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Transient hypothyroxinemia of prematurity and problem behavior in young adulthood

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ABSTRACT

Introduction

Preterm newborns are at risk of developing transient hypothyroxinemia of prematurity (THoP), which has been associated with subsequent neurodevelopmental impairments. Behavioral outcomes at adult age after THoP have never been reported.

Aim

To examine whether there is an association between THoP and problem behavior at young adult age.

Methods

This study was part of the follow-up of 19-year-old subjects born very preterm (i.e., <32 weeks) and/or with a very low birth weight (i.e.,<1500g) from the Project On Preterm and Small-for-gestational-age infants (POPS) cohort. We included 468 subjects of the POPS cohort; of whom 123 had THoP. Thyroxine (T4) concentrations were obtained through the national neonatal screening program for congenital hypothyroidism. THoP was defined as a T4 concentration <-3 SD (approximately 60nmol/L). At age 19, behavior was assessed using the Young Adult Self Report and the Young Adult Behavioral Checklist for parents.

Results

THoP was associated with a 1.8 (95% confidence interval (CI): 1.01-3.4) -fold increased odds of self-reported Internalizing behavior, as well as with a 1.9 (95% CI: 1.1-3.1) -fold increased odds of parent-reported Total problem behavior. These relations persisted after correction for demographic and perinatal variables. Similar associations were absent for the other self-reported and parent-reported syndrome and problem scales.

Conclusions

THoP was associated with more internalizing and total problem behavior at age 19. While our observations warrant more awareness of problem behavior in preterm infants, at present, it is unclear whether these associations are causal and screening for THoP does not seem necessary.

INTRODUCTION

Thyroid hormones are crucial for the developing brain, where they help to control cell migration, proliferation and differentiation.[1] According to the construct of Zoeller and Rovet (2004) [1] in the first half of pregnancy, thyroid hormones play a role in the development of visual attention and processing, and of fine motor skills. During the second half of pregnancy, thyroid hormones are proposed to be involved in the development of memory, visuospatial skills, and fine and gross motor skills [1] Because the fetal thyroid starts to become functional from the 12th week of gestation,[2] adequate maternal-fetal transfer of thyroxine (T4) in the first trimester is essential for early brain development. However, maternal T4 remains a major fraction of fetal serum T4 after the onset of fetal thyroid hormone production, and continues to play a role in fetal neurodevelopment until birth.[3]

Small reductions in the early supply of thyroid hormones might lead to permanent alterations in behavioral patterns. In animals, disruptions in the transplacental supply of thyroid hormones resulted in morphological changes in the cerebral cortex and hippocampus of the pups.[4,5] In humans, functional changes in these structures have been proposed to underlie attention deficit/hyperactivity disorder (ADHD).[6,7] Indeed, small reductions in the maternal thyroid function during early pregnancy were associated with ADHD symptoms in 8-year-old offspring.[8,9] Similarly, the risk of developing attention problems was also increased in subjects with early-treated congenital hypothyroidism (CHT).[10]

Preterm birth has been associated with attention problems and internalizing behavior. These patterns have been reported to persist into adulthood.[11] Nowadays, of all live-born children, 11.1 (range: 5-18) % are born <37 week of gestation, and 1.7% are born <32 weeks of gestation.[12]

After preterm birth, a transient reduction in the thyroid hormone level, known as transient hypothyroxinemia of prematurity (THoP), has been estimated to occur in approximately 20% of infants, although it is even more common with increasing degrees of prematurity.[13,14] It can be attributed to the sudden disruption of the transplacental T4 supply.[15-17] Additionally, hypothalamus-pituitary-thyroid axis immaturity, reduced thyroidal iodine reserves, acute illnesses, and treatment with dopamine also contribute to the development of THoP.[15,18-21] T4 concentrations are therefore lower in extremely preterm infants than in fetuses of the same post-conceptional age[22] THoP usually restores spontaneously within 6 to 8 weeks.[23] There is conflicting evidence with regard to the effects of THoP on long-term neurodevelopmental outcomes. Although THoP was associated with adverse neurodevelopment in infancy and childhood,[13,24,25] the only study that had provided follow-up into adulthood was negative.[26] Whether THoP is associated with problem behavior, in particular attention problems, has not been addressed to date.

Therefore, we aimed to investigate whether there is an association between THoP and problem behavior at young adult age. Here, we provide a prospective follow-up of a well-described cohort of males and females born very preterm (i.e., <32 weeks) and/or with a very low birth weight (i.e., <1,500 g) in whom behavioral outcomes were assessed at age 19 years and whose T4 levels were determined during a T4-based national screening program for CHT. Based on previous studies that addressed the effects of early disruptions in the supply of thyroid hormones,[8-10] we expected to find more problem behavior in subjects with THoP, especially attention problems.

METHODS

Study population

The Project On Preterm and Small-for-gestational-age infants (POPS) cohort is a nationwide birth cohort study, which comprised 94% (n=1,338) of infants who were born alive in the Netherlands in January-December 1983 with a gestational age of less than 32 weeks and/or with a birth weight below 1,500 grams.[27] In 1983, 101 out of 115 level 1 to level 3 hospitals throughout the Netherlands collected data. At age 1 year, 975 subjects (73%) were still alive, and they were followed up throughout childhood. At age 19 years, another follow-up was scheduled; 959 subjects (72%) were still alive at that point. Of these, 745 subjects had known neonatal T4 concentrations. In keeping with previous analyses in the POPS cohort with regard to THoP,[24,25] we excluded subjects whose T4 concentrations were measured before postnatal day 5 or after day 17 (n=66) or who received thyroid hormone supplementation during their hospital stay (n=5). We also excluded subjects with severe congenital malformations, such as Down syndrome, central nervous system defects or inborn errors of metabolism (n=10), severe sensory handicaps (n=8) and congenital hypothyroidism (n=1). 655 subjects were therefore eligible for our study. Figure 1 shows the flowchart of our study sample.

Iodine intake of the infants and/or their mothers was not measured in our cohort. However, iodine supplementation guidelines were intensified in The Netherlands in 1982, and iodine status was subsequently considered sufficient in a survey among school children in the 1990s.[28]

The study was approved by the medical ethical committees of the participating centers, and written informed consent was obtained from all participants.

Laboratory analysis

T4 was measured in the context of the neonatal screening for CHT. From April 1983 onward, results were prospectively collected,[24] although the T4 values of 54 subjects born before April 1983 could be acquired retrospectively. T4 concentrations from filter paper

eluates were measured in duplicate by radioimmunoassay [29] in the five laboratories connected to the national screening program. These laboratories were under permanent quality control.[30] T4 levels in the eluates were expressed as standard deviations from the mean, which was calculated on a daily basis.[31] In our sample, T4 SDS was normally distributed. The intra-assay and inter-assay coefficients of variation in the eluates were 8 and 10%, respectively. In line with previous analyses in this cohort,[24,25] THoP was defined as a T4 concentration of <-3SD (approximately 60 nmol/L).[25]

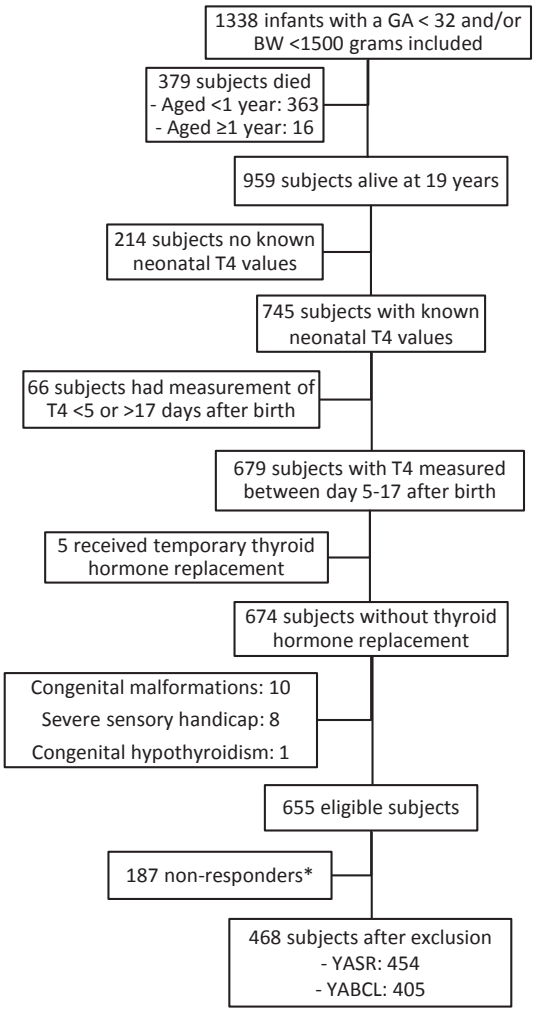

Figure 1: Flowchart of the inclusion of POPS subjects at age 19
*included in this number: subjects who were followed up but did not return the YASR or YABCL
YASR, Young Adult Self Report; YABCL, Young Adult Behavior Checklist

In a number of subjects re-tests were performed in order to ascertain the transient nature of hypothyroxinemia. Whether and when re-tests were done was at the discretion of the treating clinician, and T4 was analyzed in the same manner as the initial T4 measurements.

Study procedure

Behavior at age 19 was studied using the Young Adult Self Report (YASR) and/or the Young Adult Behavior Checklist (YABCL). The YASR was used to assess problem behavior from the perspective of the adolescent, while the YABCL assessed problem behavior from the parent's or caregiver's perspective. Both questionnaires were developed by Achenbach and provide a standardized description of behavior, feelings, thoughts and competences in people aged 18 to 30 years.[32] The YASR and YABCL contain 130 and 109 items, respectively. Each item is scored according to a 3-step scale, where 0 = "not true", 1 = "somewhat or sometimes true", and 2 = "very often or often true". The questions pertain to the preceding 6 months. From these items, 8 syndrome scales are derived: Anxious/Depressed, Withdrawn, Somatic complaints, Thought problems, Attention problems, Intrusive behavior, Aggressive behavior, and Delinquent behavior. Although the syndrome scale Attention problems assesses some aspects of ADHD, confirmation of ADHD diagnoses in childhood and/or young adulthood was not known for our cohort. Subsequently, three problem scales are calculated: the problem scale 'Internalizing behavior' is the sum of the syndrome scales Anxious/Depressed and Withdrawn, the problem scale 'Externalizing behavior' is the sum of the syndrome scales Aggressive behavior, Delinquent behavior and Intrusive behavior, and the Total problems scale is the sum of all individual items. For each syndrome and problem scale a clinical cut-off, as well as a borderline clinical cut-off has been determined on the basis of a non-referred population.[32] For this study, we used the borderline clinical cut-off, since we aimed at exploring associations even in the subclinical range. For the syndrome scales, the 95th percentile is considered the borderline clinical cut-off point. For the problem scales, the 83rd percentile is considered as the borderline clinical cut-off point. These cut-off points are gender-specific.

Statistical analysis

Multivariate logistic regression was used to study the effect of THoP on behavioral outcomes. Behavioral outcomes were dichotomized according to the borderline clinical cut-off point. The model was first adjusted for the demographic characteristics gender, socio economic status (SES), ethnicity and parity. Analyses were repeated after also adjusting for the perinatal characteristics gestational age (GA) and being born small-for-gestational-age (SGA), and for neonatal illnesses, such as infant respiratory distress syndrome (diagnosed clinically and/or radiographically), intraventricular hemorrhage

(diagnosed clinically and/or ultrasonographically) and sepsis (diagnosed hematologically and/or through blood culture). Next, analyses were repeated with T4 as a continuous variable, and after stratifying the data according to gestational age into < and ≥ 29 weeks. We based this cut-off point on a randomized placebo-controlled trial, showing gestational age-dependent effects of early levothyroxine treatment on behavior.[33] A *P* value of ≤0.05 was considered statistically significant.

Our study was not designed specifically to address the effect of THoP on behavioral outcomes. Our sample size enabled us to detect a difference of 1.3 points on the attention scale of both the YASR and YABCL, assuming a maximum SD of 4 points, with a power of 80% and a significance level of 0.05.

RESULTS

Descriptives

Of the 655 eligible subjects, 468 subjects and/or their parents (71.5%) filled in the YASR and/or the YABCL. Non-responders were more likely to be male and to have a non-Caucasian ethnicity, a lower SES and a younger maternal age at birth than responders (Table 1). Non-response was unrelated to perinatal characteristics, the T4 concentration (-2.4 SD vs. -2.4 SD, P=1.00), or the proportion of subjects with THoP (26.3 % vs. 28.3%, P=0.59).

Among the 468 participants, 391 returned both the YASR and the YABCL, 14 returned the YASR only, and 63 returned the YABCL only. Of these, 123 developed THoP, which was diagnosed in 67% of the infants with a GA <28 weeks, in 27% of the infants with a GA 28-31 weeks, and in 12% of the infants with a GA ≥32 weeks. Table 1 details the baseline characteristics of subjects with and without THoP.

Re-testing was performed in 427 of 468 subjects. None of the re-tested subjects had a T4 concentration <-3SD after 53 days postpartum, which is consistent with the known duration of THoP.[23]

YASR

Table 2 presents the self-reported behavioral outcomes at age 19. THoP was associated with a higher odds of Internalizing behavior. This relation persisted after correction for demographic and perinatal characteristics. Hypothyroxinemic subjects showed a non-significant tendency towards more Withdrawn behavior and Total problem behavior; these associations only became significant after adjustment for confounders. There were no associations between THoP and other self-reported syndrome or problem scales.

Table 1: General and perinatal characteristics

	Subjects with THoP (n=123, 26.3%)	Subjects without THoP (n=345, 73.7%)	*P* value*	Non-responders (n=187)	*P* value†
General					
Male sex (%)	64 (52.0)	154 (44.6)	0.158	115 (61.5)	0.001
White (%)	102 (85.0)	316 (91.9)	0.030	142 (75.9)	<0.001
Low socio-economic status (%)	45 (36.9)	123 (36.0)	0.856	108 (60.7)	<0.001
First child (%)	64 (52.9)	197 (57.1)	0.422	97 (51.9)	0.337
Perinatal					
Maternal age (years)	26.7±5.0	27.4±6.1	0.279	26.1±4.9	0.021
Gestational age (weeks)	29.4±2.1	31.4±2.4	<0.001	31.0±2.7	0.549
Birth weight (grams)	1,191±254	1,306±257	<0.001	1,279±251	0.876
SGA birth (%)	30 (24.6)	148 (42.9)	<0.001	76 (40.6)	0.549
Apgar score ≥7 after 5 min (%)	93 (75.6)	298 (86.4)	0.010	157 (84.0)	0.987
Part of multiple pregnancy (%)	33 (26.8)	78 (22.6)	0.345	37 (19.8)	0.277
Respiratory distress syndrome (%)	73 (59.3)	122 (35.4)	<0.001	67 (35.8)	0.168
Intraventricular hemorrhage (%)	45 (36.6)	42 (12.2)	<0.001	30 (16.0)	0.442
Sepsis (%)	54 (43.9)	88 (25.6)	<0.001	69 (36.9)	0.109
Necrotizing enterocolitis (%)	7 (5.7)	19 (5.5)	0.939	8 (4.3)	0.506
Total T4 (SD)	-3.5±0.4	-1.9±0.7	<0.001	-2.4±1.0	0.995

Values represent mean±SD or n (%). Continuous variables were compared with the unpaired t test. Dichotomous variables were compared with the Chi square test.

**P* value when comparing subjects with and without THoP

† *P* value when comparing responders (subjects with and without THoP combined) and non-responders

YABCL

Table 3 displays the parent-reported behavioral outcomes at age 19. THoP was associated with a higher score for Total problem behavior (29.0±22.6 vs. 23.3±20.6; p=0.023). Moreover, THoP was associated with a higher odds of Total problem behavior, which remained significant after adjusting for all potential confounders. THoP also increased the odds of Thought problems and Internalizing problem behavior. However, these associations lost significance after adjustment for demographic and perinatal variables. There were no associations between THoP and other parent-reported syndrome or problem scales.

When analyzing T4 SDS as a continuous variable, no association was found with any of the self- or parent-reported syndrome or problem scales (Supplementary Table 1). Stratification by gestational age did not change our results (data not shown).

Correlations between self- and parent reported behaviors ranged between 0.40 and 0.61 (all *P* values <0.001).

Table 2: Risk of problem behavior according to the Young Adult Self Report (YASR) after THoP.

	Subjects with THoP	Subjects without THoP	OR (95% CI)					
	N = 118	n = 336	Unadjusted	*P* value	Adjusted (1)	*P* value	Adjusted (2)	*P* value
Syndrome scales								
Anxious/depressed	7.6±7.1	6.3±6.2	2.5 (0.95-6.4)	0.064	2.9 (1.1-7.6)	0.034*	2.3 (0.7-7.1)	0.150
Withdrawn	2.9±2.9	2.6±2.4	1.7 (0.9-3.5)	0.112	2.0 (1.02-4.1)	0.045*	2.4 (1.1-5.2)	0.031*
Somatic complaints	3.7±3.7	3.3±3.6	1.1 (0.5-2.6)	0.806	0.9 (0.4-2.4)	0.907	1.5 (0.5-4.0)	0.459
Thought problems	0.5±1.3	0.3±0.9	1.3 (0.6-3.1)	0.528	1.5 (0.6-3.7)	0.332	1.7 (0.6-4.7)	0.283
Attention problems	2.7±2.5	2.7±2.2	1.4 (0.6-3.3)	0.455	1.7 (0.7-4.1)	0.261	1.6 (0.6-4.4)	0.371
Intrusive behavior	2.1±2.1	1.7±1.9	1.9 (0.3-11.7)	0.476	1.9 (0.3-12.2)	0.511	5.7 (0.7-47.4)	0.107
Aggressive behavior	2.7±2.7	2.5±2.9	0.5 (0.1-2.4)	0.402	0.6 (0.1-2.9)	0.544	0.9 (0.2-5.7)	0.950
Delinquent behavior	1.0±1.6	1.1±1.7	0.3 (0.0-2.3)	0.234	0.3 (0.0-2.8)	0.315	0.3 (0.0-3.3)	0.355
Problem scales								
Internalizing behavior	10.5±9.5	8.9±8.0	1.8 (1.01-3.4)	0.045*	2.0 (1.1-3.7)	0.032*	2.4 (1.2-5.0)	0.016*
Externalizing behavior	5.8±5.2	5.4±5.2	0.5 (0.2-1.3)	0.134	0.6 (0.2-1.5)	0.253	0.8 (0.3-2.4)	0.687
Total problem behavior	34.8±25.4	30.9±23.0	1.7 (0.9-3.1)	0.082	1.8 (0.98-3.5)	0.058	2.4 (1.2-5.0)	0.016*

Values represent mean±SD or OR (95% CI).
Adjusted (1): gender, SES, ethnicity and parity
Adjusted (2): adjusted (1) + gestational age, SGA-status and neonatal illnesses (IRDS, IVH and sepsis)
* $P < 0.05$

Table 3: Risk of problem behavior according to the Young Adult Behavioral Checklist (YABCL) after THoP.

	Subjects with THoP	Subjects without THoP	OR (95% CI)					
	n = 107	n = 298	Unadjusted	*P* value	Adjusted (1)	*P* value	Adjusted (2)	*P* value
Syndrome scales								
Anxious/depressed	5.9±5.4	5.0±4.9	1.3 (0.6-2.7)	0.517	1.3 (0.6-2.8)	0.508	1.4 (0.6-3.4)	0.441
Withdrawn	2.1±2.3	1.6±1.8	1.4 (0.7-3.0)	0.381	1.4 (0.7-3.0)	0.378	1.5 (0.6-3.5)	0.391
Somatic complaints	2.4±2.5	2.2±2.6	0.7 (0.3-1.8)	0.506	0.8 (0.3-1.9)	0.807	0.9 (0.3-2.5)	0.858
Thought problems	0.9±1.7	0.6±1.4	2.1 (1.01-4.2)	0.048*	2.1 (0.97-4.4)	0.059	1.8 (0.7-4.2)	0.200
Attention problems	5.3±4.3	4.4±4.0	1.5 (0.7-3.1)	0.297	1.7 (0.8-3.5)	0.192	1.8 (0.8-4.4)	0.177
Intrusive behavior	2.2±2.0	1.8±2.3	0.4 (0.1-1.9)	0.267	0.4 (0.1-2.0)	0.278	0.9 (0.2-4.7)	0.927
Aggressive behavior	4.2±5.1	3.5±4.6	1.5 (0.6-3.7)	0.435	1.5 (0.6-3.9)	0.409	1.9 (0.6-5.6)	0.241
Delinquent behavior	0.9±1.4	0.8±1.6	0.6 (0.1-4.9)	0.603	0.6 (0.1-5.0)	0.602	1.0 (0.1-12.0)	0.988
Problem scales								
Internalizing behavior	8.0±6.6	6.6±6.1	1.7 (1.03-2.7)	0.039*	1.6 (0.97-2.6)	0.068	1.7 (0.96-3.0)	0.068
Externalizing behavior	7.3±7.0	6.2±7.5	1.4 (0.8-2.5)	0.281	1.5 (0.8-2.7)	0.208	1.8 (0.9-3.6)	0.110
Total problem behavior	29.0±22.6	23.3±20.6*	1.9 (1.1-3.1)	0.018*	1.8 (1.1-3.1)	0.025*	2.4 (1.3-4.5)	0.005*

Values represent mean±SD or OR (95% CI).
Adjusted (1): gender, SES, ethnicity and parity
Adjusted (2): adjusted (1) + gestational age, SGA-status and neonatal illnesses (IRDS, IVH and sepsis)
* $P < 0.05$

DISCUSSION

We found that THoP was associated with increased odds of internalizing and total problem behavior at age 19 years. THoP was not associated with attention problems.

A recent meta-analysis found that internalizing behavior and attention problems were more common after preterm birth.[11] In several cohorts of preterm infants, including the POPS cohort, these behavioral patterns were demonstrated to persist into young adulthood.[34,35] Whether THoP has an influence on adult behavior has not been addressed to date, with the exception of our study. However, there are some data available regarding behavior after subtle impairments in the early supply of thyroid hormones. The Generation R study, which follows a community-based sample of mothers and their children, found that hypothyroxinemia in women early in gestation was associated with an increased risk for ADHD symptoms in their 8-year-old children.[8] Another study found higher rates of ADHD in children born to mothers with higher TSH levels early in their pregnancies.[9]

We found that THoP was associated with increases in internalizing and total problem behavior at age 19. However, we did not find evidence for an effect of THoP on attention problems. Since thyroid hormones appear to influence different domains of brain development at different stages during gestation,[1] it is possible that the developmental window in which a transient decrease in the T4 supply could have an influence on attention might be earlier than in (the period equivalent to) the third trimester of pregnancy,[8,36] although children with treated CHT were also at risk of attention problems.[10] An alternative explanation is that the causes of attention problems after preterm birth are complex.[37] Therefore, in our sample, a possible effect of THoP on attention problems might go unnoticed.

A randomized placebo-controlled trial in infants born before 30 weeks of gestation showed no effect of treatment with levothyroxine (at a dose of 8 mcg/kg/d during the first 6 postnatal weeks) on behavior at the ages of 5.7 and 10 years.[38,39] However, in *post hoc* analyses benefit was evident only among children of 25-26 weeks' gestation at age 5.7, but not at age 10. In our study, we did not find evidence for gestational age-dependency of our associations.

Currently, the POPS cohort is the only preterm population that has been followed up into young adulthood with regard to THoP as far as we are aware. It was previously shown that THoP is not associated with IQ or neuromotor development at age 19.[26] Presently, preterm infants are not routinely screened for THoP, and our results do not indicate this practice should be altered. On the other hand, behavioral problems were more prevalent in subjects with THoP. While the causality of these associations is still unclear, more awareness of problem behavior in preterm infants is warranted, especially since the risk of behavioral problems is already increased in these populations.[11]

Our study has several strengths and limitations. The major strength of our study is the long follow-up period, which extends into adulthood. Thus far, the long-term effects of THoP have been studied up until childhood.[13,24] Another strength of our study is the use of both the YASR and the YABCL, enabling us to study both the adolescent's and parent's, or caregiver's, perspective. Both yielded similar results. Moreover, 80% of the subjects in our cohort were still living with their parents, and previous research has shown that parents of children who were born preterm provide highly valid data,[40] suggesting a reliable parental evaluation in our sample.

Our study has several weaknesses. First, only total T4 concentrations, obtained during a single measurement, were available for analysis. It is possible that several participants in our study were misclassified as hypothyroxinemic, since the systemic total T4 level does not always parallel the tissue free T4 concentration.[20] Moreover, the reported standard deviation scores were based on the Dutch norm population. Despite this limitation, it was still possible to differentiate between lower and higher concentrations of T4. Second, thyroid function tests were not part of the assessment at age 19 years. Recent evidence in this research field indicates that school performance is influenced for an important part by the current thyroid hormone status.[36] However, in a small subset of the POPS cohort, thyroid function tests in young adulthood were not different compared to age-matched controls born at term.[41] Third, the losses to follow-up throughout the years might have introduced bias. However, the numbers lost to follow-up were acceptably low for our study. While non-response was associated with male gender, non-white ethnicity and lower socio-economic status, it was not associated with any of the perinatal characteristics.[42] Moreover, we found no differences between responders and non-responders with regard to both total T4 levels and the proportion of subjects with THoP. Furthermore, our results did not change after statistical adjustment for many of the differing factors, and we therefore believe that response bias is unlikely to explain our associations. Additionally, subjects with and without THoP differed significantly in many perinatal characteristics. Adjusting for many of these factors in our analyses did not change our results. This makes bias less likely, but the possibility cannot be excluded completely.

Although the sudden disruption of the maternal thyroid supply is considered an important factor in the development of THoP, it is unknown whether higher maternal T4 levels prior to preterm delivery protect against it. In term-born infants, maternal TSH and FT4 at the end of the first trimester were positively correlated to cord blood TSH and FT4.[43] The correlation with thyroid function in the first days of life was not studied. However, these findings cannot simply be extrapolated to preterm infants, whose thyroid function is also determined by factors related to illness, treatment and immaturity. Future research should elucidate this.

CONCLUSION

We found that THoP was associated with increases in internalizing and total problem behavior at age 19. While our observations warrant more awareness of problem behavior during the follow-up of preterm infants, at present, it is unclear whether these associations are causal. Therefore, combined with recent findings reporting on the lack of association between THoP and neurodevelopment outcomes once adulthood is reached,[26] at present, there is no indication to screen preterm infants for THoP.

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Supplementary Table 1: Risk of problem behavior across the entire range of T4 SDS

	Unadjusted	*P* value	Adjusted (1)	*P* value	Adjusted (2)	*P* value
YASR						
Syndrome scales						
Anxious	0.7 (0.4 - 1.1)	0.140	0.6 (0.4 - 1.1)	0.077	0.7 (0.4 - 1.4)	0.356
Withdrawn	1.0 (0.7 - 1.4)	1.000	0.9 (0.7 - 1.3)	0.732	0.9 (0.6 - 1.4)	0.680
Somatic complaints	1.3 (0.8 - 1.9)	0.269	1.3 (0.9 - 2.0)	0.165	1.2 (0.7 - 1.9)	0.488
Thought problems	1.1 (0.7 - 1.7)	0.664	1.0 (0.7 - 1.6)	0.881	1.0 (0.6 - 1.7)	0.967
Attention problems	0.9 (0.6 - 1.4)	0.572	0.8 (0.5 - 1.3)	0.433	0.9 (0.5 - 1.5)	0.590
Intrusive behavior	0.8 (0.3 - 2.1)	0.669	0.8 (0.3 - 2.2)	0.689	0.4 (0.1 - 1.5)	0.169
Aggressive behavior	1.7 (0.96 - 3.0)	0.068	1.8 (0.95 - 3.3)	0.070	1.6 (0.7 - 3.3)	0.231
Delinquent behavior	1.6 (0.9 - 2.9)	0.138	1.3 (0.7 - 2.6)	0.442	1.3 (0.6 - 3.1)	0.508
Problem scales						
Internal problems	0.9 (0.6 - 1.2)	0.310	0.8 (0.6 - 1.1)	0.240	0.7 (0.5 - 1.1)	0.180
External problems	1.2 (0.9 - 1.8)	0.263	1.1 (0.8 - 1.6)	0.584	0.8 (0.5 - 1.4)	0.485
Total problems	0.8 (0.6 - 1.1)	0.234	0.8 (0.6 - 1.1)	0.175	0.7 (0.5 - 1.01)	0.056
YABCL						
Syndrome scales						
Anxious	0.9 (0.6 - 1.2)	0.428	0.9 (0.6 - 1.2)	0.409	0.8 (0.5 - 1.3)	0.318
Withdrawn	0.9 (0.6 - 1.3)	0.431	0.9 (0.6 - 1.3)	0.456	0.9 (0.5 - 1.3)	0.495
Somatic complaints	1.1 (0.7 - 1.6)	0.673	1.0 (0.7 - 1.5)	0.827	1.0 (0.6 - 1.6)	0.968
Thought problems	0.8 (0.6 - 1.2)	0.249	0.8 (0.5 - 1.2)	0.241	0.9 (0.6 - 1.4)	0.579
Attention problems	0.8 (0.6 - 1.2)	0.262	0.8 (0.5 - 1.1)	0.148	0.7 (0.4 - 1.1)	0.113
Intrusive behavior	1.2 (0.7 - 2.0)	0.572	1.1 (0.7 - 2.0)	0.617	0.7 (0.4 - 1.4)	0.371
Aggressive behavior	0.9 (0.6 - 1.4)	0.595	0.9 (0.5 - 1.4)	0.565	0.8 (0.4 - 1.4)	0.381
Delinquent behavior	1.2 (0.5 - 2.8)	0.635	1.2 (0.5 - 2.8)	0.643	1.2 (0.4 - 4.1)	0.760
Problem scales						
Internal problems	0.8 (0.7 - 1.04)	0.105	0.8 (0.6 - 1.1)	0.125	0.8 (0.6 - 1.1)	0.110
External problems	0.9 (0.7 - 1.2)	0.563	0.9 (0.7 - 1.2)	0.462	0.8 (0.6 - 1.2)	0.241
Total problems	0.8 (0.6 - 1.1)	0.150	0.8 (0.6 - 1.1)	0.164	0.7 (0.5 - 0.9)	0.038*

Values represent OR (95% CI).

Adjusted (1): gender, SES, ethnicity and parity

Adjusted (2): adjusted (1) + gestational age, SGA-status and neonatal illnesses (IRDS, IVH and sepsis)

* $P < 0.05$