



## 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., <1500 g) 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 60 nmol/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.

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### 1. Introduction

Thyroid hormones are crucial for the developing brain, where they help to control cell migration, proliferation and differentiation (Zoeller and Rovet, 2004). According to the construct of Zoeller and Rovet (2004), in the first half of pregnancy, thyroid hormones play a role in the development of visual attention and process-

**Abbreviations:** CI, confidence interval; POPS, Project on Preterm and Small-for-gestational-age; THoP, transient hypothyroxinemia of prematurity; CHT, congenital hypothyroidism; YASR, Young Adult Self Report; YABCL, Young Adult Behavioral Checklist; SGA, small-for-gestational-age; SES, socio economic status.

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ing, 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 (Zoeller and Rovet, 2004). Because the fetal thyroid starts to become functional from the 12th week of gestation (Calvo et al., 2002), 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 (Morreale de et al., 2004).

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 (Auso et al., 2004; Lavado-Autric et al., 2003). In humans, functional changes in these structures

have been proposed to underlie attention deficit/hyperactivity disorder (ADHD) (Castellanos et al., 1996; Riccio et al., 1993). Indeed, small reductions in the maternal thyroid function during early pregnancy were associated with ADHD symptoms in 8-year-old offspring (Modesto et al., 2015; Pakkila et al., 2014). Similarly, the risk of developing attention problems was also increased in subjects with early-treated congenital hypothyroidism (CHT) (Rovet, 2002).

Preterm birth has been associated with attention problems and internalizing behavior. These patterns have been reported to persist into adulthood (Aarnoudse-Moens et al., 2009). 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 (Blencowe et al., 2012).

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 (Delahunty et al., 2010; Reuss et al., 1997). It can be attributed to the sudden disruption of the transplacental T4 supply (Fisher, 1998; Glinoer and Delange, 2000; Vulmsa et al., 1989). Additionally, hypothalamus-pituitary-thyroid axis immaturity, reduced thyroidal iodine reserves, acute illnesses, and treatment with dopamine also contribute to the development of THoP (Fisher, 1998; Murphy et al., 2004; Ares et al., 1997; van Wassenaer et al., 1997; Williams et al., 2005). T4 concentrations are therefore lower in extremely preterm infants than in fetuses of the same post-conceptual age (Morreale de and Ares, 1998). THoP usually restores spontaneously within 6–8 weeks (Mercado et al., 1988). 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 (Delahunty et al., 2010; Den Ouden et al., 1996; Meijer et al., 1992), the only study that had provided follow-up into adulthood was negative (Hollanders et al., 2015). 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., <1500 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 (Modesto et al., 2015; Pakkila et al., 2014; Rovet, 2002), we expected to find more problem behavior in subjects with THoP, especially attention problems.

## 2. Methods

### 2.1. Study population

The Project On Preterm and Small-for-gestational-age infants (POPS) cohort is a nationwide birth cohort study, which comprised 94% (n = 1338) 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 g (Verloove-Vanhorick et al., 1986). 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

(Meijer et al., 1992; Den Ouden et al., 1996), 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. Fig. 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 (Wiersinga et al., 2001).

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

### 2.2. Laboratory analysis

T4 was measured in the context of the neonatal screening for CHT. From April 1983 onward, results were prospectively collected (Den Ouden et al., 1996), 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 (Chopra, 1972) in the five laboratories connected to the national screening program. These laboratories were under permanent quality control (Schopman et al., 1984). T4 levels in the eluates were expressed as standard deviations from the mean, which was calculated on a daily basis (Schopman, 1979). 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 (Meijer et al., 1992; Den Ouden et al., 1996), THoP was defined as a T4 concentration of <−3SD (approximately 60 nmol/L) (Meijer et al., 1992).

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.

### 2.3. 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 18–30 years (Achenbach, 1997). 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

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