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**MARJO KARVONEN**

# MODERN AUXOLOGICAL METHODS FOR HEAD CIRCUMFERENCE GROWTH MONITORING

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## ABSTRACT

Head circumference (HC) reflects brain size in childhood, especially from birth to 6 years of age. Measuring HC is neither complicated nor costly, and HC monitoring is used globally to detect disorders causing either macro- or microcephaly. The World Health Organization (WHO) published multinational HC growth charts in 2007 that intend to depict optimal HC growth irrespective of ethnic background. Many countries have produced their own HC growth charts too. In Finland, the HC charts used before this study were based on a longitudinal HC study of 130 children born between 1953 and 1964. It remains unclear which HC reference should be used in HC growth monitoring and whether they should be updated periodically. Furthermore, evidence-based methods for HC screening are lacking.

The aims of this study were first to construct up-to-date, population-based HC references for Finnish children from birth to 7 years, and then to define the limits of normative HC growth using two model diseases: hydrocephalus and neurofibromatosis 1 (NF1), in which the former represents acceleration in HC growth or macrocephaly and the latter represents macrocephaly especially in proportion to height. The third aim was to describe offspring head growth in childhood after a common environmental factor, maternal smoking during pregnancy.

The study population used in this study to construct new Finnish HC reference charts was from the Espoo primary care and consisted of 19,715 children born from 1986 to 2008 and their growth data from birth to 7 years old. Data for the model diseases (hydrocephalus and NF1) were collected retrospectively from the records of patients at three tertiary centers. These cohorts consisted of 80 children with NF1 (HC growth from birth to age 7 years) and 61 children with hydrocephalus who had undergone cerebrospinal fluid diversion surgery before the age of 2. Data for childhood HC growth after maternal smoking during pregnancy were collected on 43,632 children from Espoo primary care and the Finnish Medical Birth Register maintained by the Finnish Institute for Health and Welfare.

In the new Finnish HC reference, there was a positive secular change compared with the former HC reference. In the new reference, the HC median was higher than the former reference during the first year of life and after the second year of life. Another difference was that the SD of the HC was larger in the new reference compared with the former reference. Finnish children had also larger heads compared with the WHO and American Centers for Disease Control and Prevention (CDC) HC references. In the NF1 cohort, an elevated (≥ 2 SDS) HC-to-height ratio (HCHR) is an early, characteristic feature compared with healthy children. At the median age of diagnosis (3.6 years), an elevated HCHR was the second most prevalent feature after café au lait macules compared with clinical diagnostic criteria. For hydrocephalus screening, the population-based (Finnish) reference was more accurate than the WHO standard, and the best diagnostic accuracy was obtained by using the new screening parameter HC SDS change over time, which was based on modeling HC growth in a healthy child population. The accuracy of the WHO standard could be augmented to the same level using population-specific HC cut-offs and combining screening by HC and HC SDS change. The HC growth of children exposed to maternal smoking during pregnancy experienced incomplete catch-up growth during their first 6 months of life and their HC was deficient up to 6 years old and will likely remain as such permanently.

This dissertation has provided new HC references for Finnish boys and girls from birth to 7 years old and established that HC should be updated periodically. Population-based references are more accurate than multi-ethnic standards. This study also characterized HC growth during childhood after exposure to maternal smoking during pregnancy and provided evidence-based methods for detecting aberrant HC growth.

**National Library of Medicine Classification**: QS 675, QZ 380, WE 705, WL 350, WS 103, WS 104

**Medical Subject Headings**: Child; Infant; Growth Charts; Cephalometry; Head/growth and development; Hydrocephalus; Microcephaly; Neurofibromatosis 1; Neonatal Screening; Finland

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## TIIVISTELMÄ

Lapsen päänympärys kuvastaa kasvavien aivojen kokoa. Päänympäryksen mittaaminen on helppo ja halpa seulontamenetelmä, jota käytetään maailmanlaajuisesti pään suuri- tai pienikokoisuutta eli makro- tai mikrokefaliaa aiheuttavien sairauksien tunnistamiseen. Mitattua päänympärystä tarkastellaan kasvukäyrien avulla. Vuonna 2007 Maailman terveysjärjestö (WHO) julkaisi monikansalliset päänympäryskäyrästöt, joiden tarkoituksena on kuvata ihanteellista päänkasvua lapsuusiässä riippumatta kansallisuudesta. Monissa maissa on muodostettu omia päänympäryskäyrästöjä. Aiemmat suomalaiset käyrät ennen tätä väitöstutkimusta oli laadittu yhteensä 130:n vuosina 1953–1964 syntyneen lapsen kasvutietojen pohjalta. Ei tiedetä, mitkä kasvukäyrät soveltuvat parhaiten kuvaamaan suomalaisten lasten pään kasvua ja tulisiko käyriä uusia aika ajoin. Lisäksi päänympäryskasvun seurantaan ei ole ollut käytössä näyttöön perustuvia seulontarajoja, joiden avulla erotetaan normaali kasvu poikkeavasta kasvusta.

Tämän väitöstutkimuksen tavoitteina oli laatia väestöpohjaiset päänympäryskäyrät suomalaisille lapsille ja tarkastella niiden soveltuvuutta verrattuna muihin laajasti käytössä oleviin päänympäryskäyriin (WHO:n käyrät ja amerikkalaiset CDC:n käyrät, Centers for Disease Control and Prevention) sekä tutkia poikkeavan päänympäryskasvun seulontarajoja

kahden päänympäryksen kasvuun vaikuttavan mallisairauden avulla. Nämä olivat hydrokefalus ja neurofibromatoosi 1 (NF1), joista edellinen edustaa makrokefaliaa tai päänkasvun kiihtymistä ja jälkimmäinen makrokefaliaa erityisesti suhteessa pituuteen. Kolmantena tavoitteena oli kuvata laajassa väestöpohjaisessa aineistossa äidin raskauden aikaiselle tupakoinnille altistuneiden lasten päänympäryksen kasvua.

Uuden suomalaisen päänympäryskäyrästön muodostamiseen käytettiin Espoon perusterveydenhuollon 19 715 lapsen kasvuaineistoa. Lapset olivat syntyneet 1986–2006, ja kasvutietoa oli syntymästä seitsemään ikävuoteen. Mallisairausaineistot kerättiin kolmesta yliopistosairaalasta: 80 lasta, joilla oli NF1 (kasvun seuranta seitsemään ikävuoteen asti) ja 61 hydrokefaluslasta, jotka oli leikattu ennen kahta ikävuotta. Äidin raskausajan tupakoinnille altistuneiden 43 362 lapsen kasvu- ja muut taustatiedot saatiin Espoon perusterveydenhuollosta, Terveyden ja hyvinvoinnin laitoksen ylläpitämästä Syntyneiden lasten rekisteristä sekä Tilastokeskuksesta.

Vuosien 1986–2008 päänympäryskäyrästöjen kohortissa oli havaittavissa ajan oloon tapahtunutta muutosta verrattuna vuosien 1953–1964 kohorttiin. Uusien käyrien mediaani oli ensimmäisellä ikävuodella ja toisen ikävuoden jälkeen isompi kuin vanhoilla käyrillä. Vanhoissa käyrissä keskihajonta oli laajempi mm. pienemmän otoskoon takia. Suomalaisten lasten päänympärykset olivat suurempia verrattuna WHO:n ja amerikkalaisiin käyriin. NF1-lapsilla kohonnut päänympäryspituussuhde (≥ 2 SDS) oli tavallinen ja varhainen löydös. Keskimääräisessä diagnoosi-iässä (3,6 vuotta) kohonnut päänympäryspituussuhde oli toiseksi yleisin NF1-piirre verrattuna käytössä oleviin NF1:n diagnostisiin kriteereihin, maitokahviläikkien jälkeen. Hydrokefaluksen seulonnassa suomalainen päänympärysreferenssi oli tarkempi kuin WHO:n käyrästö, ja paras seulontatarkkuus saavutettiin käyttämällä uutta, terveiden lasten päänympäryskasvuun perustuvaa standardoitua päänympäryksen muutoksen seulontamenetelmää. WHO:n standardi saavutti yhtä hyvän seulontatarkkuuden, kun käytettiin väestönmukaisia päänympäryksen seulonnan katkaisurajoja ja yhdistettiin tähän päänympäryksen kasvun muutosseula. Raskausaikana tupakoineiden äitien lapsilla oli

päänympäryksessä saavutuskasvua ensimmäisen puolen ikävuoden aikana, mutta päänympärykset jäivät koko kuuden vuoden seuranta-ajan pienemmiksi kuin tupakoimattomien äitien lapsilla. Ero on todennäköisesti pysyvä, koska merkittävin päänkasvu on tapahtunut jo kahden ensimmäisen ikävuoden aikana.

Tässä tutkimuksessa luotiin uudet päänympäryksen kasvukäyrät suomalaisille tytöille ja pojille syntymästä seitsemään ikävuoteen ja osoitettiin, että päänympäryskäyrät on tärkeä säännöllisesti päivittää ajankohtaisiksi ja muodostaa siitä väestöstä, jossa niitä käytetään. Lisäksi tässä tutkimuksessa kuvattiin päänympäryksen kasvutapa lapsilla, jotka olivat altistuneet äidin raskausaikaiselle tupakoinnille. Tutkimuksessa luotiin myös näyttöön perustuvia menetelmiä poikkeavan nopean tai suuren päänkasvun tunnistamiseksi.

**Luokitus**: QS 675, QZ 380, WE 705, WL 350, WS 103, WS 104

**Yleinen suomalainen ontologia**: lapset; fyysinen kehitys; pää; kasvu; mitat; seuranta; kasvuhäiriöt; neurofibromatoosi; hydrokefalia; mittausmenetelmät; seulonta

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Marjo Karvonen

# LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications:

I Karvonen M, Hannila M-L, Saari A, Dunkel L. New Finnish reference for head circumference from birth to 7 years: Ann Med. 44:369-74,2012.

II Karvonen M, Saari A, Hannila M-L, Lönnqvist T, Dunkel L*, Sankilampi U*. Elevated head circumference-to-height ratio is an early and frequent feature in children with neurofibromatosis type 1: Horm Res Paediatr. 79:97-102, 2013.

III Karvonen M, Saari A, Lamidi M-L, Selander T, Löppönen T, Lönnqvist T, Dunkel L, Sankilampi U. Screening of hydrocephalus in infants using either WHO or population-based head circumference reference charts. Acta Paediatr. 2021; 110: 881-888.

IV Karvonen M, Saari A, Sund R, Sankilampi U. Maternal smoking during pregnancy and offspring head growth in comparison to height and weight growth up to 6 years of age: a longitudinal study. Clin Epidemiol. 2021;13:959-970.

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# CONTENTS

# ABBREVIATIONS

| | |
|---|---|
| AGA | Appropriate for gestational age |
| DQ | Developmental quotient |
| ELBW | Extremely low birth weight |
| HC | Head circumference |
| IGF | Insulin-like growth factor |
| IQ | Intelligence quotient |
| LBW | Low birth weight |
| SGA | Small for gestational age |
| SD | Standard deviation |
| SDS | Standard deviation score |
| VLBW | Very low birth weight |

# 1 INTRODUCTION

Head circumference (HC) is a reliable index of brain size and growth in infancy and early childhood (1-5). Repeated measurements of HC through infancy and early childhood have been included in preventive child health care programs in both developed and developing countries for nearly a century (6). The aim of HC screening is the timely diagnosis of treatable conditions that affect head growth. Screening for disorders by measuring HC growth is inexpensive and non-invasive, yet evidence-based methods for HC growth screening are scarce.

The Finnish HC growth charts used prior to the present thesis were in use until 2015. They were constructed based on HC measurements taken from birth to 10 years of age among 130 children born between 1953 and 1964 (7). A positive change in mean HC across generations has been described in many countries (8-11) and, as such, represents a secular trend. Multinational and multiethnic HC charts intended for global use were first generated by Nellhaus in 1968 (12) and then also in 2007 by the World Health Organization (WHO) (13). However, significant differences between population-based HC charts and the multiethnic WHO HC standards have been reported in many countries (14-17).

In infancy, from birth to the closure of cranial sutures (18), hydrocephalus may manifest as a pathological enlargement of HC or as frank macrocephaly (HC > 2 SDS) before any other signs or symptoms. Thus, it can be detected by an enlargement or accelerated growth in HC (19). On the other hand, multiple environmental and genetic factors can affect HC growth possibly leading to microcephaly (HC < -2 SDS). Among the most prevalent environmental causes, maternal smoking during pregnancy is associated with reduced intrauterine fetal head growth.

The aims of this study were, first, to construct up-to-date, population-based HC references for Finnish children from birth to 7 years old. The second aim was to define limits between typical and abnormal HC growth by age and develop mathematical algorithms (screening rules) for abnormal head size and growth over time. These screening rules were

tested in two disease models, hydrocephalus and neurofibromatosis 1 (NF1); the former involves accelerated HC growth or macrocephaly and the latter macrocephaly especially in proportion to height. The third aim was to analyze head growth in childhood after exposure to maternal smoking during pregnancy, which decreases head growth prior to birth.

# 2 REVIEW OF THE LITERATURE

## 2.1 GROWTH OF HEAD CIRCUMFERENCE

### 2.1.1 Typical HC growth

HC is a reliable index of brain size from birth to 6 years, and a moderate index of brain size in childhood thereafter (1-5). HC growth is driven by underlying brain growth. The majority of the intracranial volume increase and brain growth takes place during the first 2 years after birth (20,21). The fastest growth in HC occurs during the first six months of life, then HC growth slows down gradually until the first birthday, after which it slows down further. During the first year of life, HC reaches around 80% of its final size (12,22,23).

In a study of head growth between 1 (n = 35) and 18 (n = 103) years of age (22), the mean HC in both sexes reached 87.5% of its adult size by one year of age, and by 5 years of age, it reached 93.9% of its adult size. They defined the point at which each head growth measure reached its full maturation as the age when the 95% confidence interval of the mean HC overlapped with the 95% confidence interval of the mean HC at 18 years of age. For HC, this point was 15 years of age in males and 13 years in females (22).

When creating standardized metrics, it is necessary to observe the pattern of healthy brain growth. Dekaban found that maximum brain weight is reached around the age of 19 years (20). According to this postmortem study, brain weight grows up to four times its size at birth during the first three years of life and barely reaches five times its birth size in the subsequent 15 years. After 45-50 years of age, a progressive decline in brain weight occurs. The brain reaches around 70% of its adult size during the first year of life and, after 2 years, is roughly 80% of its adult size (20,24).

Furthermore, a magnetic resonance imaging (MRI) study of brain volume revealed that brain volume grows by 25-27% from approximately 2

until 15 years, when maximum brain volume is achieved (25), and declines thereafter. Similar results were reported by Sgouros et al. (21) in an MRI study on intracranial volume changes from birth up to 15 years old. They showed that intracranial volume reaches 77% of the volume observed at age 15 by age 2 and 90% by age 5. Moreover, they found a segmental pattern of growth in intracranial volume occurring in three approximately five-year phases: 0 – 5, 5 – 10, and 10 – 15 years of age. During each period, intracranial volume growth is linear, but the rate of this growth differs in each period (21). The first period is associated with the fastest growth, the second is much slower, and the final period involves a mild spurt.

Furthermore, no significant change in the total brain volume was observed from 5 to 17 years of age in a neuroimaging study of 85 children and adolescents (26). However, they did identify a positive correlation between age and white matter volume and a negative correlation between age and grey matter volume. Reiss (1996) et al. observed a gender-based difference in total brain volume with boys having approximately 10% larger total brain volumes than girls. This gender-based difference was related to a larger volume of grey matter observed in boys. However, these analyses of the differences between boys and girls were not adjusted for body size. The difference between boys and girls in intracranial volume and brain size is consistent in the literature with boys having larger intracranial volumes or brain weights than girls (20,21,25). This finding coincides with the observed parallel HC growth patterns of boys having larger HCs than girls (12,13,27).

Macrocephaly refers to a large head, specifically, an HC more than 2 SDS over the mean. Microcephaly refers to a small head, usually defined as an HC more than 2 SDS under the mean. These designations of macro- and microcephaly are discussed in more detail in chapters 2.2.1 Genetic disorders and 2.3.2 HC growth references.

**Role of heritability in HC growth**

Longitudinal twin studies revealed, that in the first 3 months of life, environmental factors impact HC variability more than genetic ones (28,29). Thereafter, genetic factors outweigh environmental ones in

mediating HC growth. The maximum heritability estimates from these studies are 90% at 4-8 months of age (29) and 70% at 9 to 11 months of age (28,30). Taken together, these studies have shown that HC growth is strongly regulated by genetic factors during the first year of life (28,30) and later even into adulthood (29).

**Brain growth and development and main growth factors**

During the first half of gestation, prenatal brain development is dominated by neurogenesis and neuronal migration, while the latter half largely involves myelination, cortical cytoarchitectural maturation, and a burst of synaptogenesis (31-33). Moreover, the third trimester is governed by an increase in fetal brain volume (34). Postnatal brain development consists of a rapid process of axon outgrowth, axon, and dendrite branching, synaptic formation, gliogenesis, and myelination, all of which take place during the first year of life, thereby enlarging the brain and head size in a fast manner (32). Myelination and synaptic remodeling and pruning continue into early adulthood.

While many growth factors regulate metabolism and tissue growth, the insulin-like growth factor 1 (IGF-1) pathway (i.e., IGF-1 and its receptor, IGF-1R) predominates in the regulation of brain growth and development *in utero* and postnatally (35-38). IGF-1 is a hormone secreted in the liver under the control of growth hormone for endocrine functions. In addition, IGF-1 is produced in most tissues for autocrine and paracrine functions in the fetus and postnatally (39,40). Growth hormone and nutrition regulate IGF-1 secretion in the liver and other tissues (41,42). The pituitary secretion of growth hormone is controlled by the hypothalamus through inhibitory hormone somatostatin and stimulatory growth hormone-releasing hormone (GHRH). IGF-1 exerts negative feedback on the hypothalamus by inhibiting growth hormone release (38). In utero, however, IGF-1 secretion is stimulated by estrogen rather than growth hormone (43). The placenta secretes IGF-1 throughout gestation, but it is not clear whether placental-derived IGF-1 is secreted into fetal circulation (44,45). Late in gestation, the circulating IGF-1 is mainly secreted by the liver (46).

From animal studies, we know that IGF-1 mRNA is present in all cell types in the fetal and juvenile brain and declines thereafter (47). The IGF-1 pathway stimulates the proliferation of neural progenitors, the differentiation and survival of neurons, olidendrocytes, and astrocytes, synapse formation, and myelination in pre- and postnatal states (35,48,49). Much of IGF-1's actions are exerted in an auto- or paracrine way in the developing brain and vary according to both region and time (48,50,51).

Postnatally, we know that serum IGF-1 concentration is associated with nutritional state, i.e., with dietary protein and total energy intake (36,37,52,53). Studies of very preterm infants indicate that good HC growth positively correlates with early postnatal energy intake (54-56). Furthermore, good weight gain and HC growth before hospital discharge correlate with a positive neurocognitive outcome in childhood (55,57-59) and young adulthood (60). In Brandt et al. (2003), good early postnatal energy intake (days 2 to 10) in very-low-birth-weight small for gestation age SGA children was positively associated with both good HC catch-up growth 6 to 12 months after term and with developmental and intelligence quotients from 18 months to 6 years (54). Furthermore, in a study of 49 very preterm infants, the rate of increase in circulating IGF-1 concentration from birth to 35 weeks of postmenstrual age was positively correlated with brain volume and developmental outcome at 2 years of corrected age (61). However, good early postnatal energy and protein intake is not the only key to adequate growth and brain maturation because, in very preterm infants, due to their unmatured metabolism, the utilization of nutrients may be inadequate, thus leading to lowered IGF-1 concentrations and bioavailability (53).

Although the IGF-1 pathway is a crucial mediator in the growth, development, and maturation of the human brain, the role and underlying mechanisms of IGF-1 have not yet been fully explained. The auto- and paracrine actions of IGF-1 in the brain combined with the dynamic nature of its actions, render it difficult to study *in vivo* in humans (48,50,51). Our knowledge of the actions of IGF-1 on brain growth and development is almost exclusively based on animal studies. What we know about IGF-1's actions in the human brain have mostly been deciphered from reports of

defects in IGF-1-signaling (62,63). Therefore, the nuances and details of the function of the IGF-1 in the human brain have yet to be unveiled.

### 2.1.2 Catch-up growth

Concerning height growth, catch-up growth has been defined as the phenomenon of growth acceleration after restricted growth, usually in reference to postnatal growth after intrauterine growth restriction (64). For HC growth, the criteria for catch-up growth have not yet been specifically defined. The criteria for catch-up growth in height are defined in many terms; for example, a change of +0.67 SDS in a certain time period has been used, or attaining the normal range of height (>- 2 SDS or > 3 rd percentile) (65). These criteria have been variously applied in defining catch-up growth in HC. Catch-up growth in HC is sometimes defined more generally as an acceleration of growth reaching the normal range of HC growth velocity. Catch-up growth of HC has been reported to occur during the first 6-12 months of life in infants whose HC was reduced at birth due to intrauterine growth failure including prenatal exposure to maternal smoking, and/or preterm birth (54,66-77). Also, normative HC growth is fastest during the first 6 months of life.
In the children born small for gestational age (SGA) and/or preterm, good HC growth close to the normal range during the first 6-12 months of life has been correlated with a favorable neurodevelopmental outcome in adulthood (54,70,74,76,78-82). HC growth during the first year of life plays a crucial role in the neurodevelopment of the child (27,70,74,83,84). In a study by Ghods et al. (2011) on growth in SGA children, catch-up growth in HC was defined as an increment of 0.67 SDS between birth and 3 months (84). After the period of catch-up growth, which lasted 3 months, the children who had exhibited catch-up growth continued to have a higher HC up to the end of the follow-up at age 5.5 years compared with those without catch-up growth. In another study, compensational HC growth after the first year of life did not improve the neurodevelopmental outcome (27,74). Furthermore, the correlation between first-year HC

growth and cognitive outcome has mostly been stronger than that of birth HC in preterm, SGA, and term-born children. The association between birth HC and neurocognitive outcome is most often non-existent in the first place or disappears with age (27,70,71,74,83).

## 2.2 CONDITIONS AFFECTING HEAD CIRCUMFERENCE GROWTH

### 2.2.1 Genetic disorders

There is a large number of heterogenic genetic disorders that cause either macrocephaly (> 2 SDS above the mean) or microcephaly (< - 2 SDS below the mean). Mild macrocephaly or microcephaly are relatively common with a shared prevalence of approximately 5% by definition; therefore, microcephaly is often assigned in studies and in practice as an HC below – 3 SDS. These limits for micro- or macrocephaly are somewhat arbitrary since the populations of micro- and macrocephalic children usually include asymptomatic children with an IQ in the typical range (85-87). Instead of frank macro- or microcephaly in each affected individual, in many syndromes, there is a tendency toward a larger or smaller HC than in the general population. This is the case in the autosomal dominant neurocutaneous disease, neurofibromatosis type 1 (NF1, MIM # 162200) (88,89), where the distribution of HC is shifted toward a larger HC in the NF1 population compared with the general population. Of course, in an affected population, also the proportion of individuals with an HC crossing the threshold of either +2 SDS or – 2 SDS is elevated.

Macrocephaly is often genetic, and it may be syndromic or arise from multifactorial genetic background e.g., autism spectrum disorder-related macrocephaly or familial macrocephaly (90,91). Macrocephaly in general is associated with cognitive deficits. In many cases, they both are co-existing manifestations of a genetic syndrome, e.g., Sotos (MIM # 117550), NF1, storage diseases, and other metabolic disorders (91).

Microcephaly often derives from a genetic cause either as an isolated condition, e.g., genetically heterogenic autosomal recessive primary microcephaly (MIM # 251200) or as part of a syndrome, e.g., Williams

syndrome (MIM # 194050) (85,92). Microcephaly is generally associated with an increased risk of subnormal IQ or mental retardation (85,92-96), although most of these studies are based on mixed populations of cases with both genetic and environmental disease etiology. Also, the degree of microcephaly correlates with the severity of cognitive impairment (85,93,95,96). Nevertheless, no direct relationship between HC and cognitive ability has been observed (97,98).

### 2.2.2 Acquired conditions restricting HC growth

Among the several acquired conditions causing intrauterine and/or postnatal growth restriction in HC are perinatal hypoxic-ischemic insults and infections, teratogens like alcohol, antiepileptic drugs, and maternal endocrinologic disturbances (85).
In a study from the UK of 52 term-born infants with hypoxic-ischemic encephalopathy (HIE), there were no differences in neonatal HC between the affected and control infants, but at 12 months, 48% of infants with HIE had developed microcephaly compared with 3% of the controls (99). In 53% of the infants with HIE, a drop of 2 SDS in HC growth occurred during the first year of life compared with 3% in the control group. A randomized, controlled follow-up study on therapeutic hypothermia in HIE reported a statistically non-significant difference in HC between 98 treated and 86 control children (100). The children in the hypothermia group had a 0.4 SDS larger mean HC (from birth to six or seven years of age) compared with that in control children (P-value = 0.22).
Alcohol is a known teratogen, and maternal alcohol use during pregnancy causes reduced brain size and HC from birth through young adulthood (101-104). The severity of alcohol-related growth restriction correlates with the severity of the prenatal alcohol exposure and, further, with the neurocognitive outcome (103,104).

#### Exposure to maternal smoking in pregnancy

In Finland, the prevalence of maternal smoking during pregnancy after the first trimester was 10.5% between 2000 and 2015 (105). Maternal smoking

during pregnancy is a firmly established risk factor for intrauterine growth restriction in both body size and HC (67,68,77,106-119).

The mediating mechanisms between prenatal maternal smoking exposure and offspring HC growth restriction have not been fully elucidated. Lower cord plasma concentrations of IGF-1 have been measured in newborns exposed prenatally to tobacco compared with unexposed newborns (113,120). In rats, prenatally administered nicotine resulted in reduced amounts of total brain DNA, which reflected a reduced total cell number compared with controls. Furthermore, biomarkers of cellular damage (e.g., ornithine decarboxylase activity) have been elevated in the brain (121). Additionally, prenatal nicotine exposure enhances susceptibility to apoptosis (122). In addition to the direct effects of nicotine, the effects of smoking exposure on the fetus may be exerted by several indirect pathways, e.g., hypoxic-ischemic insults through the placenta due to increased carbon monoxide and carboxyhemoglobin and reduced blood flow (123,124). Smoking exposure also disturbs transplacental amino acid transport, which has been observed in intrauterine growth restriction in general (125). This may be at least in part due to decreased concentrations of IGF-1 because IGF-1 stimulates amino acid uptake in human placental trophoblasts *in vitro* (126).

Catch-up growth in HC after exposure to maternal smoking during pregnancy seems to occur during the first 6 to 12 months of life (66-68,72,77,108,127,128). In the literature, this catch-up growth in HC after prenatal smoking exposure has been either complete (66-68,77) or incomplete (108,114,128). Thus, the duration of HC growth restriction after exposure to maternal smoking during pregnancy has not been defined.

### 2.2.3 Acquired conditions increasing HC growth

The most important disorder detected behind macrocephaly or enlarging HC is hydrocephalus, which eventually leads to neurological injury and death if left untreated. Hydrocephalus may be present at birth or occur later. Most of the childhood hydrocephalus cases are congenital and occur during the first year of life, with a prevalence of approximately 0.8-1.1/1000

live births (19,129). In infancy up to approximately 2 years of age, the cranium can adjust to an elevated intracranial volume via open cranial sutures and fontanelles (18,130). Therefore, in infants, HC growth may be accelerated before other symptoms or even macrocephaly develop and thus the condition may be found by HC screening.

Another underlying cause of macrocephaly may be the benign enlargement of subarachnoid spaces (BESS) (131-133), which is sometimes called or can develop into benign external hydrocephalus (131-133). Benign external hydrocephalus seldom needs more than observation, but a transient delay in neurodevelopment may be present (131). Intracranial cysts may enlarge HC in infancy, but these are much rarer than hydrocephalus underlying a true HC enlargement (19).

## 2.3 MONITORING OF HEAD CIRCUMFERENCE GROWTH

### 2.3.1 Goals of HC growth screening

HC is measured as a part of general growth monitoring together with length/height and weight measurements in childhood, especially during infancy in growth-restricted conditions. HC is assessed together with length/height growth also when diagnosing syndromes or diseases that affect the aforementioned auxological measures or their proportionality to each other. HC is assessed independently to detect conditions affecting mainly HC growth, e.g., hydrocephalus may be detected by accelerated HC growth in infancy.

Growth screening aims to detect pathological conditions affecting growth at an early stage. Anthropometric measurements are a straightforward, non-invasive, and inexpensive means of screening. Growth screening should be evidence-based to establish reliable cut-offs for normative and abnormal growth. Screening is always a trade between sensitivity and specificity because when the latter increases, the former will decline and vice versa. To understand the essentials of screening, it is necessary to know some basic concepts on which the calculations of sensitivity and specificity are based, i.e.,

True positive (TP): the patient has the disease, and the test is positive.
False positive (FP): the patient does not have the disease, but the test is positive.
True negative (TN): the patient does not have the disease, and the test is negative.
False negative (FN): the patient has the disease, but the test is negative.
Sensitivity, i.e., the true-positive rate (TPR), is defined as

$$\text{TPR} = \frac{TP}{(TP+FN)}$$

Specificity, i.e., the true-negative rate (TNR), is defined as

$$\text{TNR} = \frac{TN}{(TN+FP)}$$

Thus, the sensitivity describes the portion of the population with the disease that the test classifies correctly as being sick, and the specificity describes the portion of the healthy population that the test classifies correctly as being healthy.

### 2.3.2 HC growth references

HC is measured as the maximum occipitofrontal diameter to the nearest 0.1 centimeter, using a non-stretchable tape (134).
The measured HC value (in centimeters) is converted into a standard deviation score (SDS) or a percentile value using an HC reference. The HC value in centimeters (cm) is plotted by age on the sex-specific HC growth chart. Also, a growth chart software using integrated reference values can be used. The SDS is calculated as

$$\text{SDS} = \frac{measured\ HC\ (cm) - mean\ HC\ (cm)\ for\ age\ and\ sex}{SD\ for\ age\ and\ sex}$$

where mean HC for age and sex and SD for age and sex are obtained from the HC reference.

HC is normally distributed in a general population similar to height. Figure 1 demonstrates the normal distribution with the main SDS or Z-score levels and corresponding percentiles. Figure 1 shows how 95% of the values of the normal distribution are within ± 2 SDS or the Z-score limits. The HC value is in the normocephalic range if it is between –2 SDS and +2 SDS or between the 2nd (-2.05 SDS) or 3rd (-1.88 SDS) and 97th (1.88 SDS) or 98th (2.05 SDS) percentile depending on the designation being used. Figure 1 also depicts how SDS values outside ± 3 SDS limits are extremely rare in the general population, only 0.2% of the population are outside those limits.

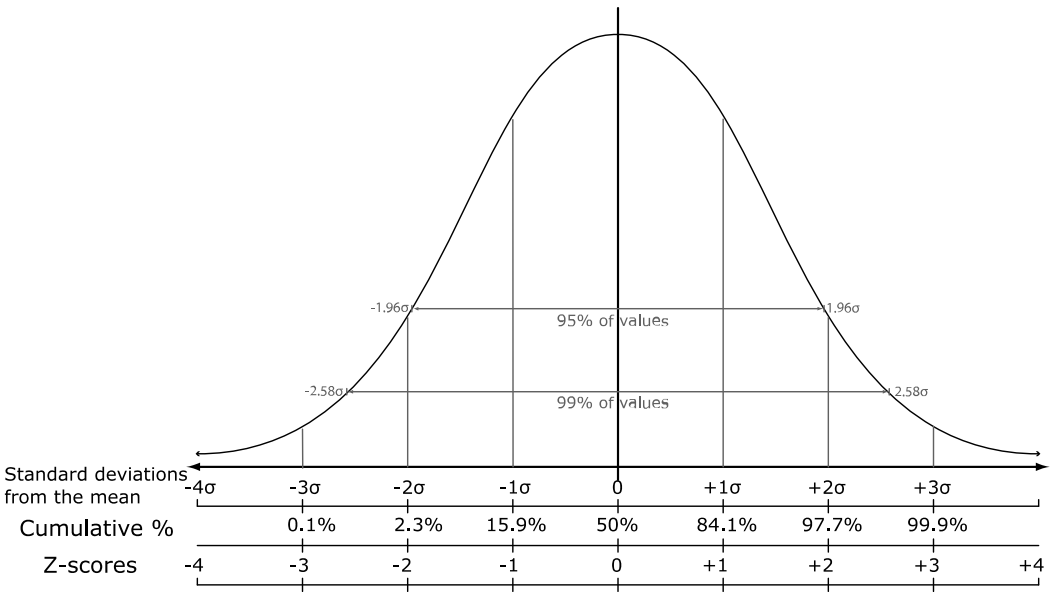


**Figure 1.** Normal distribution. Standard deviations (σ) from the mean and Z-scores are shown, and cumulative percentages stand for percentiles. Adapted from https://upload.wikimedia.org/wikipedia/commons/2/25/The_Normal_Distribution.svg. Wikimedia Commons. Web. 1 September 2021.

In anthropometric measurements, an element of measurement error is always present. This is minimized by standardized techniques and equipment. One can also imagine that some situation- or subject-specific factors may cause extra variability to the HC measurements e.g., nonoptimal cooperation of the child, a variable form of the head due to plagiocephaly in an infant, or very thick hair.

In a WHO multicentre growth study, the measurers went through standardized training and their measurement techniques were controlled every two months in standardization sessions (135). Also, in Finland, anthropometric measurements are taken at child health clinics by highly trained nurses with standardized methods and equipment (134).

Wright et al. (136) assessed whether a different measurement technique was responsible for the systematic differences observed between the WHO HC standards and the European HC references. In the meta-analysis by Natale et Rajagopalan (137), the heads of UK children were the largest relative to the WHO standard. The study of Wright et al. conducted in Scotland, UK recruited infants from the neonatal period up to two years of age. In the first setting, they measured infants with plastic tape with a tight method (WHO) and then with a loose method with the ends of the tape overlapping (UK). In the second setting, they measured infants with a metallic tape with the tight WHO method following the WHO protocol closely. The measurers were trained according to WHO standardization protocol, e.g., no more than 5 mm inter-observer differences were allowed. Then they compared these measurements with those taken during routine HC monitoring. The tighter WHO technique produced smaller HC values in both settings. The difference between HC values using the tighter or looser technique in settings 1 and 2 was similar. The authors concluded that differences in measurement technique accounted for half of the differences between the references, but even by using the WHO measuring protocol, the British children had larger HC mean than in the WHO standard. They recommended using the tight technique with a non-distensible plastic tape since the metallic tape is hardly available. They also

recommended taking three measurements at a time and writing down the average of the measurements.

The unavoidable element of measurement error can be assessed in many ways. In the WHO multicenter growth study, the reliability of measurements was studied (138). They calculated intra-observer technical error of measurement (TEM) and compared it against the TEM of an expert. They found that intra-observer TEM fell into the expert's 95% precision margin, i.e., ± 2 times the expert's TEM, thus the intra-observer TEM was considered acceptable. For HC, the intra-observer TEM for a newborn was 0.16 – 0.28 cm and for an older child up to five years of age, 0.13 – 0.29 cm. These estimates were as good as or better than in previously reported publications (138). The WHO study group also assessed possible bias in measurements. If the measurements of an observer fell out of the range of ± 2.8 x expert's TEM, it was considered a remarkable bias. There was no evidence of a bias in HC measurements acquired by the observers, but in length measurements, there tended to be a small negative bias. They also defined the inter-observer TEM and its proportion of the variability of the measurement. Then, the proportion of the inter-subject variance that is not due to measurement error is called the coefficient of reliability. The coefficient of reliability was 95% for all other measurements (including HC) except for skinfold thickness. The coefficient of reliability over 90% was considered adequate as presented by the Second National Health and Nutrition Examination Survey 1976 – 1980 (NHANES) in the US (139).

**Figure 2.** Head circumference measurement at a child health clinic.

**History of HC growth charts**

HC growth charts have been formulated since the first half of the 20th century. The first longitudinal growth study called Fels Growth Study was set up in the US in 1929, and HC measurements were part of the data collection since the beginning. Since then, several population-based HC growth charts have been constructed worldwide. Undoubtedly, the most famous HC charts were compiled by Nellhaus in 1968 (12). Nellhaus constructed "interracial and international" HC growth charts from all available HC references all over the world with appropriate data for calculations. Nellhaus took into account the knowledge of that time of a possible secular trend in body growth, therefore, he used only material that was published after 1948. They were altogether 15 HC references from Europe and North America and a reference from Japan. Nellhaus calculated common means and standard deviations from the pooled variances of the curves. When he compared the mean HC of five references from boys with different ethnic backgrounds (two African-American, one Japanese, one Alaskan Eskimo, and one Russian) with common means he had calculated from all the data, he found that the means corresponded closely to the grand mean, with a slight exception of the Alaskan Eskimo, who tended to have larger HC means. Nellhaus aimed to construct multinational HC growth charts for use everywhere in the

world because he did not find any significant ethnic or geographical differences, and indeed, these charts have been in use worldwide until almost recent years. The former Finnish HC growth curves by Takkunen (nee Kantero) (7) were included in the Nellhaus HC charts.

**Methods of constructing HC growth references and standards**

The methods for constructing growth charts were originally developed regarding childhood growth in height and weight. The methods have since been adapted to formulating HC growth charts.

Growth charts may be constructed based on cross-sectional data collection when the data are drawn from a population through a designated age range at the same time. In cross-sectional data collection, only one anthropometric measurement of each subject is included when constructing the charts. This way of collecting growth data is quick, but the growth rate cannot be assessed since all measurements come from different subjects. Longitudinal data collection allows for delineation of growth rates, and growth charts may be constructed upon smaller sample sizes than in a cross-sectional design. Longitudinal studies, however, require more time to follow-up and are prone to loss of subjects to follow-up. The modern method of collecting growth chart data is mixed-longitudinal, which has been chosen by the WHO Multicentre Growth Reference Study Group in constructing the multiethnic growth charts in 2006 and 2007 (13,140).

As part of developing new growth standards, the WHO reviewed all available statistical techniques for constructing growth centiles (141) and chose the Generalized Additive Models for Location, Scale, and Shape (GAMLSS) method (142), which is a generalization of the previously developed LMS method (143). The LMS method uses a Box-Cox transformation to normalize the distribution of the measurements at each age. The distribution is summarized by Box-Cox power ($\lambda$), mean ($\mu$), and a coefficient of variation ($\sigma$), and the method has been named according to the initials of the symbols, LMS. The LMS method corrects any skewness in the distribution; however, data with remarkable kurtosis require the more generalized GAMLSS method, as was the case for constructing the WHO

growth standards. Under the GAMLSS framework, the Box-Cox-power exponential distribution method combined with curve smoothing by cubic splines proved the most fitting in forming the WHO growth standards (140).

The methodology of constructing the WHO HC growth charts is the same as was used for weight and length/height charts (13). The construction of HC growth charts represents a “simple” application of the methods because the HC data were normally distributed and, as such, required neither skewness nor kurtosis correction.

### 2.3.3 WHO HC standards and their validation

WHO launched its multiethnic growth standards in 2006 and 2007 including HC standards from birth to 5 years of age (13,140). This WHO multicentre growth reference study was designed to create a standard of ideal child growth under optimal conditions irrespective of ethnic background. The study population was recruited from six different sites around the world (Brazil, Ghana, India, Norway, Oman, and the United States), and the study combined a longitudinal study from birth to 24 months of age with a cross-sectional study from 18 to 71 months of age and comprised altogether approximately 8500 children (13,140,144,145). The inclusion criteria for both the study site and the individual consisted of socioeconomic factors that were designated as favorable to growth. For an individual, the criteria were: lack of health-associated environmental or economic constraints of growth, i.e., a mother committed to exclusive or predominant breastfeeding for at least 4 months; introduction of complementary foods by the age of 6 months; partial breastfeeding for at least 12 months; term and single birth; absence of significant morbidity; and a non-smoking mother (before and after delivery) (13,144). WHO standards were aimed at describing child growth to the individual’s genetic potential.

However, studies from Norway, Belgium (14), the US (146), Japan (15), Czech Republic (16), the U.K. (17), Greenland (147), and recently from France (148) (Table 1) have shown a conflicting finding compared with

WHO HC standard. What is common to these studies is that HC growth has overshot WHO HC standards in all these countries. In Japan (15) and the Czech Republic (16), they aimed at replicating the WHO inclusion criteria and then comparing the study population against the WHO HC standard and their national HC references. In Japan (15), the growth of the breastfed children was followed up until 24 months of age, and from 4 months on, the mean HC of the Japanese breastfed children was above that of the WHO HC standard. Also, the mean HC in the Japanese national reference in use was above the mean HC in the WHO standard, but the proportions outside ± 2 SDS were not reported (15). In the Czech Republic (16), the mean HC of breastfed infants was above the mean of the WHO standard from birth to 12 months of age, except at one month of age.

In Norway and Belgium (14), they compared the HC growth of breastfed children together with a larger cohort of children from birth to 5 years of age, and the mean HC in both countries was above the mean of the WHO standard at all ages. Furthermore, HC growth of breastfed children was, in both countries, closer to the HC growth of the general population than to the WHO standard. This finding suggests a more significant role of the genetic and environmental background to HC growth than that of the feeding practice. This was also the case in the Czech Republic (16) where the mean HC growth of breastfed children did not significantly differ from the mean of the national HC reference.

A longitudinal study from Greenland (2018), followed up 279 children from birth to two years of age. Breastfed and formula-fed children and children whose mothers had smoked during pregnancy were recruited (147). Their HC values were significantly larger compared with the WHO standard and the Danish reference. The difference between the study population and the Danish reference was smaller than that between the study population and the WHO standard.

In the US (146), they compared the distributions of HC references in use for North America, i.e., the National Center for Health Statistics (NCHS), the Centers for Disease Control and Prevention (CDC), the WHO standard, and a growth reference they constructed from a primary care network (PCN) population of 75,412 children aged between 3 days and 3 years. In this PCN

population, the WHO HC standard was the one most shifted to left: the overall portions of subjects above the 95$^{th}$ percentile were 14.0% for the WHO standard, 8.6% for the CDC reference, 6.2% for the NCHS reference, and 4.9% for the PCN reference. The corresponding portions of subjects below the 5$^{th}$ percentile were 2.3% using the WHO standard, 2.9% using the CDC reference, 5.1% using the NCHS reference, and 4.4% using the PCN reference.

In 2014, a systematic review was published comparing the WHO growth standards with growth data from 55 countries (137). In this study, they aimed to replicate the recruitment method of the WHO including countries or ethnic groups from economically advanced circumstances. HC growth varied more than weight or height. From birth to age 5 years, the proportion of mean HC values of the growth references that were ≥ 0.5 SDS above the WHO HC mean ranged from 32 to 72% in age groups. Altogether half of all the mean HC values were above 0.5 SDS of the WHO HC standard (137). Furthermore, at the age of 2 years, in European countries, America, and the Pacific Islands, the proportions of the reference values above 2 SDS in the WHO HC standard were elevated. Correspondingly, the proportions below the WHO HC value –2 SDS at the age of 2 years were decreased in the above-mentioned countries or ethnic groups.

These findings contradict the hypothesis and framework behind the WHO multiethnic growth standards. HC in healthy subjects seems more strongly genetically determined than environmentally.

### 2.3.4 International comparisons of HC references

In addition to the comparisons made with the multiethnic WHO HC standard, also other international comparisons between HC references have been made. Ishikawa et al. (1987) constructed Japanese HC growth references from birth to 15 years of age in 1987 (149), and they made comparisons with the Nellhaus (12) HC charts and the erstwhile British HC charts (9). In Ishikawa et al. (1987), the HC values of the Japanese children were smaller than those in the UK or the Nellhaus composite charts (149).

Further on in Japan, Anzo et al. (2002) compared the 50$^{th}$ percentile values of HC and HC-to-height ratio between the 1978-1981 Japanese data, the 1954-1976 Swiss data, the 1979-1980 Dutch data, and the 1930-1982 US data (10). They found that, besides the smaller HC of the Japanese children compared with Caucasian children, the HC-to-height ratio was, in turn, larger in Japanese children. A former Japanese study had reported similar HC-to-height ratios in Japan, the US, and the UK (11).

In an Egyptian study in which they constructed new HC growth references in 2008 (150), they noticed differences in mean HC from 1 to 24 months of age compared with Swedish, American, and Saudi-Arabian references. Swedish boys had the largest HC values, next were the Americans, thereafter Egyptians, and lastly the Saudis. Among the girls, the comparisons were mainly the same.

### 2.3.5 Secular trends in HC growth

In Japan, the UK, and Sweden a positive difference in HC between generations has been described, which is generally called a secular change (8-11,149,151). The mean HC has grown nearly linearly in Japan between 1940 and 1980, 1978 to 1981, and from 1990 to 1994 following the course of a secular trend in linear growth, which seems to be plateauing (10,11). Therefore, it is predicted that the secular trend in both linear growth and HC is coming to an end in Japan (10).

**Table 1.** Studies comparing HC growth in a national population with the WHO HC standard

| Study (year) | Country | Number of participants and age | Inclusion criteria according to the WHO | Outcome measure | Results |
|---|---|---|---|---|---|
| Júlíusson (2011) (14) | Norway and Belgium | 6,985; 0-5 years | Healthy, full-term children, feeding type recorded, non-smoking mother during pregnancy | Prevalence of HC > 2 SDS and < -2 SDS by WHO standard | Belgium:<br>> 2 SDS 6.55%,<br>< -2 SDS 0.97%<br>Norway:<br>> 2 SDS 6.4%,<br>< -2 SDS 0.18% |
| Daymont (2010) (146) | US | 75,412; 3 days to 3 years | Mostly healthy, gestational age ≥33 weeks, birth weight ≥ 1,500 g | Portions of HC above 95$^{th}$ percentile and below 5$^{th}$ percentile by WHO standard. | > 95$^{th}$ percentile 14.0%,<br>< 5$^{th}$ percentile 2.3% |
| Wright (2011) (17) | UK | 15,208; 2 weeks to 36 months | Full-term children, otherwise not reported | Z-scores by WHO standard. Prevalence of HC > 98$^{th}$ and < 2$^{nd}$ percentile by WHO standard | Mean Z-scores 0.57-1.09 SDS.<br>> 98$^{th}$ percentile 8.1-16.4%.<br>< 2$^{nd}$ percentile 0-1.8% |

| Study (year) | Country | Number of participants and age | Inclusion criteria according to the WHO | Outcome measure | Results |
|---|---|---|---|---|---|
| Tanaka (2013) (15) | Japan | 647; 0-24 months | Healthy, full-term, and exclusively breastfed children | Comparison of the 50$^{th}$ percentile of HC with WHO standard | At birth and 1-month HC lower than WHO. From 4 months onwards the same or larger HC than WHO. |
| Vignerova (2015) (16) | Czech Republic | 960; 0–12 months | Met all the inclusion criteria | Z-scores by WHO standard. | Mean Z-scores 0–0.8 SDS |
| Natale et Rajagopalan (2014) (137) Review | 53 studies from 37 [1] countries or ethnic groups plus WHO and EURO-12 | Approximately hundreds of thousands (the size of the population was not always reported + included children of various ages): 0-5 years | Healthy (not stated in all studies), full-term children from economically favorable circumstances | Comparison of means with WHO HC standard and of ±0.5 SDS outliers | 18 out of 26 HC means at 2 years ≥ 0.5 SDS above WHO mean. Of 219 outlying HC mean values, 202 (98%) were ≥+0.5 SDS. In the USA, Europe, and Pacific Islands, HC distribution strongly right-shifted. |

| Study (year) | Country | Number of participants and age | Inclusion criteria according to the WHO | Outcome measure | Results |
|---|---|---|---|---|---|
| Klovgaard (2018) (147) | Greenland | 279; 0–24 months | Healthy full-term children, no feeding type data | Z-scores by WHO standard. Prevalence of HC > 2 SDS and <-2 SDS by WHO standard | Mean Z-scores 0.71-0.96 SDS in WHO standard. HC > 2 SDS 7.4-11.3%. HC <-2 SDS 0-1.5%. |
| Bergerat (2021) (148) | France | 157,762; 0–5 years | Birth weight > 2500 g | Z-scores of the mean HC values were compared with WHO standard and with former French reference | Mean HC Z-score of WHO standard -0.60 SDS below that of current French reference from birth to 5 years. Positive secular trend between the former and current French references. |

[1] Australia, Belgium, Canada, Canada (Cree population), Czech Republic, China, Denmark, Egypt, Greece, Finland (Study I from present doctoral thesis included), France, Germany, Hong Kong (2003, when separate from China), India, Iran, Ireland, Israel, Italy, Japan, Republic of Korea, Lebanon, Netherlands, Netherlands (Maroccon population), New Zealand (NZ), Norway, Nigeria, Poland, Russia, Saudi-Arabia, Singapore, Spain, Sweden, Switzerland, Turkey, United Arab Emirates, UK, USA, the WHO (Brazil, Ghana, India, Norway, Oman and USA) and EURO-12 (Austria, Croatia, France, Germany, Greece, Hungary, Ireland, Italy, Portugal, Spain, Sweden and UK).

### 2.3.6 HC in relation to other anthropometrics

HC is an important part of general growth monitoring, and it is often compared with height when assessing growth. It has been commonly assumed that normative HC and height growth do not greatly differ from each other when assessed in standard deviation scores or percentiles. Indeed, at birth and in infancy, a steady correlation between HC and body length and weight has been shown (112,152-154). Scheffler et al. (2017) replicated the finding of the correlation between length/height, body mass, and head size from birth to the age of 2 years. They performed a principal component analysis for several auxological traits from birth to 7 years old and showed that length/height, fat accumulation, and head size followed very different incremental patterns and developmental paths (153). Head size in particular followed an independent path after 2 years of age.
In Japan, as part of constructing new HC references, they compared mean HC with mean height as a ratio (11) and formulated HC-to-height references to make comparisons between different ethnic groups and generations (10). Similarly**,** as part of constructing new HC growth curves in Egypt, they (150) produced HC-to-height ratios separately for boys and girls. They noticed that there was a significant gender-based difference during infancy, with boys having larger values, that continued mostly until 12 years, whereafter the girls had greater values (150). In Norway, when publishing the former growth references, they also published a chart for HC for height (155). In an Argentinian study (156), they constructed a combined reference for boys and girls for HC-to-height ratio, which was elevated in children suffering from hypo- or achondroplasia.

In the NF1 population, there is a shift towards a larger HC combined with shorter stature relative to the general population (88,89). To our knowledge, HC-to-height ratio has not previously been assessed in NF1 using an HC-to-height reference specific for the NF1 population.

### 2.3.7 Growth monitoring practices

General recommendations on childhood HC growth monitoring are scarce. There is only one Cochrane review from 1999 on childhood growth monitoring (157) in which HC is not even mentioned. In Finland, there are national recommendations for childhood growth monitoring in child health clinics (134), which recommend measuring child HC from birth until 7 years of age. In Finland, children visit cost-free child health clinics almost every month during their first year, then at 18 months, and annually after that up to 7 years of age. During all visits, the growth of the child is measured. Virtually all families attend these visits (158). In Norway, according to the guidelines from the Norwegian Directorate of Health, HC is measured from birth up to 12 months of age, according to a schedule similar to the Finnish HC Growth Monitoring Programme (159), though in Finland, the follow-up lasts longer.

**Studies on the yield of HC growth screening**

A few studies have observed the yield of HC growth screening using study-specific screening criteria to detect HC growth disorders (Table 2). These criteria for abnormal HC growth encompass various criteria of an abnormally large or small change in HC growth over a designated period. A nationwide study in Norway (19) (Table 2) retrospectively analyzed all children (n = 298, boys 67%) under 5 years of age hospitalized due to intracranial expansion over four years. For 58% (n = 173) of the patients, hydrocephalus was the primary diagnosis. Of the total of 298 patients, 37% (n = 109) were referred because of increased HC as the only symptom, which was defined as crossing two percentile curves according to Norwegian HC screening rules. These percentiles were not defined more specifically, but from the original article in which the HC reference was published (155), we can see that in erstwhile Norwegian HC charts 2.5$^{th}$, 10$^{th}$, 25$^{th}$, 50$^{th}$, 75$^{th}$, 90$^{th}$, 97.5$^{th}$ percentiles were presented. The most common disorder underlying HC enlargement as the only reason for referral was hydrocephalus in 91% of patients. Of all hydrocephalic children on whom there was data on the exact age of diagnosis 87% (n =

141/162) experienced symptoms (increased HC or other symptoms) already before 10 months of age, and the median age of the percentile crossing criteria was 4.8 months. Only one child from the whole study cohort was referred because of increased HC after 2 years of age, and most referrals happened before the age of 10 months. The authors concluded based on this data, that HC screening is important only during the first 10 months of life.

Another population-based register study in the UK of 74,428 children aged 3 days to 3 years (160) retrospectively analyzed the accuracy of several screening criteria in detecting both intracranial expansive conditions and metabolic or genetic conditions associated with macrocephaly (Table 2). They tested the WHO standard, Centers for Disease Control and Prevention (CDC) reference, and a primary care network (PCN) reference. Only 0.11% (85 subjects) of the study population had a new diagnosis of either an intracranial expansive condition or metabolic or genetic condition associated with macrocephaly. Hydrocephalus was the most common single condition (n = 24) detected, and tumors were classified in a separate group. Crossing two increasing percentiles had the highest sensitivity, which was only 31-60% with a specificity of 54-78%. When an HC cut-off of the 97$^{th}$ percentile was used, the sensitivities of the references ranged from 34-48% and the specificities from 82-94%.

A Dutch study (161) assessed the diagnostic accuracy of certain HC screening rules in a population of 43 children who were less than one year of age when diagnosed with hydrocephalus (Table 2). The population with hydrocephalus was retrospectively collected from patient files of a tertiary center treated over 31 years with a reference population of 1,938 children. They found that a combination of a very large (> 2.5 SD) HC and/or a very large (> 2.5 SD) progressive growth of HC resulted in the best accuracy with a sensitivity of 76.7% and a specificity of 96.5%. The analysis of HC growth was limited to 20 subjects who had at least two HC measurements.

A population-based study from Turkey (162) (Table 2) studied the characteristics of macrocephaly by retrospectively reviewing the health records of 9,758 children aged 0-4 years who had been followed up in a

well-child unit over 11 years. Macrocephaly (HC > 97$^{th}$ percentile) was diagnosed in 90 (0.9%; 61% males) children. All macrocephalic children went through cranial ultrasound, and if abnormal findings were detected, computed tomography (CT) or MRI was performed. The most common diagnosis was familial macrocephaly in 57 (63.3%) subjects, the second most common diagnosis was "isolated macrocephaly" in 18 (20%) subjects with no other findings besides macrocephaly. Hydrocephalus was the third most common diagnosis found in 8 (8.9%) subjects. The median age of diagnosis was around 3 months in all macrocephalic subjects. Subjects with macrocephaly at birth were included in the analyses.

Kurata et al. (2018) studied the relationship between macrocephaly (> 2 SDS) and neurodevelopmental disorders. They included a cohort of 93 children aged 1 – 44 months who had been referred to a tertiary center because of macrocephaly during a 9.5-year period. The prevalence of neurodevelopmental disorders was 17% in children with macrocephaly and two-thirds of them presented with autism spectrum disorder or its traits (163). There was a male preponderance among the macrocephalic children. None of the patients needed immediate treatment for the cause of macrocephaly.

In a population-based cohort of 10,851 children from the UK (87), Wright and Emond (2015) studied the incidence of centile shifting in HC measurements and the incidence of HC values outside ± 2 SDS and their relationship with neurocognitive disorders (Table 2). The infants were measured at ages 6-8 weeks, 9, and 18 or 24 months of age. When using the WHO standards, upward shifts during the first time interval, from 6-8 weeks to 9 months, were much more common than downward shifts and the HC distribution was right-shifted. Thus, they used Z-scores that were adapted to the mean HC SDS values of the study population. By using these adapted Z-scores, similar proportions shifted up or down: Shifts of > 1 SDS upward or downward were very common, a proportion of 20% during the first time interval and approximately 15% during the latter (87). Still, only one-third of the shifts that occurred during the first time interval were sustained during the latter, and only 0.5% showed a sustained shift outside ±2 SDS. An average HC in an individual outside ± 2 SDS increased

the risk for a neurocognitive disorder. Still, 85% of the children with HC < -2 SDS and 91% of those with HC > 2 SDS did not have any neurocognitive disorder. Moreover, 93% of children with a neurocognitive disorder had HCs within the normal range. The authors concluded that the parents and caregivers can be reassured that most often a mildly divergent HC in a child represents no underlying pathology and a single centile shift is usually due to measurement error (87).

**Table 2**. Comparison of studies on the yield of HC screening

| Study (year) | Study design | Number of study subjects and age range | Screening cut off criteria | Main outcomes | Conclusion |
|---|---|---|---|---|---|
| Zahl (2008) (19) | Nationwide retrospective study of all referrals to pediatrics/neurosurgery clinics in 4 years because of intracranial expansive conditions | 298 children, 0-5 years | Crossing two percentiles upwards. (2.5$^{th}$, 10$^{th}$, 25$^{th}$, 50$^{th}$, 75$^{th}$, 90$^{th}$, or 97.5$^{th}$) (155) | The timing and detection rate of detecting intracranial expansive conditions according to increased HC | Of the intracranial expansive conditions, hydrocephalus was the most common to find by an increase in HC and it was mostly found during the first 10 months of life |
| Daymont (2012) (160) | Population-based retrospective study of intracranial expansive conditions or metabolic and genetic conditions associated with macrocephaly screened by WHO, CDC, and primary care network references | 74,428 children, aged 3 days-3 years | Crossing 2, 3, 4, or 6 major percentiles (5$^{th}$, 10$^{th}$, 25$^{th}$, 50$^{th}$, 75$^{th}$, 90$^{th}$, 95$^{th}$) upwards, or thresholds HC > 95$^{th}$, 97$^{th}$, or 99.6$^{th}$ percentiles | Sensitivity, specificity, positive predictive value, likelihood ratios positive and negative, number needed to screen and number needed to test | Commonly used HC percentile cut-offs had low sensitivity and low positive predictive value in the detection of pathology associated with head enlargement |
| van Dommelen (161) | Retrospective study of referrals to a tertiary hospital from 1975 to 2005 because of hydrocephalus | 43 children with hydrocephalus and a reference population of 1,938 healthy children from birth to 1 year of age | HC > 2.0 OR 2.5 SD, HC growth > 2.0 OR 2.5 SD, combinations of the above criteria. HC > 2.0 above length or weight SD | Sensitivity, specificity, and positive predictive value | Criteria of HC >2.5 SD and/or HC growth >2.5 SDS had the best accuracy in hydrocephalus screening (sensitivity 76.7%, specificity 96.5%) |

| Study (year) | Study design | Number of study subjects and age range | Screening cut off criteria | Main outcomes | Conclusion |
|---|---|---|---|---|---|
| Yilmazbas (2018) (162) | Retrospective population-based study of well-child clinic visits between January 2004 and December 2014 in order to describe characteristics of detected macrocephaly | 9,758 children, aged 0-4 years | HC > 97$^{th}$ percentile, or crossing one or more major percentiles upwards or "relative macrocephaly", when HC exceeded more than 2 centiles of height | Number of macrocephalic subjects detected and underlying causes and timing of detection | 90 (0.09%) were macrocephalic. 61% (n = 55) of macrocephalic children were males. Mean age of detection 2.7 months. The majority was familial or asymptomatic macrocephaly (83%) and 9% had hydrocephalus. The rest were miscellaneous. Most needed no treatment. |
| Wright and Emond (2015) (87) | From the Avon Longitudinal Study of Parents and Children (ALSPAC), a population-based study of more than 14,000 pregnancies recruited to the study between April 1991 and December 1992 | 10,851 children with ≥2 HC measurements at 6 to 8 weeks, 9 months, and 18/24 months. WISC-III at 8 years and data of possible statement of special educational needs at 11 years and of neurodevelopmental diagnoses | Crossing > 1 SDS upward or downward, crossing outside ±2 SDS | Correlation of centile crossing with neurocognitive disorders (NCD) | Centile crossing was common, but usually reversible and not a sign of an NCD. When the average HC during the follow-up was outside ± 2 SDS, risk for an NCD was significantly elevated, but 91% of macrocephalic and 85% of microcephalic children did not have an NCD, and 93% of those with an NCD had an HC within the normal range. |

| Study (year) | Study design | Number of study subjects and age range | Screening cut off criteria | Main outcomes | Conclusion |
|---|---|---|---|---|---|
| Kurata (2018) (163) | Retrospective study of referrals to a tertiary hospital from January 2006 to August 2015 because of macrocephaly | 93 children, aged 1-44 months | HC > 2 SDS | Prevalence ("relationship") of neurodevelopmental disorders | 17% of macrocephalic children had a neurodevelopmental disorder. Male preponderance in macrocephaly (1.9:1) and neurodevelopmental disorders (23%). |

Abbreviations: WISC-III, Wechsler Intelligence Scale for Children, 3rd edition

# 3 AIMS OF THE STUDY

The aims of this study were

I To construct new population-based HC references for Finnish children from birth to 7 years of age and to evaluate the possible secular change between this and the former Finnish HC reference and possible differences between the up-to-date Finnish HC reference and other largely used HC references e.g., the WHO. (Publication I)

II To define the limits for normative HC growth, to develop evidence-based screening criteria for abnormal HC growth, and to investigate their sensitivity and specificity in two HC growth-related disorders, neurofibromatosis type 1 and hydrocephalus. (Publications II and III)

III To study childhood HC growth after exposure to maternal smoking during pregnancy. (Publication IV)

# 4 NEW FINNISH REFERENCE FOR HEAD CIRCUMFERENCE FROM BIRTH TO 7 YEARS

## 4.1 ABSTRACT

**Background and objectives:** In the evaluation of the growth of head circumference (HC), charts depicting normal growth are of paramount importance. Current Finnish HC growth charts are based on data from only 130 children born 1953-1964. As a secular trend in HC growth has been reported, we updated the HC charts using a large sample of contemporary HC data.

**Material and methods:** Mixed cross-sectional HC data of 19,715 healthy subjects aged 0-7 years were collected from primary health care providers. References for HC for age and HC/height ratio for age were fitted using generalized additive models for location, scale, and shape (GAMLSS).

**Results:** Increased HC for age was seen particularly after 2 years of age in both genders compared to the 1953-1964 reference. The SD for HC was remarkably larger in the 1953-1964 reference. The proportion of 1986-2008 reference subjects exceeding the +2 SD limit of the 1953-1964 reference was much bigger than the proportion below -2 SD.

**Conclusions:** Because of the secular change in HC growth, the HC reference has to be renewed periodically. The new Finnish reference for HC for age should be implemented for monitoring HC growth of children in Finland.

Adapted with permission of Taylor & Francis from: Karvonen M, Hannila M-L, Saari A and Dunkel L. New Finnish reference for head circumference from birth to 7 years. Annals of Medicine. 2012 Jun;44(4):369-74. doi: 10.3109/07853890.2011.558519. Epub 2011 Apr 15. PMID: 21495784. The tables and figures are modified from the original to correspond sequential numbers of this thesis. One subtitle “4.3.1 Study population and measurements” was added to fit the sequental numbering of this thesis.

## 4.2 INTRODUCTION

In the evaluation of the growth of head circumference (HC), charts depicting normal growth are of paramount importance. Head circumference charts currently in use in Finland are based on follow-up data of only 130 children born in years 1953–1964 (7,164). Head circumference is routinely measured at health care visits during infancy and childhood until the age of 7 according to the recommendation by the National Institute for Health and Welfare. The ultimate goal of taking multiple HC measurements is the early detection of underlying pathological processes affecting head growth. Indeed, HC is a good indicator of the growth in brain volume especially in early childhood (1,4,5), and slow growth of HC may indicate primary pathology in the developing brain (92,93,165). Excessive growth in turn may indicate a pathological process affecting the circulation of the cerebrospinal fluid leading to hydrocephalus (19) Because of the small number of individuals and positive secular change in HC growth, evident in many countries (8-11,149,151), the aim of the current work was to provide an update of the HC charts, for the ages 0–7 years, based on adequate sample size and utilization of recent statistical methods.

## 4.3 MATERIAL AND METHODS

### 4.3.1 Study population and measurements

Data for the present study were collected from providers of public primary care in the city of Espoo, Finland's second largest city with a population of 241,600 inhabitants. With a significant net migration from all parts of Finland, its population has grown 10.6-fold over the past 60 years. The majority of the population (94.4%) is of Finnish origin, which mirrors the whole of Finland (97.3%). The Finnish social security system provides regular, free-of-charge visits to public primary care child health clinics to permanent residents of Finland regardless of social status or income level. Primary care nurses in Finland are specially trained in child health care and health prevention, and their duties include assessment of health and

development at scheduled visits including standardized weight, length/height, and head circumference measurements.

Children in Espoo have regular visits at child health clinics at the ages of 1–2 weeks, 3–6 weeks, and 6–8 weeks; at 2, 3, 4, 5, 6, 8, 10, 12, 18, and 24 months; and then at 3.5, 5, and 6 years of age. Children may have also extra visits if special health concerns are suspected.

Head circumference is measured using a plastic tape measure at every visit to the child health clinic as the maximum occipitofrontal circumference, and the results are rounded to the nearest 0.1 cm. Since 2003, all measurements in the Espoo area have been captured in a networked electronic patient management system named Effica (Tieto Ltd, Finland). The birth measurements, including HC as well as data on premature birth, are recorded to Effica during the first visit to the child health clinic after birth. Permission for the present study was obtained from the Espoo Municipality Institutional Review Board. No contact was made with the study subjects since the data were handled anonymously.

### 4.3.2 Database cleaning

Finnish growth references for weight and height have been recently renewed (166) The data for these references comprise subjects born 1983–2008. The original sample for the HC reference is the same. Database cleaning for the height standard encompassed three phases: first, the primary care nurses of Espoo municipality excluded the subjects with diseases or medications potentially affecting growth. The nurses had been specifically trained by a pediatric endocrinologist (L.D.). This phase of database cleaning has been reported in detail elsewhere (166) Next, measurements which were obtained outside scheduled visits were excluded. Lastly, all HC outside ± 5 SD were excluded (representing extreme outliers, i.e. physiologically improbable measurements, or being extremely pathological when true measurements). After the cleaning procedure, the data consisted of 146,790 measurements of 19,715 subjects (9,536 girls; 48.4%) born 1986–2008.

### 4.3.3 Statistical methods

In the construction of growth curves for HC (HC for age and HC/height ratio for age), distribution of response variables and technique in smoothing distribution parameter curves over age were chosen by closely following the guidelines provided by the World Health Organization (WHO) (140) Accordingly, generalized additive models for location, scale, and shape (GAMLSS) were used, choosing the distribution of response variable from the flexible Box-Cox power exponential (BCPE) distribution family and using cubic splines as a smoothing technique. BCPE distribution can be described in terms of four parameters: M for median, S for coefficient of variation, L for Box-Cox transformation power, and T as a parameter related to kurtosis.

R statistical software (GAMLSS package) (167) was used in the analysis. First, an optimal power transformation was calculated for age in relation to the response variable as it was found to improve goodness of fit. Second, optimal degrees of freedom for parameter curves were defined using the optim function and information criteria BIC (which have penalty h of log(n) in the formula −2 * l – hp, where l is the maximized likelihood, p number of parameters in the model, and n number of observations) as it seemed to give optimal smoothness for curves. We started modeling from the normal distribution (BCPE with L = 1 and T = 2), and it turned out to be sufficient for both response variables when comparing fitted percentiles to observed percentiles (Figure 6, Supplementary Figure).

## 4.4 RESULTS

A positive secular change was seen in HC reference 1986–2008 both in girls and boys as compared to the HC reference 1953–1964 (Figure 3). It was particularly clear after 2 years of age in both genders. The mean HC at birth was 34.8 cm in girls and 35.3 cm in boys in the new reference. The corresponding figures were 34.7 cm and 35.5 cm in the 1953–1964 HC reference, respectively.

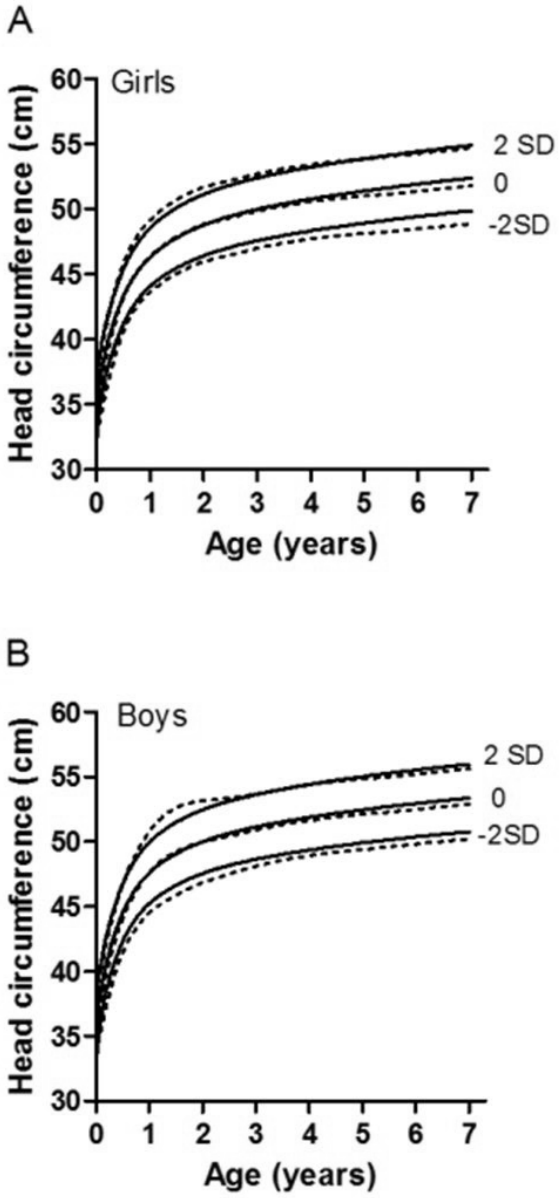


**Figure 3.** The new Finnish HC for age reference (mean ± 2 SD, solid lines). Curves based on 146,790 measurements from 19,715 full-term healthy subjects born between 1986 and 2008 compared to the current Finnish HC reference based on subjects born between 1953 and 1964 (mean ± 2 SD, dashed lines). A: girls aged 0–7 years; B: boys aged 0–7 years

The difference in mean HC between the two references is better illustrated in Figure 4 as an absolute (cm) difference. In girls the greatest difference was at about 0.15 years of age when the mean HC was 1.0 cm greater in the 1986–2008 reference than in the 1953–1964 reference (Figure 4). After that, the difference between the two references rapidly decreased until it was slightly negative between the ages of 0.60 and 2.15 years. Thereafter, the difference grew continuously to the age of 7 years, being 0.6 cm at the end. In boys the difference in HC between the 1986–2008 reference and the 1953–1964 reference followed quite the same pattern. The maximum difference of 1.0 cm was reached at 0.15 years, and around 1.35 years the mean HC of the 1986–2008 reference was at the lowest point below the 1953–1964 reference (−0.2 cm). After the age of 2 years the mean HC of the 1986–2008 reference became bigger than that of the 1953–1964, and from that point on the difference kept increasing, being 0.5 cm at the age of 7 years.

A very identical pattern was seen in the changes in mean HC expressed in standard deviation score (SDS) in both girls and boys. At 7 years, the mean HC of the 1986–2008 reference was 0.42 SDS and 0.35 SDS above the mean of the 1953–1964 reference in girls and boys, respectively. Strikingly the SD was 10%–40% bigger in the HC reference 1953–1964 compared to the new reference (Figure 5) except at birth, when the SD of the HC reference 1986–2008 was larger.

We assessed how many subjects from the 1986–2008 reference population would fall outside ±2 SD limits of the 1953–1964 HC reference (Tables 3 and 4).

In total, 2.3% (range 0.9%–6.0%) of measurements in girls were above +2 SD, which is actually the percentage expected in normally distributed head circumference. However, the proportion of measurements below −2 SD was only 0.5% (range 0.1%–0.9%).

A similar finding was found in boys, who had 3.1% (range 0.5%–7.2%) of the measurements above +2 SD limit of the 1953–1964 HC reference and only 0.5% (range 0.1%–1.8%) below the −2 SD limit of the same reference. In boys from 0.67 years (8 months) to 4 years the proportion of measurements above +2 SD was less than 2.3%. In girls, a similar result

was obtained between the age of 0.33 years (4 months) and 4 years. Nevertheless, both in boys and girls, the proportion of measurements below −2 SD was much smaller than the proportion above +2 SD. We also calculated HC-to-height ratio for age (Figure 6). This ratio was highest in the early months, and it declined quite constantly during the whole age period.


**Figure 4**. Age- and sex-specific features of the secular change in HC in Finland. Comparison between HC reference 1986–2008 and HC reference 1953–1964. Curves indicate differences from the HC reference 1953–1964 in mean HC in cm from birth to age 7 years. Dashed line = girls; solid line = boys.

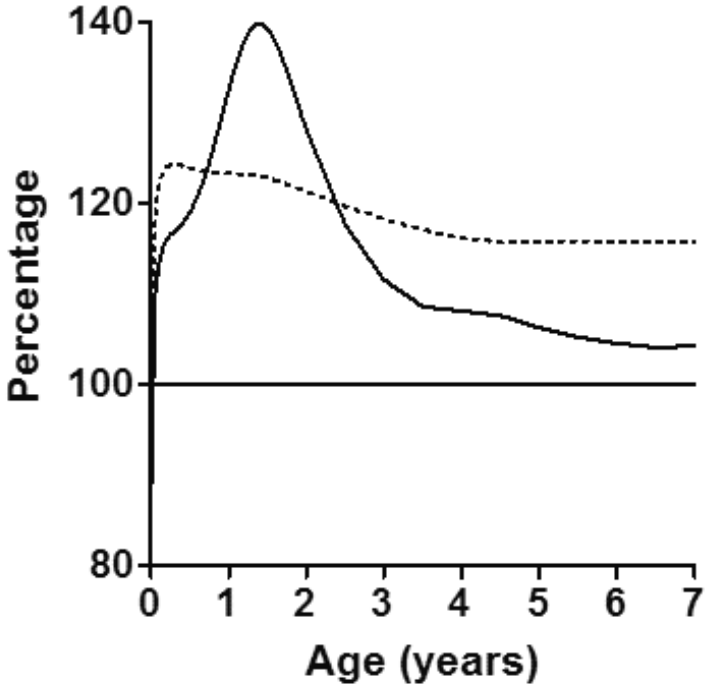


**Figure 5**. Age- and sex-specific features of the change in head circumference SD. Curves illustrate the ratio between the SD of the HC reference 1953–1964 and HC reference 1986–2008 (horizontal line). Dashed line = girls; solid line = boys.

**Table 3**. Number of head circumference measurements of girls in the head circumference (HC) reference 1986–2008 population and percentage of measurements ≤ −2 SD and ≥ 2 SD when compared to the HC reference 1953–1964.

| | HC reference 1986 - 2008 | Girls outside the ± 2SD range of the HC reference 1953-64 | |
|---|---|---|---|
| Age group | Number of measurements | Percentage ≤ - 2SDS | Percentage ≥ 2 DS |
| < 1 mo | 7,696 | 0.6 | 3.0 |
| 1 - 2 mo | 5,936 | 0.1 | 6.0 |
| 2 - 3 mo | 4,326 | 0.1 | 5.5 |
| 3 - 4 mo | 5,459 | 0.1 | 3.1 |
| 4 - 5 mo | 4,558 | 0.2 | 1.9 |
| 5 - 6 mo | 4,633 | 0.5 | 1.4 |
| 6 - 8 mo | 6,078 | 0.6 | 1.2 |
| 8 - 10 mo | 5,099 | 0.7 | 1.2 |
| 10 - 12 mo | 4,154 | 0.9 | 0.9 |
| 12 - 18 mo | 7,317 | 0.7 | 0.9 |
| 18 - 24 mo | 4,669 | 0.7 | 1.2 |
| 2 - 3 y | 4,311 | 0.9 | 1.2 |
| 3 - 4 y | 2,541 | 0.4 | 1.5 |
| 4 - 5 y | 877 | 0.7 | 3.2 |
| 5 - 6 y | 2,317 | 0.5 | 2.5 |
| 6 - 7 y | 1,498 | 0.1 | 3.5 |
| Total | 71,469 | 0.5 | 2.3 |

HC reference 1986–2008 population includes subjects born between 1986 and 2008; HC reference 1953–1964 population includes subjects born between 1953 and 1964. Birth head circumferences are included.

**Table 4**. Number of head circumference measurements of boys in the head circumference (HC) reference 1986–2008 and percentage of measurements ≤ −2 SD and ≥ 2 SD when compared to the HC reference 1953–1964.

| | HC reference 1986-2008 | Boys outside the ± 2 SD range of the HC reference 1953-64 | |
|---|---|---|---|
| Age group | Number of measurements | Percentage ≤ - 2 SDS | Percentage ≥ 2 SDS |
| < 1 mo | 8,063 | 1.8 | 2.9 |
| 1 - 2 mo | 6,200 | 0.1 | 7.0 |
| 2 - 3 mo | 4,483 | 0.1 | 7.2 |
| 3 - 4 mo | 5,868 | 0.1 | 5.5 |
| 4 - 5 mo | 4,793 | 0.1 | 3.4 |
| 5 - 6 mo | 4,795 | 0.1 | 3.6 |
| 6 - 8 mo | 6,397 | 0.3 | 2.8 |
| 8 - 10 mo | 5,395 | 0.3 | 1.9 |
| 10 - 12 mo | 4,237 | 0.3 | 0.8 |
| 12 - 18 mo | 7,785 | 0.5 | 0.6 |
| 18 - 24 mo | 5,023 | 0.4 | 0.5 |
| 2 - 3 y | 4,612 | 0.5 | 0.7 |
| 3 - 4 y | 2,693 | 0.7 | 2.2 |
| 4 - 5 y | 961 | 1.0 | 3.1 |
| 5 - 6 y | 2,453 | 0.7 | 3.4 |
| 6 - 7 y | 1,563 | 0.5 | 4.6 |
| Total | 75,321 | 0.5 | 3.1 |

HC reference 1986–2008 population includes subjects born between 1986 and 2008; HC reference 1953–1964 population includes subjects born between 1953 and 1964. Birth head circumferences are included.

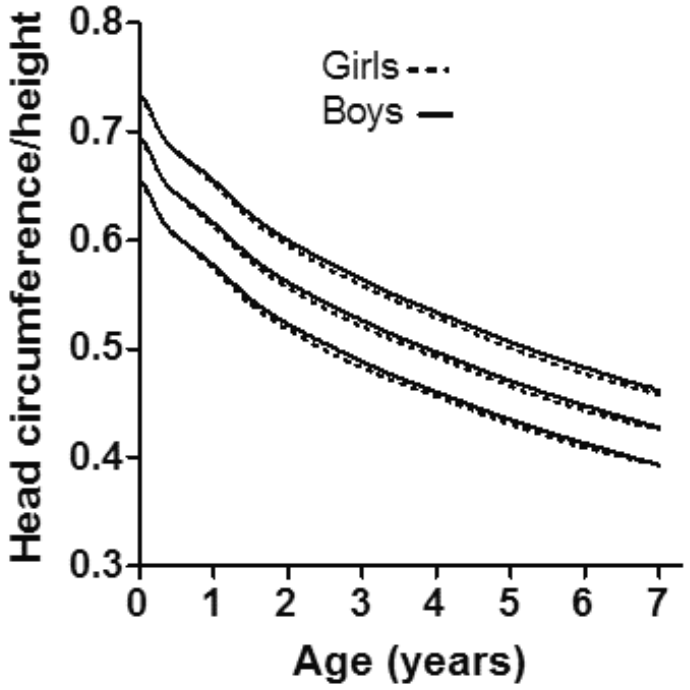


**Figure 6**. HC-to-height ratio for age in boys (solid line) and girls (dashed line) (mean ± 2 SD). Subjects born between 1986 and 2008.

## 4.5 DISCUSSION

In this study we report a positive secular change in HC between the cohorts of Finnish children born 1953–1964 and 1986–2008. Our finding is consistent with previous studies in Sweden, the UK, and Japan (8-11,149,151). In Sweden (8) the updated mean HC reference values were 0.6–1.2 SDS above the previous reference values from birth to 48 months of age. Increase in HC most likely reflects a true secular change in HC, but some methodological factors may contribute. For instance, in Sweden it was speculated that some of the increment was due to the use of a tighter steel measurement instrument for HC (8).

Through this study we demonstrated how outdated cut-off points may lead to misclassification of children. Theoretically, an uncorrected secular

trend of +0.4 SDS in mean HC without a change in SD for HC would mean that only 0.8% of children remained below the lower −2 SDS limit and as many as 5.5% were above the upper +2 SDS limit, instead of the expected 2.3% at both ends. Our observations were consistent with such a rate of misclassification by the mean ±2 SD limits.

In addition to the secular increase in mean HC we also noted a reduction in SD of the HC in the 1986–2008 reference. This further increases the rate of misclassification of outdated limits used for screening of abnormalities in the growth of HC. This results in severe underdiagnosis of conditions with microcephaly, but on the other hand it compensates the secular increase in the mean head circumference. Hence, HC growth references must be periodically updated.

Our results also highlight the importance of using national HC references in Finland, because on average the HC in Finnish children are clearly larger than those published in the multiethnic WHO HC reference or in the US-based CDC 2000 HC reference (13,168)**.** For details, please see Figure 8 (Supplementary Figure).

The strength of this study was the large, population-based, and representative sample of HC measurements of children seen in recent years at child health clinics. Head and brain growth takes place mainly in the first 2–3 years (12,20,21,25). Therefore, we think that HC growth charts from 0 to 7 years are sufficient for screening purposes.

Head circumference-to-height ratio is informative in some growth disorders. For instance, in hypochondroplasia, the HC-to-height ratio depicts macrocephaly better than the HC alone (156). Consistent with former findings, a slight difference between boys and girls was found in our data, with boys having a larger ratio. In Japan, secular trends in both height and HC growth have been reported, but the HC-to-height ratio has remained unchanged (11). Such a comparison was not possible in our study, because data for HC-to-height ratios were not available from the 1953–1964 reference.

## 4.6 CONCLUSION

In HC growth a positive secular change over the past 40–50 years was found in Finnish children. Ignoring this change in HC will lead to significant misclassification and unnecessary referral of children to specialist care because of a false suspicion of macrocephaly. Furthermore, some children with true microcephaly escape our attention when outdated HC references are used. We provide updated HC reference data as a part of the updates of the Finnish growth references.

## 4.7 DECLARATION OF INTEREST

The study was supported by EVO funds. The authors declare no other conflicts of interest.

**Supplementary material for Karvonen M, Hannila M-L, Saari A, Dunkel L. New Finnish reference for head circumference from birth to 7 years, Ann Med. 2012;44:369–374.**

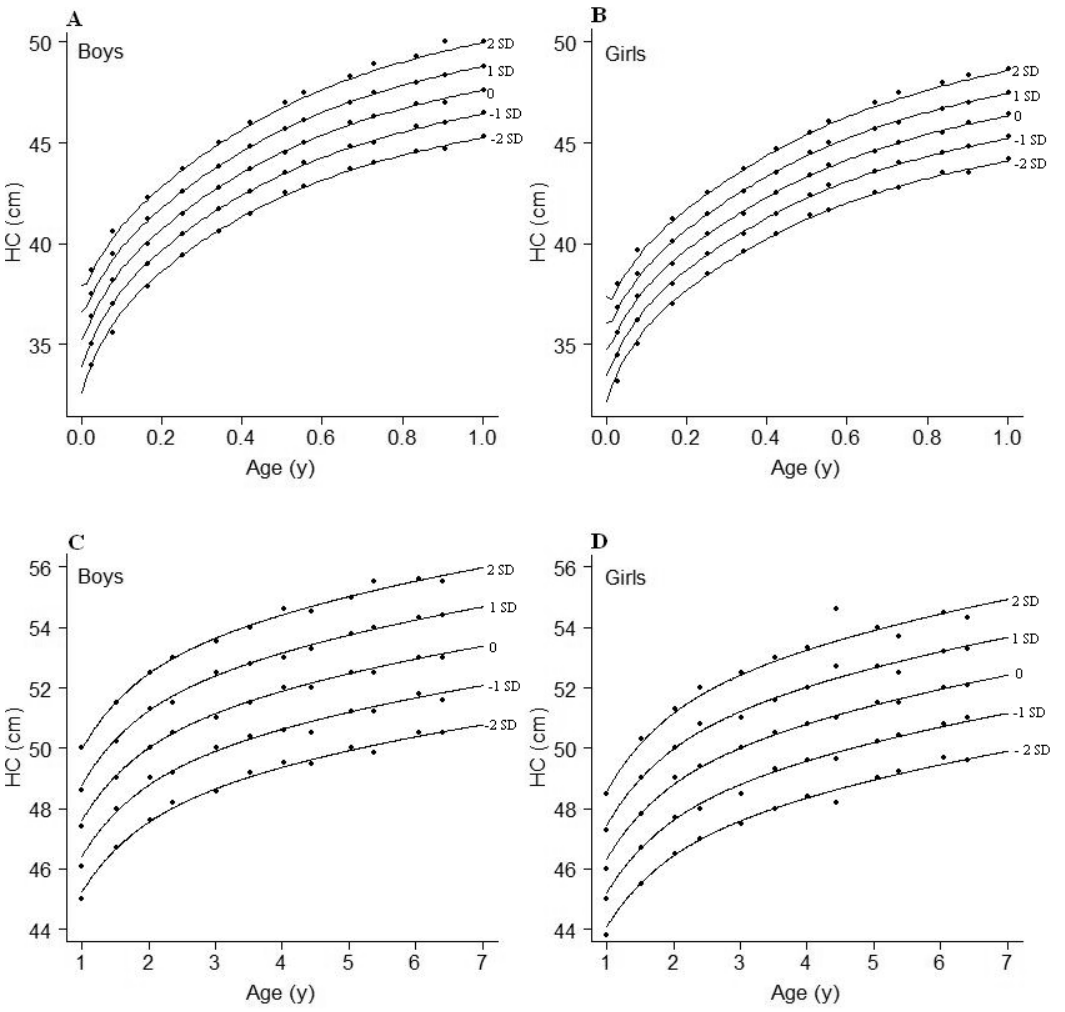


**Figure 7**. Supplementary Figure. Goodnes-of-fit. Empirical percentiles (2nd, 16th, 50th, 84th and 98th percentiles, dots) with corresponding fitted percentiles (lines). (A) Boys aged 0 – 1 year; (B) Girls aged 0 – 1 year; (C) Boys aged 1 – 7 years and (D) Girls aged 1– 7 years.

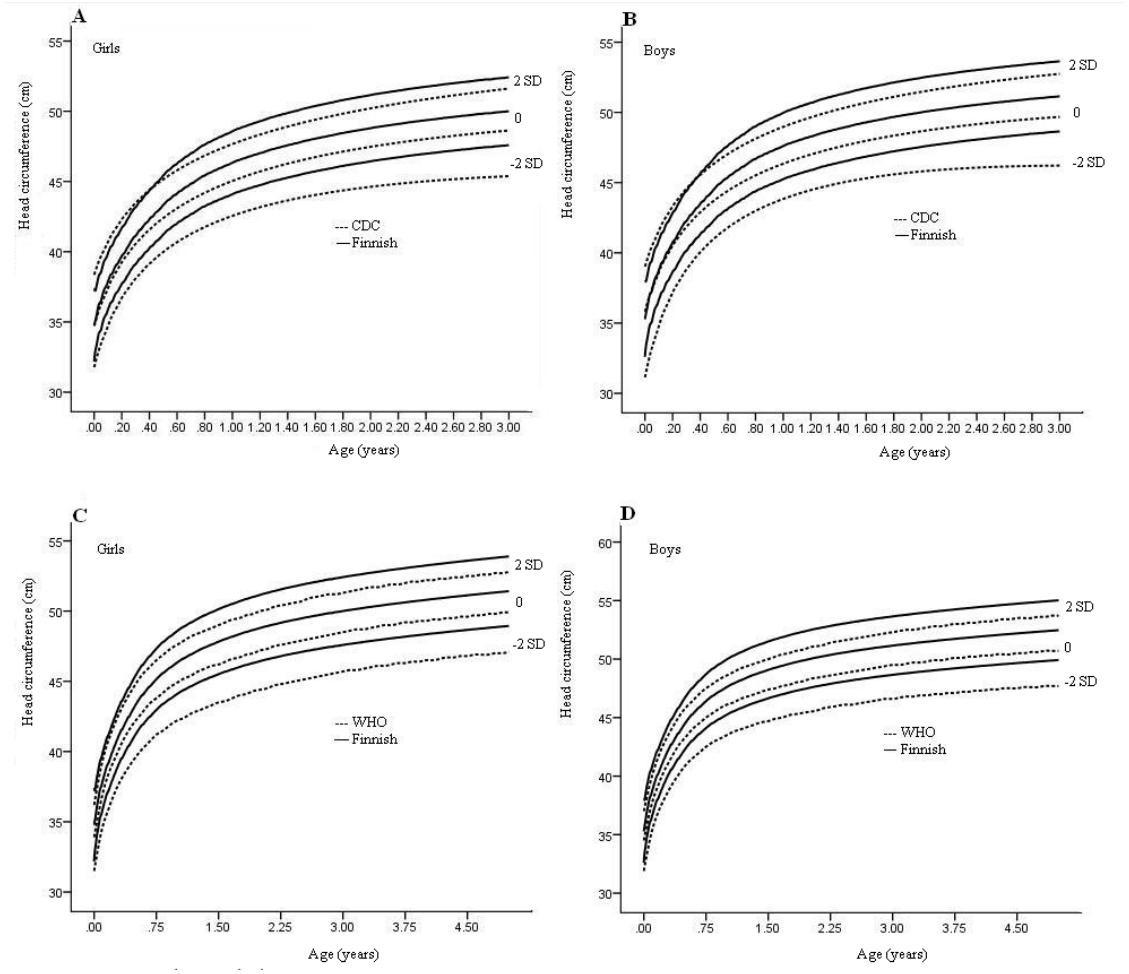


**Figure 8.** Supplementary Figure. Finnish head circumference reference 1986 – 2008 (mean, ±2 SD, solid lines) compared with the CDC 2000 and the WHO HC references (mean, 2 SD, dashed lines). Panels A and B illustrate a comparison to the CDC 2000 HC charts, (A) girls aged 0 – 3 years; (B) boys aged 0 – 3 years. Panels (C) and (D) illustrate the comparison to the WHO HC charts, (C) girls aged 0 – 5 years and (D) boys aged 0 – 5 years.

# 5 ELEVATED HEAD CIRCUMFERENCE-TO-HEIGHT RATIO IS AN EARLY AND FREQUENT FEATURE IN CHILDREN WITH NEUROFIBROMATOSIS TYPE 1

## 5.1 ABSTRACT

**Background/Aims:** Children with neurofibromatosis type 1 (NF1) tend to be macrocephalic and short. Our aim was to define the incidence and diagnostic accuracy of elevated head circumference-to-height ratio (HCHR) in children with neurofibromatosis type 1 (NF1) and to assess if elevated HCHR would facilitate early diagnosis of NF1.

**Methods:** Retrospective analysis of growth and health data of 80 NF1 patients aged 0-7 years was performed. The incidence and diagnostic accuracy of elevated HCHR for NF1 was analyzed using Receiver Operating Characteristic (ROC) curves.

**Results:** The median age when the first elevated (≥ 2.0 SDS) HCHR value was detected was 0.3 years (range 0.0 to 5.3 y). At the median age of diagnosis (3.6 y), 53.8% of NF1 children exhibited elevated HCHR. The diagnostic accuracy of HCHR alone was 0.78 (95% CI 0.72-0.84), but in comparison with the seven National Institutes of Health (NIH) diagnostic criteria for NF1, elevated HCHR was the second most prevalent feature.

**Conclusion:** Elevated HCHR is an early and frequent feature in NF1 children. Taking HCHR into account would facilitate early detection of NF1.

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## 5.2 INTRODUCTION

The assessment of growth in children is a well established and cost-effective part of the preventive health care services provided in the majority of developed countries (169,170), yet the usefulness is still unknown when it comes to the assessment of head circumference.

Assessment of head circumference (HC) is based on the comparison of HC in relation to age or to height, and it aims at an early detection of abnormal head growth, ideally before the child becomes macrocephalic or microcephalic.

Assessment of head growth with respect to height is especially important in some growth disorders, in which discordance between HC and height is a characteristic feature. For instance, in neurofibromatosis type 1 (NF1) a tendency for a larger HC and a shorter stature compared to the general population has been reported (88,89,171). NF1 (MIM # 162200) is a neurocutaneous disease with autosomal dominant inheritance that affects 1:3500 individuals worldwide (172-175). The diagnosis of NF1 is based on seven clinical criteria (Table 1), not including any auxological criteria, established by the National Institutes of Health (NIH) in 1987 (176). The clinical manifestations of NF1 increase with age (177-180), and therefore, in children the diagnosis may be delayed (177). An early diagnosis of NF1 is important because of the associated neurocognitive difficulties and the increased risk for benign and malignant tumors already in childhood.

We postulated that HC-to-height ratio (HCHR) would be elevated in NF1 children, and its assessment would help to distinguish children with NF1 from the healthy population. Furthermore, since the most rapid head growth occurs in the first 2 years of life, we hypothesized that an elevated HCHR would help to find the children with NF1 early, and to serve even as a possible new diagnostic criterion for NF1 in children.

**Table 5**. The prevalence of the National Institutes of Health (NIH) diagnostic criteria for NF1 (176) at the time of diagnosis in 80 NF1 patients, and the prevalence of elevated (≥ 2 SDS) head circumference-to-height ratio (HCHR) at the median age of diagnosis (3.6 years).

| Diagnostic criteria of NF1 (176) | Prevalence at diagnosis in 80 NF1 patients |
|---|---|
| Cafè au lait macules (≥ 6 over 5 mm of diameter in prepubertal children) | 97.5% |
| Skin fold freckling | 23.8% |
| Neurofibromas | 17.5% |
| Lisch nodules | 15.0% |
| Optic glioma | 16.3% |
| Osseus lesions | 8.8% |
| NF1 in 1˚ relative | 40.0% |
| HCHR ≥ 2.0 SDS at the median age of diagnosis (3.6 years) (N = 65) | 53.8% |

## 5.3 PATIENTS ANS METHODS

All NF1 patients (ICD-10: Q85.00) aged 0-16 years attending two university hospital pediatric or neuropediatric outpatient clinics (Kuopio and Helsinki) between January 1996 to June 2010 were included in the study. Their medical records were reviewed, and the NIH criteria on which diagnosis had been based and age at diagnosis were registered. Altogether, 105 NF1 patients were registered. The inclusion criteria for the study were (1) a confirmed NF1 diagnosis based on the NIH criteria, (2) the age at the

diagnosis had been registered, and (3) simultaneous HC and length/height data were available prior to or at the diagnosis and before the age of 7 years. In 21 patients, simultaneous HC and height/length data were not available. In two of the 84 remaining patients, the NIH criteria at diagnosis were not found in the medical records and in another two the age at diagnosis was not registered. Thus, a total of 80 of 105 patients (76.2%) fulfilled the inclusion criteria for the study. These 80 NF1 patients (40 boys, 40 girls) were born between 19th April 1982 and 15th June 2009, and the median age at diagnosis was 3.6 years (range 0.0 to 14.7 years). Six children had been born prematurely at gestational ages ranging from 32 weeks 5 days to 35 weeks 6 days, and until the age of 2 years, their growth data were corrected for the postmenstrual age. In four patients, the diagnosis had been confirmed with genetic testing.

In Finland, children visit child health clinics almost every month during their first year of life and annually after that until 7 years. At every visit, children are measured by primary care nurses with standardized methods and calibrated equipment. HC is measured as the maximum occipito-frontal circumference to the nearest 0.1 cm with a non-stretchable tape. Height is measured in children under 24 months in supine position and after that age, as standing height with a stadiometer, to the nearest 0.1 cm. The same methods are used in children's hospitals by trained nurses, who take the measurements.

Growth data from birth to 7 years of age were included in the present study. Auxological values were converted into standard deviation scores (SDS) using the contemporary Finnish growth references for HC, height and HCHR (166,181). In the reference population, there were 145,239 HCHR measurements from 19,712 children (9,535 girls, 10,177 boys, median 8 measurements per subject, range 1 to 16). A receiver operating characteristic (ROC) curve for the diagnostic accuracy of HCHR was generated by using the highest HCHR value of each NF1 patient, and comparing them with the highest HCHR values of each subject in the reference population. The ROC analyses were performed for the whole NF1 cohort and for boys and girls separately. The area under the curve (AUC) for the elevated HCHR was calculated. The cumulative percentage of

the children with an elevated HCHR was defined. The SPSS statistical software versions 17 and 19 were used in the analyses. The study had the approval of the Ethics Committee of the Hospital District of Pohjois-Savo. Informed consent was not needed because no contact was made with the study subjects.

## 5.4 RESULTS

The total number of HC and length/height measurements and calculated HCHR values was 879 in 80 NF1 patients (median 12 per patient, range 1 to 21, 484 measurements in boys and 395 in girls). Of the HC measurements, 11.8% and 2.8% were at least 2.0 SDS, and of the height measurements, 12.0% and 17.7% were -2.0 SDS or below in boys and girls, respectively (Figure 9). The distribution of HCHR in NF1 patients was shifted to the right: 20.9% of the HCHR values in boys, and 17.5% in girls were at least 2.0 SDS.

The accuracy of screening using HCHR as the only criterion for NF1 was moderate (AUC 0.78; 95% CI 0.72-0.84) (Figure 10). The AUC for boys was 0.79 (95% CI 0.72-0.87) and for girls 0.77 (95% CI 0.68-0.86), respectively. A combined cut-off value of 2.0 SDS for the elevated HCHR was chosen for boys and girls, and used in the subsequent analyses (Figure 10). At the cut-off point of 2.0 SDS, the specificity was 92.2% and the sensitivity 47.5% (in boys, 92.2% and 50.0%, and in girls, 92.2% and 45.0%, respectively). The cumulative percentage of NF1 patients with an elevated HCHR (≥ 2.0 SDS) by age is shown in Figure 11. By the age of 1 year, 34.3% of the patients had an elevated HCHR, by 2 years, the value had risen to 48.4%, and by 3 years, 52.3 % of NF1 patients had elevated HCHR values.

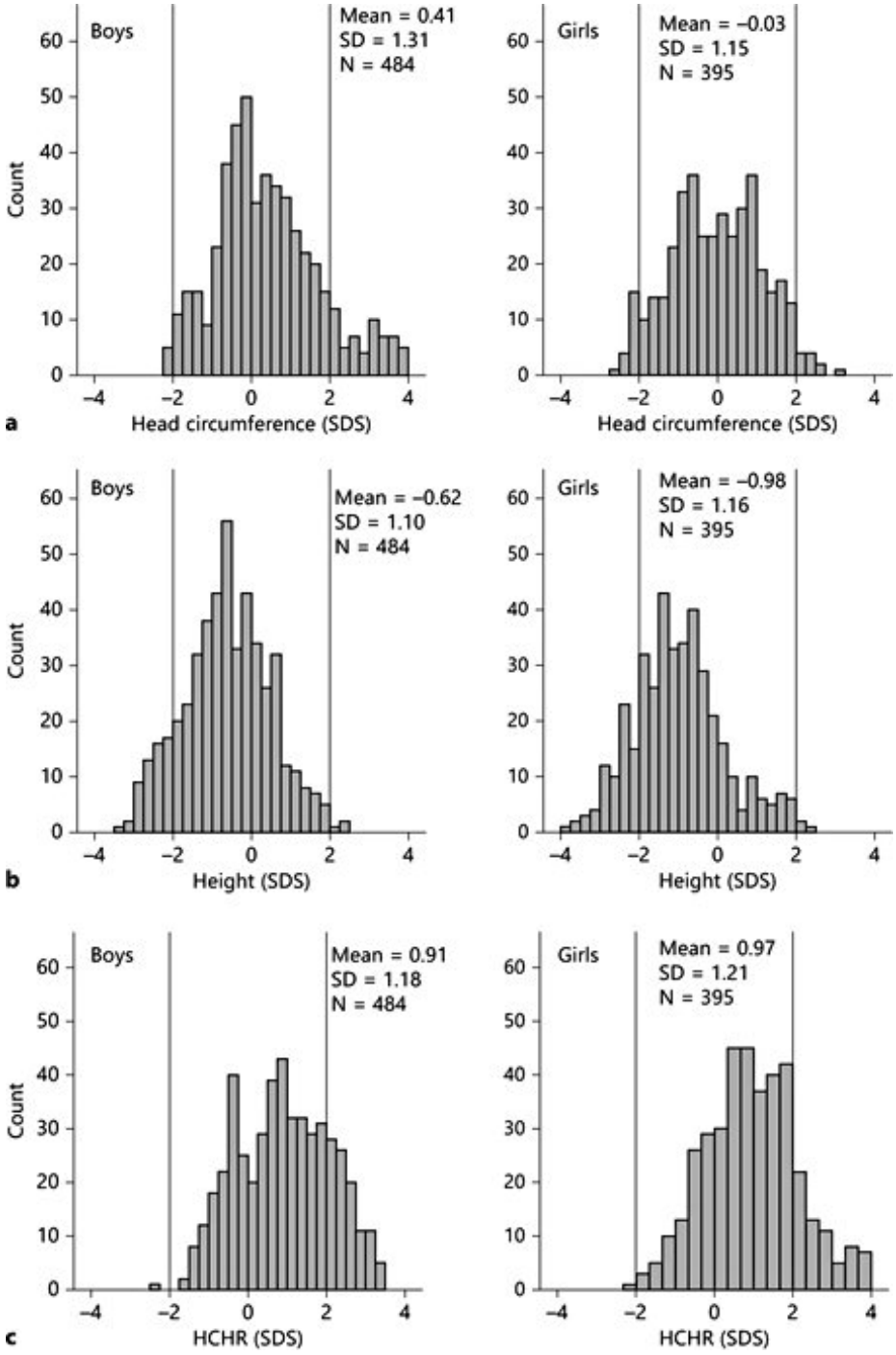


**Figure 9**. Distributions of head circumference (**a**), height (**b**), and HCHR (**c**) in 40 boys (484 measurements) and 40 girls (395 measurements) with NF1, in comparison with the contemporary population-based growth reference.

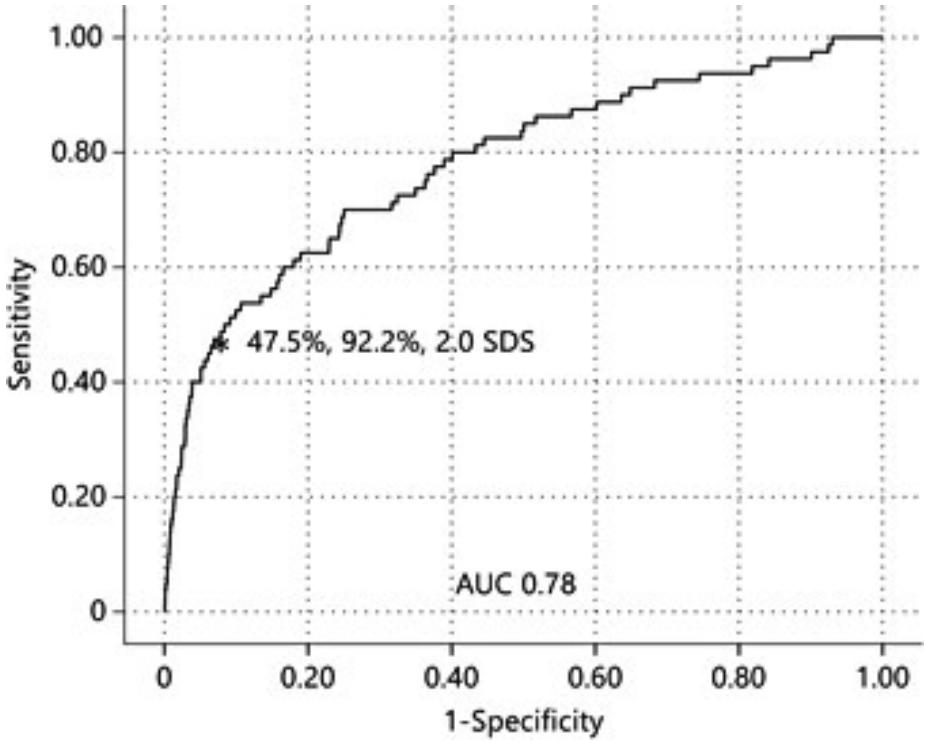


**Figure 10**. The ROC curve for the HCHR in 80 NF1 patients when using their highest HCHR SDS value from birth to 7 years of age. The AUC and the cut-off point (sensitivity-specificity pair with the corresponding SDS) are shown.

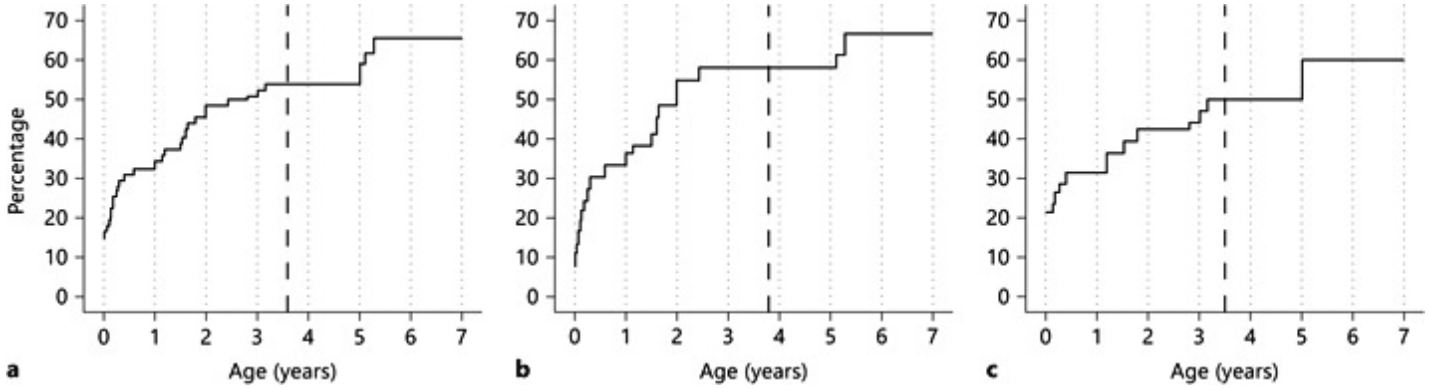


**Figure 11**. The cumulative percentage of NF1 children with an elevated head circumference-to-height ratio (HCHR ≥2.0 SDS) by age in all 80 children (**a**), in boys (n = 40) (**b**), and in girls (n = 40) (**c**). The bold dotted vertical lines indicate the median age at diagnosis (3.6 years in all children, 3.8 years in boys and 3.5 years in girls).

The prevalence of the NIH criteria at the diagnosis (median age at diagnosis, 3.6 years, range 0 to 14.7) in the 80 patients is presented in Table 5. Café au lait macules were observed in 97.5 % of the children, and the second most common diagnostic feature was an affected family member (40.0%). An elevated HCHR value was found in 53.8% of the children at the median age of diagnosis. If an elevated HCHR had been one of the criteria, it would have been the second most common clinical manifestation in our retrospective cohort. Altogether 75 of 80 patients had HCHR data available also prior to the diagnosis, and 31 of the 75 patients with available HCHR data prior to the diagnosis (41.3%) had an elevated HCHR already before the diagnosis. The median age when the first elevated HCHR value was detected was 0.3 years (range 0.0 to 5.3) in the whole study group.

## 5.5 DISCUSSION

In this retrospective cohort study of all eligible NF1 children of two university clinics, we noted that a combined auxological measure, the head circumference-to-height ratio (HCHR), is elevated in the majority of NF1 patients already at a young age. The median age of NF1 diagnosis in our cohort was 3.6 years, and only one of the contemporary NIH diagnostic criteria (café au lait spots) was more prevalent than an elevated HCHR at the diagnosis. Our data suggest that assessing HCHR along with the diagnostic NIH criteria of NF1 would facilitate the early diagnosis in children.

Auxological measures including HC are extensively available for the majority of children in developed countries (169,170). However, the use of HC alone or in combination with height as a diagnostic tool has been scarce. We found only one previous study where auxological data (macrocephaly and short stature together with hypertelorism and thoracal abnormalities) had been used for prediction of NF1 probability at the age of 6 years (182). These features were associated with NF1 at the age of 6 years, and they were indicative for the imminent diagnosis when a child

had insufficient diagnostic criteria below 6 years of age. In a recent study a strong correlation between HC and height was shown, and charts of HC for height were recommended for interpreting HC in short or tall people (183).

In our NF1 cohort, the children were on average shorter, and had a larger head circumference than the general population. Similar findings have been reported in large North American and Italian cohorts of NF1 patients (88,89,171). However, combining the two auxological variables HC and height together gives a new measurable feature, HCHR, which is useful in diagnosis of NF1. As far as we are aware, this is the first study to assess the diagnostic value of elevated HCHR in NF1. The area under the ROC curve for HCHR was 0.78, indicating a moderate diagnostic accuracy if it was used as the only criterion for NF1. Clinically, however, HCHR would be used in combination with the existing diagnostic criteria. Therefore it is reasonable to assume that the combined diagnostic accuracy and specificity would be significantly better. Compared with the other single features in our NF1 cohort, only café au lait macules were more prevalent than elevated HCHR.

There are some limitations in the study. First, around 5-10% of NF1 patients have large deletions including the entire NF1 gene and its neighbouring regions (184-186). These patients have a distinct growth phenotype with overgrowth instead of a short stature (185), as in the majority of NF1 patients with intragenic mutations. These patients with deletions of the entire NF1 gene may not have elevated HCHR. Also, a possible limitation of the study was that the study population consisted only of diagnosed NF1 cases. Another way of recruiting the study population would be from a NF1 referral pool. However, such a referral pool is difficult to collect, and would still leave a source of bias, because in practice the referral criteria would be variable.

A retrospective study setting suffers from certain limitations. For instance, the exact age of the appearance of each clinical manifestation was impossible to ascertain. Another limitation was that growth data could not be collected retrospectively straight from primary care medical records, in which it would have been more complete. The majority of the HC growth occurs before the age of 2 years, and we believe that complete

growth data with several measurements in the infancy would have further supported the diagnostic value of the elevated HCHR in NF1 children. A prospective longitudinal study among infants with prenatal diagnosis of NF1 or the suspicion of the disease due to an affected family member would be necessary to reliably document the timing of the appearance of each clinical manifestation. We are not aware of any such studies. ‘

## 5.6 CONCLUSION

This study shows that a simple and readily available auxological measure, HCHR, is elevated in the majority of NF1 patients at an early age and could help to diagnose NF1 earlier in children. Major strengths of the use of auxological criteria in diagnostics are their noninvasive nature, low costs and availability in all settings. Prospective studies confirming the diagnostic value of HCHR are warranted.

## 5.7 ACKNOWLEDGEMENTS

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## 5.8 DISCLOSURE STATEMENT

The authors have no conflicts of interest relevant to this article.

# 6 SCREENING OF HYDROCEPHALUS IN INFANTS USING EITHER WHO OR POPULATION-BASED HEAD CIRCUMFERENCE REFERENCE CHARTS

## 6.1 ABSTRACT

**Aim:** The aim was to compare the performances of the World Health Organization (WHO) and population-based (PB) references in the screening for hydrocephalus in infants aged <2 years.

**Methods:** We collected 341 longitudinal head circumference (HC) measurements of hydrocephalic infants and 120 181 measurements of 15 145 healthy infants from primary care. The measurements were converted into z-scores, and a new screening parameter, change in HC standard deviation score (SDS) over time (ΔHC SDS), was calculated. Comparisons were made using receiver operating characteristics analysis and linear mixed models.

**Results:** The mean HC $SDS_{WHO}$ was 3.5 and the mean HC $SDS_{PB}$ was 2.9 in the hydrocephalic infants, and in healthy children, those numbers were 1.0 $SDS_{WHO}$ and 0 $SDS_{PB}$ , respectively. The best screening accuracy was obtained with the PB reference in combination with the ΔHC SDS parameter (AUC 0.89). The accuracy of the WHO standard could be improved to a similar level by customising the screening cut-offs of HC SDS according to the population and combining screening parameters.

**Conclusions:** Auxology alone was not sufficient for the screening of hydrocephalus. The WHO standard should be validated in the population, and population-specific cut-offs for normality defined before its introduction.

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## 6.2 KEY NOTES

The performance of population-based (PB) head circum-ference reference or World Health Organization (WHO) standard in detecting hydrocephalus is not known.

The accuracy of the WHO standard was inferior to that of the PB reference, but was improved using population-specific screening cut-offs and a new algorithm detect-ing abnormal head growth.

The WHO standard should be validated before imple-mentation and population-specific cut-offs for normal-ity defined.

## 6.3 INTRODUCTION

Growth-monitoring programmes that include the measuring of head circumference (HC) are a fundamental part of preventive health care for children worldwide (6). The ultimate goal of HC monitoring is the timely diagnosis of treatable conditions affecting head growth. HC is a surrogate measure of brain volume, especially in early childhood (1,5), with a deviating HC growth potentially indicating pathology in the developing brain. Accurate screening for abnormal HC in infancy relies on the growth reference charts used for depicting normative head growth as well as on predefined cut-off limits for abnormality. However, these cut-off values in any given population over the course of development are not well defined (161).

Current HC references consist of population-based (PB) charts and a multiethnic HC standard generated by the World Health Organization (WHO) (13). According to the WHO, its universal standard depicts the ideal head growth in infancy and childhood irrespective of ethnic background (144,145). In an enquiry made by the WHO in 2011, 57 countries had

adopted the WHO HC standard (187). Several studies have assessed the performance of the WHO standards for linear growth in growth disorders, but we found only one study comparing the WHO HC standard values with population-based HC references (137,188). However, studies on the auxological screening of hydrocephalus (19,161) and especially on the performance of the WHO HC standard in the detection of hydrocephalus are scarce.

Hydrocephalus due to blocked cerebrospinal fluid flow is a relatively common condition, with an incidence of 0.8-1.1 cases per 1000 live births (19,129). Its first manifestation, prior to symptoms of increased intracerebral pressure or macrocephaly, is often the rapid growth of HC (19,189). Hydrocephalus is a potentially life threatening but treatable condition that has a favourable prognosis if early diagnosis and timely surgical care are provided (190-192). Thus, it is often regarded as the most important condition justifying regular HC measurement (19). The current study aimed to compare the performance of the WHO HC standard to that of the PB reference in the screening of hydrocephalus in infancy. We aimed to test different auxological screening algorithms including a novel tool for the detection of a pathologic acceleration of HC growth in hydrocephalus.

## 6.4 PATIENTS AND METHODS

The study was approved by the ethics committee of the Northern Savo Hospital District. Data were analysed anonymously without any study participant contact; therefore, according to Finnish legislation, no consent was required.

### 6.4.1 Infants with hydrocephalus

The patient registers of Helsinki, Kuopio, and Oulu university hospitals in Finland were reviewed for infants who had undergone surgery for hydrocephalus, according to the International Statistical Classification of Diseases, Tenth Revision codes G91.0-G91.1, G91.3-91.9 and G94.0-G94.2 before 2 years of age. Infants who were born from full-term pregnancies

(at 37 gestation weeks or later) and who had at least two HC measurements before the cerebrospinal fluid diversion surgery were eligible for the study. In all, 96 patients fulfilling the criteria were found (Figure 12) and clinical data were collected. Of the total cohort, six patients with congenital skull malformations were excluded, as were 29 patients with prenatal hydrocephalus detected antenatally or immediately after birth. The final cohort consisted of 61 (64%) patients with hydrocephalus (38 boys; 62%). They had been operated on at the median age of 4 months (range 0-23 months). Ten patients had been operated on after 1 year of age. The most common aetiology for the hydrocephalus was an intracranial haemorrhage (23%) (Table 6).

Like virtually all Finnish infants, the infants with hydrocephalus had participated in the nationwide free-of-charge growth-monitoring primary care programme. In the programme, infants have visits to well-baby clinic at ages 1-2 weeks and 3-6 weeks, as well as 2, 3, 4, 5, 6, 8, 10, 12, 18 and 24 months; they are measured by trained nurses using standardized methods and calibrated equipment (134). HC is measured with a non-stretchable tape as the maximum occipito-frontal diameter to the nearest 0.1 cm. At hospital visits, the auxological data from the primary care files were combined with the hospital growth data obtained using similar equipment and measurement techniques. For the current study, growth data were collected from the file of each patient until the time of surgery. Potentially false measurements, typing errors, missing values and duplicated recordings were evaluated by scatter plots alongside the plotting of each individual HC curve and were then excluded.

The HC data consisted of a total of 341 HC measurements (median of five, range 2-14 per subject).

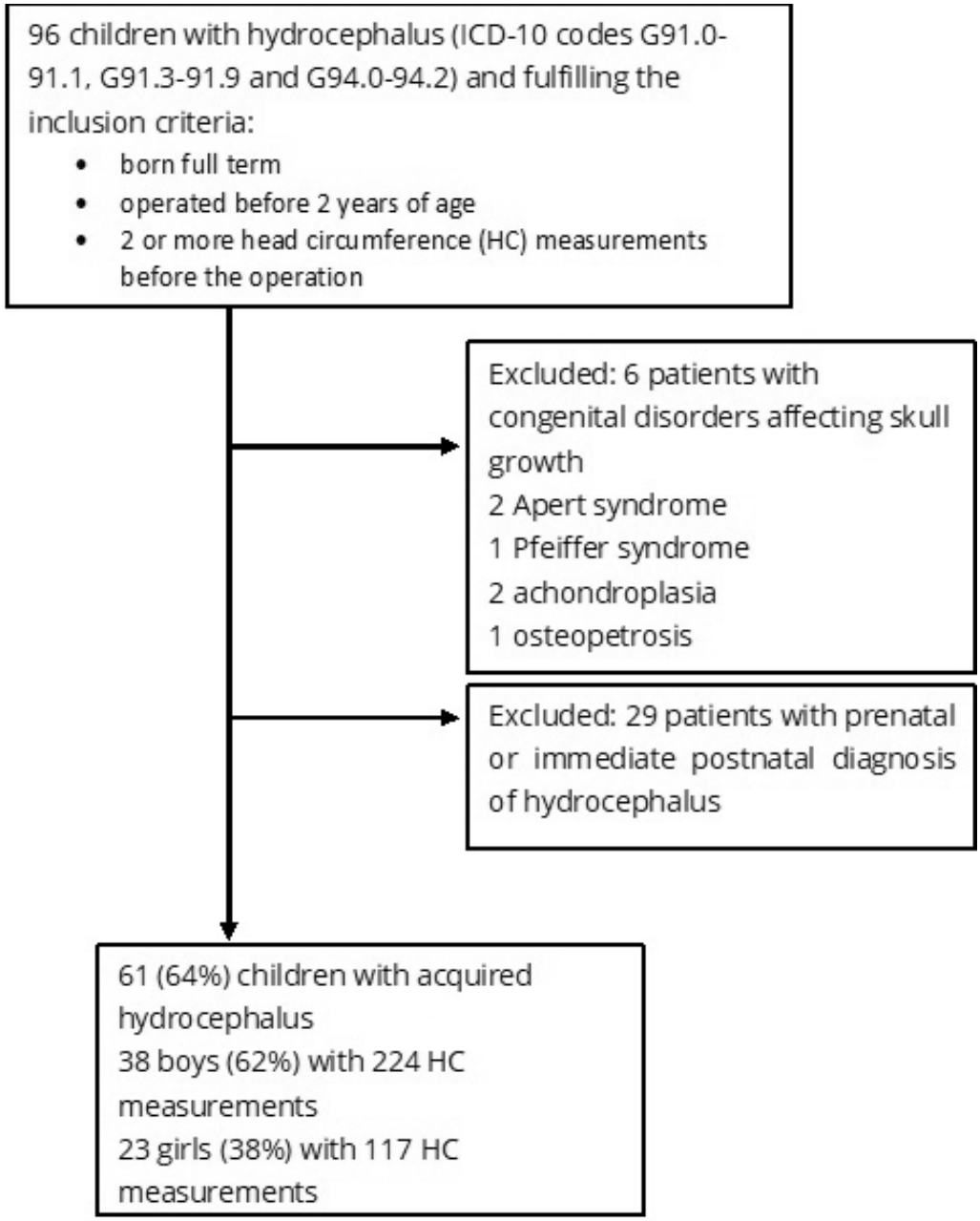


**Figure 12**. Flow chart of the exclusion procedure of the study cohort
Table 6. Characteristics of 61 infants with acquired hydrocephalus

**Table 6**. Characteristics of 61 infants with acquired hydrocephalus

| Characteristic | Value |
|---|---|
| Boys, No (%) | 38 (62) |
| Head circumference Measurements, No | 341 |
| Measurements per infant, Median (range) | 5 (2 – 14) |
| Age at surgery, Median (range), months | 4.1 (0.3 – 22.5) |
| Head circumference SDS using the population-based reference (7,20) at surgery, Mean (SD) | 2.9 (2.0) |
| Head circumference SDS using the WHO standard (7,20) at surgery, Mean (SD) | 3.5 (1.7) |
| **Etiology of hydrocephalus, No, (%)** | |
| Intracranial hemorrhage | 14 (23) |
| Arachnoid cysts | 11 (18) |
| Aqueductal stenosis | 3 (5) |
| Dandy-Walker syndrome | 6 (10) |
| Other cerebral anomaly | 2 (3) |
| Myelomeningocele | 7 (11) |
| Infection | 3 (5) |
| Tumor | 2 (3) |
| Hydrocephalus NAS | 13 (21) |

Abbreviations: No, number; SDS, standard deviation score; SD, standard deviation; NAS, not specified.

### 6.4.2 Reference population

The population used for the construction of the PB HC reference consisted of 19 715 healthy infants and children born from 1986 to 2008 with HC data registered from routine visits at well-baby or school healthcare clinics from birth to 7 years of age in Espoo, which is Finland's second largest city (median seven measurements per subject, range 1-17) (181). The data for the PB HC reference were part of length/height growth reference data that had been collected from the electronic medical records of those patients who had visited well-baby or school healthcare clinics between 10 March 2008 and 9 March 2009 in Espoo (166). All those patients who had HC measurements in the electronic medical records had been further included in the HC reference data.

Out of this population, infants who had at least two HC measurements from birth to 2 years of age comprised the population from which the reference values for the normative HC standard deviation score (SDS) change from birth to 2 years of age (ΔHC SDS) were calculated. The population consisted of 15 145 infants, with a median of nine HC measurements per subject, range 2-15, for a total of 120 181 measurements. This population was also the control population for the hydrocephalic infants in this study.

In addition, for each hydrocephalic infant, four healthy control infants matched for sex and age at each measurement, and for the number of measurements, were chosen from the control population for a detailed demonstration of longitudinal head growth up to 6 months prior to their surgery.

### 6.4.3 Development of the HC screening parameters and statistical analyses

First, using the longitudinal HC data of the reference population, we modelled the normative HC SDS change over time in healthy infants and generated standardized normal values for change in HC SDS over time (ΔHC SDS), for any time interval between two HC SDS measurements.

Cut-off values for the ΔHC SDS parameter were dependent on the time gap between the measurements and the age of the infant (Supplemental Material, Figure 17 A and 17 B). Modelling was conducted using the methodology originally developed for normative height SDS change modelling as published previously (193,194). Modelling of normative HC change is described in detail in the Supplementary Material, eMethods, while the fit of the model is presented in Figure 16.

The longitudinal HC measurements of the 61 hydrocephalic infants and the healthy control population of 15 145 infants were transformed into HC-for-age SDS using both the WHO HC standard and the PB HC reference (13,181). HC SDS is defined as the HC measurement in relation to the median of the reference population expressed in SD units. The standardized values for HC SDS change over time between every HC measurement were calculated for the infants with hydrocephalus and the healthy control population using both the PB reference and the WHO HC standard.

The two HC screening parameters, used either alone or in combination, were HC SDS and the novel HC SDS change over time (ΔHC SDS). The diagnostic accuracy of the screening was expressed as the area under the curve (AUC) values from receiver operating characteristic (ROC) analyses that were performed in comparison with the control population using either the PB reference or the WHO HC standard (166,181).

Analysis of HC SDS and ΔHC SDS in combination was carried out first by performing a binary logistic regression analysis to obtain a predictive probability value of hydrocephalus for the pair of screening parameters for each subject, and thereafter by performing a ROC analysis for these predicted probability values.

Comparison of the WHO HC standard to the PB reference in the assessment of HC growth 6 months prior to CSF diversion surgery was performed using linear mixed models.

Differences in the sensitivities of the screening parameters at the time points of 1, 2, 3, 4, 5, and 6 months prior to cerebrospinal fluid diversion surgery, as well as differences in the overall sensitivities of the screening parameters at specificity levels of 91%, 95%, and 99%, were all tested by

the McNemar test. Differences between AUC values were compared by DeLong's paired samples test.

SPSS statistical software version 25 (IBM Corp) was used for all analyses. GraphPad Prism software version 8 (GraphPad Software Inc) was used for the ROC analyses and graph drawing. AUC values depicting the accuracy of the screening were classified as fail (0.50-0.59), poor (0.60-0.69), moderate (0.70-0.79), good (0.80-0.89) and excellent (0.90-1.00). *P* values < 0.05 were considered statistically significant.

## 6.5 RESULTS

At the time of cerebrospinal fluid diversion surgery, the mean HC SDS of hydrocephalic infants was + 3.5 SDS (SD 1.7) using the WHO standard, compared to + 2.9 SDS (SD 2.0) with the PB reference (Table 6). The HC SDS of the healthy age- and sex-matched peers was depicted constantly at the + 1.0 SDS level using the WHO standard and at the 0 SDS level using the PB reference (Figure 13 A-B). An increase in the HC SDS of hydrocephalic infants was observed nearing the surgery using either of the references, with a significant deviation from their healthy peers starting three months prior to surgery.

Table 7 demonstrates the trade-off between sensitivity and specificity using several HC SDS cut-off values as screening criteria with either the WHO standard or the PB reference. If the HC SDS cut-off level for hydrocephalus screening was set at + 2 SDS, using the PB reference, the specificity would be 94% (ie around 6% of healthy children would be classified as abnormal), and around 61% of infants with hydrocephalus would be detected (sensitivity 61%). To attain the same level of specificity using the WHO standard, the HC SDS cut-off level would have to be set at + 3 SDS, but only around 52% of infants with hydrocephalus would be detected (sensitivity 52%).

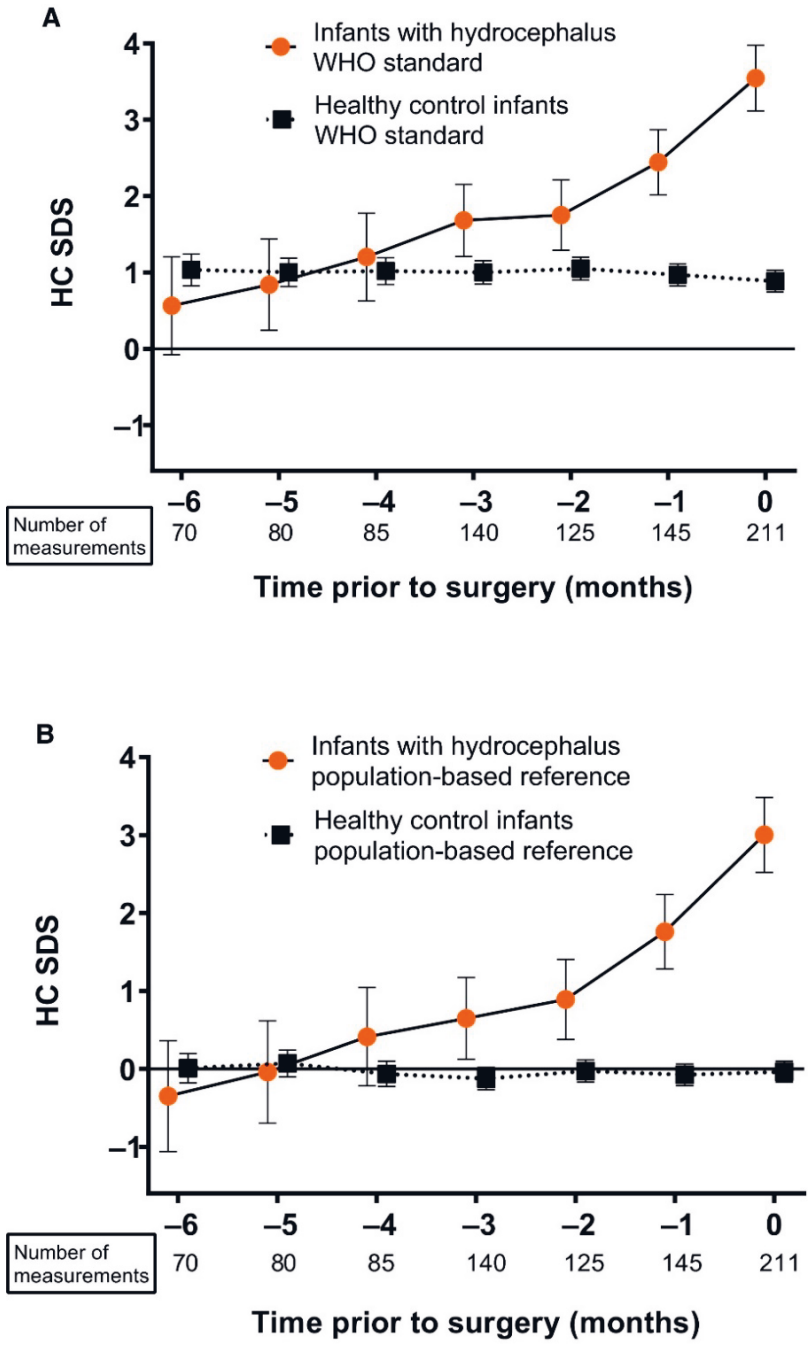


**Figure 13**. Mean HC SDS (95% CIs) in infants with hydrocephalus and age- and sex-matched healthy controls 0-6 mo prior to the surgery according to (A) the WHO standard and (B) the population-based reference. Because the median age at surgery was 4 mo, data from only 26 hydrocephalic infants with 47 observations are available at earlier time points

**Table 7**. Specificity and sensitivity of hydrocephalus screening using either WHO HC standard or population-based HC reference with different head circumference (HC) SDS cut-off levels.

| **Standard deviation score (SDS)** | **WHO HC standard** | | **Population-based HC reference** | |
|---|---|---|---|---|
| | Specificity (%) (95% CI) | Sensitivity (%) (95% CI) | Specificity (%) (95% CI) | Sensitivity (%) (95% CI) |
| 1.5 | 46 (44.8-46.4) | 85 (73.8-93.0) | 86 (85.1-86.3) | 70 (57.4-81.5) |
| 2.0 | 69 (68.3-69.7) | 75 (62.7-85.5) | 94 (93.8-94.5) | 61 (47.3-72.9) |
| 2.5 | 85 (84.3-85.4) | 72 (59.2-82.9) | 98 (97.5-98.0) | 51 (37.7-63.9) |
| 3.0 | 94 (93.7-94.5) | 52 (39.3-65.4) | 99 (99.2-99.5) | 41 (28.6-54.3) |

Abbreviations: CI, confidence interval.

When a specificity level of over 90% was targeted, the sensitivities with the WHO standard were similar to those obtained with the PB reference, at best around 65% (Figure 14 A). Then, the HC SDS screening cut-offs using both growth references had to be adjusted to that target. Using the customised cut-off levels for the current Finnish population, screening for hydrocephalus using the HC SDS parameter resulted in good overall accuracy using either of the references: $AUC_{WHO}$ was 0.81 (95% CI, 0.74-0.88) and $AUC_{PB}$ was 0.83 (95% CI, 0.76-0.89) ($P$ = 0.08, Figure 15). However, with either of the references, accepting lower specificity (ie lowering the cut-off for abnormal HC SDS from + 3.0 to + 1.5) did not improve the sensitivity to acceptable levels (Table 7), indicating that screening based on only HC SDS criterion is poor.

The new ΔHC SDS parameter performed better with the PB reference than with the WHO standard: At the 90% specificity level, around 80% of hydrocephalic infants were detected as being abnormal compared to around 60% using the WHO standard (P = 0.002-0.031 at specificity levels

91%-99%) (Figure 14 B). The best overall screening accuracy was obtained when the ΔHC SDS parameter was used together with the PB reference ($AUC_{PB}$ 0.89, 95% CI, 0.83-0.95, $P$ = 0.02 in comparison with the HC $SDS_{PB}$ parameter alone) (Figure 15 B). This indicates that when using the PB reference in combination with the ΔHC SDS parameter and the cut-off that classifies 9% of children as abnormal (specificity level 91%), 75% of hydrocephalic infants are correctly detected. The ΔHC SDS parameter in combination with the WHO standard did not yield as high an accuracy ($AUC_{WHO}$ 0.85, 95% CI, 0.79-0.91, $P$ = 0.04 in comparison with $AUC_{PB}$) (Figure 15 B). However, the best accuracy with the WHO standard was obtained when the HC SDS and ΔHC SDS parameters were used in combination, yielding an AUC of 0.87 (95% CI, 0.80-0.93) (Figure 15 C) which was significantly higher than the accuracy when HC $SDS_{WHO}$ was used alone ($P$ = 0.01), and as good as those obtained with the population-based reference.

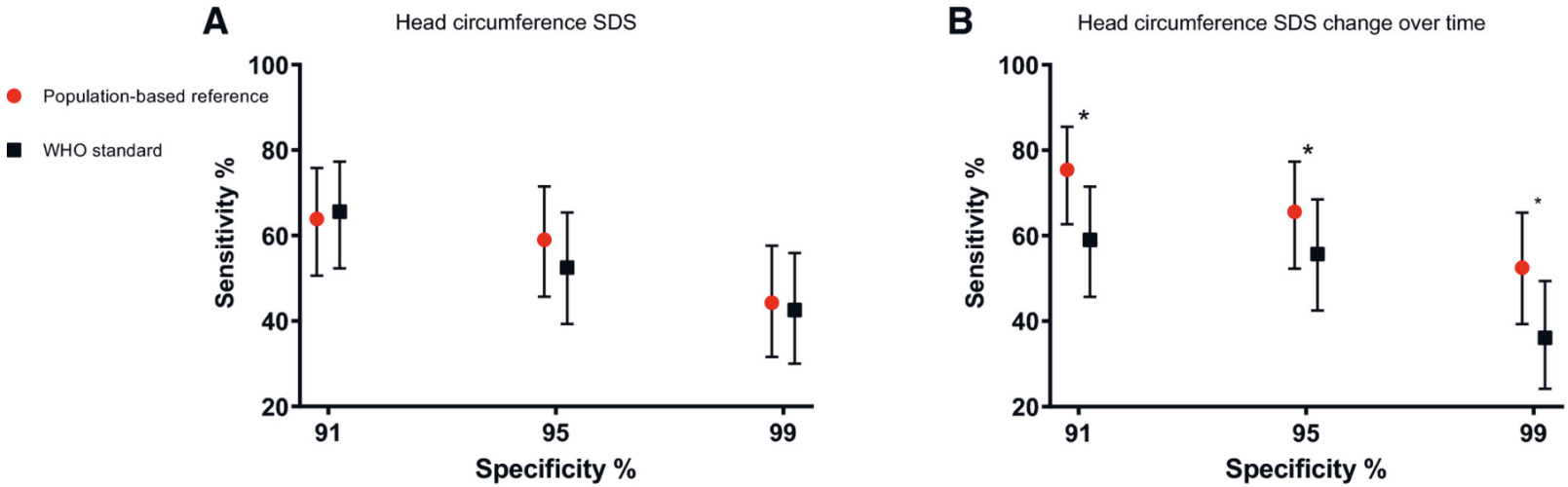


**Figure 14**. Sensitivities at 91%, 95% and 99% specificity levels for (A) the head circumference standard deviation score (HC SDS) parameter, B) the HC SDS change parameter using either the population-based reference or the WHO HC standard in 61 infants who underwent surgery for hydrocephalus before 2 y of age compared to 15 145 healthy peers *$P < 0.05$)

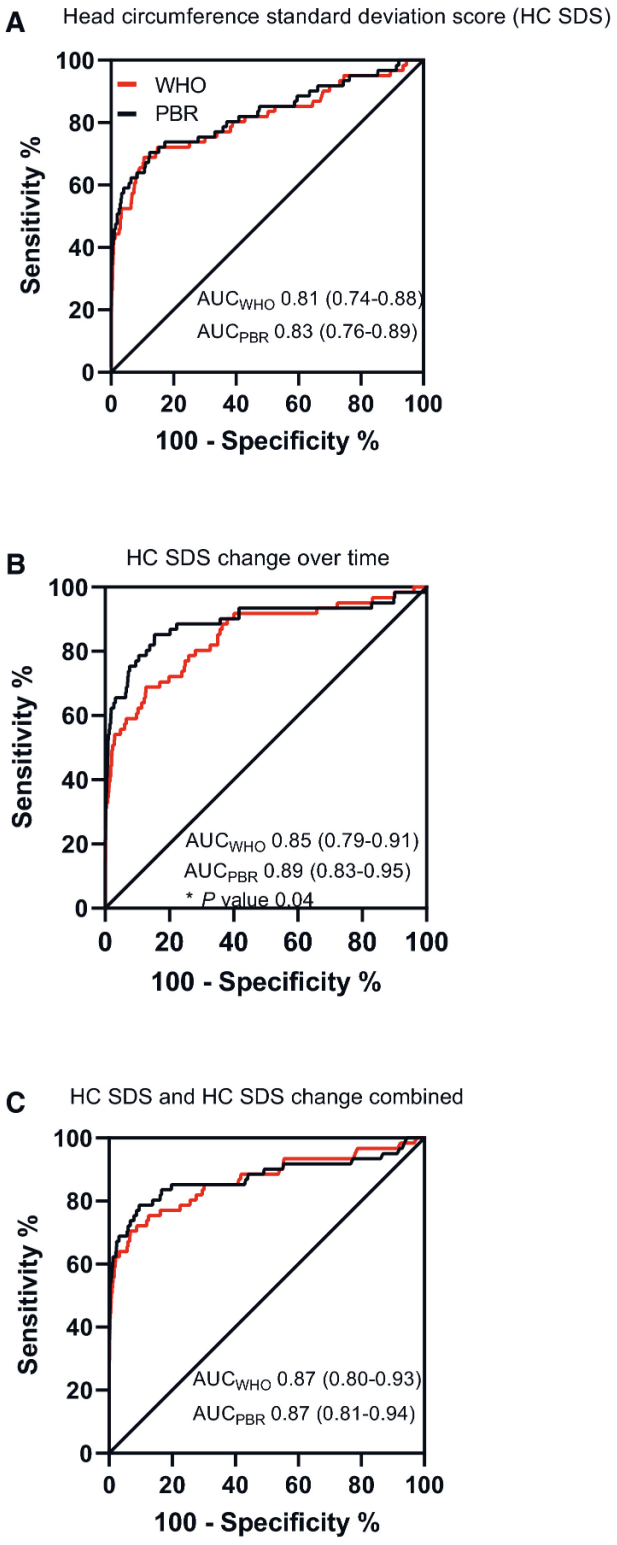


**Figure 15**. Performance of screening for abnormal head growth in 61 hydrocephalic infants using either the WHO standard (red line) or the population-based reference (black line) with the screening parameters (A) head circumference standard deviation score (HC SDS), B) head circumference SDS change over time (ΔHC SDS) and C) combination of HC SDS and ΔHC SDS

## 6.6 DISCUSSION

In this study, we showed that the WHO HC standard is not as accurate as the population-based (PB) HC reference in screening for hydrocephalus in Finnish infants. However, the performance of the WHO standard could be augmented to the same level as the PB reference with two actions. First, the HC SDS cut-offs were customised to the population. Second, a new screening parameter, the standardized change of HC SDS over time (ΔHC SDS), was used. Even at their best, auxological methods alone are not sufficient for screening for hydrocephalus in infancy. Therefore, they must be supplemented by other screening methods including careful clinical assessment.

The WHO HC standard has been adopted for use in many countries despite the lack of an initial validation or knowledge on how well it represents the relevant population (187). We have shown that the contemporary Finnish head growth reference substantially deviates from the multiethnic WHO standard (181). For example, a head circumference of 49 cm (ca. 0 SDS) in a 2-year-old female corresponds to more than + 1 SDS in the WHO standard. Similar observations have been reported in at least 18 countries (14,16,17,137,195), some of which have adopted the WHO charts in their growth assessments. In 2019, after too many inaccurate referrals because of macrocephaly, Norwegian health authorities replaced the WHO HC standard with a population-based reference (196).

When setting up a screening protocol for a condition in a population, it is crucial to define the acceptable proportion of false positives. These are individuals who are healthy but are identified as abnormal and will be subject to unnecessary examinations. The severity and treatability of the target condition—in this case, acquired hydrocephalus—may warrant the acceptance of lower specificity. When the specificity of the screening test is, for example, 90%-95%, then 5%-10% of the population would be identified as abnormal. If abnormal head size or growth over time is suspected, the first examination would be a cerebral ultrasound, which is an inexpensive and non-invasive examination. In infants older than 1 year of age, magnetic

resonance imaging of the brain would be performed, usually under general anaesthesia.

The screening accuracy of any test is always a trade-off between specificity and sensitivity. In the present study, the best diagnostic accuracy was obtained using the PB reference in combination with the HC SDS change over time parameter with a specificity of 91% and a sensitivity of 75%. This means that 9% of healthy infants would have required further examinations and, still, 25% of hydrocephalic infants would not have been detected. That is obviously not optimal. On the other hand, if the prevalence of hydrocephalus in a given population is one per 1000 children, the negative predictive value of hydrocephalus screening would be very high. This means that a normal result in head circumference screening almost certainly indicates that the infant does not have hydrocephalus. A positive predictive value of any test for a relatively rare condition in a population is always low, even though the test is positive.

To our knowledge, this was the first study to systematically evaluate HC growth over time (ΔHC SDS) as a screening parameter for hydrocephalus. The major strength of this novel monitoring parameter was the ability to adapt it to any measurement interval from birth to 2 years of age. We are aware of only a few hydrocephalus screening studies that used change in HC, and these studies used constant, predefined criteria for percentile crossing or change in the SDS level. A Dutch study (161) of 43 hydrocephalus patients explored several predefined referral criteria for HC and the change in HC SDS. The researchers found that the combination of a very large HC (>2.5 SDS) and/or very large progressive growth of HC (SDS change > 2.5) had the best screening accuracy in terms of sensitivity (77%), specificity (97%) and positive predictive value. The sensitivity of the combined parameters (HC SDS and ΔHC SDS) in our study using a population-based reference was 67%, with specificity at 97%. It was not as optimal as that seen in the Dutch study. There are, however, several possible methodological explanations for the observed difference. These include the use of only infants under 1 year of age in the Dutch population, when head enlargement is greater due to more open cranial sutures. In addition, in contrast to our study, the Dutch population included preterm

infants (21%). Preterm infants often exhibit catch-up growth, that is growth crossing percentiles or SDS levels as a normal phenomenon, with further pathological head enlargements potentially causing even larger changes in HC SDS. Lastly, in contrast to our study, the Dutch study did not account for the timeline, so the 'large' or 'very large' change in HC may have occurred over either a shorter or longer time interval.

In our study, there was an overrepresentation of boys 38 (62%) in hydrocephalic infants. This is not a new finding, as a similar gender difference has been described in prevalence studies in infantile (129) and congenital hydrocephalus (197).

The potential limitations of this study include its retrospective nature, its relatively small study population and the collection of the data from patient files. We also could not assess the diagnostic yield of screening, but this would optimally be done in a prospective population-based longitudinal setting.

However, we believe that the growth data retrieved from the electronic health records were not biased. The systematic growth monitoring has been operative in Finland for over 50 years, and in the quality assessment, false measurements, typing errors and missing values were scarce (158). We also believe that despite the retrospective setting, the main observations concerning the need for the customisation of the WHO standard cut-offs according to the population, as well as the augmented accuracy of screening using the novel ΔHC SDS, are, in any case, relevant.

## 6.7 CONCLUSION

Screening for abnormal head growth by measuring HC is easy, inexpensive and non-invasive. It can facilitate the timely diagnosis of hydrocephalus in infancy, provided that an adequate growth reference is used, along with pre-established screening criteria with validated cut-off limits. Before the multiethnic WHO HC standard is implemented in any population, its performance within the specific population should be validated. Also, the population-specific cut-offs for abnormality should be defined and used. Because evidence-based head growth screening includes complex

algorithms, this process should ideally be computerised and implemented within electronic health record systems. However, the screening process can be converted and simplified for settings that use manual tools.

At its best, auxology alone is not sufficient for the screening for hydrocephalus in infancy. Other means are needed, such as careful clinical evaluation of the early clinical signs of hydrocephalus in primary care.

## 6.8 ACKNOWLEDGEMENTS

We thank research nurse Eeva Heikkilä, who assisted with collecting the data.

## 6.9 CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

## 6.10 SUPPLEMENTARY ONLINE CONTENT

eMethods, Decsription of normative head circumference standard deviation change modeling in a healthy population

**Figure 16**. Fit of the model of normative change in head circumference standard deviation score from birth to A) one year of age, and to B) 7 years of age.

**Figure 17**. Cut-off values for abnormal change in head circumference SDS A) from birth to 12 months of age B) from 12 to 24 months of age

### eMethods, Description of normative HC SDS change modeling in a healthy population

Modeling of the normative HC SDS change was performed using longitudinal HC growth data from the healthy control population and was based on the presumption that the expectation value for the change in HC

SDS between repeated measurements of the same person is 0, and on the fact that the distribution of the change in HC SDS in a fixed age interval is normally distributed with a mean of zero and a SD of $\sqrt{(2*(1-r))}$, where r is the correlation between the HC SDS measurements at the ends of the interval (198). Age groups according to the usual schedule of routine measurements in primary health care (monthly until one year and then yearly until age of 7 years) were formed to obtain approximations for the correlations of fixed age intervals. The correlations were calculated for all possible pairs of age groups and modeled with regression analysis, in which the dependent variable was their Fisher transformation $z = 0.5*\log((1+r)/(1-r))$, since it produced a normally distributed function. The explanatory variables were the averages of the age difference and the averages of the pair of ages and/or some transformations of these values (199). Separate models were created for the two age group classifications (age less than one year and more than one year). The predicted correlation could be further calculated by $r = (\exp(2*z)-1)/(\exp(2*z)+1)$ for the predicted value of z. Furthermore, the predicted value for SD for change could be calculated using the above formula $\sqrt{(2*(1-r))}$. The standardized value of change in HC SDS is then the actual change divided by its predicted value of SD. The model fit was evaluated by plotting different residual plots, and plotting the fitted SD curves together with the data points of the original data. Since the models for both sexes were very close to each other, a common model was calculated. The fit of both models is shown in Figure 16. According to these formulas, the change in HC SDS ($\Delta$ HC SDS) was standardized by age distance and mean age between two measurements. The resulting cut-off values for growth rate are scalable for age without the limitation of fixed time intervals.

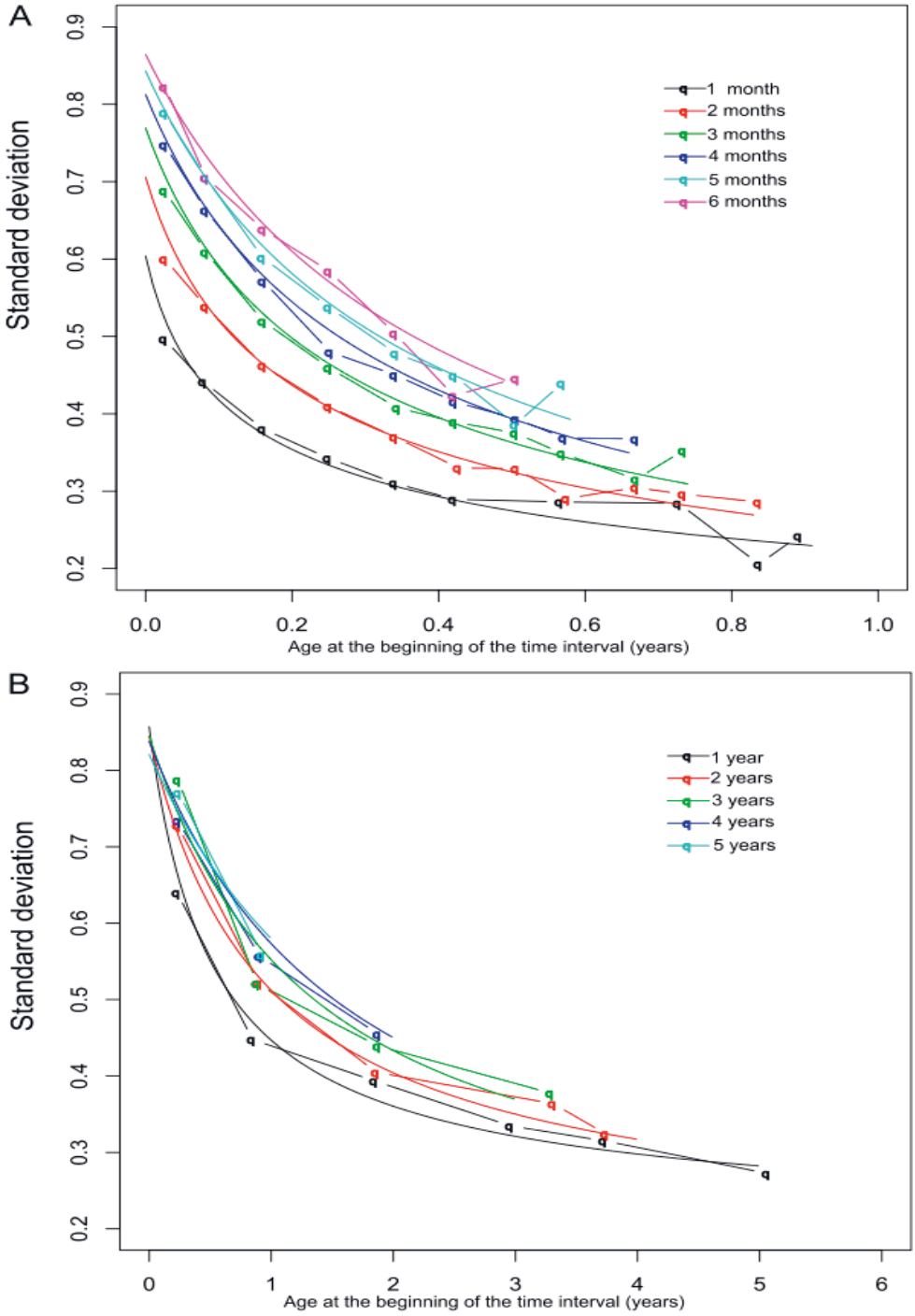


**Figure 16.** Model fit of the normative change in head circumference standard deviation score from birth A) to one year of age and B) to 7 years of age. The fitted SD curves (continuous lines) are plotted together with the data points of the original data (lines marked with q). Each color represents a specific time interval in which the normative change of HC SDS is depicted.

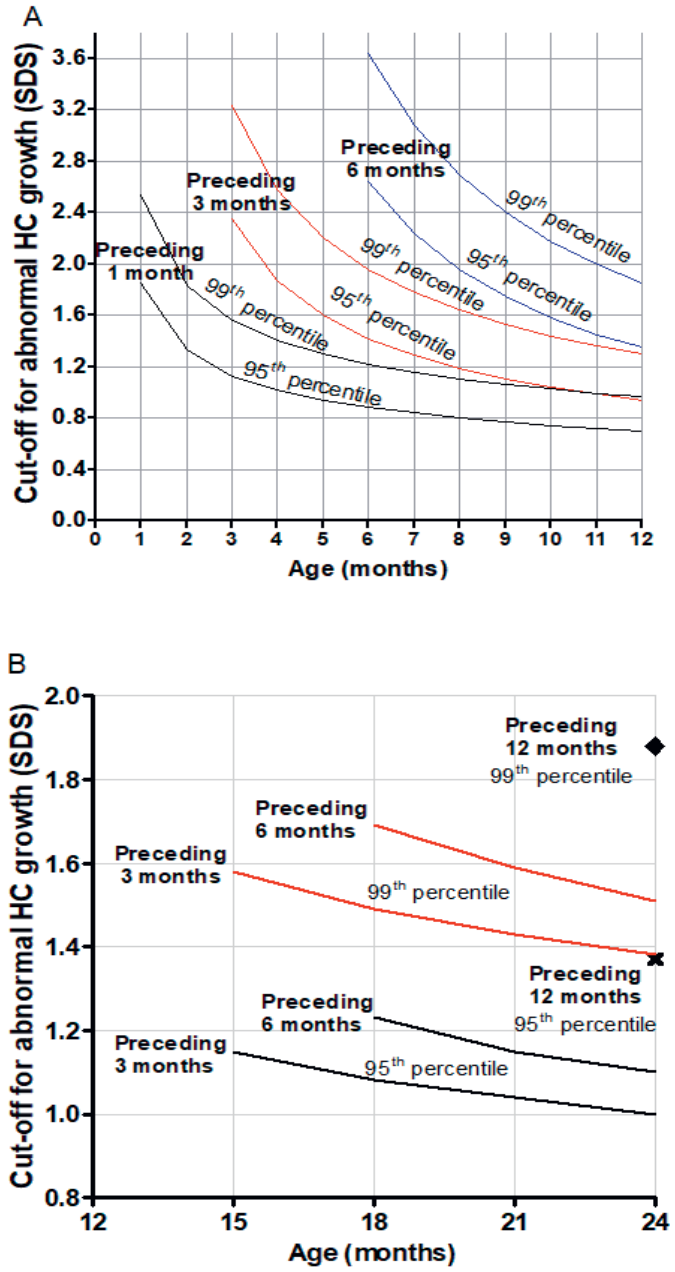


**Figure 17.** Cut-off values for abnormal change in HC SDS from A) birth to 12 months of age and B) from 12 to 24 months of age. The change of HC SDS by either the 95$^{th}$ or 99$^{th}$ percentile limit is calculated during the preceding A) 1, 3 or 6 months B) or 3, 6 or 12 months and compared with the cut-off value given by the curve.

# 7 MATERNAL SMOKING DURING PREGNANCY AND OFFSPRING HEAD GROWTH IN COMPARISON TO HEIGHT AND WEIGHT GROWTH UP TO 6 YEARS OF AGE: A LONGITUDINAL STUDY

## 7.1 ABSTRACT

**BACKGROUND:** Maternal smoking during pregnancy causes fetal growth retardation. Thereafter, it has been associated with excessive childhood weight gain and decreased linear growth in the offspring. However, it is not known whether head circumference (HC), the surrogate of brain size in childhood, is altered after intrauterine tobacco exposure. We assessed the association of maternal smoking during pregnancy with offspring HC growth up to age 6 years in comparison with length/height growth and weight gain.

**STUDY DESIGN AND SETTING:** We combined data from Medical Birth Register and longitudinal growth data from primary care of 43,632 children (born 2004-2017). Linear mixed effects models were used for modeling, adjusting for potential perinatal and socioeconomic confounders.

**RESULTS:** At birth**,** maternal smoking during pregnancy was associated with a mean deficit of -0.19 standard deviation score (SDS) (95% CI -0.25, -0.12) in HC, -0.38 SDS (95% CI -0.43, -0.32) in length, and -0.08 SDS (95% CI -0.14, -0.02) in weight-for-length. HC in smokers' children failed to catch up to that of non-smokers' children. Height of smokers' infants reached that of non-smokers' infants by 12 months but declined thereafter. Weight-for-height of smokers' infants exceeded the level of non-smokers' infants at 3 months and remained significantly elevated thereafter. HC in the offspring

of mothers who quit smoking in the first trimester was not deficient, but their weight-for-height was elevated.

**CONCLUSIONS:** HC of smokers' children is still deficient at age 6 years. Because most of the head growth occurs during the first 2 years of life, the defect may be permanent. In smokers' children, weight gain was excessive up to 6 years and height was deficient at 6 years consistent with previous literature. Efforts should be made to encourage pregnant women to quit smoking in the beginning of the pregnancy.

Adapted with permission of Dove Medical Press from Karvonen M, Saari A, Sund R, Sankilampi U. Maternal smoking during pregnancy and offspring head growth in comparison to height and weight growth up to 6 years of age: a longitudinal study. Clin Epidemiol. 2021;13:959-970. https://doi.org/10.2147/CLEP.S327766. The tables and figures are modified from the original to correspond sequential numbers of this thesis.

**Key words**: maternal smoking, tobacco exposure, child growth, head circumference, weight, height

**Plain English Summary**

Maternal smoking during pregnancy is associated with reduced weight, length and head circumference of the newborn. Postnatally, these children tend to gain excessive weight whereas their height growth is not increased in a similar way. The impact of maternal smoking during pregnancy on head growth in childhood is less well characterized. Head circumference is an indicator of brain size in childhood.

The aim of this study was to clarify how maternal smoking in pregnancy is associated with child head growth, in comparison with growth in weight and height from birth to age 6 years in a population of 43,632 children.

We showed that maternal smoking after the first trimester of pregnancy was associated with a slightly smaller head size in offspring at least until the age of 6 years.

Most of the head and brain growth occur during the first two years of life, and the persisting deficit in head size at 6 years may be permanent.
No deficit was observed in the head size of those children whose mothers had quit smoking in the first trimester of pregnancy.

Efforts should be taken to encourage pregnant women to quit smoking in the beginning of the pregnancy.

## 7.2 INTRODUCTION

Maternal smoking during pregnancy is among the most common risk behaviors that harm unborn fetuses. In Europe, the prevalence of smoking in pregnancy varies from less than 5% in Lithuania to 19% in Scotland; in the U.S., the numbers range from 2% in California up to 27% in West Virginia (200-202). Intrauterine exposure to tobacco smoke has been associated with neurodevelopmental issues including cognitive deficits and behavioral problems (203,204). These associations have been linked to biological factors such as impaired brain growth due to fetal hypoxia (123,205), alterations in brain structure and function (206), and epigenetic changes (207). On the other hand, familial and genetic factors have largely explained the associations between maternal smoking in pregnancy and offspring neurobehavioral problems such as attention deficit hyperactivity disorder (ADHD) (203). However, there is consistent evidence of a causal environmental effect of maternal smoking in pregnancy on fetal growth resulting in reduced weight, length, and HC at birth (77,107,203,208). Maternal smoking during pregnancy has been associated with excessive childhood weight gain and obesity in the offspring (108,209) as well as with a deficit in postnatal height growth up to adolescence (69,114,210,211). Head circumference (HC) is a surrogate measurement of brain size at birth and during childhood (1,5), and it is not known whether maternal smoking during pregnancy alters the growth of the developing brain permanently. A complete catch-up in HC during the first year of life has been observed in some studies (66-68,77), whereas others have reported suboptimal head growth during the first year of life (108,114). These studies with conflicting results have limitations, such as relatively small study samples from less than 200 to around 2000 infants with short follow-up times mostly limited to infancy, or lack of controlling for confounding factors that could affect head growth.

The aim of this study was to assess the association of maternal smoking during pregnancy with postnatal head growth in comparison with postnatal length/height growth and weight gain in a large population-based cohort of mothers and children, using up-to-date growth references

and auxological methodology and controlling for perinatal and socio-demographic confounding factors.

## 7.3 MATERIAL AND METHODS

### 7.3.1 Study design and population

The original study population comprised all 51,489 children (51.5% boys) born in Finland between January 1, 2004, and August 31, 2017, and living in the city of Espoo, Finland, on September 14, 2017 (Figure 18). This study links perinatal and birth outcome data of the Finnish Medical Birth Register maintained by the Finnish Institute for Health and Welfare (THL) with data on the socioeconomic status of the mothers from Statistics Finland and the longitudinal growth data from birth to 6 years of age obtained from primary care electronic health records. The exclusion criteria included a preterm or post-term birth (before 37 or after 42 gestation weeks, n = 4,705), a major congenital anomaly or syndrome (diagnostic codes Q00-07, Q75, Q85-87, and Q90-99 according to the International Classification of Diseases, 10th version, ICD-10, n = 603), or in vitro fertilization (n = 1821). We also excluded mother-child pairs for whom data was not available on socioeconomic status (n = 72) or maternal smoking during pregnancy (n = 656). The final population comprised 43,632 children (51.2% boys) (Figure 18).

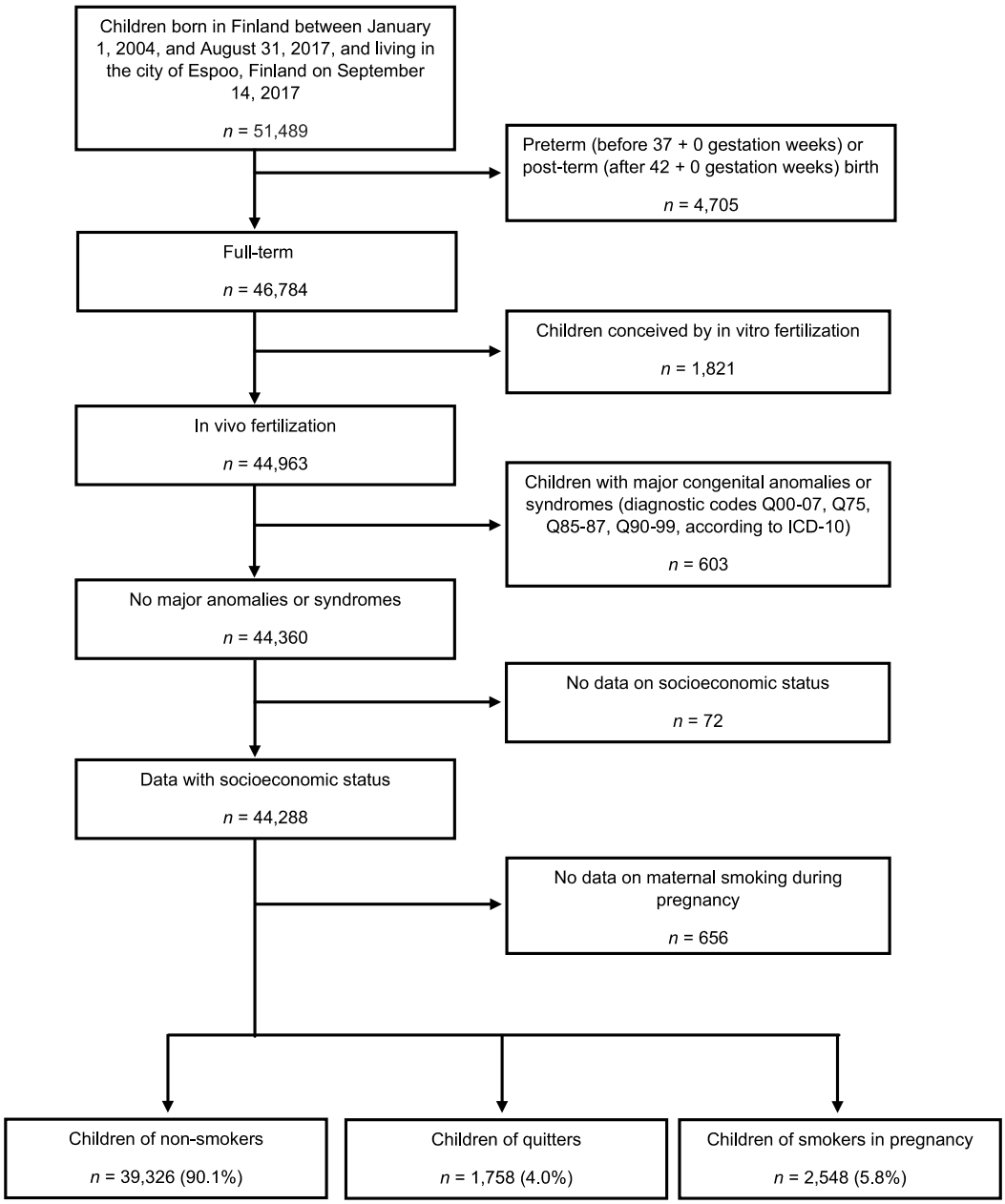


**Figure 18**. Flow diagram of the study population. Perinatal data were obtained from the Finnish Medical Birth Register. Non-smokers did not smoke at all during pregnancy, quitters stopped smoking during the first trimester, and smokers continued smoking after the first trimester. ICD-10, International Classification of Diseases, 10$^{th}$ version.

### 7.3.2 Auxological measurements

Birth weight, length, and head circumference of all newborns were measured at the birth hospital and registered in Medical Birth Register and primary care files. After birth, all infants and children in Finland are provided regular free-of-charge primary care visits, which include auxological evaluations by trained nurses. HC, weight, and length/height are measured using standardized techniques. There is a minimum of 11 visits during the first 24 months of life, and thereafter annual visits up to 6 years of age. Longitudinal growth data of the study population were gathered from the electronic health records of Espoo primary care. In the 43,632 children, there were 575,421 HC measurements, 572,938 length/height measurements, and 572,699 weight measurements between 0 and 6 years of age (median 14 HC, length/height and weight measurements per subject, range 1–37; range 1–36 in weight measurements). HC, weight, and length/height measurements were converted into SDS units using population-based growth references (166,181,212).

### 7.3.3 Covariates

The information regarding maternal smoking habits during pregnancy was self-reported by the mothers and gathered in Medical Birth Register by primary care nurses who meet the mothers regularly during the pregnancy. Smoking status was classified as 1) non-smokers who did not smoke at all during pregnancy, 2) quitters who stopped smoking during the first trimester, and 3) smokers who continued smoking after the first trimester. Previous studies have shown a good agreement of Medical Birth Register smoking data with the medical records (213,214). Data on the quantity of smoking were not gathered in the register.

Medical Birth Register data on potential risk factors that may affect fetal or postnatal growth were used as exclusion criteria (Figure 18) or covariates in the statistical analyses. Maternal age, height, and pre-pregnancy body-mass index (BMI), which was calculated according to

maternal pre-pregnancy height and weight (weight (kg)/[height (m)]$^2$), were used as continuous variables. The rest were categorical variables: parity (primi- or multiparous), living status (cohabiting or single), dichotomous indicators for any hypertensive or diabetic condition of the mother or for assisted fertility treatments (after excluding those conceived by in vitro fertilization), birth asphyxia (defined as umbilical pH < 7.05 or ICD-10 codes O68, P20, or P21), or plurality (twinning or single birth). Child's age and sex were included in the HC, weight, and length/height SD conversion algorithms (166,181,212). Diagnoses of maternal hypertensive or diabetic conditions were set by doctors in primary care and maternal outpatient clinics during pregnancy.

Data on socioeconomic status (SES) based on the occupation of the mother were obtained from Statistics Finland. SES was classified into 4 categories: SES I) upper white-collar worker, SES II) lower white-collar worker, SES III) blue-collar worker, and SES IV) others, including entrepreneurs, students, pensioners, homemakers, and those not included in SES I-III.

### 7.3.4 Statistical analyses

The association of maternal smoking during pregnancy with postnatal longitudinal head growth as well as with length/height and weight-for-length/height growth were evaluated using linear mixed effect models for repeated measures with heterogeneous autoregression correlation structure. Growth data were grouped by age categories, between which the within-subject correlation was taken into account in the models. During the first 6 months of life infants and their families visit child health clinic every month or even more frequently. To simplify the analyses, we used less frequent intervals to form the age groups: birth (until third day after birth), 3 months (fourth day after birth – 0.38 years), 6 months (0.39-0.75 years), 12 months (0.76-1.25 years), 18 months (1.26-1.75 years), 2 years (1.76-2.50 years), 3 years (2.51-3.50 years), 4 years (3.51-4.50 years), 5 years (4.51-5.50 years), and 6 years (5.51-7.00 years; the median age of the last age group was 6.0 years). If several measurements were available for a

child within the age category, only one measurement nearest to the intended age was used in the analyses. For example, all measurements between 2.51 (circa 30 months) and 3.50 years (42 months) were considered possible for representing the 3-year measurement, but the measurement closest to the age of 3 years was chosen for analyses.

The number of HC, length/height, and weight measurements by age group is provided in the supplemental materials (Tables 10-12). Also, scatter plots of 5% random samples of the HC, length/height and weight measurements by age are provided in the supplemental materials (Figure 20). Multivariate models were adjusted for potential confounding factors: maternal height, age and pre-pregnancy BMI, parity, living status, SES, maternal hypertensive or diabetic condition, birth asphyxia, assisted fertility treatments (after excluding those conceived by in vitro fertilization), and plurality (twinning or single birth).

Linear mixed models were used also for unadjusted analyses for HC, length/height, and weight-for-length/height as a baseline comparison.

All analyses were performed using SPSS statistical software version 27 (IBM Corp., Armonk, NY).

## 7.4 RESULTS

### 7.4.1 Tobacco exposure during pregnancy

Altogether, 43,632 children were included in the final study population. Mothers of 39,326 children (90.1 %) were non-smokers during pregnancy, mothers of 1,758 children (4.0%) stopped smoking during the first trimester (“quitters”), and mothers of 2548 (5.8%) children smoked after the first trimester (Figure 18). Mothers who smoked during pregnancy were the youngest, and those who did not smoke during pregnancy were the oldest mothers. (Table 7). Smokers belonged less often to the highest SES group than did non-smokers [4.6% (95% CI: 3.8, 5.5) vs. 34.8% (95% CI: 34.3, 35.2)] and were less often multiparous [51.3% (49.4, 53.3) vs. 56.3% (95% CI: 55.8, 56.8), respectively)]. Smokers had a slightly higher pre-pregnancy BMI compared with that of quitters or non-smokers [median

23.1 kg/m² (interquartile range (IQR) 20.5, 26.7) vs. 22.8 kg/m² (IQR 20.8, 25.9) and 22.4 kg/$m^2$ (IQR 20.5, 25.0)], respectively). Smokers and quitters were also slightly shorter than non-smokers. A greater proportion of smokers than non-smokers were single [19.3% (95% CI 17.6, 20.9)] vs. 3.5% (95% CI 3.3, 3.6)].

**Table 7**. Characteristics of the study population (N = 43,632) by maternal smoking status

| Characteristics | Non-smokers n=39,326 (90.1%) | Quitters n=1,758 (4.0%) | Smokers n=2,548 (5.8%) | Total n=43,632 (100%) |
|---|---|---|---|---|
| **Maternal characteristics** | | | | |
| Age at delivery, years (median, IQR) | 31.4 (28.3–34.6) | 28.2 (24.4–32.1) | 26.6 (22.7–31.7) | 31.2 (27.8-34.4) |
| Pre-pregnancy BMI, kg/m² (median, IQR) | 22.4 (20.5-25.0) | 22.8 (20.8-25.9) | 23.1 (20.5-26.7) | 22.5 (20.6-25.1) |
| Height, cm mean (SD) | 166.0 (± 6.1) | 165.6 (± 5.9) | 165.3 (± 6.0) | 166.0 (± 6.1) |
| **Socioeconomic status, n (%)** | | | | |
| SES I | 13,670 (34.8) | 236 (13.4) | 118 (4.6) | 14,024 (32.1) |
| SES II | 13,995 (35.6) | 710 (40.4) | 692 (27.2) | 15,397 (35.3) |
| SES III | 3,346 (8.5) | 304 (17.3) | 627 (24.6) | 4,277 (9.8) |
| Other | 8,315 (21.1) | 508 (28.9) | 1,111 (43.6) | 9,934 (22.8) |
| Single, n (%) | 1,272 (3.5) [a] | 146 (9.6) [b] | 423 (19.3) [c] | 1,841 (4.5) [d] |
| Primiparous, n (%) | 17,175 (43.7) | 1,119 (63.7) | 1,240 (48.7) | 19,534 (44.8) |
| Maternal hypertension, n (%) | 1,504 (3.8) | 89 (5.1) | 94 (3.7) | 1,687 (3.9) |
| Maternal diabetes, n (%) | 3,545 (9.0) | 199 (11.3) | 246 (9.7) | 3,990 (9.1) |
| Assisted fertilization method, n (%) | 991 (2.5) | 30 (1.7) | 27 (1.1) | 1,048 (2.4) |
| Gestational age, weeks, (median, IQR) | 40.1 (39.3, 40.9) | 40.3 (39.4, 41.0) | 40.1 (39.1, 41.0) | 40.1 (39.3, 40.9) |
| Boys, n (%) | 20,159 (51.3) | 899 (51.1) | 1,282 (50.3) | 22,340 (51.2) |
| Twins, n (%) | 553 (1.4) | 28 (1.6) | 43 (1.7) | 624 (1.4) |
| Birth asphyxia, n %) | 1,794 (4.6) | 105 (6.0) | 135 (5.3) | 2,034 (4.7) |

Notes: Abbreviations: IQR, interquartile range; BMI, body-mass index; SDS, standard deviation score; CI, confidence interval; [a] n=36,858; [b] n=1,519; [c] n=2,194; [d] n=40,571

### 7.4.2 Head circumference

At birth, the mean unadjusted HC SDS was significantly smaller in smokers' newborns (mean -0.31 SDS, 95% CI: -0.37, -0.25) than in non-smokers' newborns (mean -0.06 SDS, 95% CI: -0.07, -0.04) (Table 8). The unadjusted HC SDS in the smokers' children continued to be smaller than in the non-smokers' children throughout childhood. At 6 years, the mean unadjusted HC SDS of the smokers' children was -0.29 SDS (95% CI: -0.33, -0.25), whereas that of the non-smokers' children was -0.07 SDS (95% CI: -0.09, -0.06) (Table 8).

After adjusting for confounding factors, the differences in HC SDS between smokers' and non-smokers' offspring remained significant from birth to 6 years of age (Figure 19 A, Table 9). The adjusted HC of smokers' infants at birth was on average 0.19 SDS smaller (95% CI: 0.12, 0.25) than in non-smokers' (Figure 19 A). The mean difference between the HC of smokers' and non-smokers' offspring at 6 years of age was -0.15 SDS (95% CI: -0.19, -0.10) (Figure 19 A) corresponding to 2 mm.

In the children of quitters, the mean unadjusted or adjusted HC SDS did not differ from HC SDS of non-smokers' children from birth to 6 years of age (Figure 19 D, Tables 8 and 9).

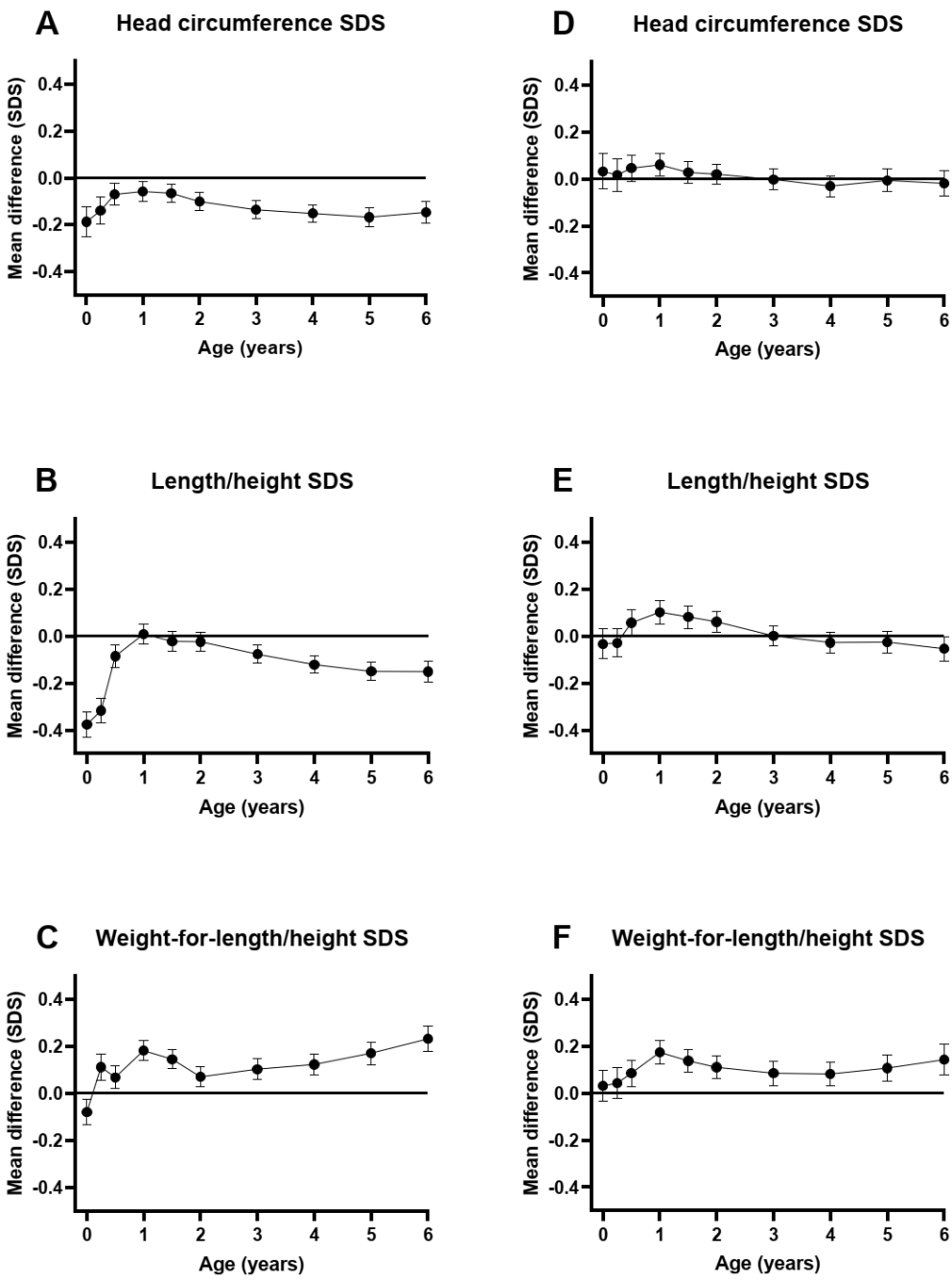


**Figure 19**. The mean difference in HC, length/height, and weight-for-length/height SDS from birth to 6 years of age between children of mothers who smoked during pregnancy and those of non-smoking

mothers (marked as a line at zero), panels A–C, and between children of mothers who quit smoking during first trimester and those of non-smoking mothers (marked as a line at zero), panels D–F. Solid lines indicate the mean difference in (A and D) head circumference (HC), (B and E)length/height, and (C and F) weight-for-length/height. Error bars indicate 95% confidence intervals. Mean differences are derived from linear mixed models with adjustments for age at visit, maternal height, age at delivery, pre-pregnancy BMI, parity, socioeconomic status, housing (single or cohabiting), maternal hypertensive and diabetic conditions, fertility treatments (children conceived by in vitro fertilization had been excluded), twinning, and birth asphyxia.

**Table 8.** Mean unadjusted standard deviation scores (head circumference, length/height, and weight-for-length/height) by maternal smoking status from birth to 6 years of age

| Age | Non-smokers | Quitters | Smokers |
|---|---|---|---|
| **Head circumference standard deviation score, (95% CI)** | | | |
| Birth | -0.06 (-0.07, -0.04) | -0.06 (-0.14, 0.01) | -0.31 (-0.37, -0.25) |
| 3 months | -0.13 (-0.14, -0.11) | -0.15 (-0.22, -0.08) | -0.33 (-0.39, -0.28) |
| 6 months | -0.11 (-0.12, -0.09) | -0.10 (-0.15, -0.04) | -0.24 (-0.29, -0.20) |
| 1 year | -0.13 (-0.14, -0.12) | -0.11 (-0.16, -0.06) | -0.25 (-0.29, -0.21) |
| 1.5 years | -0.17 (-0.18, -0.16) | -0.18 (-0.23, -0.14) | -0.30 (-0.34, -0.26) |
| 2 years | -0.13 (-0.14, -0.12) | -0.15 (-0.20, -0.11) | -0.30 (-0.34, -0.26) |
| 3 years | -0.11 (-0.12, -0.10) | -0.16 (-0.20, -0.11) | -0.32 (-0.35, -0.28) |
| 4 years | -0.09 (-0.10, -0.08) | -0.17 (-0.21, -0.12) | -0.31 (-0.35, -0.28) |
| 5 years | -0.09 (-0.10, -0.08) | -0.13 (-0.18, -0.09) | -0.32 (-0.36, -0.28) |
| 6 years | -0.07 (-0.09, -0.06) | -0.14 (-0.19, -0.08) | -0.29 (-0.33, -0.25) |
| **Length/height standard deviation score, (95% CI)** | | | |
| Birth | -0.09 (-0.10, -0.08) | -0.10 (-0.16, -0.03) | -0.44 (-0.50, -0.39) |
| 3 months | -0.14 (-0.16, -0.13) | -0.14 (-0.21, -0.08) | -0.44 (-0.49, -0.38) |
| 6 months | -0.17 (-0.18, -0.15) | -0.08 (-0.14, -0.02) | -0.23 (-0.27, -0.18) |
| 1 year | -0.10 (-0.11, -0.09) | 0.03 (-0.03, 0.08) | -0.07 (-0.12, -0.03) |
| 1.5 years | -0.09 (-0.10, -0.08) | 0.02 (-0.03, 0.07) | -0.09 (-0.13, -0.05) |
| 2 years | -0.11 (-0.12, -0.10) | -0.02 (-0.07, 0.03) | -0.11 (-0.15, -0.07) |
| 3 years | -0.05 (-0.05, -0.04) | -0.01 (-0.06, 0.03) | -0.10 (-0.14, -0.06) |
| 4 years | -0.01 (-0.02, 0.00) | -0.01 (-0.05, 0.04) | -0.11 (-0.14, -0.07) |
| 5 years | 0.00 (-0.01, 0.01) | 0.00 (-0.05, 0.05) | -0.13 (-0.17, -0.09) |
| 6 years | 0.00 (-0.01, 0.01) | -0.02 (-0.07, 0.03) | -0.13 (-0.17, -0.08) |
| **Weight-for-length/height standard deviation score, (95% CI)** | | | |
| Birth | -0.01 (-0.02, 0.01) | 0.06 (0.00, 0.13) | -0.02 (-0.08, 0.03) |
| 3 months | -0.04 (-0.06, -0.03) | 0.04 (-0.03, 0.10) | 0.13 (0.08, 0.19) |
| 6 months | 0.00 (-0.01, 0.01) | 0.13 (0.07, 0.18) | 0.14 (0.09, 0.18) |
| 1 year | -0.10 (-0.11, -0.09) | 0.11 (0.07, 0.16) | 0.15 (0.11, 0.19) |
| 1.5 years | -0.12 (-0.13, -0.11) | 0.06 (0.01, 0.10) | 0.09 (0.05, 0.13) |
| 2 years | -0.11 (-0.12, -0.10) | 0.04 (0.00, 0.09) | 0.03 (-0.01, 0.07) |
| 3 years | -0.03 (-0.04, -0.02) | 0.10 (0.05, 0.15) | 0.15 (0.10, 0.19) |
| 4 years | -0.09 (-0.10, -0.08) | 0.03 (-0.02, 0.08) | 0.10 (0.06, 0.14) |
| 5 years | -0.16 (-0.17, -0.14) | -0.01 (-0.07, 0.04) | 0.09 (0.04, 0.13) |
| 6 years | -0.19 (-0.20, -0.18) | -0.01 (-0.08, 0.05) | 0.11 (0.06, 0.17) |

Notes: All standard deviation score values are derived from linear mixed models analyses.
Abbreviations: CI confidence interval.

**Table 9**. Mean adjusted standard deviation scores for head circumference, length/height, and weight-for-length/height by maternal smoking status from birth to 6 years of age

| Age | Non-smokers | Quitters | Smokers |
|---|---|---|---|
| Mean head circumference standard deviation score, (95% CI) | | | |
| Birth | -0.07 (-0.12, -0.02) | -0.04 (-0.13, 0.05) | -0.26 (-0.34, -0.18) |
| 3 months | -0.14 (-0.19, -0.09) | -0.13 (-0.21, -0.05) | -0.28 (-0.36, -0.21) |
| 6 months | -0.12 (-0.17, -0.07) | -0.07 (-0.15, 0.00) | -0.19 (-0.26, -0.13) |
| 1 year | -0.14 (-0.19, -0.10) | -0.08 (-0.15, -0.02) | -0.20 (-0.26, -0.14) |
| 1.5 years | -0.18 (-0.23, -0.14) | -0.16 (-0.22, -0.09) | -0.25 (-0.31, -0.19) |
| 2 years | -0.15 (-0.20, -0.10) | -0.13 (-0.19, -0.07) | -0.25 (-0.31, -0.19) |
| 3 years | -0.13 (-0.18, -0.08) | -0.13 (-0.20, -0.07) | -0.27 (-0.33, -0.21) |
| 4 years | -0.11 (-0.16, -0.06) | -0.14 (-0.20, -0.08) | -0.26 (-0.32, -0.21) |
| 5 years | -0.11 (-0.15, -0.06) | -0.11 (-0.18, -0.04) | -0.27 (-0.33, -0.21) |
| 6 years | -0.09 (-0.14, -0.05) | -0.11 (-0.18, -0.04) | -0.24 (-0.30, -0.18) |
| **Mean length/height standard deviation score, (95% CI)** | | | |
| Birth | -0.22 (-0.27, -0.18) | -0.25 (-0.33, -0.18) | -0.59 (-0.66, -0.53) |
| 3 months | -0.27 (-0.32, -0.23) | -0.30 (-0.37, -0.23) | -0.59 (-0.65, -0.52) |
| 6 months | -0.30 (-0.34, -0.25) | -0.24 (-0.31, -0.17) | -0.38 (-0.44, -0.32) |
| 1 year | -0.23 (-0.28, -0.19) | -0.13 (-0.20, -0.06) | -0.22 (-0.28, -0.16) |
| 1.5 years | -0.22 (-0.27, -0.18) | -0.14 (-0.20, -0.08) | -0.24 (-0.30, -0.18) |
| 2 years | -0.24 (-0.29, -0.20) | -0.18 (-0.24, -0.12) | -0.26 (-0.32, -0.20) |
| 3 years | -0.18 (-0.22, -0.13) | -0.17 (-0.23, -0.11) | -0.25 (-0.31, -0.19) |
| 4 years | -0.14 (-0.19, -0.10) | -0.17 (-0.23, -0.11) | -0.26 (-0.31, -0.20) |
| 5 years | -0.14 (-0.18, -0.09) | -0.16 (-0.22, -0.10) | -0.28 (-0.34, -0.22) |
| 6 years | -0.13 (-0.18, -0.08) | -0.18 (-0.25, -0.11) | -0.28 (-0.34, -0.22) |
| **Mean weight-for-length/height standard deviation score, (95% CI)** | | | |
| Birth | -0.14 (-0.19, -0.10) | -0.11 (-0.19, -0.03) | -0.22 (-0.29, -0.16) |
| 3 months | -0.18 (-0.22, -0.13) | -0.13 (-0.21, -0.06) | -0.07 (-0.14, 0.00) |
| 6 months | -0.13 (-0.18, -0.09) | -0.05 (-0.11, 0.02) | -0.06 (-0.13, 0.00) |
| 1 year | -0.23 (-0.28, -0.19) | -0.06 (-0.12, 0.01) | -0.05 (-0.11, 0.01) |
| 1.5 years | -0.25 (-0.30, -0.21) | -0.12 (-0.18, -0.05) | -0.11 (-0.17, -0.05) |
| 2 years | -0.24 (-0.28, -0.19) | -0.13 (-0.19, -0.06) | -0.17 (-0.23, -0.11) |
| 3 years | -0.16 (-0.20, -0.11) | -0.07 (-0.14, -0.01) | -0.06 (-0.11, 0.00) |
| 4 years | -0.22 (-0.27, -0.18) | -0.14 (-0.20, -0.07) | -0.10 (-0.16, -0.04) |
| 5 years | -0.28 (-0.33, -0.24) | -0.18 (-0.25, -0.11) | -0.12 (-0.18, -0.05) |
| 6 years | -0.32 (-0.36, -0.27) | -0.17 (-0.25, -0.10) | -0.09 (-0.15, -0.02) |

Notes: All standard deviation score values are derived from linear mixed models analyses with adjustments for age at visit, maternal height, age at delivery, pre-pregnancy body-mass index, parity, socioeconomic status, housing (single or cohabiting), maternal hypertensive

and diabetic conditions, fertility treatments (children conceived by in vitro fertilization had been excluded), twinning, and birth asphyxia. Abbreviations: CI confidence interval.

### 7.4.3 Length/height and weight-for-length/height

Smokers' infants were shorter at birth compared with non-smokers' infants (unadjusted and adjusted values, see Tables 8 and 9). At birth, the mean adjusted difference in weight-for-length was -0.08 SDS (95% CI: -0.14, -0.02) and in length -0.38 SDS (95% CI: -0.43, -0.32) (Figure 19 B-C). The smokers' offspring showed a distinct linear growth pattern during infancy. They caught up completely in weight and length by 1 year of age. Thereafter they continued to gain weight while the linear growth in height was stunted in comparison to non-smoking mothers' offspring. Eventually, at 6 years of age, smokers' children were heavier [weight-for-height difference 0.23 SDS (95% CI: 0.18, 0.29)] and shorter [height-for-age difference -0.15 SDS (95% CI: -0.20, -0.11), corresponding to 7 mm] than children whose mothers did not smoke during pregnancy (Figure 19 B-C).

Offspring of those who quit smoking during the first trimester did not differ significantly in height growth from non-smokers' offspring from birth to 6 years of age (Table 9, Figure 19 E). However, offspring of quitters had an increased weight gain that was comparable to that of smokers' children (Table 9, Figure 19 F).

## 7.5 DISCUSSION

We demonstrated that maternal smoking during pregnancy has a longstanding association with the offspring head circumference. After exposure to tobacco via maternal smoking during pregnancy, the HC catch-up growth during infancy and childhood was incomplete, resulting in a smaller HC in the smoker's children than in the unexposed children at 6 years of age. This deficit was, however, small, corresponding to 0.2 cm at the age of 6 years. Reassuringly, HC growth of children whose mothers quit smoking during the first trimester did not differ from that of the offspring of non-smokers. Birth length and weight were reduced in newborns who

had been exposed to maternal smoking, but they seemed to catch up to their unaffected counterparts during the first years of life.

The major strength of this study was the large study population with a long follow-up. The study cohort was assessed by a well-organized primary care system that performed repeated auxological checks. Compared to previous studies assessing association of maternal smoking during pregnancy with postnatal head growth, this study was larger, and the follow-up time was longer (68,69,114,128). The analyses were adjusted for potential confounders including socioeconomic status according to mother's occupation.

A possible limitation of this study was that we did not have information on postnatal tobacco exposure by passive smoking or through breast milk. However, in a study of maternal smoking during lactation and growth, in a cohort of 1,494 children (67) , feeding type (bottle or breast) or postnatal exposure to tobacco smoke in the household did not play a significant role in growth from birth to 1 year of age. Moreover, mothers who quit smoking during pregnancy tend to start smoking again during the first months postpartum (215). Thus, our finding of the deficit in HC limited only to the offspring of smokers, not of quitters, suggests a stronger association between prenatal rather than postnatal tobacco exposure and offspring HC. Furthermore, we did not have information on the number of cigarettes smoked by the mother, which is why dose-response relationship could not be assessed. Another limitation of the study was that we did not have information on several other potential confounders, including other substance use, maternal psychiatric or neuropsychiatric conditions, or paternal characteristics. Socioeconomic status of the mother's partner was not available, either. Even though we aimed to control for potential confounders, the association between maternal smoking in pregnancy and postnatal head growth of the offspring may involve residual confounding related to SES or to other familial confounding. As we were not able to use a family-based study design, it attenuates inferring of causality of the association. Furthermore, in the study population, non-smokers' offspring was mildly under the mean SDS values of the growth references, which did not, however, affect the comparisons between the smoking groups. This

observation might be due to ethnic differences between the Finnish growth reference of children born between 1983 and 2008, and the present cohort of children born between 2004 and 2017, the latter being probably more multi-ethnic. Average HC in children of Finnish origin has been shown to be larger than average HC depicted by the multiethnic WHO growth charts or reported from some other, especially non-Caucasian people (137,181). We could not include ethnicity in the analyses, because in Finland ethnicity is not recorded in perinatal or child health data. We know that since 2000 the part of Finland in which the study was conducted has had growing yearly net migration from abroad and in 2017 more than a quarter of childbirths were of foreign language speaking mothers (216). Smoking in pregnancy seems, though, to be rarer in migrants compared to the general population in Finland (217).

In most previous studies, which assessed cohorts of 326 to 2,151 infants, the catch-up in HC growth after maternal smoking during pregnancy was seen within 12 months (67-69,77). In children of heavy smokers, an HC deficit until 2 years of age (114) or up to 5 years of age (210) has been reported. In the latter study, statistical testing or adjustments for confounding factors were not done. Consistent with our study, a persisting deficit in HC was reported by a small prospective cohort study of 363 children (128), but, unlike our study, they did not observe any catch-up growth in smokers' children. This previous study suffered from methodological issues concerning the longitudinal HC growth analysis; growth curves were made using the study's own data for standardization, and no adjustments for confounding factors were made. In the cross-sectional analysis, they failed to show significant differences in HC between the offspring of smokers and non-smokers from 6 months to 5 years of age. Methodologically, the study most similar to ours was performed by Durmuş et al. (2011) (108). Consistent with our findings, they reported an HC deficit at 1 year of age [-0.10 SDS (95% CI: -0.18, -0.01)] in the infants of smokers when compared with those of non-smokers. However, HC was not followed any further. Height growth in children of smokers was similarly deficient at 4 years of age in the study of Durmus et al. (108) (-0.10 SDS, 95% CI: -0.19, -0.01) and in ours (-0.12 SDS, 95% CI: -0.16, -0.08), and

continued to be stunted in our study (mean difference at age 6 years -0.15 SDS, 95% CI: -0.20, -0.11). Our finding of higher weight-for-length/height in the children of smokers after 3 months of age compared with children of non-smokers was also consistent with Durmuş et al. (2011) and other studies (209). On the contrary to the finding of Durmus et al. (2011), in our study, also the children of mothers who had quit smoking during the first trimester had an increased weight gain comparable to that of smokers' children. An elevated risk for childhood overweight after maternal smoking during early pregnancy has been previously reported (218).

HC is a surrogate measurement of brain size in childhood (1,5), and pre- and postnatal head growth is positively associated with neurocognitive outcome (70). Catch-up growth in HC after exposure to maternal smoking during pregnancy occurs during the first 6–12 months of life (67,72,77), when HC reaches already around 80% of its final size. In animal studies, prenatally administered nicotine resulted in reduced amounts of brain cells, and later neurons seemed to be replaced by glia (121,124). Thus, what was lost during fetal life, could not be fully repaired later. Studies investigating structural changes in offspring brain after maternal smoking during pregnancy have demonstrated reduced regional volumes in several cortical areas of the brain, in cerebellum, and corpus callosum (206,219-221). Deficits in total brain volume and in HC were observed still at ages 10–14 (N = 35) in children who had been prenatally exposed to tobacco, but the study failed to show significance when the results were adjusted for other substance use (219). Insulin-like growth factor-1 (IGF-1) is a major regulator of brain growth and development pre- and postnatally , and reduced plasma concentrations of IGF-1 have been measured in newborns after prenatal tobacco exposure (120). The risk of childhood overweight and obesity after prenatal tobacco exposure seems to be related with metabolic programming, through changes in epigenome (222) and in IGF-growth factor axis (38). Metabolic programming may be involved with the stunted linear growth of these children as well (38).

## 7.6 CONCLUSIONS

Despite partial catch-up growth during the first months of life, head size in children of smoking mothers fails to achieve that of unexposed children. Because most HC growth occurs during the first 2 years of life, it is likely that the persisting gap between the HC of children of smoking and non-smoking mothers from birth to 6 years of age may be permanent. A defect in HC growth might be a rough measure of underlying cascades. All efforts should be taken to encourage pregnant women to quit smoking in order to protect the offspring brain.

## 7.7 STATEMENT ON ETHICS

This register-based study has been approved by the ethics committee of the Northern Savo Hospital District (DNr 64/2010) and permissions have been obtained from the register holders, the National Institute for Health and Welfare (THL/582/5.05.00/2009; THL/504/5.05.00/2010;THL/1010/5.05.00/2018), Statistics Finland (TK-53-839-18 / u1183_a) and Espoo Municipality Institutional Review Board (4.9.2008/ DNo 1224).

## 7.8 ACKNOWLEDGEMENTS

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## 7.9 DISCLOSURE

The authors report no conflicts of interest in this work.

## 7.10 FUNDING SOURCES

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Hospital, State Research Funding and National Graduate School of Clinical Research.

## 7.11 SUPPLEMENTAL MATERIAL

**Table 10**. Number of HC measurements in the analyses of 43,632 children by age and maternal smoking status

**Table 11**. Number of length/height measurements in the analyses of 43,632 children by age and maternal smoking status

**Table 12**. Number of weight-for-length/height measurements in the analyses of 43,632 children by age and maternal smoking status
Figure 20. Scatter plot of a sample of 5% of the A) head circumference (cm), B) length/height (cm) and C) weight (kg) measurements. Fit lines were drawn for the smoking groups (children of non-smokers, quitters and smokers) with LOESS method.

**Table 10.** Number of HC measurements in the analyses of 43,632 children by age category and maternal smoking status

| | Birth | 3 months | 6 months | 1 year | 1.5 years | 2 years | 3 years | 4 years | 5 years | 6 years |
|---|---|---|---|---|---|---|---|---|---|---|
| Non-smokers | 39,311 | 37,486 | 36,144 | 34,248 | 29,382 | 26,909 | 18,754 | 18,303 | 15,254 | 12,142 |
| Quitters | 1,758 | 1,650 | 1,582 | 1,492 | 1,248 | 1,169 | 820 | 817 | 634 | 503 |
| Smokers | 2,547 | 2,363 | 2,269 | 2,110 | 1,712 | 1,611 | 1,103 | 1,149 | 920 | 708 |
| Total | 43,616 | 41,499 | 39,995 | 37,850 | 32,342 | 29,689 | 20,677 | 20,269 | 16,808 | 13,353 |

**Table 11**. Number of length/height measurements in the analysis of 43,632 children by age category and maternal smoking status

| | Birth | 3 months | 6 months | 1 year | 1.5 years | 2 years | 3 years | 4 years | 5 years | 6 years |
|---|---|---|---|---|---|---|---|---|---|---|
| Non-smokers | 39,209 | 37,452 | 36,125 | 34,234 | 29,371 | 26,895 | 18,745 | 18,299 | 15,250 | 12,137 |
| Quitters | 1,755 | 1,650 | 1,582 | 1, 491 | 1, 248 | 1, 168 | 820 | 817 | 634 | 503 |
| Smokers | 2,536 | 2,355 | 2,267 | 2,109 | 1,711 | 1,608 | 1,102 | 1,148 | 919 | 708 |
| Total | 43,500 | 41,457 | 39,974 | 37,834 | 32,330 | 29,671 | 20,667 | 20,264 | 16,803 | 13,348 |

**Table 12**. Number of weight-for-length/height measurements in the analyses of 43,632 children by age category and maternal smoking status

| | Birth | 3 months | 6 months | 1 year | 1.5 years | 2 years | 3 years | 4 years | 5 years | 6 years |
|---|---|---|---|---|---|---|---|---|---|---|
| Non-smokers | 39,237 | 37,443 | 36,109 | 34,213 | 29,355 | 26,886 | 18,738 | 18,285 | 15,236 | 12,126 |
| Quitters | 1,756 | 1,649 | 1,578 | 1,490 | 1,247 | 1,167 | 819 | 816 | 634 | 501 |
| Smokers | 2,543 | 2,360 | 2,267 | 2,104 | 1,705 | 1,605 | 1,102 | 1,146 | 919 | 707 |
| Total | 43,536 | 41,452 | 39,954 | 37,807 | 32,307 | 29,658 | 20,659 | 20,247 | 16,789 | 13,334 |

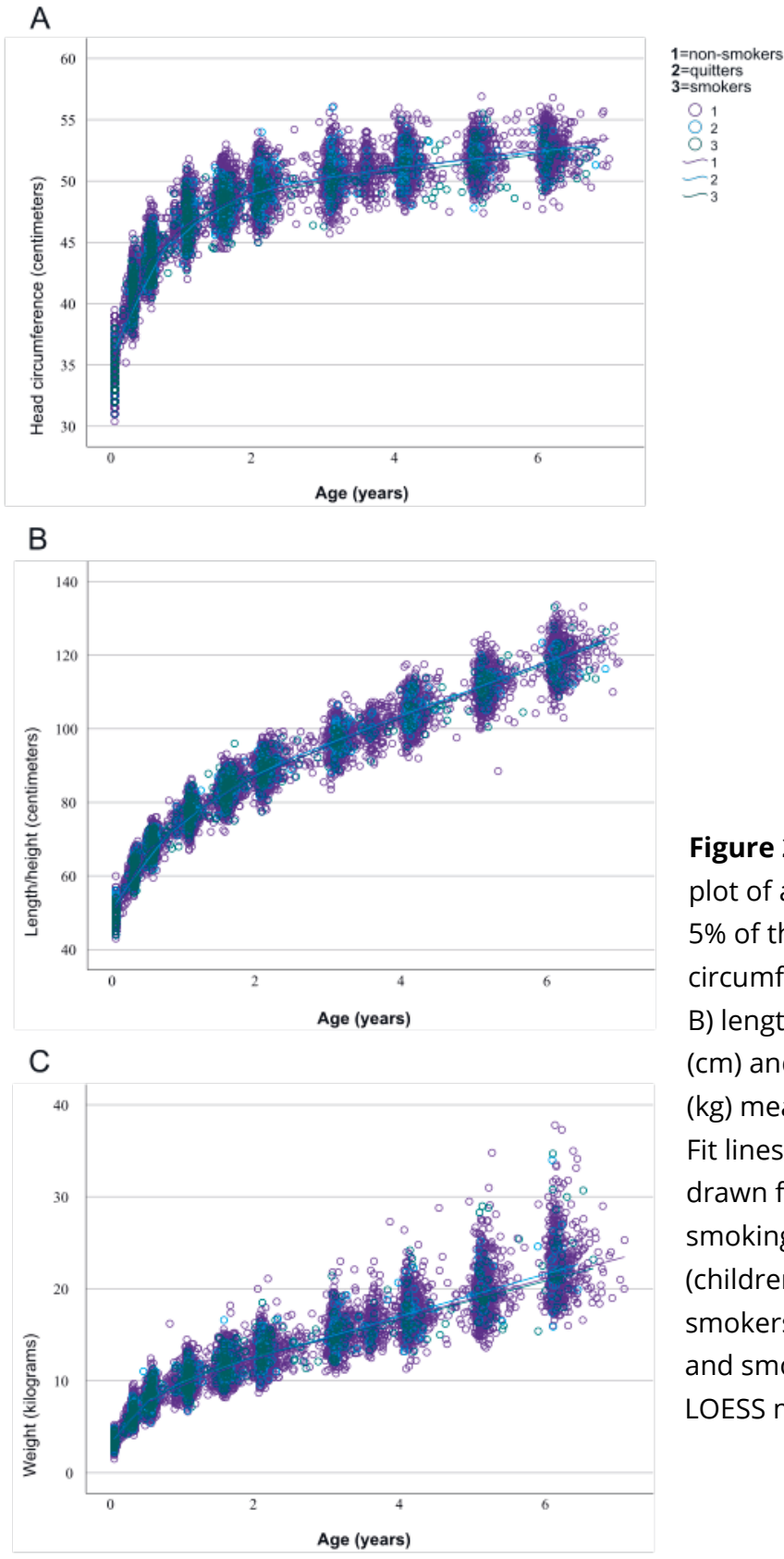


**Figure 20**. Scatter plot of a sample of 5% of the A) head circumference (cm), B) length/height (cm) and C) weight (kg) measurements. Fit lines were drawn for the smoking groups (children of non-smokers, quitters and smokers) with LOESS method.

# 8 GENERAL DISCUSSION

## 8.1 SUMMARY

### 8.1.1 Study setting and populations

Data for the new Finnish HC reference from birth to 7 years were obtained from electronic health registers from Espoo primary care (child health clinics and school health care) consisting of 146,790 measurements from 19,715 subjects (9,536 girls; 48.4%) born 1986–2008.

The data on patients with NF1 were retrospectively obtained from pediatric and neuropediatric outpatient clinics of children aged between 0 and 16 years visiting two tertiary centers (Kuopio University Hospital and Helsinki University Hospital) between January 1996 and June 2010. The resulting data consisted of 80 patients with NF1 (40 boys, 40 girls) born between 19$^{th}$ April 1982 and 15$^{th}$ June 2009. They had 879 HC and length/height measurements and calculated HC-to-height values. The study population for the Finnish HC reference was used as a reference population for the NF1 growth data analysis. In the reference population, there were 145,239 HC-to-height measurements from 19,712 children (9,535 girls, 10,177 boys).

The data on hydrocephalus patients were retrospectively obtained from three tertiary pediatric clinics (Kuopio, Helsinki, and Oulu) from visits between 1996 and 2010 in Kuopio and Helsinki and from 1980 to 1991 in Oulu. Infants with hydrocephalus who had been operated on before their 2$^{nd}$ birthday and who had at least 2 HC measurements were included. The final data consisted of 61 patients (38 boys, 62%) with altogether 341 HC measurements. The Finnish HC reference data were used as reference data in this study, both for the growth analyses and the calculation of reference values for the normative HC SDS change over time. The population for the calculation of normative HC SDS change consisted of 15,145 infants who had at least 2 HC measurements before their 2$^{nd}$ birthday, a total of 120,181 measurements from birth to 2 years of age.

The data for the analysis of HC growth in childhood after maternal smoking during pregnancy were retrospectively obtained from Espoo primary care and from the Medical Birth Register of children born between January 1, 2004, and August 31, 2017, and lived in Espoo on September 14, 2017. The final data comprised 43,632 children (51.2% boys) with 575,421 HC measurements, 572,938 length/height measurements, and 572,699 weight measurements between 0 and 6 years of age. Mothers of 39,326 children (90.1%) had not smoked during pregnancy, mothers of 1,758 children (4.0%) had stopped smoking during the first trimester, and mothers of 2,548 (5.8%) children had smoked after the first trimester of pregnancy.

### 8.1.2 New Finnish HC reference

A positive secular trend in HC was shown between the former Finnish HC reference cohort of 130 children born between 1953 and 1964 and the contemporary cohort of 19,715 children born between 1986 and 2008. The finding of a positive secular trend was in line with previous studies in Sweden, the UK, and Japan (8-11,149,151). It remains unclear for how long the positive secular trend in HC growth will continue. In Japan, the secular trend in HC growth has followed that of height growth and , in which a plateau has been observed (10,11). Thus, the secular trend in growth has been predicted to come to its end.

We also showed that the HC in Finnish children is larger than in the multiethnic WHO HC standard or in the US-based CDC 2000 HC reference (13,168)**.** The difference between the Finnish HC reference and the WHO standard was in line with the studies of Júlíusson et al. (2011) from Norway and Belgium (14) and of Daymont et al. from the US (146). In Norway and Belgium, the distribution of the WHO HC standard was shifted to the left (14). The study by Daymont et al (2010) from the US (146) compared the WHO HC standard with the CDC HC reference in a primary care population. Both the WHO and CDC references were shifted to the left, but the WHO standard was even more left-shifted than the CDC reference. The finding of the CDC HC reference also being shifted to the left compared with the

primary care growth data were similar to our results. The finding of larger heads in both Finnish and US primary care children may arise in part from the positive secular trend – the CDC reference data consisted of pooled data from four different surveys mainly from the 70s and extending partly even decades further back to the Fels Longitudinal study (168).

After publication I of this doctoral thesis, the distribution of the WHO HC standard being shifted to left has been further replicated in many European countries, Japan, and among Pacific Islanders in New Zealand (15,15-17,137,147,148).

### 8.1.3 Head-circumference-to-height ratio in NF1

In publication II, we showed that elevated (≥ 2 SDS) HC-to-height ratio (HCHR) was a typical and early finding in children with NF1.

At the median age of diagnosis (3.6 y), 54% of NF1 children exhibited elevated HCHR. The diagnostic accuracy of HCHR alone was moderate (0.78, 95% CI 0.72-0.84), but compared with the seven National Institutes of Health (NIH) diagnostic criteria for NF1, elevated HCHR was the second most prevalent feature after café au lait macules (97.5%) at the median age of diagnosis. Altogether, 75 of 80 patients had HCHR data available prior to the diagnosis, and 31 (41.3%) of them had an elevated HCHR already before the diagnosis. The median age when the first elevated HCHR value was detected was as early as 0.3 years (range 0.0 to 5.3) in the whole study group.

In our NF1 cohort, the children were on average shorter and had a larger head circumference than the general population as has been reported in large North American and Italian cohorts of patients with NF1 (88,89,171). To our knowledge, this was the first time to combine these two auxological features to a measurable feature, HCHR. We found only one previous study assessing auxological measurements (macrocephaly and short stature together with hypertelorism and thoracal abnormalities) for the prediction of NF1 probability at the age of 6 years (182). These features were associated with NF1 at the age of 6 years, and they were indicative for the imminent diagnosis when a child had insufficient diagnostic criteria

below 6 years of age. Another study showed a strong correlation between HC and height and recommended charts of HC for height when interpreting HC in short or tall people (183).

A shortfall for the generalization of the results of publication II was considered that around 5% of patients with NF1 have a total microdeletion of the NF1 gene often with the accompanying deletion of neighboring regions (184-186). These patients have a distinct growth phenotype with overgrowth instead of short stature (185) in contrast to the patients with NF1 with intragenic mutations. We discussed in publication II that these patients with NF1 with a microdeletion would not probably have an elevated HCHR. After publication II, a study of the growth of 282 patients with NF1 including 56 patients with a microdeletion in the NF1 gene was published (223). In that study, the heights of NF1-microdeletion patients between ages 2 and 18 years were expectedly above the general population median, but surprisingly, the length growth until 2 years of age did not differ from the rest of the NF1 population and was below the population mean for their age and sex. HC values were unfortunately reported only from 2 to 18 years, and they were similar to those in patients with non-deletion NF1.

Nowadays in developed countries, NF1 diagnosis is often confirmed by genetic testing. However, in developing countries, the diagnosis most probably remains clinical. The use of HCHR would facilitate the early diagnosis of NF1 in developing countries and support the early detection of NF1 in developed countries.

### 8.1.4 Screening of hydrocephalus with WHO or population-based HC reference

In publication III, we showed that a population-based reference was more accurate in hydrocephalus screening than the WHO HC standard. By using the WHO HC standard, too many false positives would have been detected, lowering the specificity remarkably and subjecting too many infants to unnecessary investigations. The best screening accuracy was attained using the new standardized HC SDS change over time in combination with

a population-based (Finnish) HC growth reference. Reassuringly, the accuracy of the WHO HC standard could be augmented to a similar level by using population-specific HC cut-offs for screening and combining screening with both HC SDS and HC SDS change over time.

However, even at best, the screening of hydrocephalus by HC was unfortunately not very accurate. When a specificity level over 90% was targeted, the sensitivities of either the WHO or a population-based HC reference varied from around 40% to 65% leaving a remarkable number of sick patients undetected. When using HC SDS change over time as a screening tool and targeting a specificity of 90% or more, the combination of this screening parameter with a population-based HC reference performed significantly better than with the WHO HC standard. The optimal specificity-sensitivity pair using HC SDS change together with the population-based HC reference was around 91% for specificity and a sensitivity of 75%. Using this threshold, still, 9% of the healthy population would end up under investigation and 25% of subjects with the disease would be left undetected.

Previous studies screening for hydrocephalus by a change in HC have been scarce. Few studies have examined the screening value of constant predefined criteria for percentile crossing or change in HC regarding hydrocephalus screening (161), intracranial expansive conditions, metabolic or genetic conditions related to macrocephaly (160), or with neurocognitive disorders (87). The studies of Wright and Emond (2015) and of Daymont et al. (2012) though not focused on the same disease as our study, demonstrate the variability in HC growth in infancy. Wright and Emond (2015) showed that shifts upward or downward were very common, 20% of children showed an up- or downward shift of > 1 SDS between 2 and 9 months and approximately 15% between 9 and 18 or 24 months (87). In addition, they also showed that the WHO standard did not fit the study population and, thus, they used internally standardized reference values.

Daymont et al. (2012) compared the diagnostic accuracy of several major percentile crossing criteria and several percentile thresholds using the WHO, CDC, and a PCN HC reference in a primary care population of

children aged from 3 days to 3 years old. They showed that screening for intracranial expansive conditions and metabolic or genetic conditions related to macrocephaly was most accurate using the PCN HC reference, in terms of specificity, positive predictive value, and positive likelihood ratio. However, the yield of the screening was eventually low regardless of the screening criterion or HC reference used. The authors speculated that the issue was the large variability of the HC in the normal range in combination with the observation that many of the infants with the condition potently causing macrocephaly were actually normocephalic. The authors suggest that a means of measuring the rate of change in HC over time more precisely than crossing predefined (percentile) lines would be beneficial.

In publication III, we developed a means for defining the normality of the change in HC SDS over time compared with the healthy population. As a model disease, we used progressive hydrocephalus that needed surgery. Still, hydrocephalus screening using HC growth even at best was not accurate as demonstrated above. This may be due to the large normal variation in HC growth during infancy. In addition, measurement error and changing measurers may cause additional wavering of the HC SDS values in repeated measurements. In the early phase of hydrocephalus, the distinction between a random HC SDS shift and a pathologic change in HC may thus be difficult to distinguish from each other. Wright and Emond (2015) and Daymont et al. (2012) suggest contradictory solutions: the first suggests not measuring HC repeatedly during infancy when in the normal range because of the large variability in HC due to measurement error and the low predictive value of the HC measurement, whereas the latter raises the concern of infants within the normocephalic range with underlying intracranial expansion and warrants a screening tool for detecting pathologic changes in HC. Daymont et al. (2012) included intracranial expansive conditions, whereas Wright and Emond (2015) only neurocognitive disorders, which may explain the difference in the concern.

The large variability of HC growth within the normal range was also reported by Jaffe et al. (1992) in a cohort of 415 healthy term-born infants, whose HC growth was followed up over the first 2 years of life (224). They reported that half (51%) of the infants showed either deceleration or

acceleration of the HC curve, which was defined as a change of the HC curve of at least one percentile for at least 2 months. Deceleration occurred more often than acceleration and it was permanent in most cases, whereas acceleration was permanent in around half of the cases (54%). None of the subjects had HC acceleration exceeding the threshold of 2 SDS, and only 5% decelerated below the -2 SDS threshold (224).

Based on our study and previous literature, limiting the screening of HC to infancy – to the first two years of life would be advisable. When hydrocephalus was the main concern in publication III and still the detection of a pathological change in HC could be to a large extent covered by the large variability of HC growth lowering the yield of screening – due to both true changes within normal variation in HC growth and measurement error – screening for other conditions or beyond this age period would probably provide no additional benefit. But when a screening cut-off of standardized change in HC SDS over time alarms, the continuing tendency toward head enlargement in repetitious measurements during a short time period would be even more alarming and would warrant further investigation. Furthermore, careful clinical assessment along with HC growth screening is still essential.

### 8.1.5 Childhood HC growth after exposure to maternal smoking in pregnancy

In publication IV, we showed in a large population-based cohort of 43,632 children, that maternal smoking continuing after the first trimester of pregnancy was associated with a deficit in offspring HC from birth up to 6 years of age. This deficit might be permanent since most of the brain and head growth takes place during the first two years of life (20,21). Catch-up growth in HC occurred until 6 months but not thereafter. The timing of the catch-up growth coincided with the literature. Previous studies on childhood HC growth after exposure to maternal smoking during pregnancy have been inconsistent, reporting either complete (66-68,77) or incomplete (108,114,128) catch-up growth. These studies often used

smaller sample sizes of subjects, shorter follow-up times, and often the analyses were not controlled for sociodemographic and perinatal factors.

Reassuringly, in the offspring of mothers who reported having quit smoking during the first trimester, HC growth did not differ from their unaffected counterparts. This finding is in line with the literature. In a population-based prospective study of 5,342 children, maternal smoking in the first trimester only was not associated with a deficit in HC at birth or during the follow-up of 12 months (108). Maternal smoking during pregnancy has been associated with fetal growth deficit in HC from the second trimester on (208,225), and the growth restriction can be prevented if the mother quits smoking after becoming pregnant.

The association between maternal smoking during pregnancy and neurocognitive and behavioral problems among her offspring, such as ADHD (attention deficit hyperactivity disorder), is well established, but the causality and underlying mechanisms are difficult to disentangle (226-228). In family-based study designs, familial and genetic factors have largely explained the above associations (203). Still, from what we know from animal models, nicotine exposure modulates several neurotransmitter systems in the developing brain (121,229,230), which can result in neurobehavioral consequences through structural and functional changes in the brain. In human studies, the structural changes in the brain associated with prenatal smoking exposure include reduced regional volumes in the cerebellum, frontal, temporal, and parietal lobes, cerebral cortex, and corpus callosum and altered white matter microstructure (219-221,231-233). In Ekblad et al. (2010), the infants were born preterm, and possibly preterm birth contributed to the fact that the birth HC of the infants of smoking mothers did not differ from that of their unaffected counterparts, only regional reductions in the brain volume (in frontal lobe and cerebellum) were observed (220). In another study of 35 subjects, deficits in total brain volume and in HC were observed at ages 10 – 14 months in children prenatally exposed to tobacco (221), but the study failed to reach statistical significance when the results were adjusted for other substance use (221). The persisting deficit in the average HC of the

child population exposed to maternal smoking during pregnancy may be a robust indicator of underlying cascades.

## 8.2 STRENGTHS AND LIMITATIONS OF THE STUDY

The strength of this doctoral thesis is the large population-based reference cohort of healthy children from the primary care for the construction of the HC references and the growth analyses of the model diseases, NF1 and hydrocephalus. Similarly, in publication IV on childhood HC growth after exposure to maternal smoking during pregnancy, we were able to obtain data from a large population-based cohort of children from primary care, combined with perinatal data from the Medical Birth Register and socioeconomic data from Statistics Finland. The register data and electronic health records enabled retrospective data collection from large cohorts.

When collecting the data on the NF1 and hydrocephalus populations, we were not able to obtain data on the exact date of diagnosis, because the data were collected from patient records. The retrospective nature of these studies may be another limitation because e.g. changing professionals taking the measurements and probable missing data. In Finland, in child and school health clinics, growth monitoring is highly supervised and performed by well-trained professionals. Thus, besides unavoidable measurement error, we do not think the growth data were biased. The retrospective nature of the data collection may have caused some loss of data. Despite some obvious loss of data on NF1 and hydrocephalus patients, the number of patients with adequate data was comparable to previous studies. Another limitation in using large population-based data is that the concept of a healthy child is not of course definite. The data for the HC reference may have included children who later developed some developmental problems. In large datasets, however, these subjects are not strongly weighted.

Another limit in studying the screening of HC growth is that the disorders affecting HC growth do not comprise large patient groups but mostly are heterogeneous and a large variety of rare or “almost rare”

diseases and conditions. Anonymized register data of rare or severe diseases would facilitate research concerning those patient populations.

Limitations to publication IV were the lack of data on some postnatal confounding factors. We were not able to use a family-based design, e.g., a sibling study or an extension of a twin study, which attenuated inferring causality. The lack of some other potential confounders did not hamper the observed association between maternal smoking during pregnancy and offspring head growth, as discussed in more detail in the discussion section of publication IV in chapter 7.5.

## 8.3. FUTURE PERSPECTIVES

HC growth charts should be updated periodically by constructing them from the current population. In doing so, the existence of any secular trend would be observed, since the continuance of the positive secular trend in HC has been predicted to come to its end following the trend of linear growth.

In the future, a study validating the new screening parameter of HC SDS change over time in a microcephalic disorder should also be conducted, as in hydrocephalus.

Furthermore, to define the optimal pattern of HC screening and up to which age children should be screened, a large prospective, register-based, follow-up study of a primary care population should be conducted to observe the yield of HC screening and assess the currently developed tools for HC screening.

# 9 CONCLUSIONS

From the results of publications I-IV, the following may be concluded:
The HC references for childhood HC screening should be up-to-date and constructed from HC growth data of the population they will be used in. Reference charts for HC-to-height ratios are likely the most accurate means of assessing HC in proportion to height. In screening for hydrocephalus, the new screening tool HC SDS change over time in combination with a population-based HC reference is the most accurate screening method. However, even at best, hydrocephalus screening by auxological methods is not optimal and should be accompanied by a careful clinical assessment. Maternal smoking during pregnancy is associated with a persisting deficit in the HC of the offspring up to the age of 6, indicative of underlying cascades related to maternal smoking in pregnancy.

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**MARJO KARVONEN**

Despite widely used practice of monitoring head circumference (HC) as part of child growth, evidence-based methods are scarce and it has been unclear which HC reference should be used. In this study we formed a new population-based HC reference for Finnish children from birth to 7 years. We explored the limits for normative HC growth by using two disease models; hydrocephalus and neurofibromatosis 1; involving accelerated HC growth, macrocephaly or macrocephaly relative to height. We also analyzed HC growth in childhood after maternal smoking during pregnancy.

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