Adjusted[1] linear regression models of thyroid function which was consistent over at least two study bloods and the Bayley-III main and subtest domains

Bayley-III main domains	N	Effect estimate	T statistic	p value	95% confidence interval Lower	higher
Cognitive Score						
Hypothyroxinaemic	31	-8.4	-2.818	0.005	-14.3	-2.6
Mixed dysfunction	561	-2.1	-1.864	0.063	-4.3	0.1
Euthyroid	398	reference				
Motor Composite Score						
Hypothyroxinaemic	31	-9.4	-3.262	0.001	-15.1	-3.8
Mixed dysfunction	560	-1.6	-1.440	0.150	-3.7	0.6
Euthyroid	398	reference				
Language Composite Score						
Hypothyroxinaemic	31	-10.7	-3.175	0.002	-17.2	-4.1
Mixed dysfunction	560	-1.8	-1.446	0.149	-4.3	0.6
Euthyroid	397	reference				
Receptive Language Subtest						
Hypothyroxinaemic	31	-1.8	-2.927	0.004	-2.9	-0.6
Mixed dysfunction	560	-0.4	-1.788	0.074	-0.9	<0.1
Euthyroid	397	reference				
Expressive Language Subtest						
Hypothyroxinaemic	31	-1.9	-3.132	0.002	-3.1	-0.7
Mixed dysfunction	559	-0.2	-1.013	0.311	-0.7	0.2
Euthyroid	397	reference				
Fine Motor Subtest						
Hypothyroxinaemic	31	-1.8	-3.184	0.001	-2.9	-0.7
Mixed dysfunction	559	-0.3	-1.213	0.226	-0.7	0.2
Euthyroid	398	reference				
Gross Motor Subtest						
Hypothyroxinaemic	31	-1.3	-2.587	0.010	-2.4	-0.3
Mixed dysfunction	560	-0.2	-1.227	0.220	-0.6	0.1
Euthyroid	398	reference				

[1] adjusted for gender, gestational age, level of nursing care required on day 14, whether or not in receipt of iodine supplement, whether or not treated with L-Thyroxine during the neonatal period or at 2 years of age, assessor and hospital of birth