# General introduction

# General introduction

The concept of the Developmental Origins of Health and Disease postulates that early developmental events shape our future health and well-being because our organs and its functions undergo programming during embryonic and fetal life [1]. The brain is one of the organs that starts developing soon after conception. Brain development is complexly regulated by neurotransmitters and hormones, such as thyroid hormone, which is produced by the thyroid gland positioned in the front of the neck [2]. The fetus is highly dependent on the placental transfer of thyroid hormone from the mother before mid-gestation, because the fetus is not able to produce sufficient amounts of thyroid hormone itself yet [3]. Before the fetal thyroid gland is fully functional, the brain is already expressing nuclear thyroid hormone receptors, which suggests a prominent role of thyroid hormone for brain development [2]. Exposure of the fetus to insufficient concentrations of thyroid hormone may disturb brain developmental processes such as the migration, the proliferation, and the differentiation of neuronal cells [4,5]. An impressive example of the importance of thyroid hormone for fetal brain development is cretinism. Individuals with this severe condition suffered from intellectual disability, hearing and speech problems, disorders of stance and gait, hypothyroidism, and/or stunted growth. A high rate of mothers that gave birth to cretins also had abnormal thyroid enlargement, so called goiter, which made it likely that these women had a malfunctioning thyroid gland [6].

> *"Goiter is a disease which, when once acquired and not cured, can be transmitted even to the third and fourth generation of posterity, therefore people with this disease should not be permitted to indulge in parenthood"* – Quote from the Boston Medical Surgical Journal from 1918 [7].

Diffuse goiter can develop when the thyroid hormone concentration in the circulation is too low. This low concentration is "sensed" by the hypothalamus, which subsequently increases the thyroid-releasing hormone (TRH) production. TRH acts on the thyrotrophic cells of the anterior lobe of the pituitary gland and stimulates the secretion of thyroid stimulating hormone (TSH). High stimulation of the thyroid by TSH can cause the thyroid to grow with the goal to restore normal concentrations of thyroid hormone in the circulation. When TSH binds to the TSH receptor on thyroid follicular cells, the thyroid gland will synthesize and secrete two types of thyroid hormones: thyroxine (T4) and the biologically active triiodothyronine (T3). T4 and T3 circulate around in serum either bound to thyroid transport proteins or in free form (FT4 and FT3) and T3 exerts thyroid hormone action by further binding to nuclear receptors in target organs. Once the thyroid hormone concentration in the circulation reaches normal values, the release of both TRH and TSH will be inhibited. This way, a homeostatic balance of thyroid hormone concentrations in serum is reached in healthy persons.

Research from the 19th and 20th century revealed that iodine is an important trace element required for the production of thyroid hormones [8]. Historically, goiter was more prevalent in areas where drinking water had a low concentration of iodine. Hence, low iodine intake was identified as the cause of goiter. Because of this relationship, the role of iodine deficiency in the etiology of endemic cretinism was investigated. For example, a double blinded controlled trial, in which families were randomized either to a placebo or iodine treatment, found that the prevalence of goiter and cretinism was lower in those families that received an injection of iodized oil [9]. However, timing of treatment mattered. Some women that were treated in the third trimester gave birth to a cretin, while no cretins were born to mothers treated before or in early pregnancy. Thyroid dysfunction in children with cretinism could also be reversed by iodine supplementation [10]. The hypothesis therefore is that endemic cretinism is caused by an inadequate thyroid hormone transfer from mother to fetus during pregnancy, that iodine deficiency is an important risk factor, and that timely iodine intervention can prevent severe iodine deficiency disorders in the child [11]. For this reason, thyroid function tests are performed in early pregnancy and recommendations were made for higher iodine intake in pregnancy, and for routinely checking the thyroid axis in all newborns.

> *"On a worldwide basis, iodine deficiency is the single most important preventable cause of brain damage"* – ICCIDD/UNICEF/WHO [12]

Thyroid dysfunction in pregnancy is relatively common due to a change in thyroid physiology, especially in case of iodine deficiency [13]. The current guidelines recommend treating pregnant women with overt hypothyroidism, which is characterized by a high TSH and a low FT4 concentration, with levothyroxine [14]. This recommendation is based on evidence from observational studies that revealed associations of overt hypothyroidism with severe pregnancy complications [15,16], including fetal death. Untreated overt hypothyroidism has also been associated with a 7-point lower IQ score in the offspring [17]. Universal screening and treatment of women with milder forms of thyroid dysfunction is, however, not routinely performed. Subclinical hypothyroidism, characterized by high TSH and a normal FT4 concentration, has been associated with adverse pregnancy outcomes in thyroid peroxidase positive women; see an overview of studies elsewhere [14]. Depending on the TSH concentration and/or the thyroid peroxidase antibody (TPOAb) status, treatment is considered [14,18]. The evidence for an association of subclinical hypothyroidism with child neurodevelopmental outcomes is inconsistent. By contrast, isolated hypothyroxinemia, characterized by a low FT4 and a normal TSH concentration, has been associated with a variety of adverse neurodevelopmental outcomes, such as lower IQ or a delay in cognitive functioning [19–23], worse psychomotor development [21,24], schizophrenia [25], autism spectrum disorder or autistic traits [26–28], and attention-deficit hyperactivity disorder (ADHD) or related symptoms [17,28–30]. Despite the evidence from observational studies, universal screening to detect low FT4 concentrations in pregnant women

and treatment is not recommended [14], because the existing randomized controlled trials failed to show beneficial effects of levothyroxine treatment of women with hypothyroxinemia on cognitive development of the offspring [31,32]. An observational study embedded in the Generation R cohort, which involves an iodine-sufficient population, showed in addition to a low maternal FT4 concentration, that also a high FT4 concentration during pregnancy was associated with a lower child IQ score and lower gray matter volume and cortex volume in the offspring [19]. Though this is in line with findings from animal studies [33–38], it has not yet been replicated in other cohort studies and it is not known whether associations differ in countries with a different iodine status.

Reference ranges of thyroid function tests are established to identify women with abnormal thyroid function. The international thyroid guidelines advise that reference ranges should be based on the 2.5th and 97.5$^{th}$ percentile of the population with an optimal iodine intake [14]. However, there is insufficient evidence to determine whether these reference ranges are affected by iodine status. Iodine nutrition in populations is most frequently assessed by a measurement of the urinary iodine concentration (UIC) in a single spot urine sample. According to the classification of the World Health Organization, a population with a median UIC below 150 µg/L is considered iodine deficient. Mild-to-moderate iodine deficiency during pregnancy is still a common problem [39,40] and has been associated with lower scores of verbal IQ, reading accuracy, and reading comprehension [41], poorer spelling [42,43], reduced receptive and expressive language skills [44], worse executive function [45], internalizing and externalizing problems [46], poorer fine mother skills [46], and higher ADHD symptom scores [47]. However, not all prospective birth cohort studies show an association between UIC and child neurodevelopmental outcomes [48–50]. Differences in results between studies might be related to methodological differences (e.g., selected reference group and available data on confounders), the age of assessment of the neurodevelopmental outcome of interest, the timing of the iodine measurements, and the severity of iodine deficiency in the population. What remains unknown is whether the association of maternal iodine status with child neurodevelopmental outcomes varies during different periods of gestation and what the consequences of iodine excess are for child neurodevelopment.

# Objectives

The aims of this thesis are:

1. To explore the determinants of iodine status during early pregnancy in populations of differing iodine status.
2. To assess the association between maternal iodine status and maternal thyroid function during pregnancy in a mild-to-moderate iodine deficient population and to determine variation in thyroid function reference ranges according to iodine status.

3. To assess the association maternal iodine status with childhood IQ, autistic traits, and ADHD symptoms in populations of differing iodine status.
4. To assess the association of maternal thyroid function with childhood IQ, autistic traits, and ADHD symptoms in populations of differing iodine status.

# Setting

Most studies presented in this thesis are embedded within the EUthyroid project entitled "Towards the elimination of iodine deficiency and preventable thyroid-related diseases in Europe". For this three-year Horizon 2020 project, which started in June 2015, data were harmonized and combined from three major European prospective birth cohort studies: INfancia y Medio Ambiente (INMA, Spain), Generation R (the Netherlands), and Avon Longitudinal Study of Parents and Children (ALSPAC, United Kingdom). These cohort studies had detailed information on maternal iodine status, thyroid function during pregnancy, and child neurodevelopmental outcomes and were selected because of the differing iodine status in these populations, ranging from iodine sufficiency to mild-to-moderate iodine deficiency. Not part of the EUthyroid project was the Swedish Environmental Longitudinal, Mother and child, Asthma and allergy (SELMA) cohort. This cohort study had information on maternal iodine status and more extensive data on thyroid function tests during pregnancy (e.g., TSH, (F)T4, (F)T3, and markers of thyroid autoimmunity) than INMA, Generation R, or ALSPAC. Data on child neurodevelopmental outcomes in SELMA could however not be used. These four cohort studies were designed to study the role of early environmental or genetic causes of normal and abnormal development from fetal life onwards. Combining individual-participant data of multiple cohorts permits hypothesis testing on a larger scale, may overcome difficulties associated with individual studies (e.g., low statistical power, range restriction), and may increase our confidence in the generalization of the results when it replicates the findings of individual studies. Hence, this thesis may provide an opportunity to generate a trustworthy foundation for conclusions and scientific progress.

## INMA

INMA is a network of birth cohorts in Spain of which three birth cohorts were included in this thesis: Valencia, Sabadell, and Gipuzkoa [51]. Pregnant women were recruited in Valencia between November 2003 to June 2005, in Sabadell from July 2004 to July 2006, and in Gipuzkoa from April 2006 to January 2008 during the first pre-natal visit. INMA was used for the analysis of the first, third, and fourth aim of this thesis.

### Generation R

The Generation R study is a population-based birth cohort study in Rotterdam, the Netherlands [52]. Pregnant women with a delivery date from April 2002 until January 2006 were eligible for participation. Enrollment was possible throughout gestation. Generation R was used for the analysis of the first, third, and fourth aim of this thesis.

### ALSPAC

ALSPAC is a population-based birth cohort in Avon, United Kingdom [53,54]. Pregnant women with an expected date of delivery between April 1991 and December 1992 were eligible for inclusion (phase I). After pregnancy, additional recruitment phases (II and III) took place to enroll those who would have fitted the original eligibility criteria. All mother-child pairs that were recruited during pregnancy were used for the analysis of the first, third, and fourth aim of this thesis.

### SELMA

The SELMA study is a population-based longitudinal prospective cohort study in the county of Värmland, Sweden [55]. Pregnant women were recruited from September 2007 to March 2010 during the first prenatal visit at an antenatal care center around week 10 of pregnancy. Women beyond week 22 in their pregnancy were excluded from the SELMA study. This study was only used for the second aim of this thesis.

## Outline

Chapter 2 explores the determinants of iodine status in populations of differing iodine status. Chapter 3 focuses on the association between maternal iodine status and maternal thyroid hormone concentrations in a mild-to-moderate iodine deficient pregnant population from the SELMA study and variation in reference ranges by iodine status is investigated. In chapter 4, we study the associations of maternal iodine status during pregnancy with child neurodevelopmental outcomes. Chapter 4.1 describes the association of maternal iodine status with child IQ, while chapter 4.2 evaluates the association of maternal iodine status with child ADHD and autistic traits. Chapter 5 evaluates the association of maternal thyroid function with child neurodevelopmental outcomes. In chapter 5.1, we examine the association of maternal thyroid function with child IQ and autistic traits. In chapter 5.2, the association of maternal thyroid function with child ADHD is assessed. In chapter 6, the main findings are summarized, and the clinical implications and direction for future research are described. Finally, a summary of this thesis is included in chapter 7.

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