Early-life endocrine regulation and neurodevelopmental outcomes

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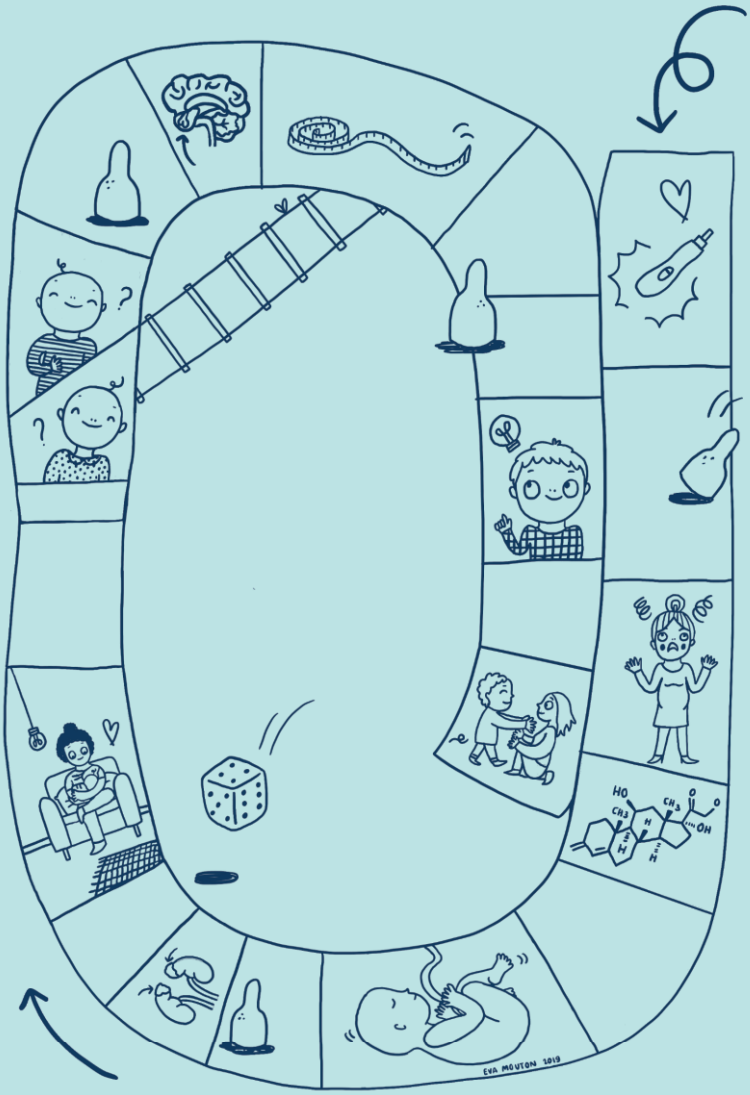
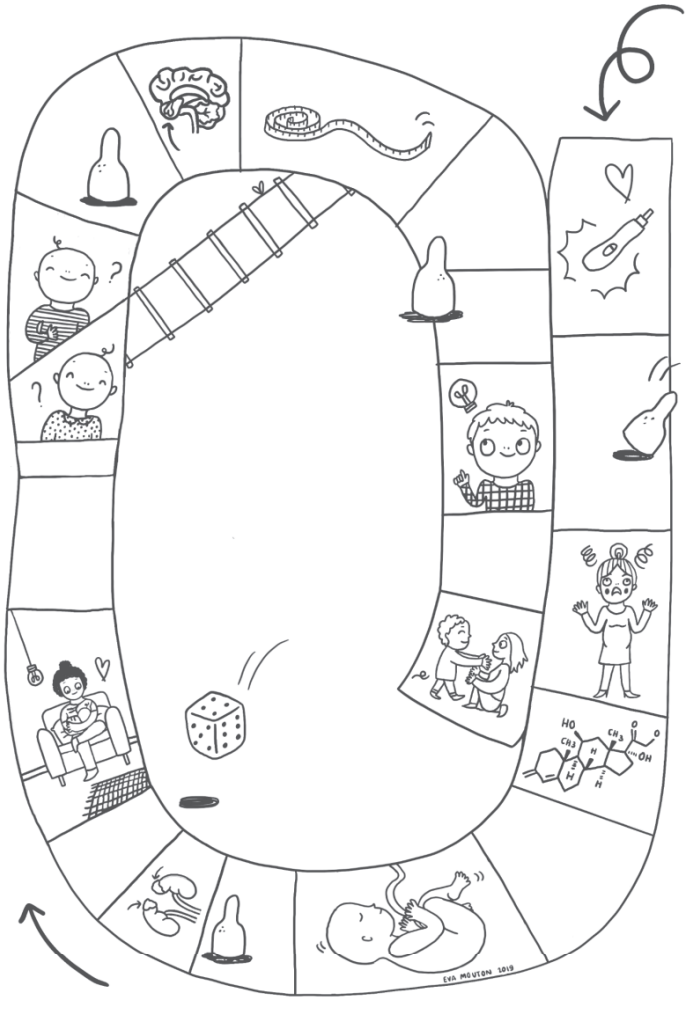
Part 3

Early-life thyroid regulation in preterm infants

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No association between transient hypothyroxinemia of prematurity and neurodevelopmental outcome in young adulthood

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ABSTRACT

Context

Transient hypothyroxinemia of prematurity (THoP) has been associated with neurodevelopmental impairment in infancy and childhood. It is not known whether these relations persist into adulthood.

Objective

The objective was to examine whether there is an effect of THoP on intelligence quotient (IQ) score and motor functioning at a young adult age.

Design

This study was part of the 19-year follow-up of the Project On Preterm and Small-for-gestational-age birth (POPS) cohort, which included infants born very preterm (ie, <32 wk) and/or with a very low birth weight (ie, <1500 g).

Setting

This was a multicenter study.

Patients

There were 398 19-year-old participants of the POPS cohort, of whom 120 had THoP.

Exposure

T4 concentrations were obtained through the national neonatal screening program for congenital hypothyroidism. THoP was defined as a total T4 concentration < −3 SD of the daily mean (approximately 60 nmol/L).

Main Outcome Measures

Main outcome measures were IQ and motor functioning, measured with the digital Multicultural Capacities Test-Intermediate Level and a revised version of Touwen's examination of minor neurological dysfunction, respectively.

Results

THoP was not associated with IQ score (mean difference, 0 [95% confidence interval, −3.8 to 3.8] points) or motor function (mean difference, 0.6 [95% confidence interval, −1.3 to 2.5] points) after adjustment for demographic and perinatal characteristics.

Conclusions

No associations between THoP and neurodevelopmental outcome at age 19 years were found.

INTRODUCTION

Preterm infants often develop transient hypothyroxinemia of prematurity (THoP). This is characterized by a temporary reduction in thyroxine (T4) that may last for 6-8 weeks,[1,2] whereas TSH remains low to normal.[3] After the severance of the umbilical cord, the transplacental supply of maternal T4 stops immediately.[4] Other mechanisms contributing to THoP are hypothalamus-pituitary-thyroid axis immaturity, reduced thyroidal iodine reserves, and acute illnesses.[2,5-8] Continuing debate exists about whether THoP is harmful for the developing brain.

THoP has been associated with delayed nerve conduction velocity,[9] later achievement of developmental milestones,[10] lower scores in cognitive tests,[11] and increased risks of school failure[12] and cerebral palsy.[13] However, there are currently no evidence-based guidelines on the screening for THoP. Moreover, the few trials that have addressed neurodevelopmental outcome after levothyroxine supplementation in preterm newborns were negative.[14-16] Nevertheless, a *post hoc* analysis suggested that the effects of this therapy were dependent on the degree of prematurity.[15] More specifically, it was found that infants of 25–26 weeks' gestation had a higher score on the Mental Developmental Index of the Bayley Scales of Infant Development at 2 years of age if treated with levothyroxine when compared with untreated controls. By contrast, treated infants of 27–29 weeks' gestation scored, on average, 10 points lower than untreated infants. Similar gestational age-dependent effects were observed for motor functioning, [15] and all of the associations found at 2 years were reported to persist at ages 5.7 and 10 years.[17,18]

It is not known whether the neurodevelopmental effects of THoP persist into adulthood. We therefore studied the effects of a low T4 concentration, obtained during a T4-based neonatal screening program for congenital hypothyroidism, on intelligence quotient (IQ) and neuromotor function at 19 years of age in a large cohort of very preterm (<32 weeks' gestation) and/or very low birth weight (<1,500 g) infants in The Netherlands. Based on previous observations in this cohort,[12] we expected to find worse neurodevelopmental outcomes after THoP.

METHODS

Population

The Project On Preterm and Small-for-gestational-age infants (POPS) cohort comprised 94% of the infants born alive in The Netherlands in 1983 with a gestational age <32 weeks and/or a birth weight <1,500 g.[19] The original cohort consisted of 1,338 infants, of whom 959 (72%) survived to age 19 years.

From April 1983 onward, neonatal screening results for congenital hypothyroidism were prospectively collected.[12] In addition, the screening results of 54 subjects born before April 1983 could also be retrieved. T4 was therefore known for 745 of the surviving subjects (78%). In line with previous analyses in the POPS cohort, we excluded the data of subjects whose T4 concentrations were measured before postnatal day 5 or after day 17 (n=66).[10,12] Subjects were also excluded if they received thyroid hormone supplementation during their stay in the hospital (n=5), as were subjects with severe congenital malformations, such as Down's syndrome, central nervous system defects or inborn errors of metabolism (n=10), severe sensory handicap (n=8), and congenital hypothyroidism (n=1). This left 655 eligible subjects for our study, of whom 398 (61%) underwent a neurological examination and/or IQ testing at one of the 10 participating centers. For the analyses of neuromotor function, we also excluded subjects taking drugs with a high risk of extrapyramidal side effects (n=2). The flowchart of the study sample is shown in Figure 1.

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

Laboratory investigations

T4 concentrations from filter paper eluates were determined in duplicate by radioimmunoassay.[20] Five accredited laboratories processed an average of 125 samples per day; they were all under permanent quality control.[21] Samples were not analyzed continuously. T4 levels in the eluates were expressed as standard deviations (SD) from the mean, which was calculated on a daily basis.[22] The intra-assay and interassay coefficients of variation in the eluates were 8 and 10%, respectively. Sampling time of day was not taken into account. Consistent with previous analyses in this cohort, hypothyroxinemia was defined as a T4 concentration of >3 SD below the daily reference mean (approximately 60 nmol/L).[12] TSH was measured only in infants with the lowest 20% T4 values. These values were not used because they do not aid in the identification of infants with THoP.[14]

Intelligence quotient

Intellectual functioning was assessed with the use of the computerized version of the Multicultural Capacity Test (MCT)–Intermediate Level.[23] In all, this test provides an overview of a person's capacities and skills: i.e., verbal and numerical intelligence, spatial visualization, speech fluency, memory, reasoning, and speed of perception. The MCT is validated for individuals aged ≥16 years from different backgrounds, whose level of education ranges from 5 years of secondary school to university level. In the Dutch norm population, the MCT reports an IQ score of 100±15.

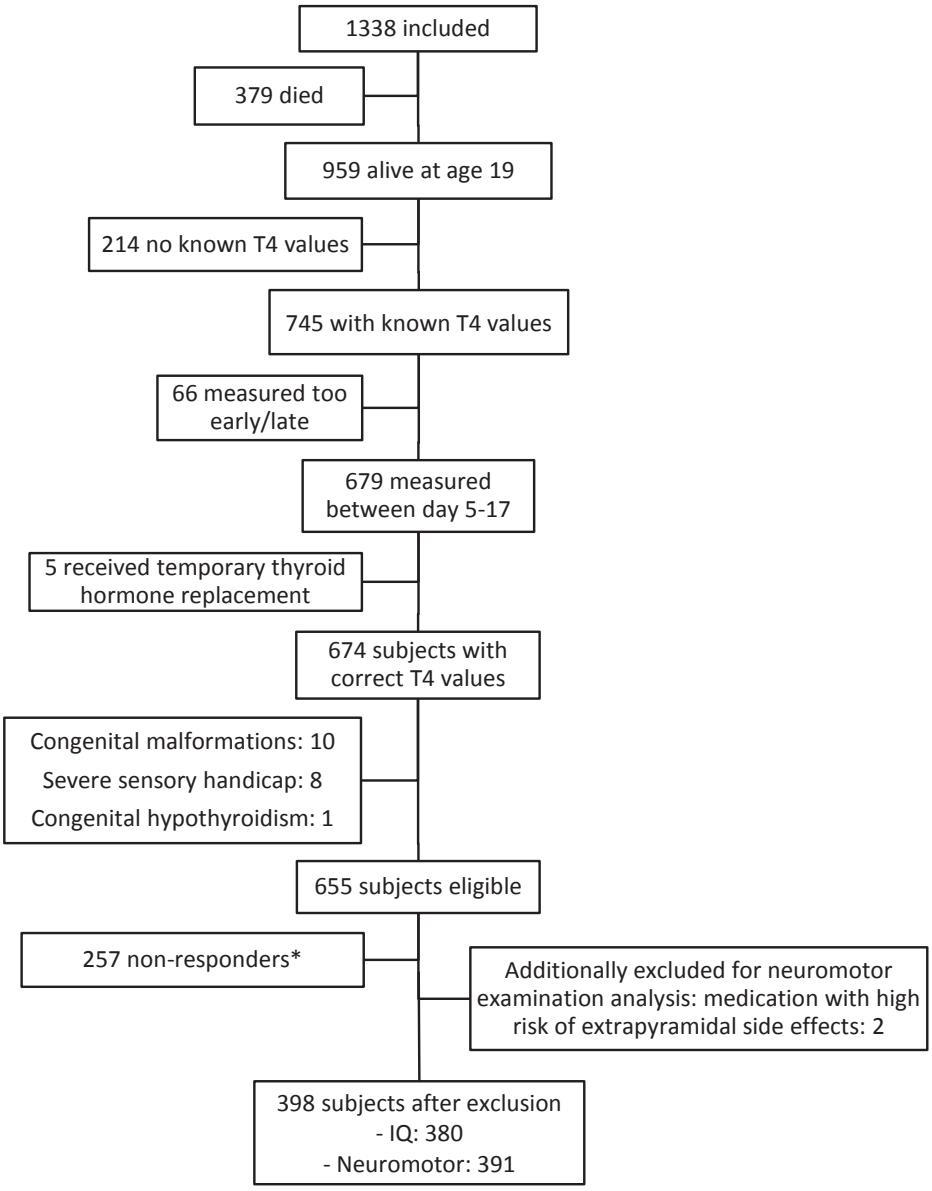

Figure 1: Flowchart of the inclusion of POPS subjects at age 19 years.
* Included in this number are subjects who only returned the (parental) questionnaires

Neuromotor performance

Neuromotor function assessment was based on a revised version of Touwen's examination of minor neurological dysfunction.[24,25] This examination focuses on five subcategories of function: hand function, quality of walking, coordination, posture, and passive muscle tone. The test comprises 34 items, each of which is scored on a 3-point scale. Two points are assigned for optimal performance, 1 point for slightly reduced performance, and 0 points for poor performance. The maximum total score is 68.

Statistical analysis

All outcomes showed fairly normal distributions. Linear regression analysis was used to study the effects of hypothyroxinemia and of T4 standard deviation score (SDS) across the entire range on continuous outcomes. Logistic regression analysis was used to study the effects of neonatal thyroid function parameters on the odds of having an IQ <85 points. Analyses were repeated after adjustment for the demographic characteristics gender, socioeconomic status (SES), ethnicity, and parity. Next, perinatal characteristics, including gestational age, being born small-for-gestational-age (SGA), and neonatal illnesses like infant respiratory distress syndrome, intraventricular hemorrhage, and sepsis, were added as covariates to the model. A *P* value of ≤0.05 was considered statistically significant.

Analyses were repeated after including only the subjects who participated in the POPS follow-up at age 5 (n=377 for IQ, n=387 for neuromotor functioning).[12] Additionally, analyses were repeated after stratification of gestational age into <and ≥ 29 weeks. This cut-off point was based on studies showing gestational age-dependent effects of levothyroxine treatment in preterm newborns.[26]

Our sample size enabled us to detect a difference of 5.0 IQ points, assuming an SD value of 15 points,[23] and a difference of 3.1 points on the neuromotor examination, assuming an SD of 9.5 points,[27] with a power of 80% and a significance level of 0.05.

RESULTS

Table 1 shows the general and perinatal characteristics of responders and nonresponders. Nonresponse was associated with male gender, non-Caucasian ethnicity, lower SES, and younger maternal age at birth. It was unrelated to the perinatal characteristics, the T4 concentration, or the proportion that exibited THoP. Hypothyroxinemia was associated with a lower gestational age and birth weight and the presence of neonatal morbidities. However, hypothyroxinemic infants were less often born SGA.

Table 1: General and perinatal characteristics of hypothyroxinemic vs. non-hypothyroxinemic groups, and of responders vs. non-responders

	Hypothyroxinemic (n=104)	**Non-hypothyroxinemic** (n=294)	***P* value***	**Non-responders** (n=257)	***P* value†**
General					
Male sex (%)	50 (48.1)	129 (43.9)	0.46	154 (59.9)	<0.001
White (%)	87 (86.1)	265 (90.4)	0.23	208 (80.9)	0.002
Low socio-economic status (%)	37 (35.9)	105 (36.0)	0.99	134 (54.3)	<0.001
First child (%)	55 (53.4)	167 (56.8)	0.55	136 (53.1)	0.48
Perinatal					
Maternal age (yrs)	26.3±4.8	27.4±6.1	0.102	26.6±5.1	0.22
Gestational age (wks)	29.4±2.2	31.3±2.4	<0.001	31.1±2.6	0.23
Birth weight (g)	1,170±241	1,297±261	<0.001	1,297±250	0.11
SGA birth (%)	27 (26.2)	127 (43.2)	0.002	100 (38.9)	0.98
Apgar score ≥7 after 5 min (%)	81 (77.9)	254 (86.4)	0.09	213 (82.9)	0.55
Part of multiple pregnancy (%)	31 (29.8)	66 (22.4)	0.13	51 (19.8)	0.18
Respiratory distress syndrome (%)	60 (57.7)	101 (34.4)	<0.001	101 (39.3)	0.77
Intraventricular hemorrhage (%)	32 (30.8)	34 (11.6)	<0.001	51 (19.8)	0.29
Sepsis (%)	45 (43.3)	80 (27.3)	0.003	86 (33.5)	0.60
Necrotizing enterocolitis (%)	7 (6.7)	17 (5.8)	0.73	10 (3.9)	0.23
Total T4 (SD)	-3.5±0.3	-2.0±0.7	<0.001	-2.4±1.0	0.75
THoP (%)	104 (100%)	0 (0%)	<0.001	72 (28.0%)	0.60

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 between hypothyroxinemic and non-hypothyroxinemic groups

† *P* value between responders and non-responders

Table 2: Associations between neonatal thyroid function parameters and neurodevelopmental outcomes at age 19 years

	Unadjusted	*P* value	Adjusted (1)	*P* value	Adjusted (2)	*P* value
T4 SDS						
IQ						
IQ total score	-1.4 (-3.1 to 0.2)	0.084	-1.3 (-2.9 to 0.4)	0.129	-1.4 (-3.3 to 0.4)	0.131
Linguistic capacity *z* score	-0.01 (-0.10 to 0.08)	0.806	-0.01 (-0.10 to 0.08)	0.819	-0.04 (-0.14 to 0.05)	0.389
Mathematical capacity *z* score	-0.09 (-0.20 to 0.01)	0.088	-0.08 (-0.19 to 0.02)	0.120	-0.11 (-0.23 to 0.01)	0.074
Logical reasoning *z* score	-0.08 (-0.18 to 0.02)	0.098	-0.09 (-0.18 to 0.01)	0.088	-0.11 (-0.22 to 0.00)	0.054
Spatial visualization *z* score	-0.03 (-0.13 to 0.06)	0.501	-0.02 (-0.11 to 0.08)	0.690	-0.03 (-0.14 to 0.07)	0.547
Neuromotor function						
Neuromotor sum score	0.3 (-0.6 to 1.1)	0.524	0.2 (-0.6 to 1.1)	0.603	-0.1 (-1.0 to 0.9)	0.904
Hand function	0.08 (-0.03 to 0.18)	0.137	0.07 (-0.03 to 0.17)	0.164	0.06 (-0.05 to 0.18)	0.280
Quality of walking	-0.02 (-0.14 to 0.10)	0.736	-0.03 (-0.15 to 0.10)	0.685	-0.08 (-0.22 to 0.06)	0.276
Coordination	0.13 (-0.34 to 0.61)	0.579	0.12 (-0.36 to 0.61)	0.614	-0.01 (-0.56 to 0.55)	0.986
Posture	0.02 (-0.11 to 0.16)	0.765	0.03 (-0.10 to 0.17)	0.636	0.00 (-0.16 to 0.15)	0.958
Passive muscle tone	0.00 (-0.18 to 0.17)	0.936	-0.03 (-0.21 to 0.15)	0.769	-0.06 (-0.27 to 0.14)	0.544

Table 2: Associations between neonatal thyroid function parameters and neurodevelopmental outcomes at age 19 years (continued)

	Unadjusted	*P* value	Adjusted (1)	*P* value	Adjusted (2)	*P* value
Hypothyroxinemia						
IQ						
IQ total score	0.0 (-3.5 to 3.5)	0.980	0.1 (-3.4 to 3.6)	0.972	0.0 (-3.8 to 3.8)	0.995
Linguistic capacity *z* score	-0.03 (-0.23 to 0.16)	0.741	0.02 (-0.20 to 0.17)	0.861	0.04 (-0.16 to 0.24)	0.692
Mathematical capacity *z* score	0.06 (-0.17 to 0.29)	0.584	0.07 (-0.17 to 0.30)	0.583	0.10 (-0.15 to 0.36)	0.429
Logical reasoning *z* score	0.07 (-0.15 to 0.28)	0.533	0.10 (-0.11 to 0.31)	0.353	0.13 (-0.10 to 0.36)	0.158
Spatial visualization *z* score	-0.10 (-0.30 to 0.10)	0.323	-0.10 (-0.30 to 0.10)	0.314	-0.08 (-0.29 to 0.14)	0.470
Neuromotor function						
Neuromotor sum score	-0.13 (-1.9 to 1.6)	0.887	0.0 (-1.8 to 1.8)	0.998	0.6 (-1.3 to 2.5)	0.544
Hand function	-0.12 (-0.34 to 0.10)	0.276	-0.10 (-0.32 to 0.12)	0.392	-0.05 (-0.29 to 0.18)	0.653
Quality of walking	0.05 (-0.21 to 0.32)	0.686	0.06 (-0.22 to 0.33)	0.683	0.13 (-0.16 to 0.43)	0.381
Coordination	0.20 (-0.82 to 1.21)	0.700	0.22 (-0.82 to 1.26)	0.676	0.50 (-0.63 to 1.63)	0.384
Posture	0.00 (-0.29 to 0.29)	0.987	-0.01 (-0.30 to 0.29)	0.970	0.09 (-0.22 to 0.41)	0.561
Passive muscle tone	-0.09 (-0.47 to 0.28)	0.626	-0.07 (-0.46 to 0.31)	0.715	-0.01 (-0.43 to 0.41)	0.967

Values represent beta (95%CI).

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

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

The hypothyroxinemic group had an IQ score of 100.8±14.9 points and a neuromotor score of 58.4±8.4 points. These scores were not different from those of the non-hypothyroxinemic group, which were 100.7±15.4 and 58.5±7.6 points, respectively. Fifty-three subjects had an IQ score <85 points.

Table 2 presents the associations between neonatal thyroid function parameters and continuous outcomes at age 19 years. No associations with total scores or subscores were found. Furthermore, neonatal thyroid function parameters were not associated with the odds of having an IQ <85 points (data not shown).

Analyses when including only the subjects who participated in the POPS follow-up at age 5 did not change our results (data not shown). Moreover, stratified analyses provided no evidence for gestational age-dependent effects of neonatal thyroid function parameters on outcomes (data not shown).

DISCUSSION

The main finding from our study is that previous observations linking THoP to neurodevelopmental outcome in infancy and childhood were not confirmed in young adulthood.

A limitation of our study is that only total T4 concentrations obtained during a single measurement were available for analysis. It is therefore possible that several participants in our study were misclassified as being hypothyroxinemic, because local tissue concentrations of unbound T4 can still be adequate despite a low circulating total T4 level.[2] Moreover, the reported SDS were based on the Dutch norm population. Although these scores do not reflect normality for prematurity, it was still possible to differentiate between lower and higher concentrations of T4. However, samples were not analyzed continuously, with means being calculated on a daily basis, which could lead to day-to-day fluctuation in the absolute level of total T4. However, laboratories were under permanent quality control,[21] and therefore these fluctuations were probably minimal.

Another limitation of our study is the loss to follow-up that is almost inevitable in life-course studies. Nonresponse was associated with male gender, nonwhite ethnicity, and lower parental socioeconomic class, but not with any of the perinatal characteristics. Moreover, both total T4 levels (-2.4 SD vs. -2.4 SD, P=0.75) and the proportion of children with THoP (26.1 vs. 28.0%; P=.60) did not differ between responders and nonresponders. Furthermore, our results did not change after statistical adjustment for many of the differing factors, as well as after analyzing the data while only including those subjects who participated at age 5. Therefore, we believe that response bias is unlikely to explain our associations. Hypothyroxinemic and non-hypothyroxinemic groups differed significantly in many perinatal characteristics, with hypothyroxinemia being associated with a greater proportion of neonatal morbidities. An explanation for these associations is

nonthyroidal illness.[2,7,8] Statistical adjustments for many of these factors did not change our results.

A recent meta-analysis showed that a birth weight <2,500 g was associated with a 4.98-point reduction in IQ at adolescence or young adulthood after taking publication bias into account.[28] This difference became smaller with increasing age. Among the studies included in the meta-analysis were several that had included only subjects born very preterm, and their results were similar. Another meta-analysis demonstrated that very preterm birth was associated with motor impairment in childhood.[29] Our data suggest that these relations cannot be explained by THoP.

A possible explanation for the lack of association in our study is that the total T4 concentration does not always reflect the availability of free T4 in tissues. However, previous analyses in the POPS cohort showed that a total T4 concentration <-3 SD was associated with adverse outcomes in childhood.[10,12] Alternatively, it could be possible that neurodevelopmental impairment after THoP improves with age, although our results should be interpreted carefully due to losses to follow-up. Therefore, replication of our findings in an independent sample is warranted, preferably in a prospectively designed study with serial measurements of free T4.[3]

It has been demonstrated in a placebo-controlled randomized trial that treatment with levothyroxine (at a dose of 8 µg/kg/d during the first 6 postnatal weeks) of infants born <30 weeks gestation does not improve long-term neurodevelopmental outcome.[15,17,18] However, it was suggested from a small subgroup analysis that treatment could be beneficial for infants in the extremely preterm range. Our study showed no evidence for a gestational age-dependent effects of THoP on IQ or neuromotor function at 19 years of age.

In a recent study among infants born <28 weeks gestation, three different doses of levothyroxine (of 4, 8, and 16 µg/kg/d for 6 wk), either continuous or as bolus, as well as iodide, were compared to placebo.[16] The groups on levothyroxine also received triiodothyronine (T3) continuously, at a dose of 1 µg/kg/d, during the first 14 days. Although mental and motor performance at age 3 years did not differ between treated and untreated children, or between the treatment arms, it was concluded that "further trials are warranted." Our findings, showing that the neurodevelopmental sequelae of THoP could not be extrapolated to young adult age, question whether new trials are necessary.

In conclusion, we did not find an association between THoP and neurodevelopmental outcome in young adulthood.

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