SARA SAMMALLAHTI

# GROWTH AFTER PRETERM BIRTH AND COGNITIVE FUNCTIONING AND MENTAL HEALTH IN ADULTHOOD

UNIVERSITY OF HELSINKI

# Growth after preterm birth and cognitive functioning and mental health in adulthood

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*To my late grandmother Maila,*
*who always thought little girls should be a bit stubborn*

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I Sammallahti, S., Pyhälä, R., Lahti, M., Lahti, J., Pesonen, A-K., Heinonen, K., Hovi, P., Eriksson, J. G., Strang-Karlsson, S., Andersson, S., Järvenpää, A-L., Kajantie, E. & Räikkönen, K. Infant growth after preterm birth and neurocognitive abilities in young adulthood. The Journal of Pediatrics. 2014;165(6):1109-1115.e3.

II Sammallahti, S., Lahti, M., Pyhälä, R., Lahti, J., Pesonen, A.-K., Heinonen, K., Hovi, P., Eriksson, J.G., Strang-Karlsson, S., Järvenpää, A.-L., Andersson, S., Kajantie, E., Räikkönen, K. Infant growth after preterm birth and mental health in young adulthood. Plos One. 2015;10(9):e0137092.

III Sammallahti, S., Heinonen, K., Andersson, S., Lahti, M., Pirkola, S., Lahti, J., Pesonen, A.-K., Lano, A., Wolke, D., Eriksson, J. G., Kajantie, E., Räikkönen, K. Growth after late-preterm birth and adult cognitive, academic, and mental health outcomes. Pediatric Research. 2017:81(5):767-774.

IV Sammallahti, S., Kajantie, E., Matinolli, H.-M., Pyhälä, R., Lahti, J., Heinonen, K., Lahti, M., Pesonen, A.-K., Eriksson, J.G., Hovi, P., Järvenpää, A.-L., Andersson, S., Räikkönen, K. Nutrition after preterm birth and adult neurocognitive outcomes. Plos One. 2017:12(9):e0185632.

**Abstract**

*Background:* Preterm birth (before 37 weeks of gestation) is a major cause of infant mortality and morbidity worldwide, and preventing its burden is a health care priority. Even in adulthood, individuals who were born preterm perform, on average, worse on tests of cognitive functioning than term-born peers do, and may have more mental health problems.

Early growth failure is common among preterm individuals, and some studies have suggested that those preterm individuals who grow poorly in infancy have more neurodevelopmental problems later on in childhood. It is unclear whether these associations persist into adulthood and whether they extend beyond the smallest and most immature of preterm infants, to the majority of preterm infants who are born late preterm (at 34-36 completed weeks of gestation). It also remains unknown whether early postnatal growth patterns predict mental health outcomes - some partly conflicting evidence suggests that *intrauterine* growth restriction at least associates with mental health problems.

The mechanisms explaining the associations between growth and neurodevelopment are also unclear. Early growth reflects a number of intertwined early-life environmental factors and individual characteristics, and while altering neonatal nutrition can affect growth, it is not known whether changes in nutrition can improve long-term neurodevelopmental outcomes. It has even been suggested that faster growth and higher nutritional intakes during the early postnatal period can present a trade-off between improved neurodevelopment and increased cardiovascular risk.

*Methods:* The 157 participants of the Helsinki Study of Very Low Birth Weight Adults (HeSVA, birth weight <1500g) and the 108 participants of the Arvo Ylppö Longitudinal Study (AYLS, gestational age 34-36 completed weeks) examined in this thesis were born in Finland between 1978 and 1986. They were invited to adult follow-up visits between 2004 and 2012. Among these young adults, I examined whether growth in weight, length, and head circumference between different early growth periods (between preterm birth, term age, and 12 months of corrected age in HeSVA, and between late preterm birth, 5 and 20 months of corrected age, and 56 months of age in AYLS) was associated with performance in neuropsychological tests, with self-rated symptoms of depression, attention deficit hyperactivity disorder, and other mental health problems, or with diagnosis of mental disorder based on a psychiatric interview in adulthood. In the AYLS cohort, the participants also reported final grade point average and special education in

comprehensive school. I further examined whether daily intakes of energy in total, of energy from human milk, and of carbohydrates, protein, and fats during the initial hospitalization, which were relatively low compared to modern recommendations, predicted adult cognitive functioning (HeSVA). As growth variables, I used standardised residual change scores from linear regression models where weight, length, and head circumference *z* scores were regressed on corresponding measures at previous time points, creating uncorrelated residuals that reflect growth conditional on previous history. These growth variables were then used as independent variables in linear and logistic regression models to predict the outcomes, while taking into account several potential confounders including child and parental background characteristics and neonatal morbidity.

*Results:* Faster growth during the first months of life was associated with better adult cognitive functioning in both cohorts. The size and direction of the effects were similar: for each SD faster growth in weight, head circumference, and length between birth and term age, the HeSVA participants had 0.23-0.41 SD higher general intelligence quotient, executive functioning component, and visual memory scores. For each SD faster weight gain and head growth from birth to 5 months, and head growth from 5 to 20 months, the AYLS participants had 0.19-0.41 SD higher general intelligence quotient and executive functioning component scores and grade point average. Those who grew faster also had lower odds of having received special education at school. Growth after these time periods did not predict cognitive functioning or school outcomes. In contrast, there were no consistent associations between early growth and adult mental health in either cohort.

Even when taking into account several important neonatal complications and illnesses, the associations between early growth and adult cognitive functioning could not be wholly explained. Neonatal morbidity however seemed to largely account for the associations between higher energy intake between the first six weeks of life and better cognitive functioning among the HeSVA participants.

*Conclusions:* Faster growth during the first weeks and months of life after preterm birth is associated with better cognitive functioning, and these associations persist into adulthood. The mechanisms explaining these associations are largely unclear, but seem outcome-specific. Early intakes of nutrition may reflect or possibly even mediate the effects of neonatal morbidity on neurodevelopment, however the neonatal morbidities commonly associated with preterm birth do not wholly account for the associations between early growth and long-term neurodevelopment.

**Keywords:** premature birth; infant, very low birth weight; gestational age; birth weight; cognition; intelligence; executive functioning; memory; mental health; depression; attention deficit disorder with hyperactivity; substance-related disorders; anxiety disorders; education; growth; weight gain; body height; cephalometry; energy intake; milk, human; infant; adult; risk factors; follow-up studies; longitudinal studies; developmental origins of health and disease

## Tiivistelmä

*Tausta:* Ennenaikainen syntymä (ennen 37 täyttä raskausviikkoa) on tärkeimpiä pienten lasten kuolleisuuden ja sairastavuuden syitä ympäri maailman, ja sen haittojen ehkäisy on terveydenhuollossa ensiarvoisen tärkeää. Vielä aikuisuudessakin ennenaikaisesti syntyneet suoriutuvat keskimäärin ikätovereitaan heikommin kognitiivisten toimintojen testeissä ja heillä on mahdollisesti enemmän mielenterveysongelmia.

Varhainen syntymänjälkeinen kasvuhäiriö on tavallista ennenaikaisesti syntyneillä imeväisillä, ja joidenkin tutkimusten mukaan niillä ennenaikaisesti syntyneillä lapsilla, joiden kasvu on heikkoa imeväisiässä, on myös enemmän kehityksellisiä ongelmia myöhemmin lapsuudessa. On epäselvää, säilyykö tämä yhteys aikuisuuteen, ja koskeeko se pelkästään kaikkein pienimpinä ja ennenaikaisimpina syntyneitä lapsia, vai myös hieman ennenaikaisena syntyneitä (34–36 täyttä raskausviikkoa). Ei myöskään tiedetä, onko varhainen kasvu syntymän jälkeen yhteydessä mielenterveyteen - osittain ristiriitaiset tutkimustulokset viittaavat siihen, että ainakin syntymää edeltävä kasvuhäiriö liittyy mielenterveyden häiriöihin.

Mekanismit, jotka selittävät kasvun ja aivojen kehityksen välistä yhteyttä tunnetaan huonosti. Varhainen kasvu heijastelee useita varhaisia, toisiinsa kytkeytyneitä ympäristötekijöitä ja yksilöllisiä ominaisuuksia. Vaikka varhainen ravitsemus voi vaikuttaa kasvuun, ei tiedetä, voidaanko ravitsemusta muuttamalla vaikuttaa myönteisesti ja kestävästi aivojen kehitykseen ja kognitiivisiin taitoihin. On jopa ehdotettu, että nopeampi kasvu ja suurempi energiansaanti imeväisiässä voi vaikuttaa myönteisesti aivojen kehitykseen, mutta toisaalta lisätä sydän- ja verisuonisairastavuuden riskiä.

*Menetelmät:* Tämän väitöskirjan kohteena olevaan kahteen aineistoon kuului Pikku-K-tutkimuksen (engl. *Helsinki Study of Very Low Birth Weight Adults*) 157 pikkukeskosena syntynyttä osallistujaa (<1500g) ja Arvo Ylppö -tutkimuksen (engl. *Arvo Ylppö*

*Longitudinal Study*) 108 hieman ennenaikaisena syntynyttä osallistujaa (34–36 täyttä raskausviikkoa). Nämä osallistujat syntyivät Suomessa vuosien 1978 ja 1986 välillä, ja heidät kutsuttiin aikuisiän seurantavaiheeseen vuosien 2004 ja 2012 välillä. Tutkin, miten varhainen painon, pituuden ja päänympäryksen kasvu eri ajanjaksoina ennusti suoriutumista kognitiivisten toimintojen testeissä, itse raportoituja masennuksen ja tarkkaavuus- ja ylivilkkaushäiriön oireita ja muita mielenterveyden ongelmia sekä psykiatrisen haastattelun perusteella diagnosoituja mielenterveyden häiriöitä aikuisuudessa. Lisäksi Arvo Ylppö -tutkimuksessa osallistujat raportoivat peruskoulun päättötodistuksensa keskiarvon ja kertoivat, olivatko saaneet erityisopetusta. Pikku-K-aineistossa tutkitut kasvukaudet sijoittuivat ennenaikaisen syntymän, lasketun ajan ja 12 kk korjattua ikää vastaavan ajankohdan välille. Arvo Ylppö -aineistossa kasvukaudet sijoittuivat hieman ennenaikaisen syntymän, 5 ja 20 kk korjattua ikää vastaavien ajankohtien, sekä 56 kk iän välille. Lisäksi selvitin Pikku-K-aineistossa, ennustaako päivittäinen keskimääräinen energiansaanti ja hiilihydraattien, proteiinin, rasvojen, ja ihmismaidosta saatavan energian määrä syntymää seuranneena sairaalassaoloaikana aikuisiän kognitiivisia taitoja. Nämä ravitsemustasot olivat aineistossani nykypäivän suosituksiin verrattuna matalia.

Kasvumuuttujina käytin standardoituja residuaalimuuttujia. Ne olivat peräisin lineaariregressiomalleista, joissa standardoitua paino-, pituus- ja päänympärysmittaa kasvukauden lopussa ennustettiin vastaavilla standardoiduilla mitoilla aiempina ajankohtina. Näin syntyi residuaalimuuttujia, jotka olivat riippumattomia aiemmasta kasvuhistoriasta. Näitä residuaalimuuttujia käytettiin riippumattomina muuttujina lineaari- ja logistisissa regressiomalleissa ennustamaan aikuisiän vastemuuttujia samalla huomioiden useita mahdollisia sekoittavia tekijöitä, kuten lapsen ja hänen vanhempansa taustaan ja varhaiseen sairastavuuteen liittyviä tekijöitä.

*Tulokset:* Nopeampi kasvu ensimmäisten elinkuukausien aikana oli yhteydessä parempaan aikuisiän kognitiiviseen testisuoriutumiseen molemmissa aineistoissa. Näiden yhteyksien kokoluokka ja suunta olivat samankaltaiset: yhden keskihajonnan verran nopeampi painon, päänympäryksen ja pituuden kasvu syntymän ja lasketun ajan välillä oli Pikku-K-aineistossa yhteydessä 0.23–0.41 keskihajontaa suurempaan älykkyysosamäärään sekä toiminnanohjausta ja visuaalista muistia kuvaaviin komponenttipisteisiin. Arvo Ylppö -aineistossa yhden keskihajonnan verran nopeampi painon ja päänympäryksen kasvu syntymän ja 5 kk välillä, ja pään kasvu 5 ja 20 kk välillä oli yhteydessä 0.19–0.41 keskihajontaa korkeampaan älykkyysosamäärään, toiminnanohjauskomponenttipisteisiin ja päättötodistuksen keskiarvoon, ja niillä jotka

kasvoivat nopeammin, oli myös pienempi todennäköisyys saada erityisopetusta. Kasvu näiden ajanjaksojen jälkeen ei ennustanut neurokognitiivisia tai koulusuoriutumiseen liittyviä tuloksia. Kasvun ja aikuisiän mielenterveyden välillä ei havaittu johdonmukaisia yhteyksiä kummassakaan aineistossa.

Tutkimuksessa otettiin huomioon useita varhaiseen sairastavuuteen liittyviä tekijöitä, jotka eivät kuitenkaan täysin selittäneet kasvun ja aikuisiän kognitiivisten taitojen välistä yhteyttä. Vastasyntyneen sairaudet kuitenkin vaikuttivat selittävän suurelta osin ne yhteydet, jotka havaittiin ensimmäisen kuuden elinviikon aikaisen korkeamman energiansaannin ja paremman aikuisiän neurokognitiivisen suoriutumisen välillä Pikku-K-aineistossa.

*Johtopäätökset:* Nopeampi kasvu ensimmäisten elinviikkojen ja -kuukausien aikana on yhteydessä parempiin kognitiivisiin taitoihin aikuisilla, jotka ovat syntyneet ennenaikaisesti. Kasvun ja kognitiivisten taitojen ja mielenterveyden kehityksen yhteyttä selittävät mekanismit ovat suurelta osin epäselviä, mutta vaikuttavat eroavan riippuen siitä, millaiset aikuisiän ominaisuudet ovat tarkastelun kohteena. Varhainen energiansaanti voi heijastella tai jopa välittää vastasyntyneisyyskauden sairastavuuden vaikutuksia kognitiiviseen kehitykseen, mutta ennenaikaiseen syntymään tavallisesti liittyvät komplikaatiot eivät vaikuta kokonaan selittävän varhaisen kasvun ja aikuisiän kognitiivisten taitojen välisiä yhteyksiä.

**Avainsanat:** ennenaikainen syntymä; pikkukeskonen; raskausviikot; syntymäpaino; kognitio; älykkyys; toiminnanohjaus; muisti; mielenterveys; masennus; tarkkaavuus- ja ylivilkkaushäiriö; päihdehäiriöt; ahdistuneisuushäiriöt; koulutus; kasvu; painonnousu; pituus; päänympäryksen mittaus; energiansaanti; ihmismaito; imeväisikäinen; aikuinen; riskitekijät; seurantatutkimukset; pitkittäistutkimukset; varhainen ohjelmoitumishypoteesi

## Abbreviations

| | |
|---|---|
| ADHD | Attention deficit hyperactivity disorder |
| AGA | Appropriate for gestational age |
| APIC | Adults Born Preterm International Collaboration |
| APQ | Adult Problem Questionnaire |
| ASD | Autism spectrum disorder |
| ASR | Achenbach System of Empirically Based Assessment Adult Self-Report |
| AYLS | Arvo Ylppö Longitudinal Study |
| BDI | Beck Depression Inventory |
| BMI | Body mass index |
| BPD | Bronchopulmonary dysplasia |
| CA | Corrected age |
| CES-D | Center for Epidemiological Studies Depression Scale |
| CHD | Coronary heart disease |
| CI | Confidence interval |
| CNS | Central nervous system |
| CP | Cerebral palsy |
| CPT | Conners' Continuous Performance Test II |
| DOHAD | Developmental origins of health and disease |
| ELBW | Extremely low birth weight |
| EUGR | Extrauterine growth restriction |
| ESPGHAN | European Society of Paediatric Gastroenterology, Hepatology, and Nutrition |
| GA | Gestational age |
| GH | Growth hormone |
| GPA | Grade point average |
| HeSVA | Helsinki Study of Very-Low-Birth-Weight Adults |
| IGF | Insulin-like growth factor |
| IQ | Intelligence quotient |
| IUGR | Intrauterine growth restriction |
| IVH | Intraventricular haemorrhage |
| LMP | Last menstrual period |
| NEC | Necrotising enterocolitis |
| NICHD NRN | National Institute of Child Health and Human Development Neonatal Research Network |
| NICU | Neonatal intensive care unit |
| OR | Odds ratio |
| PDA | Patent ductus arteriosus |
| PMA | Postmenstrual age |
| p-PROM | Preterm premature rupture of membranes |
| PVL | Periventricular leukomalacia |
| RDS | Respiratory distress syndrome |
| ROCF | Rey-Osterrieth Complex Figure test |
| ROP | Retinopathy of prematurity |
| SD | Standard deviation |
| SES | Socio-economic status |
| SGA | Small for gestational age |
| TMT | Trail Making Test |
| VLBW | Very low birth weight |
| WAIS-III | Wechsler Adult Intelligence Scale, 3rd edition |
| WHO | World Health Organization |
| WMI | White matter injury |

# 1. INTRODUCTION

Preterm birth is associated with an increased risk of early morbidity and neurodevelopmental impairment, but the majority of preterm infants come to cope well as adults. Previous studies have suggested that growth failure after preterm birth is very common and may reflect a multitude of factors such as prenatal adversity, early illness, and inadequate nutrition, and it is also associated with poorer cognitive functioning in childhood. However it remains unknown whether the associations between early growth and neurodevelopment persist into adulthood, and whether they extend beyond smallest and most immature of preterm infants. It is also unclear whether increased nutritional intakes, which can improve short-term growth, translate into long-term neurodevelopmental benefits.

Individuals who are born preterm may also have more mental health problems, but the aetiology of these problems seems somewhat different from that underlying cognitive vulnerability. It may be that intrauterine growth restriction and its prenatal causes - rather than preterm birth *per se* - is associated with mental health adversity, however the evidence is somewhat conflicting. Few studies have evaluated whether growth restriction after preterm birth, during the early period which coincides with late gestation among term-born individuals, predicts mental health outcomes.

In the four studies that are included in this thesis, I have examined whether growth after preterm birth predicts cognitive and mental health outcomes among two cohorts of preterm adults. The participants of the Helsinki Study of Very Low Birth Weight Adults (HeSVA, birth weight <1500g, maximum n=157) and of the Arvo Ylppö Longitudinal Study (AYLS, gestational age 34-36 completed weeks, maximum n=108) were born in Uusimaa, Finland between 1978 and 1986, and they were invited to adult follow-up visits between 2004 and 2012. I review the previous body of literature in Section 2, list the aims of the current study in Section 3, describe the cohorts and the methods in Section 4, summarise the main results in Section 5, and shortly discuss the findings in Section 6. The original publications are presented in the Appendix.

# 2. REVIEW OF THE LITERATURE

## 2.1. Definitions and prevalence of preterm birth

*Preterm birth is defined as birth before 37 completed weeks of gestation.[1] The rate of preterm birth varies greatly by region, from just above 5% in northern Europe to up to 18% in some areas of Sub-Saharan Africa: worldwide, one in every ten infants is born preterm.[2]*

Preterm birth can be further sub-divided into extremely preterm (gestational age [GA] <28 weeks), very preterm (28 to <32 weeks, or, alternatively, <32 weeks), moderately preterm (32 to <34 weeks, or, alternatively, 32 to <37 weeks), and late preterm (34 to <37 weeks) birth (Figure 1).[1] The majority of preterm children are born close to the 37-week limit of term birth: an estimated 84.3% of preterm births are moderate to late preterm, while only 15.6% of preterm births occur at <32 weeks, and 5.2% at <28 weeks.[2] The cut-offs separating different subgroups of preterm individuals based on gestational age, or even that dividing infants into preterm and term-born are, of course, somewhat arbitrary: different organs experience developmental spurts at different times, and together these interlinked changes form the rapid, continuous process of fetal maturation.

In the case of non-live birth, the lower limit of preterm birth, in contrast to miscarriage, has varied by region and over time, making it more difficult to reliably estimate the rates of preterm birth worldwide. One widely accepted definition, in line with the International Classification of Diseases, 10th revision, proposes that all deliveries at ≥22 weeks of gestation or at ≥500 grams of birth weight, and any delivery of a newborn who shows signs of life, be considered a birth.[2]

***Figure 1.*** *Gestational age categories.*

| *Category* | *Gestational weeks* |
|---|---|
| Preterm | < 37 |
| Late preterm | 34 to < 37 |
| Moderately preterm | 32 to < 34 *or* 32 to < 37 |
| Very preterm | < 32 *or* 28 to < 32 |
| Extremely preterm | <28 |

Over the last 30 years - since around the time the preterm participants of this study were born - understanding of gestational age as a crucial determinant of infant survival and morbidity has increased, and the assessment of gestational age has become more reliable.[1] Before, GA simply referred to the time elapsed between the mother's last menstrual period (LMP) and birth, and preterm birth was defined as birth at fewer than 259 days since the first day of the mother's last menstrual period.[1] Currently, the single

most reliable way of assessing GA is routine ultrasound measurement of fetal size during the first trimester.[1] Although less reliable due to variation in menstrual cycles among women and in the timing of conception in relation to ovulation, as well as recall errors, LMP continues to be the most widely used way of estimating GA, and the best available approach in many low-income settings.[1] External and neurological assessment of the neonate, such as the Dubowitz examination, can also help the clinician establish gestational age.[1] The best estimate of gestational age is often the result of a combination of all the available information.

In addition to gestational age, birth weight has also been used to pick out the most vulnerable neonates. The limit of extremely low birth weight (ELBW) is one kilogram, and the limit of very low birth weight (VLBW) is 1.5 kg, at which birth weight nearly all infants are born preterm; the limit of low birth weight is 2.5 kg (Figure 2).[1,3] Easy to measure, low birth weight was previously used as a primary indicator of early adversity. However, while useful as markers of neonatal vulnerability and immaturity, birth weight cut-offs cannot be used interchangeably with gestational age classifications. Firstly, birth weight at a given gestational age can vary by several hundred grams between individuals and still be considered within normal range. For example, for those born at 37 weeks of gestation, the lower limit of term birth, the 10$^{th}$ and 90$^{th}$ centile range of birth weight spans from 2.33 to 3.32 kg for girls and from 2.38 to 3.45 kg for boys.[4] Secondly, even children who are born too small are not necessarily born too early: instead of or in addition to low gestational age, lower-than-normal birth weight can reflect a non-optimal intrauterine environment which has led to prenatal growth restriction.

The rate of preterm birth has been increasing during the last decades in most countries with reliable data, but the reason for this is not fully understood.[2] This trend may be partly due to increased registration of extremely preterm births, perhaps because even more immature infants now have a chance of survival.[2] Changes in obstetric practices, increased maternal age and obesity, and increased rates of multiple gestation may also explain why the rates of moderate and late preterm birth, in particular, have increased in some, but not all high- and middle-income countries.[2,5] Fortunately, the most recent data suggest that rates of preterm birth may finally be in

***Figure 2.*** *Birth weight categories.*

| *Category* | *Birth weight* |
|---|---|
| Low birth weight (LBW) | < 2500 g |
| Very low birth weight (VLBW) | < 1500 g |
| Extremely low birth weight (ELBW) | < 1000 g |

decline even in some countries that have previously shown an increasing trend, including the US.[6]

Currently in Finland, where this study was conducted, 5.9% of all children are born preterm, and 0.8% are born with VLBW.[7] These rates have remained quite stable for decades: in 1987, when the Finnish national register of births was first established, the rate of preterm birth was 5.6%, and 0.9% of children were born with VLBW.[7]

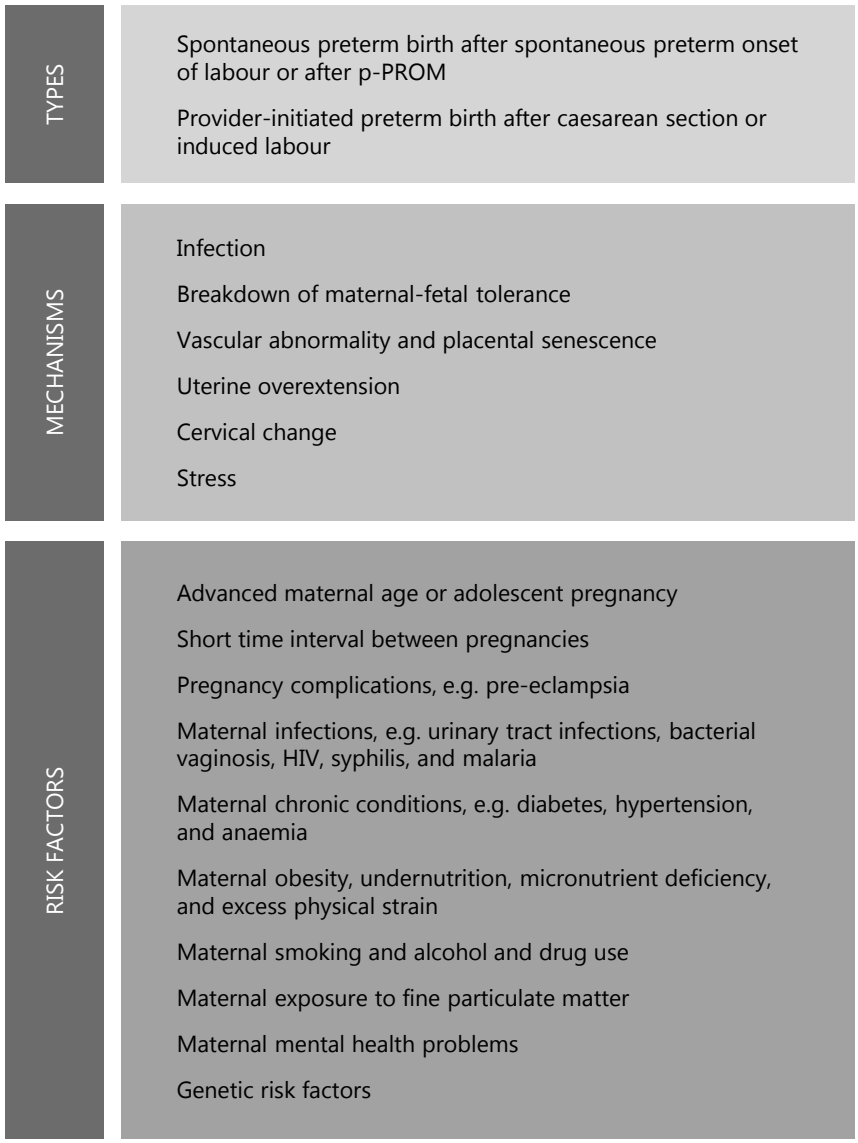
### 2.2. Aetiology of preterm birth

*Preterm birth can be spontaneous or provider-initiated. Several mechanisms including infection, breakdown of immunological tolerance of foreign genetic material, vascular abnormality and placental senescence, uterine overextension, cervical changes, and stress-related hormonal changes are likely to contribute to the risk of preterm birth. Underlying the activation of one or several of these interlinked pathways are a multitude of shared risk factors, many of which remain poorly understood.*

Preterm birth is commonly divided into two major subtypes based on its immediate cause: the spontaneous and the provider-initiated preterm birth. Spontaneous preterm birth occurs after spontaneous onset of labour (regular contractions and cervical change before 37 weeks of gestation, accounting for 40-45% of preterm births), or after preterm premature rupture of membranes (p-PROM, spontaneous rupture of membranes at least 1h before the onset of contractions and before 37 weeks of gestation, accounting for 25-30% of preterm births).[8] One third (30-35%) of preterm births are provider-initiated: these include induced labour and caesarean section for maternal indications such as pre-eclampsia, for fetal indications such as intrauterine growth restriction and distress, and for non-medical reasons.[8–11] However, underlying these different types of preterm delivery can be several interlinked pathophysiological pathways and a multitude of risk factors.[12,13] Although producing an exhaustive list of these aetiological factors - some of which almost certainly still remain undiscovered - is not possible, a variety of key mechanisms and risk factors for preterm birth are listed in Figure 3.

The timely onset of labour is orchestrated by a complex pathway of parturition. As the result of changes in endocrine and paracrine signalling, such as a decline in progesterone action and a complex inflammatory response, the uterine myometrium awakes from its quiescence to a contractile state, the cervix ripens to allow for dilation, and the decidua becomes activated in preparation for membrane rupture and for the separation of the

***Figure 3.*** *Main types, proposed mechanisms and key risk factors of preterm birth.*



chorioamniotic membranes and of the placenta from the uterus.[13,14] However, what prompts these changes at 40 weeks of gestation, and what causes them to sometimes occur prematurely, remains largely unknown: endocrine clocks, inflammatory and mechanical factors, and cell senescence have been implicated as interlinked components of the pathway leading to parturition, and premature activation of one or several of the components can lead to spontaneous preterm birth.

Infection plays a key role in preterm birth. In more than one in every three cases of very preterm birth, placental lesions consistent with acute chorioamnionitis are present, suggesting possible infection.[15] Transabdominal amniocentesis studies have revealed microbial invasion of the amniotic cavity in 10-34% of cases with preterm labour with intact membranes, and in 17-58% of cases with p-PROM, however reliably estimating the rate of microbial invasion is challenging.[8,15] Infections can both activate an inflammatory pathway to spontaneous preterm birth, and lead to fetal or maternal distress and provider-initiated preterm delivery. The pathogens causing these infections seem to mainly originate from the mother's normal microbiota, and can ascend from the lower genital tract, or, more rarely, spread through the placenta, through the fallopian tubes, or during an invasive procedure.[8] Non-intra-amniotic infections and changes in the normal microbiota of the mother can also increase the risk of preterm birth, partly by predisposing to intra-amniotic infections. These conditions include, for example, bacterial vaginosis (OR for preterm delivery 2.19, 95% CI 1.54-3.12),[16] periodontal disease,[17] malaria,[1] and viral infections including but not limited to maternal human immunodeficiency virus infection.[18,19]

The inflammatory pathway to parturition can be activated also in the absence of any demonstrable microbial or parasitic infection. One potential reason for this seems to be the breakdown of the maternal tolerance of paternal antigens expressed by the placenta or by the fetus. This can lead to an immunological response similar to an allograft rejection, during which maternal T-cells attack against the foreign material and cause inflammatory placental lesions and an increased risk of preterm birth.[20]

Placental vascular defects have also been implicated in the aetiology of preterm birth. In some cases, during early pregnancy, the utero-placental arteries which supply blood to the placenta and thus deliver oxygen and nutrients from the mother to the fetus are not formed and remodelled properly. It has been suggested that placental arterial defects accelerate placental senescence, which in turn partly triggers the onset of labour through

sterile inflammatory signals.[21] In addition to increased risk of spontaneous preterm birth, defective vascular architecture also contributes to pre-eclampsia and fetal growth restriction, which are important indications of provider-initiated preterm birth.[22–24] These problems are also discussed in section 2.4.3.2.

Abnormal cervical tissue architecture and remodelling are also likely to contribute to the risk of preterm birth. For unknown reasons, the cervix may "ripen", or be functionally remodelled prematurely.[25] Cervical surgery can also increase the risk of p-PROM, especially if performed during pregnancy.[26]

Multiple pregnancy is a major risk factor for preterm birth, carrying a nine-fold increased risk of preterm birth compared with singleton pregnancy.[27] A proposed mechanism behind the high rates of spontaneous preterm delivery in twin and higher-order multiple pregnancies is uterine over-distension, resulting in an inflammatory activation of parturition.[13] Risk factors for multiple pregnancy include certain ethnic backgrounds, advanced maternal age, and the use of assisted reproductive technology and the transfer of two or more embryos in particular.[28,29]

The release of maternal, placental, and fetal stress-related hormones such as the corticotropin-releasing hormone, cortisol, urocortins, and oxytocin is mandatory for maintaining homeostasis in the face of diverse external or internal threats to the mother and to the fetus. Glucocorticoid signalling in particular has been shown to shape fetal development and long-term outcomes.[30,31] It would seem that the physiological stress response pathways can contribute to the activation of the spontaneous pathway to parturition and to complications that call for provider-initiated preterm birth.[32] However, the physiological stress response can be triggered by a variety of physical and psychological stimuli in interaction with the genetic and epigenetic build-up of an individual,[33] and the specific effects of these stimuli on the risk of preterm birth remain largely unclear. Physical strain may increase the risk of preterm delivery during complicated pregnancies, but for the great majority of expectant mothers, regular moderate-intensity physical exercise carries minimal risk and has significant benefits such as a reduced risk of gestational diabetes.[34] Psychosocial stress - and, some argue, subjective perception of stress in early pregnancy in particular - may predict preterm delivery to a moderate degree, and behavioural, infectious or inflammatory, and neuroendocrine mechanisms have been hypothesised to underlie this association: however, the relationship remains controversial.[35–38]

Furthermore, several aspects of the mother's background and medical history may help estimate the risk of preterm delivery even though the mechanisms underlying these associations are unclear. One of the strongest and most obvious risk factors for preterm delivery is having had a preterm delivery in the past: women who have given birth to a preterm singleton have a recurrence risk of 20% in the current singleton pregnancy.[39] Another, weaker maternal background risk factor is low education.[40] For example, in Finland in the late 1980's, soon after the birth of our cohort members, the risk of preterm delivery was somewhat higher for women with basic, compared with tertiary education (OR 1.44 [95% CI 1.17-1.77] for very preterm birth, and OR 1.58 [95% CI 1.41-1.76] for moderately preterm birth).[41] Other markers of low socioeconomic status, such as residence in poor neighbourhoods have also been shown to associate with preterm delivery (OR 1.23, 95% CI 1.18-1.28 for most vs least deprived quintile).[42] Black women may be twice as likely as white women to give birth preterm (OR 2.0, 95% CI 1.8-2.2), based on studies conducted mainly in the US: both genetic and environmental factors may contribute.[43] Overweight and obesity increase the risk of preterm delivery, and the higher the body mass index (BMI), the higher the risk: for example, for extremely preterm delivery, mothers with an early-pregnancy BMI of 25-30 had an adjusted OR of 1.23 (95% CI 1.13-1.35), and mothers with a BMI >40 had an OR of 2.91 (95% CI 2.21-3.83), compared with normal-weight mothers in a large Swedish register cohort.[44] Maternal smoking is also a risk factor for preterm birth, especially when continued throughout the pregnancy.[45] Maternal exposure to ambient fine particulate matter may also increase the risk of preterm birth.[46]

Finally, genetic factors influence the duration of pregnancy.[47] A very recent genome-wide association study identified six loci that are associated with gestational duration and preterm birth: the implicated genes have previously been shown to play a role in uterine development, inflammatory and immunological pathways, and vascular function.[48] Nonetheless, the genetic determinants of preterm birth remain largely elusive.

### 2.3. Early mortality and morbidity among preterm infants

*Preterm birth is a key risk factor for neonatal mortality and morbidity including, for example, respiratory morbidity, infection, gastrointestinal problems, metabolic disturbances, and retinopathy. The brain of the preterm neonate is also susceptible to lesions and to disturbances in maturation. Underlying this vulnerability are a number of immaturity-related factors, many of which remain unclear. With decreasing*

*gestational age at birth, the frequency and severity of these problems tend to increase, and some illnesses are quite specifically confined to the most immature of preterm infants.*

### *2.3.1. Mortality*

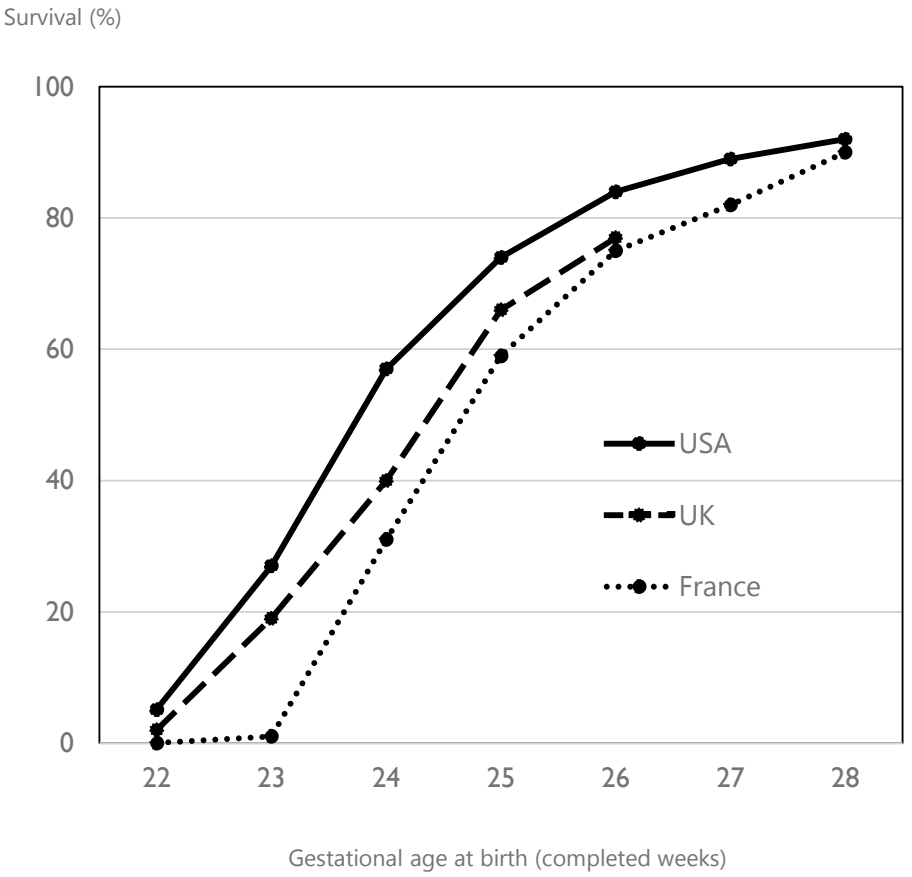
Preterm birth is the leading cause of neonatal death in the world, and the most common cause of child death in almost all high- and middle-income countries.[1] Worldwide, more than a million children die each year from complications of preterm birth, making preterm birth second only to pneumonia as the most common cause of child death.[1] For those who survive, the long-term risk of morbidity including neurodevelopmental problems is increased. In principle, the lower the gestational age at birth, the greater the risk of immaturity-related health problems and long-term morbidity, and the higher the costs of early care.

Degree of prematurity is also the most obvious and important determinant of mortality among preterm infants. In large (>1000 individuals) European and US cohorts born in the 21st century, rates of survival to discharge improve from 5% or less for infants born at 22 weeks of gestation, to 90-92% for those born at 28 weeks of gestation, as shown in Figure 4.[49–51] In Finland, detailed national perinatal data that are currently available for the first week of life reveal 1st week mortality rates of 15% for extremely preterm (<28 weeks), 2.1% for very preterm (28 to <32 weeks), 0.49% for moderately (32 to <34 weeks), 0.30% for late preterm (34 to <37 weeks), and 0.032% for term (37 to <42 weeks) infants born alive in 2015.[7]

Close to the lower limit of viability, survival rates across hospitals and countries vary considerably. In low-income countries, more than two in every three very preterm infants, and almost all extremely preterm infants die during the neonatal period.[1] Even in high-income settings, differences can be quite striking: for example, in a recent large Japanese cohort, much higher discharge survival rates than those depicted in Figure 4 were reported (37% and 64% for infants born at 22 and 23 weeks of gestation, respectively).[52] The differences between countries and hospitals are likely to arise heavily from differences in treatment practises. To illustrate, one US study found that the interquartile ranges for hospital rates of active treatment within the US alone were 8-100% among infants born at 22 weeks, 52-97% among infants born at 23 weeks, and 95-100% among infants born at 24 weeks of gestation.[53]

Survival rates have increased over time, reflecting improved maternal and infant care.[49,54] Since the late 1970s and early 1980s, when our cohort members were born, the chances of survival have increased for extremely preterm infants in particular. In 1978-1985, 71% of VLBW infants survived into early childhood in the Finnish region of Uusimaa, where our participants were recruited: 20% of all the VLBW infants died within the first week of life.[55] In 2011-2013 in the same region, 92% of VLBW and/or very preterm infants survived to the age of one year: 5% died within the first week of life.[56]

***Figure 4.*** *Rates of survival to discharge in proportion to the number of live births according to gestational age at birth in the EPICure (born in the UK in 2006),[49] EPIPAGE-2 (born in France in 2011)[50] and NICHD NRN (born in the USA in 2000-2011)[51] cohorts.*



### *2.3.2. Respiratory morbidity*

When a newborn takes his or her first breaths, the alveoli fill up with air, putting in motion a cascade of physiological changes that enable infants to rely on their own lungs for gas exchange, instead of depending on the placenta. However, lungs are slow to reach this ability to adapt to the extrauterine environment, compared with many other vital organs, and respiratory problems often form the most immediate threat to the preterm neonate. It is no surprise that improvements in the treatment of these problems have become some of the most important hallmarks of neonatology. In the late 1980s and 1990s, exogenous surfactant, which prevents the collapse of alveoli, became commercially available, and the antenatal administration of corticosteroids, which promote fetal lung maturation, became standard treatment for women at high risk of preterm delivery.[1,49,54] Respiratory support strategies have also changed: non-invasive ventilation, such as nasal continuous positive airway pressure have reduced the need of mechanical ventilation and, in some cases, its complications.[57]

Even so, respiratory distress syndrome (RDS) affects almost all extremely preterm infants,[58] and even infants born late preterm at 34 weeks of gestation have a 40-fold risk of RDS, compared with term-born infants.[59] Among preterm neonates, the cause of RDS (previously called hyaline membrane disease), is the deficiency of alveolar surfactant combined with the structural immaturity of the lungs, commonly leading to cyanosis, grunting, retractions, and tachypnoea very soon after birth.[57] In severe cases and if untreated, RDS may result in progressive hypoxia, respiratory failure, and death, but for most neonates, problems usually begin to resolve within a few days.[57]

Among very preterm infants, early respiratory distress may also be followed by a chronic pulmonary disease, bronchopulmonary dysplasia (BPD). First described by Northway et al. in 1967 as lung injury in preterm infants resulting from oxygen and mechanical ventilation,[60] BPD in the 1970s and 1980s used to present with typical radiographic findings of pulmonary cysts and hyperinflation from approximately one week of age onwards, along with cyanosis and a prolonged need for oxygen treatment.[60–62] However, after the prevention and management of respiratory distress improved in the 1990s, the radiographic findings became more rare, and BPD was re-defined as the use of supplemental oxygen at 36 weeks of postmenstrual age.[63] Nowadays, somewhat more detailed, severity-based criteria are often used, recognizing mild BPD after prolonged oxygen treatment even when the infant at 36 weeks is breathing room air.[61] Using this definition, two-thirds of extremely preterm infants suffer from BPD, and severe BPD

affects about 18% of extremely preterm infants, according to a large US study of infants born in 2003-2007.[58] Close to the upper limit of very preterm birth, severe BPD becomes increasingly rare, affecting only a few percent of infants born at 29 to 31 weeks.[50]

In late preterm infants, BPD is absent, but the risk of respiratory distress and failure, transient tachypnoea of the newborn, persistent apnoea and bradycardia, pulmonary hypertension, pneumothorax, pneumonia, and the need for interventions is still higher than in term-born peers, and sparse evidence suggests that the risk of long-term respiratory consequences may be increased.[59,64,65]

### *2.3.3. Central nervous system morbidity*

Intraventricular haemorrhage (IVH), or periventricular-intraventricular haemorrhage, results from bleeding in the germinal matrix, a layer from which first neurons and later glial cells arise during fetal development.[66,67] This highly vascularised fetal structure generally disappears by term age, but in the very preterm infant, its capillaries' fragility and inability to auto-regulate cerebral blood flow make is susceptible to bleeding, especially during the first few days after birth.[66,67] In addition to low gestational age, disturbances in cerebral blood flow and haemostasis contribute to the pathogenesis of IVH, and its risk factors include hypoxia, severe RDS, patent ductus arteriosus (PDA), high ventilator pressure, prolonged labour, vaginal delivery, septicaemia, and thrombocytopenia, whereas antenatal corticosteroid use protects against IVH.[67–70] Further, genetic and epigenetic differences in the areas of the genome that contribute to coagulative and inflammatory pathways have been implicated in the pathogenesis of IVH,[71] and it may be that preterm birth not only causes IVH, but the two also share common underlying genetic and prenatal environmental risk factors.

The modified Papile grading system describes the severity of IVH. In grade I, the haemorrhage is confined to the germinal matrix, and in grade II, blood is seen in the lumen of a lateral ventricle, but it has not distended the ventricle.[67,72,73] In grade III, IVH extends over more than half of the ventricle on a parasagittal view, leading to ventricular dilation, and in grade IV, a parenchymal haemorrhagic infarction is seen in the periventricular tissue, apparently caused by venous obstruction by the haematoma: together, types III and IV can be referred to as severe IVH.[67,72,73]

Neonatal cranial ultrasound to detect IVH was introduced in 1979,[74] and earliest studies in the 1980s reported that 30-50% or even more very preterm or VLBW infants had IVH,

and approximately one in ten had severe IVH.[75,76] In recent years, a large US study reported that 16% of extremely preterm infants who survived the first 12 hours had grade I-II IVH and 16% had severe IVH.[58] In France and Sweden, quite similar rates of severe IVH or other intra-parenchymal haemorrhage were reported among extremely preterm infants (10-13%),[50,77] with rates dropping below 1% at the 32-week limit of very preterm birth.[50] Among late preterm infants, the risk of IVH is very small (absolute risk 0.41%, according to a recent meta-analysis), but still higher than among term-born infants (0.09%).[65] Progressive severity of IVH is associated with progressively higher odds of neonatal death and of neurodevelopmental impairment, and severe IVH, in particular, is a risk factor for cognitive delay and cerebral palsy.[66] The association between IVH and cognitive functioning is also discussed in section 2.5.3.1.

A subset of preterm infants with IVH, including approximately one in four preterm infants with severe IVH, develop hydrocephalus, in which the flow of cerebrospinal fluid is disrupted and intracranial pressure rises.[78,79] Increased orbitofrontal head circumference, fontanelle fullness, and suture splaying may follow as the immature skull gives room for the accumulating fluid, and treatments ranging from serial lumbar punctures and temporary shunts to permanent ventriculo-peritoneal shunts are used to relieve the pressure.[78]

Other potential early complications of IVH (both resulting from IVH and adding to the damage caused by IVH) are neonatal seizures or convulsions, however hypoxic-ischemic encephalopathy and infarction, infections and malformations of the central nervous system (CNS), and metabolic disturbances can result in neonatal seizures also in the absence of haemorrhage.[67,80] Difficult to reliably detect in the preterm infant, reported rates of neonatal seizures vary: a recent study using continuous electroencephalography together with video monitoring reported seizures in 5% of 120 very preterm infants,[81] and an older study reported clinically diagnosed seizures in 6% of VLBW neonates born in the 1980s,[82] but amplitude-integrated electroencephalography studies have reported rates as high as 48% among very preterm infants.[83] Among late preterm infants, the risk of recorded seizures or convulsions is low (0.20%), much like among term-born infants (0.12%).[65]

White matter injury (WMI) is common among preterm infants. The aetiology of WMI is multifactorial and likely to partly overlap with that of IVH. Hypoxia and ischaemia, inflammation, nutritional deficiencies, and hormonal disturbances have been suggested to disrupt the myelinisation and maturation of white matter, leading to both cognitive and

motor problems, such as cerebral palsy.[84–86] In the 1980s, cerebral ultrasound made the diagnosis of cystic periventricular leukomalacia (PVL) possible, but later, as neonatal treatment and imaging have improved, this severe form of injury has become uncommon (affecting about 2% of very preterm infants[50]), and instead, more subtle and diffuse lesions without macrocystic areas have become the predominant form of WMI, detected on magnetic resonance imaging in about one-third of very preterm neonates.[84,86]

Preterm birth also increases the risk of grey matter abnormalities, including the reduced growth, abnormal structure, and altered functional connectivity of the cerebral cortex and of the subcortical structures including the cerebellum, the hippocampus, the basal ganglia, and the thalamus.[86,87] White matter injury can predispose to grey matter abnormalities, but the two also share common risk factors, such as severe immaturity and hypoxia.[86,87] Unlike IVH and cystic PVL, grey matter injury cannot be readily detected or ruled out using neonatal cerebral ultrasound, and early prevalence rates are poorly available, but it seems plausible that insults to the structure and maturation of grey matter during the early critical period of development plays a role in the aetiology of neurodevelopmental problems among preterm infants. The term encephalopathy of prematurity has been used to describe the complex constellation of developmental and destructive brain injury typical to premature infants, a combination of both PVL and neuronal and axonal disease of the cerebral cortex and of the subcortical structures.[85]

#### *2.3.4. Patent ductus arteriosus*

In the fetus, the ductus arteriosus connects the main pulmonary artery to the descending aorta, diverting the majority of blood pumped by the right ventricle of the heart away from the lungs. Ordinarily, within the first hours or days after birth at term, the pulmonary blood flow and the partial pressure of oxygen in arterial blood increase and the vasodilating prostaglandin levels decrease, and the smooth muscle of the ductus arteriosus constricts, causing the closure of the shunt.[88] Then, within the next 2-3 weeks, the ductus closes also anatomically, becoming the fibrous ligamentum arteriosum.[88]

In the preterm infant, compared with the term-born, ductus arteriosus is less sensitive to the increased oxygen concentration and more sensitive to circulating vasodilators, and often fails to close (functionally, as well as anatomically) during the first three days of life: this is called PDA, or persistent PDA.[89] PDA is a common finding in very preterm infants. For example, US and US/Canadian cohort studies have reported PDA in 46% of extremely preterm infants born in 2003-2007,[58] in 31% of VLBW infants in born in

1990[90] and in 2004-2005,[91] and in 1.3% of late preterm infants in a meta-analysis[92] of two studies conducted in the 1980s.[93,94]

PDA can be a symptomless finding on an echocardiograph and close spontaneously without causing any harm,[91] but in some infants - especially those already struggling with RDS and other complications of immaturity - high-volume left-to-right shunting through the PDA increases pulmonary blood fluid volume and the risk of pulmonary oedema and (possibly) BPD, and adds to the workload of the heart.[88,89] PDA is also associated with IVH, WMI, necrotising enterocolitis (NEC), and renal failure, but understanding of when and which treatment for PDA actually reduces morbidity is limited: indomethacin and ibuprofen remain the first option in many places, with surgical ligation often used as a last resort.[89,95]

### *2.3.5. Systemic infections*

The risk of infection is increased among preterm infants because of several reasons. The immune system of the preterm infant is immature and innate pro-inflammatory and antiviral responses are attenuated, and the maternal transfer of antibodies which mainly takes place during late gestation and continues through breast-feeding is disrupted.[96] Preterm infants also often need medical interventions such as mechanical ventilation and intravenous lines, which breach the physical barriers against pathogens.[96]

Sepsis, or septicaemia, refers to symptoms of a systemic inflammatory response accompanied by an infection (which has spread to the blood stream): the "gold standard" definition of neonatal sepsis is the combination of both clinical signs (such as tachypnoea or apnoea, hypo- or hyperthermia, tachy- or bradycardia) and the detection of pathogens in the blood (i.e. positive blood culture), but non-specific clinical findings and sometimes misleading blood culture results make for a diagnostic challenge.[97] In preterm neonates, a late onset, usually associated with gram-positive organisms such as coagulase-negative staphylococci is common.[98–100] In the US in 1993-2012, 32% of extremely preterm infants who survived the first three days had blood culture positive late-onset sepsis, but rates have declined over the last decade.[54] Early onset within the first three days is less common and more lethal, with quite stable rates of 2% among extremely preterm US infants in 1993-2012 at least:[54] important pathogens, contracted from the birth canal or from infected amniotic fluid, include *Escherichia coli* and group B streptococci.[98,100,101] Corresponding rates of sepsis were reported among extremely preterm infants in Sweden in 2005-2007.[102] Among late preterm infants admitted to neonatal intensive care, sepsis

is often suspected, at least enough to merit blood culture workup, but the risk of culture positive sepsis is quite low (0.36%, compared with 0.13% in full-term infants).[65,100]

Neonatal meningitis is an inflammatory response of the CNS, often in response to the spread of the same pathogens which cause sepsis.[103] Mortality from neonatal meningitis is high, and 20-50% of survivors have long-term complications, such as visual and hearing deficits, cerebral palsy, cognitive impairment, and epilepsy.[103] The US Neonatal Research Network and the international Vermont-Oxford Trial Network reported rates of 1-3% among VLBW or extremely preterm infants born in 1987-1988,[104] 1990,[90] and 2003-2007.[58]

### *2.3.6. Necrotising enterocolitis*

NEC is a life-threatening gastrointestinal disease that primarily affects premature infants. The typical patient is a very premature infant, aged approximately one week to one month, who has previously tolerated enteral feeds, but then deteriorates in a matter of hours or days and develops feeding intolerance, abdominal distension, and bloody stools.[105,106] Abdominal radiography may shows gas within the wall of the bowel, in the portal vein, and even in the free peritoneal space: surgery reveals a necrotic, sometimes perforated portion of the intestine.[105] Mortality among patients is high (15-63%, depending mainly on the degree of prematurity), and survivors have an increased risk of intestinal problems such as strictures, stoma complications, and short bowel syndrome, growth delay, and neurodevelopmental impairment.[105]

NEC is thought to occur as a result of an exaggerated inflammatory response of the immature intestinal epithelium to altered microbiota, and very preterm birth, bacterial colonization, and formula feeding apparently act as major risk factors.[105] Although the first descriptions of "gangrenous enterocolitis" among preterm infants date back to the 1800s, NEC, much like the survival of very preterm infants in general, apparently remained rare until the 1960s and 1970s.[107,108] Mizrahi and colleagues first used the term NEC to describe the disease in 1965,[109] and Bell and colleagues combined clinical and radiographic data to describe the stages and surgical treatment of the disease in 1978.[110] In some of the earliest estimates, 6-8% of VLBW infants born in the US in 1975-1978[111] and in 1987-1988[104] were diagnosed with NEC. Since the late 1980s, a large body of research has shown regional differences both in incidence rates of NEC, and in the temporal trends of NEC incidence. For example, a register study of all children born in Sweden in 1987-2009 reported an initial decrease in the incidence of NEC, followed by a

steady increase from about 1995 onwards among preterm infants:[112] for extremely preterm infants, the increase continued throughout the study period,[112] reaching an overall incidence of 5.8% among extremely preterm infants born in Sweden in 2003-2008.[102] In comparison, the Neonatal Research Network in the US reported an increase from 7% in 1993 to 13% in 2008, and a decrease to 9% in 2012, among extremely preterm VLBW infants.[54] Among late preterm infants, the risk of NEC is very small (approximately 0.11%) but apparently still higher than among term-born infants (less than 0.01%).[65]

### *2.3.7. Retinopathy of prematurity*

In very preterm infants, the immature retinas are susceptible to abnormal vascularization and retinal detachment, and consequent visual impairment, which together form the retinopathy of prematurity (ROP).[113] Low gestational age at birth, high oxygenation targets, and poor growth and nutrition during the neonatal period increase the risk of ROP.[113] The majority of extremely preterm infants may develop some degree of ROP,[58,113] and severe ROP, characterised by extraretinal fibrovascular proliferation and a risk of retinal detachment, has been reported among 6-34% of extremely preterm infants.[49,50,58,102] There is no clear evidence that the overall incidence would have changed substantially over the last few decades.[113]

### *2.3.8. Metabolic disturbances*

Finally, preterm birth increases the risk of several types of early metabolic disturbances in the neonatal period, such as hypoglycaemia,[114] hypothermia,[115] and hyperbilirubinemia or jaundice requiring phototherapy or, in extreme cases, blood exchange transfusion.[116] Metabolic problems are very common among very preterm neonates, but the risks are increased also among late preterm infants.[65] While often transient in nature, these disturbances reflect the problems the preterm infant has in adapting to the extrauterine environment. Some of the disturbances, such as severe hyperbilirubinemia,[117] may quite directly harm the health and neurodevelopment of the infant, while others, such as neonatal hypoglycaemia,[118,119] seem to have little independent effect on neurodevelopmental outcomes.

## 2.4. Growth and nutrition of preterm infants

*Unprepared to adjust to the postnatal environment, preterm infants struggle to keep up with the growth trajectories that would be expected of term-born individuals during late gestation and early infancy. This early period represents a time of rapid growth and organ maturation, regulated not only by genetic build-up but also by environmental factors both before and after birth. Among preterm infants, growth problems can reflect a number of factors that include early postnatal morbidity and inadequate nutrition.*

### *2.4.1. Different growth measures reflect different qualities*

The interaction of a multitude of genetic and environmental factors, including sex, ethnicity, nutrition, physical activity, and chronic and transient illnesses affect the rate and timing of human physical growth. Different measurements of growth, such as weight, height (or length, when referring to infants), and head circumference (which usually refers more specifically to the occipito-frontal circumference), reflect partly different underlying factors and develop differently during the prenatal period, infancy, childhood, adolescence, and adulthood.

For example, weight gain is quick to reflect the balance between energy expenditure and intake throughout the lifespan. In contrast, head growth is quite closely correlated with the growth of the brain, except in cases with hydrocephalus: for example, one study of very preterm infants reported a linear correlation coefficient of 0.68 for head circumference and brain tissue volume based on MRI at term.[120] Head growth mirrors the early growth spurt of the brain, which takes place during the last trimester of gestation and the first postnatal months, and unlike height and length growth, most head growth occurs during this early period.[120–122]

Length or height gain has been modelled using three additive main components:[123] the fetal-infant component, which reflects the "nutrition-dependent" phase of growth during which length growth is described to mark the growth of lean body mass, protein accretion and organ growth and development,[124,125] the childhood component, which reflects the "growth-hormone-dependent" phase of growth during which disturbances along the growth hormone (GH) and insulin-like growth factor (IGF) axis become most apparent,[125] and the puberty, during which the conjoint and independent effects of sex steroids and the GH-IGF axis induce a rapid growth spurt and the end of height growth.[126] However, it is apparent that this model is quite the simplification: growth is regulated by

both environmental factors and a complex endocrine system - including not only GH and IGF but also other hormones such as the thyroid hormone, insulin, and cortisol - during the entire growth period.

### *2.4.2. Comparing growth against the population norm*

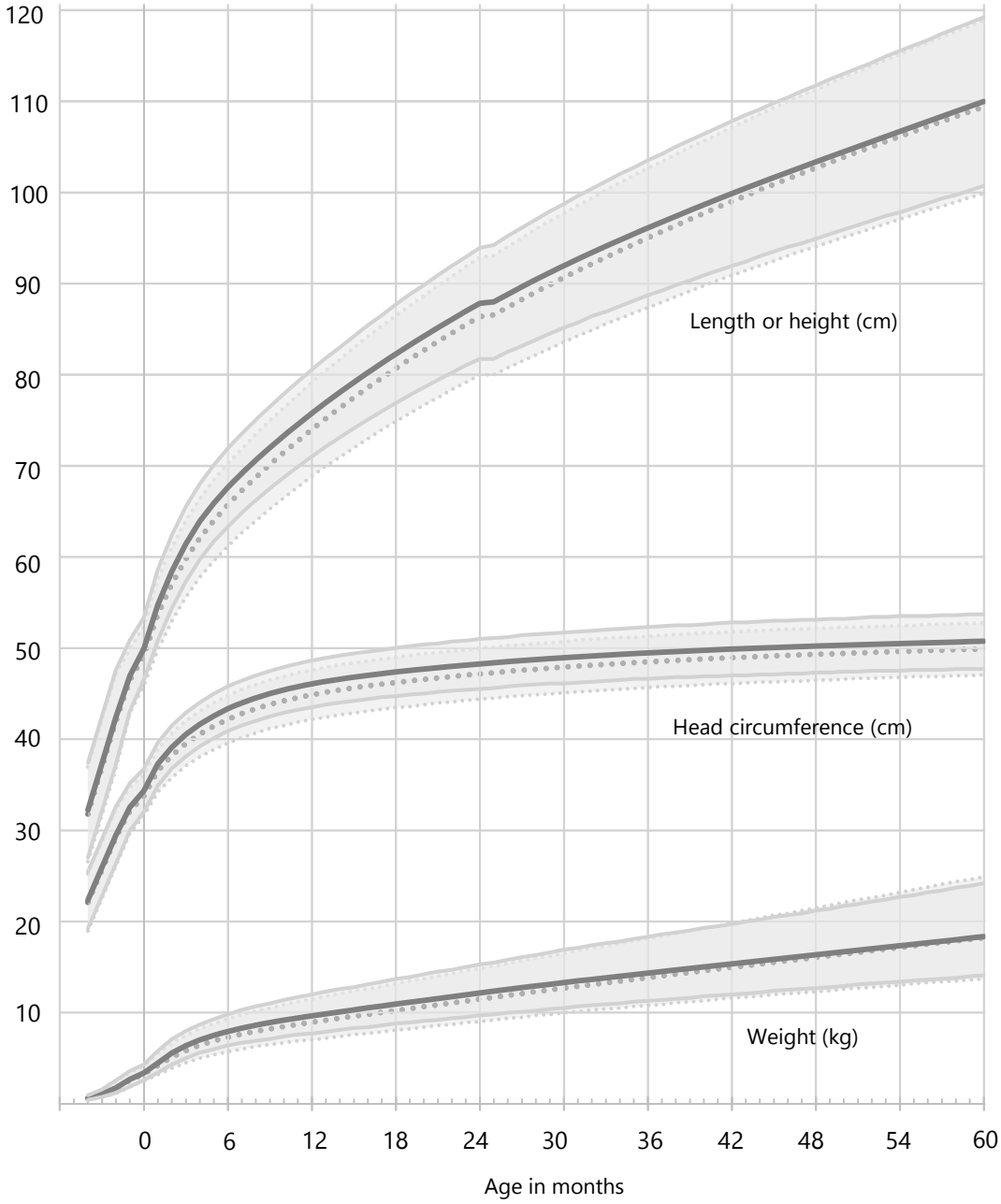
To assess the growth of an individual against that of a population, two major types of growth charts are used: *standard* growth curves (or charts) aim to describe optimal growth among healthy individuals and under ideal conditions, whereas *reference* growth curves (or charts) describe average growth among a given population, including both healthy and non-healthy individuals.[127] Further, growth charts for neonates may either describe average or optimal size *at birth* (which reflects growth in utero), or average or optimal *extrauterine growth* (which is influenced both by pre- and postnatal factors).

Recently, the INTERGROWTH-21st Consortium released its international neonatal standard charts which describe optimal weight, length, and head circumference at birth according to gestational age, spanning from 24 to 32 weeks (published in 2016)[128] and from 33 to 42 weeks of gestation (published in 2014).[4] Quite smoothly in line with these charts are the standard growth curves released by the World Health Organization (WHO) in 2006 that describe optimal growth in weight, length, head circumference, and several other growth indicators from birth to 5 years of age.[129,130] Based on these data, Figure 5 shows normal human growth in length or height, head circumference, and weight from 24 weeks of gestation to 5 years of age.

Any measurements can, of course, be subject to measurement error and this can interfere with reliable growth monitoring. For example, the INTERGROWTH-21st Consortium reported that among their trained observers, inter- and intra-observer technical error of measurement values ranged from 0.3 to 0.4 cm for neonatal head circumference, and from 0.3 to 0.5 cm for length.[131] The WHO Multicentre Growth Reference study group reported quite similar levels of technical error of measurement.[132] To interpret these values, one can expect that two-thirds of the time, differences between replicate measures will be within ± the value of the technical error of measurement.[132]

Growth charts are (usually) created separately for boys and for girls. Country-specific charts aim to take into account regional and ethnic differences in physiological rates of growth. Some have also suggested that other background factors should be taken into account when creating growth charts: for example, parity and multiple birth are associated with fetal growth rates.[133,134] However, others will argue that some of these

***Figure 5.*** *Mean length-for-age or height-for-age (cm), head circumference-for-age (cm), and weight-for age (kg) in boys (solid lines) and in girls (dotted lines). The range from -2 to +2 standard deviations is shown in light grey for each indicator, and for boys and for girls separately. Data were derived from international standard curves that describe normal size at birth among infants born at 24, 28, and 32 weeks of gestation*[128] *and at 36 and 40 weeks of gestation,*[4] *and normal growth among children from 1 to 60 months of age.*[129,130]



differences in growth reflect pathological rather than physiological processes and separate growth charts will not help identify high-risk individuals. The multitude of factors associated with growth are discussed in more detail throughout this part 2.4.

To assess the growth and development of a preterm infant against a term-born population, the degree of prematurity needs to be taken into account. Postmenstrual age (PMA) is used to describe the combined duration of gestation (GA) and of time elapsed since birth.[135] Corrected age (CA), also called age corrected or adjusted for prematurity, describes the duration of the postnatal period from the expected date of delivery (PMA 40 weeks) onwards.[135] Finally, calendar or chronological age refers simply to the time elapsed since birth.[135] For example, a preterm infant who is born 10 weeks before the expected day of delivery ("due date"), will have a GA of 30 weeks at birth. On the due date, the same infant will have a calendar age of 10 weeks, a PMA of 40 weeks, and a CA of 0 days: this time point is also called term age or term equivalent age.

PMA is used to describe the age of preterm infants soon after birth, especially during the extrauterine period between birth and term, while CA is used later, after term age.[135] No consensus exists over when to stop using CA and use calendar age instead: the American Academy of Pediatrics recommends that CA only be used for children up to 3 years of age,[135] however one should consider the context and the focus of the assessment when deciding when to stop correcting for prematurity.[136,137]

In this thesis, I have used birth size reference charts published by Pihkala et al, based on data on infants born in 1979-1983, and infant growth reference charts published by Sorva et al, based on data on children born in 1959-1971.[138–140] These charts were chosen because they were based on data from Finland from approximately the time when our study participants were born. Since then, new Finnish growth charts have been published, based on data from children born between 1996 and 2009.[141,142] These new growth references show that Finnish children nowadays are slightly larger at birth (about 130 g heavier and 0.3 cm longer, at term),[141] slightly taller in infancy, childhood, and adulthood (reaching, eventually, an about 1.8-1.9 cm higher average adult height),[142] and slightly heavier in proportion to height from about 10-12 years of age onwards, but not before this age,[142] compared with the earlier Finnish reference populations born around the 1960s and 1970s. These temporal trends are hypothesised to reflect changes in maternal and child nutrition and health. In the late-preterm cohort, growth was monitored until the age of 56 months, and the WHO child growth standard charts published in 2006 were used to standardise size at follow-ups.

### *2.4.3. Prenatal growth*

#### 2.4.3.1. The normal course of prenatal growth and development

Growth during the prenatal period is determined both by the fetal genome and by the prenatal environment, which in turn is the result of an interplay between maternal, placental, and fetal factors. The first eight weeks of development (called the preimplantation and embryonic period, or just the embryonic period) are characterised by the formation of the all major organ systems. The rest of the gestation, the fetal period, is characterised by rapid fetal growth and functional maturation. During the fetal period, the second trimester represents the period of most rapid length growth for the fetus, whereas the most pronounced weight gain occurs during the third trimester of gestation.[143] On average, healthy males grow slightly faster than healthy females, and at term, the gender difference in birth weight, length, and head circumference is about 120 g, 7 mm, and 6 mm, respectively.[4]

The growth and development of the brain continues throughout and after the prenatal period. During the 3rd week of embryonic development, the neural plate is formed, and during the 4th, it folds to form the neural tube.[143] The neuroepithelium of the neural tube begins to proliferate, producing the precursors of most of the different cells of the CNS: first, the young neurons which migrate and develop into the grey matter of the CNS, then, the glia cells, and last, the ependymal cells lining the ventricles.[143] The surface of the cerebral hemispheres is smooth until the 4th month, when the first indentation on the lateral wall begins to form to separate the temporal lobe: by the 6th month, additional clefts to separate the frontal, parietal, and occipital lobes have emerged, and during the last few months, intense further folding in addition to increase in total volume occurs, to allow for a rapid increase in the cortical area.[143]

Both the mother, the fetus, and the placenta produce hormones to respond to continuous changes in the demands of the fetus, the needs of the mother, and the resources of the surrounding environment, as also discussed earlier in section 2.2. IGF, produced by the mother, the fetus, and the placenta, is important in regulating fetal growth, both directly and indirectly through changes in placental capacity.[144,145] Insulin is important in promoting tissue growth by increasing glucose and amino acid uptake and utilization, and while the mother provides glucose (the primary source of energy for the fetus), the fetus itself produces its insulin.[144,145] The thyroid hormone is also growth stimulatory, and the placenta seems to modulate, to some degree, the responsiveness of the maternal hypothalamic-pituitary-thyroid axis and also act as barrier between the maternal and

fetal hypothalamic-pituitary-thyroid axes.[32,144] In contrast, glucocorticoids are predominantly catabolic, limiting growth and inducing structural and functional maturation of the lungs, the brain, and other organs in preparation for life outside the womb.[31,144] Glucocorticoids are produced both by the fetus and by the mother, and their action is regulated by the placenta: in addition to modulating transport from mother to child, the placenta can respond to cortisol by *increasing* the production and release of placental corticotropin-releasing hormone, which in turn can activate the fetal (and maternal) hypothalamic-pituitary-adrenal axes.

In the mother, the effect of placental growth hormone together with other endocrine changes promote IGF production, insulin-resistance, and the mobilization of maternal nutrients in spite of accumulating maternal fat stores to ensure a sufficient supply of energy for the fetus, while placental lactogen and prolactin in turn promote insulin production and increase energy intake.[146] It would seem that in the malnourished mother, the placenta will up-regulate energy uptake to maintain a sufficient supply for the fetus, while in the hyperglycaemic mother, the fetus will increase insulin production, speeding up anabolism and weight gain.[145,147] Meanwhile in the hypoxic or anaemic mother, the placenta will change its metabolism to spare oxygen for fetal use and reduce glucose transport.[145,147] However, direct human evidence of how the placenta, mother, and fetus orchestrate the regulation of fetal growth is scarce, and the exact mechanisms, such as epigenetic alterations and nutrient-sensing pathways of placental adaptation remain largely unclear.[145,147]

#### 2.4.3.2. Intrauterine growth restriction

Intrauterine growth restriction (IUGR) can be defined in several ways. An antenatal ultrasound examination may reveal a relatively small fetus and, if repeated, an aberrant growth rate. At birth, infants are usually called small-for-gestational-age (SGA) if their birth weight is below the 10$^{th}$ percentile, or two or more standard deviations (SD) below the mean birth weight, when taking into account gestational age and sex.[148,149] SGA status is widely used as a proxy of IUGR, however small size at birth may also reflect normal physiological variation, rather than a pathological process.[148,150]

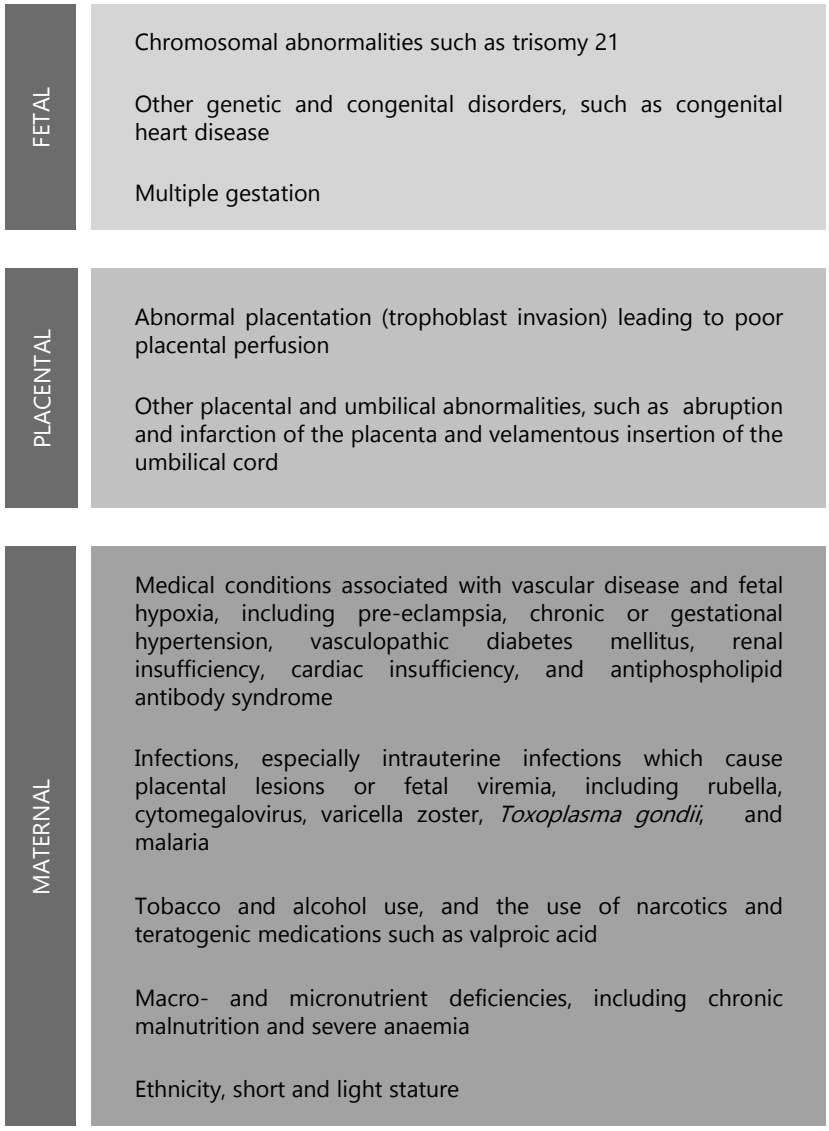
Several other background factors can affect growth rates: for example, first-born infants and twins tend to be slightly smaller than the offspring of multiparous mothers and singletons are, and maternal size correlates positively with neonatal size. It has been argued that some of these associations reflect physiological rather than pathological differences and should be taken into account when identifying individuals at risk of

adverse outcomes.[133] For example, one large study suggested that the lower cut-off for optimal birth weight (at which mortality and morbidity is lowest) is about 150 g lower for twins than it is for singletons.[134] In contrast, adjusting for parity results in lower rates of SGA birth among primiparas, but it is unclear whether this adjustment will improve the identification of high-risk infants.[151] The question of ethnicity is also complicated: for example, the INTERGROWTH-21 collaboration have argued that their standards describe how all fetuses everywhere should grow when there are minimal constraints,[4] but others have suggested that ethnic disparities in fetal growth rates are the result of both genetic and environmental differences, occur to a small degree even under optimal circumstances, and should be taken into account when judging whether SGA status might reflect non-pathological variation.[148,152,153]

Figure 6 lists the key risk factors for IUGR.[145,149,150] Suboptimal utero-placental transfusion is thought to represent a common pathway through which many of the risk factors for IUGR affect growth.[149] A variety of chronic disorders associated with vascular disease can cause reduced utero-placental blood flow.[149] Maternal use of tobacco, alcohol, and narcotics during pregnancy represent crucial and modifiable risk factors: maternal smoking, for example, is associated with a 3.5-fold increase in the risk of SGA birth.[149] Problems in early trophoblast invasion lead to abnormal placental vascular architecture and reduced perfusion: this defective remodelling of the placental spiral arteries has been implicated in the pathogenesis of pre-eclampsia and increases the risk of IUGR.[145,154] Pre-eclampsia and many of the other risk factors for IUGR also increase the risk of preterm birth - both spontaneous and provider-initiated, as previously discussed in section 2.2.

IUGR may involve more than just weight gain, and the assessment of other growth indicators such as length and head circumference can help determine the cause, timing, and prognosis of IUGR. For example, insufficient placental perfusion will often lead to "asymmetrical" IUGR, in which the fetus redistributes its limited resources to prioritise brain development, at the cost of weight gain and other non-vital processes, and this so-called "brain sparing effect" then leads to head size at birth that is closer to normal than weight is.[150] In contrast, early insults such as embryonic infections and exposure to teratogens are more likely to underlie "symmetrical" IUGR, characterised by poor weight gain as well as poor head growth (and, often, poor length growth).[150] Any condition that impacts the important processes of fetal brain growth, including the proliferation, differentiation, and death of cells can lead to microencephaly ("small brain"), which in turn leads to primary microcephaly ("small head"), defined as a head circumference that is two or more SD below the mean for gestational age at birth.[155] To distinguish severe,

***Figure 6.*** *Key risk factors for intrauterine growth restriction.*



so-called "true microcephaly", a cut-off of 3 SD is also used, leading to incidence estimates varying generally from 0.001% to 0.2%.[155] Recently, amidst the Zika virus epidemic and related local increases in microcephaly, some controversy regarding the definition and diagnosis of microcephaly has arisen.[156,157]

#### 2.4.3.3. Macrosomia

Macrosomia refers to large size at or before birth. To identify those at risk of birth asphyxia, meconium aspiration, stillbirth, and caesarean section, for example, studies may use simple birth weight cut-offs of 4000, 4500g or 5000g.[158] To take into account gestational age, neonates can also be classified as large-for-gestational-age if their birth weight is above the 90$^{th}$ percentile (or two or more SD above mean birth weight for gestational age), to distinguish them from appropriate-for-gestational-age (AGA) and SGA infants.[158] The most important risk factors for macrosomia and for being born large-for-gestational-age include maternal diabetes mellitus (both pre-pregnancy and gestational), obesity, and high weight gain during pregnancy.[158–162] Multiparity, advanced maternal age, non-smoking status, maternal height, and rare genetic syndromes have also been identified as risk factors for macrosomia.[158–162]

### *2.4.4. Postnatal growth*

#### 2.4.4.1. Targeting fetal growth rates

The early postnatal period for the preterm infant coincides with the period of rapid fetal growth for the term-born individual: between 24 and 40 weeks of gestation, a fetus will experience a more than 50% increase in length and head circumference and will more than quintuple its weight.[4,128] Even at 34 weeks, the earliest limit of late preterm birth, cortical volume is only about half and total volume only 65% of the term brain, with major maturation still to occur.[121]

Both the European Society of Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN),[163] and the American Academy of Pediatrics[164] recommend that the target growth for preterm infants parallel the rate of intrauterine growth. Weight gain is usually described in terms of weight gain velocity, which (usually) refers to the velocity of weight gain relative to size, measured in grams of weight gain, per kilogram of bodyweight, per day.[165] A relatively stable early weight gain velocity of about 17-18 g/kg/day is generally recommended before term age.[166] As size increases, relative velocity decreases, however, going down to only about 4-5 g/kg/day by 50 weeks PMA.[166] The rates of head growth and length growth (also called linear growth), in contrast, are usually described in centimetres per week regardless of attained size: both should follow the fetal rate of approximately one cm per week.[124,165] Change in *z* scores over time can also be used to see

whether size is getting closer to fetal expectiations.[165] However, some controversy exists over whether these recommendations are actually optimal for later health and development, or whether growth targets for preterm infants, especially concerning weight and length, should differ from the fetal norm.[124]

#### 2.4.4.2. Birth slows down growth

Some disruptions from the fetal growth pattern seem unavoidable even among healthy preterm infants, who lack the continuous nutrient infusion of the fetus and the maturity and fat stores of the term-born infant. Firstly, immediately after birth, both preterm and term-born neonates experience a short initial period of weight loss, which probably reflects both fluid loss and a transient nutritional deficit.[167,168] The lowest weight of a preterm infant is usually recorded towards the end of the first week, and after this nadir, healthy preterm infants regain their birth weight during the 2nd or 3rd week of life, extremely preterm infants more slowly than others.[167] A recent study of healthy preterm neonates followed from birth to 21 days of life suggested that the initial weight loss offsets the growth trajectory by about 0.8 *z* scores, and after this drop from the original birth weight percentile curve (which a fetus of the same size at the same PMA would be expected to follow) to a slightly "lower curve" (which a slightly smaller fetus would have been expected to follow), the shape of the healthy, well-nourished preterm neonate's growth curve parallels the fetal growth curve.[167]

In turn, a few weeks before full-term birth, a fetus (whose weight is also rapidly increasing but growth velocity decreasing) will experience a dip in weight gain velocity, followed by the normal initial weight loss immediately after birth, and then a period of faster weight gain to "get back on track"- meanwhile, a preterm infant around the same PMA will merely carry on exhibiting a steadily declining growth velocity relative to size.[166,169] The normal slowing down of growth that occurs among term-born individuals as birth approaches has been attributed to limited placental supply, an increase in corticosteroid action to promote organ maturation near birth, and even some methodological problems of cross-sectional data, which may exaggerate the magnitude of this "dip".[145,166]

Head circumference measurements can also show a small decrease during the first days of life, due to resolving of oedema and moulding of the head.[170] In one small study, occipito-frontal head circumference reduced by 2.0% during the first week of life among 9 preterm infants born by elective caesarean section, and by 0.7% among 25 preterm infants born by vertex vaginal delivery, after which head circumference began to increase.[171]

#### 2.4.4.3. Extrauterine growth restriction

Poor postnatal growth is one of the most common problems among preterm infants, and can be defined and described in several ways. Extrauterine growth restriction or retardation (EUGR),[166,172–176] or simply postnatal growth failure,[58,177–179] is often defined as weight below the 10th percentile at discharge,[172,173,175,177] but different time points such as 36 weeks PMA[58,178,179] or 28 days after birth,[176] or a combination of several time points[166,174] have also been used. Based on SD scores, poor early growth (called, for example, preterm growth restraint,[180] early neonatal growth failure,[181] or severe postnatal growth failure[182]) has also been defined as weight below -2 SD at 3 months CA, for example,[180] or as a >1 SD[181] or >2 SD[182] decrease in weight *z* scores between birth and discharge. In addition to weight, EUGR and related classifications have also been extended to similarly describe small head circumference and length.[172,180,181]

Rates of EUGR have decreased over time, but are still high. In a large US study of infants born at 23 to 34 weeks of gestation in 1997-2000, 28%, 34%, and 16% had weight, length, and head circumference below the 10th percentile at discharge, respectively.[172] The problem is especially pronounced among the most immature infants: 79% of the extremely preterm survivors of the National Institute of Child Health and Human Development Neonatal Research Network (NICHD NRN) cohort born in the US in 2003-2007 (GA 22-28 weeks)[58] and 75% of the extremely preterm survivors of the ELGAN study born in the UK in 2002-2004 (GA 23-27 weeks)[176] had weight <10th percentile at PMA 36 weeks[58] and at 28 days of life,[176] respectively.

Worse yet, among the VLBW infants of the NICHD NRN born in 1995-1996, 97% had weight <10th percentile at PMA 36 weeks.[179] Among the VLBW participants of the North American Vermont-Oxford collaboration born in 2013, 50.3% had weight below the 10th percentile at discharge, and 27.5% had weight below the 3rd percentile: this was a significant improvement from 2000, when 64.5% and 39.8% of the VLBW infants of the same collaboration study had discharge weight below the 10th and the 3rd percentile, respectively.[177] Differences in fetal growth references can affect the number of preterm infants who are classified as having EUGR. Moreover, infants who are SGA at birth are understandably more likely to be below the 10th percentile in weight also at discharge, i.e. have EUGR.[172,183] As a result, the large proportion of SGA children can help explain why cohorts in which birth weight cut-offs are used as an inclusion criterion (e.g., VBLW cohorts) report poorer growth outcomes than cohorts with a gestational age cut-off (e.g. extremely preterm cohorts) do: the latter has become the more common inclusion criterion during the recent decades.

#### 2.4.4.4. Early growth and illness

Several illnesses are associated with growth problems, and together with the patterns of prenatal growth, immaturity-related early morbidity seems important in explaining variance in growth during the initial hospital stay after preterm birth.[168,184]

Some studies have observed no clear association between IVH and postnatal head sparing[102] or EUGR for weight,[102] during the initial hospitalization, however others have reported that infants with severe IVH[183] and cystic PVL[185] have poorer weight gain and head growth up to about 2 years of age. BPD and a long period of oxygen treatment have been associated with poor growth in weight, length, and head circumference at the Neonatal Intensive Care Unit (NICU), however the differences may at least partly even out by 18-22 months CA.[172,183,185–187] NEC disrupts early weight gain quite dramatically and also affects length and head growth.[172,186,187] Neonatal infections such as sepsis are also associated with growth problems, including restricted neonatal head growth.[186–188]

These associations between illness and growth are explained by a number of intertwined mechanisms. Several underlying factors can result both in poor growth and in morbidity: they include low gestational age, intrauterine growth restriction, certain congenital malformations, and genetic disorders.[172,189] These factors can act as confounders behind both growth and morbidity, but they can also increase the likelihood of illness which then acts as a mediator affecting growth.[190]

One of the ways through which illness can lead to poor growth is by disrupting the nutritional balance. Firstly, this can be through inadequate intake. For example, the severely ill infant may lack the ability or the stamina to suckle breast milk or actively take in other forms of enteral nutrition, may not tolerate enteral feeds even when given them passively, and may receive parenteral nutrition that is not optimal for growth.[191–193] Secondly, illness may increase nutritional needs: for example, BPD and sepsis increase energy expenditure.[194,195]

Illness can affect growth also through inflammatory pathways. Chronic inflammation, neurotoxic effects of the cytokine response, and disturbed regulation of the GH-IGF axis caused by early illness have been implicated in the aetiology of brain injury and reduced head growth, reduced length growth, and changes in body composition, but direct evidence from preterm infants is scarce.[124,187,188]

Medications and other treatments used in the management and prevention of illness may also reduce growth. For example, the administration of catabolism-promoting corticosteroids to prevent BPD may disrupt growth, and the concern for NEC and other

complications may lead to interruption of enteral feeds and to suboptimal nutrition.[172,196–198] Even aspects of the hospital environment itself may inhibit normal growth. For example, the pain, noise, and lack of normal interaction with parents that the hospitalised preterm infant experiences have been implicated as risk factors for postnatal growth failure.[199–201]

The microbiota of the preterm infant seems like a promising crossing point for these different pathways between preterm birth, illness, and growth, and has raised an intense interest in the recent years. The early development of the gut microbiota in the preterm infant is affected by the structural and immunological immaturity of the gut itself, and by factors which alter microbial exposure and growth, such as pre- and postnatal antibiotics and other medications, caesarean section, infection control measures, and altered nutrition including reduced breast-feeding.[202–204] Together, these factors contribute to the development illnesses such as NEC and late-onset sepsis, as discussed in section 2.3, and may contribute both to early growth failure and later acceleration of growth among preterm infants.[202–204]

#### 2.4.4.5. Early growth and nutrition

Adequate nutrition is, of course, the prerequisite of adequate growth. But what is adequate? Neonatal growth, especially in weight, can certainly be increased by providing more macronutrients than what the average human milk contains (and what the preterm neonate would be able to suckle), both through parenteral and enteral supplementation. ESPGHAN recommends increased daily intakes of energy (110-135 kcal/kg) and protein (4.0-4.5 g/kg of body weight below 1000g and 3.5-4.0 g/kg of body weight between 1000-1800g) for preterm infants to make growth as similar to fetal growth rates as possible.[163] However, evidence of nutritional interventions that would have any long-term effects on growth, let alone improve other aspects of development, is scarce.

Most evidence seems to exist for the effects of human milk: compared with (enriched) formula, on its own it seems to result in slightly *slower* early weight and length growth.[163,205,206] However, human milk (vs formula) reduces the risk of NEC and is associated with other potential benefits (discussed in sections 2.5.3.4 and 2.5.3.5), and is thus the recommended choice of enteral nutrition.[163,205,206] Quite fascinatingly, during the first weeks after delivery, mothers of preterm infants provide, on average, milk that has a higher energy and protein content than milk produced by mothers of term infants has.[207] However, this little nudge from nature is insufficient for meeting the recommended levels of intake for preterm infants, and ESPGHAN thus recommends that maternal milk be fortified or, if neither maternal or donor human milk is available,

enriched "preterm formula" be provided to preterm infants, until they attain at least about 1800g of bodyweight.[163,208]

Indeed, multinutrient-enriched human milk (vs non-fortified human milk) before, but not after hospital discharge, has been associated with slightly faster in-hospital growth rates in weight, length, and head growth among preterm infants, but the very limited data that span beyond infancy have shown no long-lasting benefits.[209,210] Limited evidence indicates that multinutrient-enriched preterm formula (vs ordinary term formula) increases weight, length, and head circumference up to 18 months, but in the absence of evidence of substantial long-term benefits, the use of preterm formula is not recommended after discharge.[211] Higher intake of protein[212,213] and glutamine[214] (from either parenteral or enteral feeds,[214] formula,[213] or fortified human milk[212]) seems to accelerate early weight, length, and head growth, but trial evidence of any substantial long-term benefits is yet again lacking.[212–214] Early parenteral nutrition increases in-hospital weight gain at least in observational studies, and energy- and protein enriched parenteral nutrition may increase head growth during hospitalization, but again there is no evidence of long-term benefits.[215,216] Provision of additional calcium,[217] phosphorus,[217] or taurine[218] has not been shown to significantly influence growth even during the neonatal period.

#### 2.4.4.6. Early growth and gender

Some,[172,219] but not all studies[220] have suggested that preterm males are more likely than preterm females to be shorter[172,219] and lighter[172,219] and have a smaller head circumference[172] than same-sex fetal or full-term reference populations at discharge[172] and even after infancy.[219] Of course, the growth references against which preterm infants are compared are different for boys and girls. Males are expected to be slightly larger than females throughout gestation and infancy, with a postnatal peak in length growth velocity soon after birth. This peak difference in growth velocity between the sexes mirrors in magnitude and coincides in timing with a transient surge in testosterone levels at about 1 month of age, suggesting that there is a transient "mini-puberty" and a resulting "mini growth spurt".[126,221] In girls, a similar transient activation of the hypothalamic-pituitary-gonadal axis, and subsequent follicle development is seen immediately after birth, but testosterone levels are lower.[221,222]

Interestingly, the mini-puberty of infancy is different for preterm and term infants. It would appear that preterm boys and girls experience a much higher surge in follicle-stimulating hormone levels than term-born infants do, resulting also in more pronounced

gonadal activation: in boys, this occurs around one month after birth, regardless of gestational age, and in girls, the surge is observed immediately after birth, decreasing after about one month in term-born girls, and after about three months in preterm girls.[222,223] It has been hypothesised that this surge is needed to complete genital development. For example, the "mini-puberty" could promote the spontaneous descent of undescended testes (a condition much more prevalent among preterm vs term-born boys),[224] but these are speculations, and the role of this mini-puberty remains unclear.

#### 2.4.4.7. Catch-up growth and growth beyond infancy

After an initial period of EUGR, IUGR, or both, many preterm infants will begin to "catch up", as if attempting to get back on some set pathway of growth that they were momentarily diverted from. The term "catch-up growth" describes the general phenomenon of accelerated growth after a transient period of growth restriction,[225] be it during or after infancy, among preterm or term-born individuals, and after prenatal or postnatal growth failure. A common definition of catch-up growth describes it as an increase in weight, length, or head circumference *z* score over time that occurs after a previous period of growth restriction (such as IUGR or EUGR) and that results either in size above the -2 SD cut-off at some chosen time point, or in a growth rate that is greater than the median for age and gender.[148]

Catch-up in weight usually begins in early infancy among preterm individuals and may continue, to a lesser degree, throughout childhood and even during adolescence.[219,226] After adolescence, the BMI of preterm individuals is not significantly different from that of term-born peers, suggesting overall catch-up weight gain that is proportionate to height, at least in young adulthood.[227]

The individual patterns of length and height catch-up growth vary considerably, and many preterm individuals fall short of their expected final height. Some individuals are born short and remain short throughout and after infancy, reflecting perhaps genetic build-up, while others exhibit periods of both growth acceleration and deceleration, which could reflect an attempt to reach the maximal genetic potential while struggling with illnesses and other environmental factors.[198,228]

Adult findings highlight the importance of the early period of height growth among preterm individuals for final attained height. Among term-born, healthy, well-nourished humans, adult height is thought to mainly reflect genetic potential, and can be predicted quite accurately based on sex and mid-parental height. However, among extremely preterm individuals, size at 2 years of age is a stronger predictor of adult height than mid-

parental height is, and poor growth - both in utero and in infancy - seems to mainly account for the persisting difference in adult height between preterm and term-born adults.[180,226,229,230] In addition to the differences in infant length growth, some evidence suggests that preterm adolescents undergo puberty slightly earlier than term-born adolescents do.[231] This could further contribute to the difference in adult size, including the difference in final attained height.

The magnitude of this adult height gap varies between studies:[219,226,229,230,232] regional and temporal differences in height as well as differences in the distribution of gestational age, size for gestational age at birth, and sex among the participants in different studies are likely to contribute. In a large Swedish register study, very preterm AGA women were 1.7 cm shorter, and moderately and late preterm AGA women were 0.5 cm shorter than term-born women, but when maternal factors were taken into account or when preterm women were compared with their term-born sisters, moderately or late preterm birth no longer affected adult height, however very preterm birth continued to result in a 2.0-2.4 cm reduction in adult height.[233] Large Swedish and Norwegian studies among men have reported similar results: very preterm men were about two centimetres shorter than term-born men, and being short for gestational age at birth further increased the odds of being short in adulthood.[234,235]

Infancy is a crucial time period for head growth, coinciding with the brain growth spurt of late gestation and early infancy.[120–122,124] Even at term, the brain is only about a quarter of its adult volume: most of the remaining growth results from the myelination of the nerve fibres, with some additional growth due to the increase in the size of neuronal cells and the proliferation of neuronal processes.[143] Fortunately, even among infants who struggle to keep up and catch-up with weight and length growth, head growth is often spared.[187,236,237] Gestational age is again meaningful. Among extremely preterm infants, head size *z* scores tend to be slightly below the reference throughout infancy, but still closer to expected values than weight scores, and preterm infants with higher gestational age do not seem to significantly differ from term-born peers.[236,237] Grouped together, ELBW adults[232] (or adolescents)[238] have been reported to have about 1-2 cm smaller head circumference, compared with term-born peers.[232,238] SGA birth has also been associated with smaller head circumference in adulthood.[239] While some short-term evidence of the effects of enriched early nutrition exists, it remains unclear how early nutrition might best promote head growth in the long term, as discussed in section 2.4.4.5.

More worrying than the difference in head circumference are the underlying differences in the development of the brain, of which head circumference is a crude proxy. As

described in section 2.3.3, the brain of the preterm infant is vulnerable to injury, and those who grow poorly, also show delayed cortical grey matter maturation.[240] Adult imaging studies have reported, rather consistently, that the volume of the whole brain and of specific regions including the grey and white matter of the temporal, frontal, insular, and occipital areas, thalamus, caudate nucleus, putamen, globus pallidus, and corpus callosum is reduced among young adults who were born preterm, as summarised by Raju et al. in a 2017 review of the literature.[241]

## 2.5. Adult health and wellbeing among former preterm infants

*Individuals who were born preterm continue to differ from term-born peers in terms of health and well-being even as adults, but the differences are more subtle than during the neonatal period. Both preterm birth and intrauterine growth restriction may be associated with increased risk factors for cardiovascular disease and with a risk of mental disorders. Preterm birth is also associated with poorer cognitive functioning and academic attainment in adulthood. Immaturity-related morbidity and social environmental factors seem to partly explain these differences, but identifying early on those individuals who will have persisting difficulties is not straightforward. Research concerning postnatal growth or nutrition among preterm infants and adult physical or mental health is scarce and somewhat conflicting, however a few studies suggest that faster growth during early infancy may be associated with better cognitive functioning beyond early childhood.*

### *2.5.1. DOHAD*

The Developmental Origins of Health and Disease (DOHAD) hypothesis claims that early life events alter the risk of later health. Something of a paradigm, the DOHAD framework is now used to examine and understand how humans and other organisms attempt to adapt to their surroundings throughout the lifespan, using early environmental cues.[242] The DOHAD framework stems largely from the work of David Barker, Clive Osmond, and colleagues in 1980s and 1990s, when birth weight, a reflection of the prenatal life, was shown to predict the risk of diabetes and cardiovascular illness later in life in a manner that was robust, consistent, and surprising at the time.[243–245] First called the Fetal Origins of Adult Disease hypothesis, or simply the Barker hypothesis, the framework later became known as DOHAD, as it became apparent that the role of events during the early postnatal period could also be understood from this perspective.[242,246]

To explain the association between early growth restriction or preterm birth (as birth weight *per se* does not differentiate between the two) and later cardiovascular risk, many DOHAD researchers suggest that when struggling with scant resources, the fetus or infant is "programmed" to survive on the limited resources that are expected also in the future. However, under the lavish conditions of modern society, this programming will prove somewhat maladaptive, leading to high blood pressure, accumulation of adipose tissue, and other risk factors for cardiovascular disease and diabetes. Early epigenetic alterations of key regulatory genes which evoke a "thrifty phenotype" have been suggested to be the central mechanism behind this programming.[242,246,247]

Gluckman and colleagues have presented the "predictive adaptive response hypothesis", which many would argue fits quite well within the DOHAD framework.[242,246,248] They suggest that the early programming response that results in this thrifty phenotype may actually serve two purposes: it can both represent an adaptive response for immediate survival (under harsh conditions) and a predictive response to ensure survival to reproductive age. As an example, they argue that the earlier age of menarche among low birth weight individuals who experience catch-up growth may lead to better reproductive success: in uncertain times, rapid postnatal growth could increase fitness, outweighing any harmful effects in late adulthood.[248]

In contrast, supporters of the "maternal capital hypothesis" argue that any external cues that the fetus receives of its surrounding environment are passed on and modified by the mother, and the maternal phenotype (rather than the nutritional resources of the outside environment itself), dictates the surrounding that the fetus must adapt to.[249] This early adaption does not occur to ensure "fit" to the environment that awaits the individual later on in life, but rather to ensure an early "fit" between the nutritional needs of the offspring and the capacity of the mother, making the offspring more "affordable" for the mother and thus more likely to survive the crucial early period of development.[249] However, according to this maternal capital hypothesis, if environmental constraints are relaxed, the offspring will change its strategy of adaption and catch-up.[249]

From the perspective of DOHAD and of the debate within and surrounding it, as well as from the point of view of the clinicians and parents who care for preterm babies, the long-term outcomes of preterm infants, both SGA and AGA, the effects of the early postnatal environment, and the role of postnatal growth are interesting. Do preterm birth and IUGR affect adult health and wellbeing? Is there a trade-off between rapid early growth leading to perhaps cardiovascular disease or diabetes later on, and some benefit

of that rapid growth? Are the effects associated with early growth merely the effect of prenatal events, or can the trajectory of development be altered after birth?

### *2.5.2. Physical health*

#### 2.5.2.1. Preterm birth poses a risk to adult physical health

Preterm birth and IUGR have been shown, independently of each other, to be risk factors for type 2 diabetes in several studies of mostly middle-aged individuals born much before the era of modern neonatology.[250] As discussed in the previous section, these studies stem from the work of David Barker and colleagues, who studied low birth weight as a risk factor for cardiovascular disease and related morbidity in the 1980s and 1990s.[243–245] Since then, studies concerning the risk of coronary heart disease (CHD) and stroke after preterm birth specifically have reported somewhat conflicting results. In a large Finnish study, stroke and CHD before 65 years of age were not associated with preterm birth, except that early preterm women had an elevated risk of CHD.[251] In a large Swedish register study, ischaemic heart disease was associated with SGA birth, but not with gestational age *per se*.[252]

Preterm adults also exhibit risk factors for adult cardio-metabolic disease, which are easier to study also among young adults.[250] Clearest perhaps is the slightly elevated blood pressure.[227] The large Adults Born Preterm International Collaboration (APIC), which also includes the cohort of VLBW individuals examined in this thesis, reported recently that VLBW adults had 3.4 mmHg higher systolic and 2.1 mmHg higher diastolic blood pressure.[253] The finding was not limited to a specific subgroup such as SGA individuals.[253] A non-optimal lipoprotein profile is another cardio-metabolic risk factor seen among very preterm adults.[227,254] Impaired glucose regulation has been reported in some studies,[250] including our own cohort,[255] but a recent meta-analysis failed to show significant differences in fasting glucose or insulin levels.[227] As lifestyle risk factors, VLBW adults are less physically active and may have less healthy diets, yet as protective factors, they report smoking less and using alcohol less frequently, and have sleep rhythms which indicate a morning preference.[250]

Preterm birth also seems to have long-lasting effects on pulmonary health. Preterm adults have poorer lung function and more asthma compared with term-born peers.[241] Those who have suffered BPD in infancy are at an increased risk, and cohorts of the early 1990s report poorer outcomes than those from the turn of the millennium.[241] Finally,

preterm birth and IUGR are risk factors for reduced nephron numbers in the developing kidney and kidney disease in later life.[256]

#### 2.5.2.2. Early growth and adult physical illness

Research concerning early growth and adult physical illness among the preterm population is scarce and somewhat conflicting. Among the VLBW adults studied in this thesis, growth between birth and term was not associated with adult blood pressure (after taking into account gestational age).[257] Lower flow-mediated dilation, an early marker of atherosclerosis, was associated with slower weight gain during the first 2 weeks in our VLBW cohort,[258] but a British study reported the opposite effect among 216 preterm adolescents.[259]

Glucose regulation was unrelated to early growth in our VLBW cohort, except among the 31 SGA participants among whom faster growth was associated with higher fasting and 2-hour insulin concentrations in the oral glucose tolerance test.[255] In the Dutch POPS cohort of 346 very preterm young adults, rapid weight gain between birth and 3 months CA was weakly associated with higher insulin levels,[260] and weight gain from birth to 3 months and from 3 to 12 months CA was associated with higher adult weight, height, BMI, waist circumference, fat mass, fat-free mass, and percentage body fat.[261] In another Dutch cohort of 169 preterm young adults, a weak association was also observed between weight gain between birth and term and insulin secretion, but the association was attenuated to non-significance after adjustment for a number of potential covariates including fat mass.[262] Within the same cohort, faster weight gain relative to length growth was associated with a non-optimal adult lipid profile and body composition.[263] In line, in a US study, more rapid increase in BMI but not in length, between preterm birth and 4, 12, and 18 months, was associated with higher odds of obesity among 633 young adults.[264]

#### 2.5.2.3. Early nutrition and adult physical illness

Little evidence exists of the adult health effects of early nutrition in the preterm population, but the existing data do not support the hypothesis that discouraging weight gain during hospitalization would reduce the risk of cardio-metabolic morbidity.[265] Among the participants of our observational VLBW cohort, higher protein intake during the first three weeks after birth was associated with a healthier body composition and a higher metabolic rate in young adulthood.[266]

In an series of two separate randomised controlled trials, Lucas and colleagues compared preterm formula against standard formula[267] and preterm formula against donor milk,[268] in a total of 926 British preterm infants born in the early 1980s (birth weight <1850g).[269] In an adolescent follow-up study of about 23% of these infants at 13-16 years, no difference in proinsulin, insulin, or glucose levels between these different feeding groups were observed, but 32-33 split proinsulin concentrations were higher among those who had been allocated to nutrient-enriched diets.[269] Also, donor milk (compared with preterm formula) was associated with lower mean arterial blood pressure.[270]

### *2.5.3. Cognitive functioning and academic outcomes*

#### 2.5.3.1. Preterm birth poses a risk of long-term neurodevelopmental problems

The nature and origins of individual differences in cognitive functioning are a controversial topic, and mixed terminology is used to describe these phenomena. Psychometric tests that identify individual differences in cognitive functioning can cover domains such as verbal and non-verbal reasoning, processing speed, executive function, memory, and spatial ability.[271] Performance across these tests show a substantial and positive correlation, and the underlying 'general cognitive ability', also called simply 'general intelligence', 'g', or described in terms of an 'intelligence quotient' (IQ),[271] is thought to reflect a general broad capability to reason, plan, solve problems, think abstractly, comprehend complex ideas, and learn quickly and from experience.[272]

Several studies have shown that the average IQ of very preterm,[273–275] extremely preterm,[276,277] ELBW,[277] and VLBW[275,278–280] young adults is lower than that of term-born peers. For example, as reported by Pyhälä and colleagues in the VLBW cohort studied in this thesis, VLBW adults had 0.57 SD lower full-scale IQ, 0.68 SD lower performance IQ, and 0.29 SD lower verbal IQ, compared with term-born controls (which would correspond to about 8.6, 10, and 4.4 IQ points, respectively), after adjustment for sex and age.[280]

Large Norwegian and Swedish register studies among male conscripts have shown that with increasing gestational age up to full term, the average cognitive performance improves, and even late preterm adults perform poorer than term-born peers.[281,282] These differences seem persistent: in a Finnish study of 919 elderly men and women, late preterm birth was associated with the risk of mild cognitive impairment.[283]

Some have reported that visuospatial functioning among (early) preterm adults may be more impaired,[279] while others have reported a somewhat bigger difference in verbal

functioning scores:[274] most studies (including that in our VLBW cohort) report that both are affected.[273,279,280] Performance in tests of executive functioning (including tests reflecting, for example, verbal fluency,[273–275,280] response inhibition,[274,275] and processing speed[274–276,280]) seems also poorer among preterm adults, compared with term-born adults, and although adjustment for IQ attenuates the differences, it does not make them disappear altogether.[275,280] Studies on memory function are scarce: in our cohort, performance in tests that reflect visual memory encoding, but not so much storage and retrieval, was poorer among VLBW young adults, compared with term-born peers.[280] Further, late preterm birth was associated with poorer memory performance in late adulthood in the previously mentioned Finnish study.[283]

Preterm birth also affects academic outcomes. With decreasing gestational age, the odds of completing high school or having a university degree decrease.[284] Even when adjusting for some potential confounders or after excluding severely impaired individuals, extremely preterm,[276,277,285] very preterm,[274] ELBW,[277] and VLBW[279,280] adolescents and young adults perform worse in tests of reading, spelling, and mathematical or arithmetic skills,[277,285] and are more likely to have received special education,[279,280,285] and to choose practical upper secondary school programmes rather than pursue more academically challenging programmes.[276] According to some[276] but not all[280] studies, preterm adolescents also receive lower final grades than term-born peers. Poor educational outcomes and cognitive impairments together can mediate the effects of preterm birth on adult socioeconomic attainment in a broader sense, possibly contributing to lower incomes of extremely preterm adults in adulthood.[286]

Late preterm individuals' long-term educational attainment has received less attention than that of early-preterm individuals. One meta-analysis of the few available studies suggested that late preterm adults are (very slightly) less likely to have completed high school than term-born peers,[287] in line with a Finnish study that found that late-preterm elderly adults had lower life-time socioeconomic attainment than term-born adults.[288] According to childhood studies, late preterm children have poorer school skills and an increased need of special education.[287] Interestingly, educational attainment also seems to moderate the association between late preterm birth and cognitive impairment so that this association may only be seen among less educated (and not highly educated) elderly adults, perhaps reflecting differential cognitive reserve or neuroplasticity.[283]

The existing literature does not suggest consistent sex differences in the association between preterm birth and adult cognitive ability.[273,276,280] Some,[278] but not all[275,280] studies have reported that SGA status is an additional risk factor for poorer cognitive

functioning: it may be that this is true for those SGA preterm infants who also had small head size at birth.[278]

Of perinatal variables, severe (grade III-IV) IVH is an important and independent predictor of poorer adult IQ.[277,289] In a study of very preterm or VLBW adults, severe IVH decreased adult IQ by an average of 9 points, after taking several other neonatal health, treatment, and family factors into account.[289] Two studies that looked at any IVH, rather than severe IVH, reported no association however,[274,276] and one can hypothesise that the seemingly conflicting results could be due to the small number of participants with severe IVH in those studies which did not detect a difference (n=7 in one[274] and n=6 in the other study[276]). Further, one study specifically compared 93 preterm adults who had had mild IVH against 273 preterm adults without IVH and reported that mild IVH has very little independent predictive value over adult neurodevelopment, after adjusting for demographic factors.[290] Studies on adolescents and children however support the importance of neonatal brain abnormalities (both severe IVH and more subtle changes including but not limited to grade II IVH) in predicting neurodevelopmental outcome including IQ, executive functioning, verbal memory, and poorer academic attainment and skills in childhood.[285,291–293] This discrepancy between child and adult studies could be taken as a sign of compensation and plasticity (resulting in the diminished role of early brain insults in predicting adult cognitive functioning), or as a result of methodological reasons. A great number of things concerning the health, survival, imaging, and treatment of preterm infants has changed over the years, and not enough adult follow-up studies are present to draw well-based conclusions.

Concerning other perinatal variables, some evidence suggests that although a long period of mechanical ventilation and BPD can predict poorer adult cognitive functioning independently of several potential confounders,[276,289] the effects may be limited to those who receive postnatal corticosteroid treatment,[277] and one adolescent study found no association between BPD and cognitive outcomes at all.[291] Trial evidence would certainly be needed to weigh any potential long-term risks of corticosteroid treatment against benefits.[277] Altogether, evidence concerning the independent effects of illness-related neonatal variables such as corticosteroid treatment, BPD, or neonatal infection on neurodevelopment is not uniform and is mostly limited to studies among young children.[294]

Parental education[277,278,282] and other proxies of parental socio-economic status (SES) such as parental occupation[275,277,282] are predictive of IQ, as should be expected based on studies among the general population, but the association between preterm birth and

cognitive functioning remains even when differences in SES are taken into account. One recent study of very preterm and VLBW adults reported that being born to a family with high SES was associated with approximately 9 points higher IQ, and coming from a lower SES background with 2 points lower IQ, compared with the comparison group whose family was classified as middle-SES based on parental education and occupation (after taking into account several other potential confounders).[289] Together, the morbidity, treatment, and social environmental factors identified within the first few months of life alone explained more than a third of the variance in cognitive abilities among VLBW adults.[289]

It is important to keep in mind that mostly these deficits between preterm and term-born infants are quite subtle, and the majority of preterm adults cope as well as any term-born peer. For example, even those VLBW adults who quite clearly perform more poorly than term-born peers in neuropsychological tests that assess executive functions, but who are free of major disabilities, do not themselves report experiencing any more problems related to executive functioning in their everyday lives.[295]

However, preterm birth is also associated with a small but elevated risk of severe neurocognitive impairment. Intellectual disability is an umbrella term for a collection of developmental disabilities characterised by early onset, low IQ, and difficulties in independent daily life. In a large Norwegian register study of adults born in 1967-1983, 4.4%, 1.8%, 1.0%, 0.7%, and 0.4% of those born at 23-27, 28-30, 31-33, 34-36, and ≥37 completed weeks of gestation, respectively, had an intellectual disability.[284] Although environmental insults can contribute to intellectual disability, its severe forms tend to have genetic causes which can have widespread effects not only on cognitive ability, but also on perinatal and postnatal complications and growth.[296]

Finally, preterm birth is associated with neurodevelopmental problems beyond cognitive functioning. The prevalence of cerebral palsy (CP) is about 9%, 6%, 2%, 0.3% and 0.1% among adults born at 23-27, 28-30, 31-33, 34-36, and ≥37 completed weeks of gestation, respectively.[284,297] Likely etiological risk factors for CP include genetic susceptibility and early hypoxia, growth restriction, and infection, and while CP can present without any effect on cognitive ability, it increases the risk of comorbid cognitive impairment.[297–299] Blindness and deafness are rare in modern high-income settings, affecting less than 1% of even extremely preterm individuals in a Swedish study,[77] but milder hearing and visual impairments such as somewhat reduced visual acuity and contrast sensitivity are more common.[300–302] Of course, CP and sensory impairments can also limit the options for reliable neuropsychological assessment.

#### 2.5.3.2. Effects of early growth after preterm birth on cognitive and academic outcomes in adulthood

Very few studies have looked at the association between early growth after preterm birth and adult cognitive functioning. In the first publication that I am aware of, Brandt and colleagues compared head circumferences among the preterm SGA participants of the Bonn Longitudinal Study born in Germany in 1967-1978 (birth weight <10$^{th}$ percentile, nearly all VLBW).[239] They first classified the SGA infants into "head catch-up" (n=27) and "no head catch-up" (n=19) groups based on whether or not the infant's head circumference significantly differed from that of VLBW AGA (n=65) and term-born (n=85) controls at 12 months CA, using a method which was not detailed in the publication. They then compared these two groups of SGA individuals and observed that those in the "head catch-up" group had 16 points higher IQ than those in the "no head catch-up" group at the mean age of 23 years, even though head circumference had not been different at birth (statistically significantly, at least). Infants with major malformations or chromosomal abnormalities were excluded, and birth weight, gestational age, optimality scores that reflect pre- and neonatal adversity, or parental head size were not different between these two groups, but the "head catch-up" group were more likely to be born after pre-eclampsia and to have a higher energy intake during the first 10 days of life than the "no head catch-up" group. The follow-up rate was an impressive 93% of adult preterm survivors. In another study among the same participants, the adult IQ of those SGA individuals who showed "height catch-up" (n=21, height *z* scores steadily increased to adulthood) did not differ from that of the "no height catch-up" group (n=25, height *z* scores decreased or remained unchanged).[228] While these studies represent an era when under 40% of VLBW neonates survived, and the choice of methodology was not optimal for revealing the effects of postnatal growth independently of earlier growth, they hinted that early head growth after preterm birth could provide an early, perhaps even modifiable marker of adult outcome.

The next adult study suggested that also AGA preterm infants who grow faster have higher adult IQ.[278] In this study, Weisglas-Kuperus and colleagues assessed weight and length gain among the very preterm or VLBW, AGA (birth weight and length above -2SD) adults of the POPS study born in the Netherlands in 1983, when neonatal survival rate was already 77%.[278] Those who had weight and length above -2SD also at 3 months CA (n=274) had 4.1 points higher IQ at 19 years, compared with those who were short, light, or both at 3 months CA (n=79), after adjusting for gestational age, sex, and parental factors including SES. 59% of adult survivors underwent neuropsychological assessment.

Belfort and colleagues showed that post-term growth in length, but not in BMI, predicted adult IQ among preterm adults with birth weight ≤2500g.[264] The participants were 633 young adults born in the US in 1984-1985, representing 60% of those preterm infants who had originally taken part in the Infant Health and Development Program.[264] A larger increase in length z scores between term and 4 months CA was associated with lower odds of having low IQ (<85 points) at 18 years (OR 0.78). Length growth between 4 and 12 or 12 and 18 months, adjusted for earlier growth, or BMI increase during any of these periods did not predict low IQ in adulthood. Child and maternal age, sex, gestational age, maternal smoking, and parental factors including SES and a maternal IQ estimate, as well as participation in the educational intervention were adjusted for.

Finally, Stein et al. reported educational outcomes among adults from low- and middle-income countries (Brazil, Guatemala, India, Philippines, and South Africa).[229] They noted that among the 492 preterm adults with schooling data available, those who had faster length growth in infancy, independently of birth length, sex, or study location were more likely to have completed secondary school.[229]

#### 2.5.3.3. Effects of early growth on cognitive and academic outcomes: evidence from childhood follow-up studies

In line with these adult studies are the many studies on preterm,[303] early preterm (<33 weeks),[304] very preterm,[184,305–307] extremely preterm,[181,308,309] VLBW,[184,306,310] and ELBW[187,311–313] children, which have shown that poor growth in infancy is associated with poor cognitive functioning at 16-36 months CA[187,304,310,313,309] and at 5-10 years[181,184,303,305–308,311,312] (calendar age, in most studies). However, four studies on preterm,[314] VLBW[315,316] and ELBW[236] children showed no statistically significant associations between growth after birth and cognitive functioning at approximately 2 years[236,316] or 4-8 years.[314,315] Most of these growth studies and some studies on size as a predictor of cognitive functioning were reviewed (and presented in table format) by Ong and colleagues in 2015.[317]

Almost all of these studies associated growth with general estimates of cognitive functioning and development[181,184,187,303–308,310–313,309] (such as IQ[303,305–308,311]). Some additionally showed that early growth is associated with both general estimates of both verbal and non-verbal reasoning.[303,305] Visuo-motor integration showed a weaker, if any association with growth in the few studies that additionally examined it.[303,305] Further, a few studies reported that faster early growth predicts better school outcomes, including a lower rate of teacher-reported learning problems[312] and better reading and spelling

skills.[303,308] In addition to the cognitive outcomes, in some,[181,187,236,304,308,310,313,309,316] but not all[305,311] studies, poor early growth was associated with poor motor development.

More specifically concerning the timing and measure of growth, several (but not all[181,307,310,315,316]) studies reported that better cognitive functioning[184,187,304–306,308,312,313,309] and school outcomes[308,312] are associated with faster *head growth* during time periods that included the very first weeks and months of life: from birth to discharge,[187] to 4 months CA,[312] to 2 years CA,[306,308] and to 6-10 years,[184,305] from NICU admission to discharge,[309] from the 1st week of life to term,[304] and from the day of regaining birth weight to discharge.[313] What about time periods that did not include the first few weeks or months of life? Several studies reported that head growth from discharge to 3 months,[307] term to 2 years,[306] and from discharge to 16-36 months CA,[309] to 5 years CA,[181] or to 6-10 years[184] was associated with better cognitive outcome, whereas one reported effects between before but not after term.[304] Head growth after infancy (which occurs to a much lesser degree) was not associated with improved performance.[307,308,312,315]

Faster *weight gain* after birth has also been associated with better cognitive functioning. These associations have been found in studies that have looked at growth periods extending from birth to discharge,[181] to 2-3 years CA,[303,306,310] and to 5-10 years,[184,311] from the 1st week of life to term,[304] and from the day of regaining birth weight to discharge.[313] However, other studies have reported that weight gain from birth to 1-2 years[236,308,316] or to 4-7 years[314] was *not* associated with cognitive outcome, and more rapid weight and BMI gain after term seems unrelated to general estimates of cognitive functioning.[304,308] It has been suggested that rapid early postnatal weight gain (along the intrauterine rates) is a good marker of sufficient nutrition and good health during a time when almost all preterm infants are below the expected mean weight, but the increase in fat-free-mass, rather than the accumulation of fat mass, is the component of weight gain that better predicts neurodevelopment among hospitalised preterm infants.[318]

Rapid *length growth* after birth was *not* associated with childhood cognitive functioning in a number of studies which examined growth from birth to approximately 2 years CA[306,310,316] or to 5 years[311], and from the 1st week of life to 12 months CA.[304] One study reported that length gain between birth and discharge, but not between discharge and 6-10 years, was associated with better cognitive functioning in school-age very preterm children.[184] Offering some support to this was a study of VLBW children that reported that length in infancy, but not at birth, was predictive of neurodevelopment at 2 years: however, this latter study did not, strictly speaking, examine growth *per se* (but rather, reported the effects of length at different time points, after showing that size at birth did

not significantly differ among the participants), and the authors only adjusted for birth head size and weight when analysing the effects of birth length, but not when analysing those of later length.[319] Further, the adult study by Belfort et al. (described in the previous section) also reported childhood outcomes, showing that length growth from term to 4 months, but not later in infancy, was associated with higher IQ at 8 years.[264]

The few studies that have specifically looked for sex differences in the association between growth and neurodevelopment have found none.[304,310] Comparisons of AGA and SGA children have not reported consistent results. One US study compared relatively healthy preterm AGA children with or without postnatal weight growth restriction and SGA children with or without weight catch-up growth.[303] They reported that the children who had both prenatal and postnatal growth problems (n=43) had the poorest cognitive outcome, whereas SGA infants with good catch-up growth (n=68) performed similarly to AGA children with no growth problems (n=434).[303] Among AGA children, those with postnatal growth problems (n=110), performed worse than those without.[303] Somewhat in line, one Australian study of early preterm children (gestational age <33 weeks) reported that faster infant weight and BMI gain was strongly associated with better cognitive functioning among SGA children (n=50), but found much weaker effects among AGA children (n=511).[304] In contrast, a Finnish study found that faster infant weight and head growth were associated with higher IQ only among AGA children (n=122), but not SGA children (n=59) in a cohort of very preterm and VLBW children.[306] Finally, somewhat similarly, a Dutch ELBW study reported that AGA children whose weight *z* scores remained normal (≥-2SD at birth and at 5 years, n=53) had higher IQ, compared with those AGA children whose weight decreased below the -2SD cut-off (n=27), but catch-up weight gain among SGA (n=21) children was unrelated to IQ.[311] The latter study reported a non-significant trend in the same direction among their small SGA group as among their larger AGA group (i.e., increasing and non-decreasing *z* scores were associated with better neurodevelopment),[311] but the Finnish study did not.[306] Because the cohorts and methodology varied in many ways, and potential interactions were not statistically addressed, it is difficult to get to the bottom of why these results conflict.

The approach to dealing with potential confounders has varied quite considerably across studies. One recent study that specifically looked at the effects of adjustment for early illness (IVH, BPD, sepsis, NEC, and postnatal steroids) concluded that these had a significant role in explaining the associations between head growth sparing and infant neurodevelopment, even more so with cognitive than with motor outcomes.[187] The others who found evidence of an association usually adjusted for some illnesses such as severe

IVH or other neonatal brain abnormality,[181,184,304,308,310,313] postnatal corticosteroids,[304,308,313] BPD,[304,310,313] and the length of ventilation.[181] Most who reported associations also adjusted for basic child characteristics (such as sex, age at assessment, and gestational age)[181,184,187,303,304,306,310,313,309] and SES,[181,184,187,303,304,306,308,313] and one even included maternal smoking during pregnancy and breast-feeding status at discharge.[304] Some studies did not report adjusting for potential confounders:[305,307,311,312] this was perhaps because some aimed to simply describe the prognosis for growth restricted children, rather than untangle the effects of underlying factors, or because associations between growth and neurodevelopment were presented quite briefly as additional information. In one study, the associations remained after Bonferroni correction:[303] others did not report correction for multiple testing.

Further, study populations varied in many ways. Associations were found even in populations where disabled or severely ill participants had been excluded (depending on the study, this meant congenital malformations,[187,304,306–308,310,313,309] chromosomal abnormalities,[304,306,308] cerebral palsy,[184,308] visual/hearing impairment,[308] hydrocephalus with shunt placement,[187,309] or even anyone with low Apgar scores,[310] long-lasting corticosteroid medication,[306] microcephaly at birth,[309] or any severe illness or neurological impairment at all[303]). However, several studies did not mention any pre-defined exclusion criteria.[181,305,311,312] This can make interpretation more difficult, because some of these underlying conditions can affect growth, neurodevelopment, and perhaps even more worryingly, the reliability of neuropsychological assessment.

Further, there was heterogeneity in the way growth variables were constructed, and even the choice of growth standards used across studies could have impacted the results.[310] There are also a number of studies which claimed to study growth, but actually looked at size at some specific point of development (rather than change in size). Size can certainly be relevant in a number of situations, however, for the purpose of this thesis, I specifically wanted to address the question of whether growth predicts adult outcomes, and I have thus not included all those studies that studied size in my literature review: they answer a different question.

To give an idea of the background setting of the studies, I have listed the years of birth, the country, city or cohort name, and the number of participants who were included in the childhood follow-up analyses that were described in this section in Table 1.

***Table 1.*** *Background information of studies on growth after preterm birth and childhood cognitive functioning.*

| Reference | Years of birth | City, area, or cohort name, and country | Number of participants |
|---|---|---|---|
| Stathis et al (1999)[312] | 1977-1986 | Brisbane, Australia | 87 |
| Cooke (2006)[315] | 1980-1981 | Merseyside, UK | 194 |
| Latal-Hanjal et al (2003)[316] | 1983-1994 | Zürich, Switzerland | 219 |
| Casey et al (2006)[303] | 1984-1985 | IHDP, US [a] | 655 |
| Kan et al (2008)[308] | 1991-1992 | Victorian Infant Cohort, Australia | 179 |
| Cooke & Foulder-Hughes (2003)[305] | 1991-1992 | Liverpool, UK | 268 |
| Huang et al (2013)[314] | 1993-1996 | Hebei, Zhejiang, Jiangsu, China | 654 |
| Ehrenkranz et al (2006)[313] | 1994-1995 | NICHD NRN GOS, US | 495 |
| Lidzba et al (2016)[184] | 1995-1997 | Tübingen, Germany | 136 |
| Franz et al. (2009)[181] | 1996-1999 | Ulm, Germany | 219 |
| Claas et al (2011)[311] | 1996-2005 | Utrecht, the Netherlands | 101 |
| Sices et al. (2007)[236] | 1997-1999 | Ohio, US | 154 |
| Belfort et al (2011)[304] | 2001-2005 | DINO, Australia | 613 |
| Leppänen et al (2013)[306] | 2001-2006 | PIPARI, Finland | 181 |
| Neubauer et al (2016)[307] | 2003-2009 | Tyrol, Austria | 273 |
| Nash et al (2011)[310] | 2004-2006 | Sunnybrook, Canada | 289 |
| Meyers et al (2016)[187] | 2009-2010 | NICHD NRN GDB+F, US | 658 |
| Raghuram et al (2017)[309] | 2009-2011 | CNN and CNFUN, Canada | 1973 |

[a] *Belfort et al. later reported adult outcomes in this cohort, as described in the previous section.* [264]

*Abbreviations: CNFUN: the Canadian Neonatal Follow-Up Network; CNN: the Canadian Neonatal Network; DINO: DHA for the Improvement of Neurodevelopmental Outcome; IHDP: Infant Health and Development Program; NICHD NRN GDB: the National Institute of Child Health and Human Development Neonatal Research Network's Generic Database and Follow-up Studies; NICHD NRN GOS: the National Institute of Child Health and Human Development Neonatal Research Network Growth Observational Study; PIPARI: Development and Functioning of Very Low Birth Weight Infants from Infancy to School Age*

It is noteworthy that while temporally varied, the results available for this review of childhood outcomes were almost exclusively based on cohorts born in wealthy Western countries, except for one study whose participants were born in China.[314] That study

differed from the majority of others in many additional ways: it was one of the few not to report significant associations, the only to include (a majority of) late preterm infants in the study group, one of the few to look at weight gain from birth to 4-7 years without earlier measurement points, and the only one to adjust for maternal IQ among a large number of other family-related covariates.[314] Because of these several differences, it is difficult to say why they reported findings that were different from most others. It is hardly only because of adjustment for maternal IQ: the adult study by Belfort and colleagues suggested significant associations between growth and cognitive functioning even when maternal IQ was adjusted for.[264] It seems unlikely, also, that early growth after preterm birth would not matter in lower-income-settings, but it certainly may reflect partly different underlying mechanisms, as nutritional and medical resources are different and fewer extremely preterm or severely ill infants survive to assessment at all.[229] Further, even among preterm infants born in low- and middle income countries, faster early growth predicts better adult educational attainment, as described in the previous section.[229] One can even argue that in terms of survival and neonatal care, the cohorts born in high-income countries in the 1970s and early 1980s are more similar to the infants of low- and middle-income countries today, and that their results could generalise more to lower-income settings (with basic maternal and neonatal care), rather than to current preterm infants born in high-income countries where intensive care is available.

Taken together, these adult and child studies suggest that growth in early infancy predicts cognitive functioning, more so than growth after this early period does. Further, head growth seems perhaps the most consistent growth marker of neurodevelopment, followed by weight gain, and only then, length growth. However, the first two have also received more research attention, and different growth measures may be differentially associated with neurodevelopment at different time points, and evidence regarding these effects is somewhat conflicting. Further, due to methodological differences, estimating any effects sizes is difficult. Only a few studies have looked at how these effects might persist into adulthood, what kind of measurements best predict what kind of outcomes, or whether some subset of preterm infants benefits more than others, and evidence regarding late preterm infants is lacking. Finally, and perhaps most interestingly, it is unclear what underlies the effects between growth and neurodevelopment - is it nutrition, intrauterine events and growth patterns, genetic potential, or illness, for example - and can something be done to help?

#### 2.5.3.4. Effects of early nutrition after preterm birth on cognitive and academic outcomes in adulthood

Only a few studies have looked at the effects of early nutrition among preterm infants on adult cognitive outcome - or any other adult outcomes, for that matter.

For the purpose of this review, the most interesting perhaps are the results from the feeding trials conducted by Lucas and colleagues among preterm infants (birth weight <1850g) born in the UK in the early 1980s. The trials and some of their other findings were also described in section 2.5.2.3.

In these two separate randomised controlled trials, researchers compared multinutrient-enriched preterm formula against standard formula commonly used for term-born infants,[267] and preterm formula against unfortified donor milk.[268] All mothers were given the opportunity to provide maternal milk, and the studied products were given as a supplement, or as the sole diet when no maternal milk was available. Later, the researchers combined data from both trials and showed that those randomised to receive multinutrient-enriched formula (vs term-formula or donor-milk) had higher VIQ at 13-20 years of age.[320,321] These positive effects contrast somewhat with the earlier findings within that same population, which did not find that fortified formula would consistently improve neurodevelopmental scores at 18 months[322] or at 7.5-8 years.[323] While it could be that some effects of early nutrition only become apparent with age, attrition complicates the interpretation of these findings: of the total of 926 infants who were originally enrolled in the trials, data for only 95 participants[320] and 76 participants[321] were available for analysis at 13-20 years.

Data from this adult/adolescent follow-up were also used to report observational findings: in a subsample of 50 participants of the 13-20 year follow-up, those who had received more maternal milk in infancy had higher VIQ.[324] Maternal milk intake was understandably not randomised, and one can speculate that intake was limited by early illness and the amount of milk the mothers were able to provide, for example. Data on neonatal complications were not available in these publications.

Two others, to my knowledge, have reported findings from adult observational cohorts. In the study by Brandt and colleagues that was also discussed in section 2.5.3.2., energy intake during the first 10 days of life was not associated with IQ at 23 years among 46 VLBW SGA individuals born in 1967-1975, after adjusting for SES only.[239] Neonatal complications were not addressed, but the VLBW survival rate of less than 40% at the time suggests that only the healthiest members of the cohort could be followed-up.[239]

Finally, Breeman and colleagues very recently compared a range of neonatal predictors of cognitive functioning among the 260 very preterm or VLBW adults of the Bavarian Longitudinal Study born in Germany in 1985-1986, as also noted in section 2.5.3.1.[289] They reported that a longer duration of parenteral nutrition was associated with higher adult IQ (with an effect size of 0.19 IQ points per day), when a large variety of other factors related to neonatal health and family environment such as gestational age, size at birth, BPD, RDS, and the duration of mechanical ventilation were taken into account.[289] Further, they reported that although those who were being breast-fed at the 5-month follow-up had higher adult IQ than those who were not in unadjusted models, the effects attenuated to non-significance after taking the multiple other predictors such as SES and illnesses into consideration.[289]

#### 2.5.3.5. Early nutrition after preterm birth and cognitive and academic outcomes: evidence from childhood studies

Literature concerning nutrition after preterm birth and neurodevelopmental outcomes in infancy is quite abundant. Some studies have also extended their follow-up to school-age.

In observational settings, among ELBW[190,325] and VLBW[326] children, higher energy,[190,325] protein,[325] and lipid[326] intakes during the first weeks of life predict better neurodevelopmental scores at 12-22 months. However, it would seem that these effects are mainly driven by the most critically ill neonates, among whom nutritional intake could reflect or mediate the effects of illness severity.[190] Further, some have reported that ELBW infants born after the introduction of a more aggressive nutrition protocol (which changed, in particular, the provided amount of protein, amino acids, and total energy), rather than before this shift in protocol, receive better neurodevelopmental scores at 2-3 years, after adjusting for some basic potential confounders,[327] whereas others did not reported differences that would survive adjustment.[328] Certainly, the risk of residual confounding in these studies remains.

Perhaps the most compelling evidence exists for feeding with *maternal milk*, which is the recommended primary basis of nutrition for preterm and term infants alike.[163,205,206,329] Of course, randomised controlled trials of breastfeeding would be unethical and practically quite impossible to conduct. Thus, evidence of benefits is mostly based either on observational studies, or on studies that have compared donor human milk versus formula as a source of nutrition when sufficient amounts of maternal milk are not available. Although donor milk is pasteurised and may not provide the immunological

and mother-child-interaction benefits of maternal milk and direct breast-feeding, both maternal and donor milk are recommended over formula use, however both need to be fortified during the early period to enable the preterm infant to meet growth expectations, as discussed in section 2.4.4.5.[163,205,206,329]

Many observational studies have indeed linked breastfeeding and maternal milk with better neurodevelopment. Among very preterm[330,331] and extremely preterm infants,[285] and infants with birth weight <1850g,[332] with VLBW,[333] and with ELBW,[334] those who received more or any maternal milk during the initial hospitalization,[285,330,332,334] who were breast-fed at discharge,[331] and who were breastfed for at least eight months[333] had better cognitive test scores[330–334] and school skills[285,330] than comparison groups at 2.5 years,[334] 2 or 5 years,[331] and 7-11 years.[285,330,332,333] All of these studies adjusted for some maternal background factors (such as maternal age, maternal education, marital status, employment status, income status, maternal or child ethnicity, and parity) and infant characteristics (such as gestational age and gender) and early complications (such as severe IVH, PVL, sepsis, BPD, and NEC), and a few studies also included maternal smoking during pregnancy[333] and neonatal weight gain.[330] Missing from this list of potential confounders is maternal IQ, which has been suggested to contribute to the observed associations between breast-feeding and child neurodevelopment.[335] One observational study compared VLBW children who had been breast-fed (n=125) with those who had received maternal milk from a bottle but had never been actually breast-fed (n=142) or who had never received maternal milk (n=153) in infancy.[335] In the first group, they found significantly better general, verbal, visuo-spatial, and motor skills at 6-8 years, but these associations were attenuated to non-significance after adjusting for SES-related factors and an estimate of maternal verbal IQ, except that visuo-motor integration scores were slightly better.[335]

A few other studies have also conflicted with the studies that have reported that maternal milk or breast-feeding benefit neurodevelopment among preterm infants. One study found no association between the amount of maternal milk intake during the first month of life and cognitive outcomes at 20 months CA among 98 VLBW infants,[336] and another reported no association between the duration and amount of breast-feeding during the first year of life and cognitive outcomes at 12 months CA among 148 VLBW infants.[337] These two studies adjusted for potential confounders that were similar to the ones listed in the previous paragraph, but interestingly, both assessed outcomes earlier than the studies which reported positive findings. It is possible that some subtle effects of breast-feeding only become evident with age. However, it is also possible that the effects of SES

and other family factors on cognitive functioning become more evident with age, and breast-feeding in our society is a reflection of these others environmental factors, not a (major) causal agent behind improved neurodevelopment.

Somewhat in line with this pessimistic view, donor milk vs formula trials among preterm infants have been unable to show that one would offer clear cognitive benefits over the other, although feeding with donor milk is otherwise beneficial (it is associated with a lower risk of feeding intolerance and NEC, which, one could argue, indirectly promotes also optimal neurodevelopment), as reported by a Cochrane review in 2014.[205] The only neurodevelopmental data available to that systematic review were from the studies by Lucas et al., described also in the previous section, which compared unfortified *donor milk against preterm formula before discharge* among preterm children, either as a sole diet (sub-trial A) or as a supplement to any maternal milk the mother chose to provide (sub-trial B). At first, those who were given preterm formula as a supplement had less developmental problems than peers who were given unfortified banked donor milk as a supplement (B), based on the Knobloch screening inventory at 9 months CA, but there were no significant differences between those who received only donor milk vs preterm formula as a sole diet (A).[268] In the follow-up however, when neurodevelopment was tested at 18 months CA, no significant developmental differences emerged between any of the four diet groups in either sub-trial A or B.[322] Unfortunately, to my knowledge, the researchers did not provide comparisons of these original donor milk vs formula trial groups at later follow-ups.

Despite intense interest, other randomised controlled studies and their meta-analyses have also failed to show that any other specific nutritional intervention would significantly benefit neurodevelopment. One Cochrane review from 2016 examined *fortification of human milk (with protein, energy, and usually micronutrients) during hospitalization*[210] for preterm infants, and concluded that based on the published[338] and unpublished data from the trials by Lucas and colleagues - again, the only ones to report neurodevelopmental outcomes at or after 1 year of age - multi-nutrient fortification of human milk before discharge did not affect neurodevelopmental status at 18 months.[210] A trial by Tan and al. further suggested that an intervention which increased both the energy and protein content of enteral and parenteral nutrition during initial hospitalization of very preterm infants was not associated with cognitive or motor outcomes at 9 months CA.[339]

Two other Cochrane reviews from 2012 and 2013 examined whether *nutrient-enriched formula (vs standard term formula) after discharge*[211] *or multinutrient-enriched human milk (vs unfortified human milk) after discharge*[209] had an impact on preterm infants' neurodevelopment. The first review identified four relevant studies which reported no effects on neurodevelopmental outcomes at 12-18 months CA,[340–343] and concluded that there was no evidence to support the use of preterm formula after discharge.[211] In line, nutrient-enriched formula trial findings published after the publication of the 2012 Cochrane review also showed no effects at 2 years CA.[344] Similarly, the 2013 Cochrane review found no evidence of benefits of fortifying human milk after discharge but rather stated that it had the potential to interfere with breast-feeding,[209] however they also cautioned that only one small study had examined neurodevelopmental outcomes (and found no difference among the fortified vs non-fortified milk groups in mental, motor, or behaviour rating scales).[345]

Trials of *increasing the amount of amino acids* in parenteral nutrition[346–348] or the amount of amino acids in parenteral nutrition and of protein in enteral nutrition[349] have also not shown differences in neurodevelopment, assessed at approximately 2 years CA among ELBW or VLBW neonates.[346–349] One Cochrane review from 2016 examined the potential effects of *supplementation with one common amino acid, glutamine,* specifically.[214] The authors identified three trials that assessed neurodevelopmental outcomes after early infancy, and none of them showed significant differences in these outcomes. One of the three studies reported no differences between early parenteral amino acid provision (n=154, ≥3g/kg/day at ≤5 days of life) vs late provision (n=714) in terms of neurodevelopment at 18 months CA among ELBW infants, in a secondary analysis of the NICHD NRN glutamine trial data.[350] The two other studies were from a single trial that compared glutamine supplementation in milk or formula (n=40, 0.3g/kg/day at 3-30 days of life) against placebo supplement (n=32) during the first month of life after very preterm or VLBW birth, and found that neither general neurodevelopment at 2 years CA,[351] nor IQ, executive functioning, or parent- or teacher-rated behavioural, mental health, and learning outcomes at 7.5 years were different between the groups:[352] however visuo-motor ability was *poorer* in the glutamine supplement group.[352]

Another Cochrane review from 2014 examined *higher versus lower protein intake* during the initial hospital stay in formula-fed preterm or low-birth-weight infants and found two small studies on preterm infants, and yet again reported that these offered no convincing evidence of cognitive benefits.[213] One of the studies reported no difference between high-

protein (3.2 g/kg/d, n=16) vs low-protein (2.6 g/kg/d, n=14) fed VLBW children at 2 years.[353] Another study reported, among a subset (n=15) of the 16 VLBW infants in the high-protein (3.1-3.8 g/kg/day) vs 7 infants of the low-protein (2.6 g/kg/d) group, that those who received more protein had higher scores on the Neonatal Behavior Assessment Scale.[354] Methodological problems such as the very small number of participants and the unreliability of neonatal assessment for any long-term neurodevelopmental outcome make any conclusions difficult to draw. Further, two studies have reported that very preterm infants fed protein-enriched human milk (4.8 g/kg/day, n=19) vs a control supplement (3.5 g/kg/day, n=13),[355] and infants with birth weight <2000g who were fed very high protein (6.0-7.2 g/kg/d, original n=152) vs high protein (3.0-3.6 g/kg/d, original n=152) diets[356] had *lower* IQ scores at 3 months CA[355] and at 5-7 years,[356] suggesting that effects of increasing protein content (considerably) could even be detrimental. Unfortunately, full text versions of these single studies which were mostly published decades ago were unavailable to me, and the number of participants may have been smaller in the cognitive outcome analyses.

*Long-chain poly-unsaturated fatty acid enrichment* has also been investigated in several studies, some of which initially seemed to suggest beneficial effects, but later proved less encouraging. One important study was the DINO trial which initially reported improved neurodevelopment at 18 months CA among girls who received more docosahexaenoic acid,[357] but later concluded that supplementing enteral feeds with docosahexaenoic acid before term age did not result in any differences in IQ, attention, executive functioning, behaviour, visual-spatial perceptual skills, educational progress, or quality of life at 7 years CA among the 657 preterm (<33 weeks) participants enrolled in the study: if anything, girls who received the supplement had *more* parent-rated behavioural problems.[358] The lack of long-lasting effects was confirmed in three different meta-analyses published in 2008-2012 that overlapped in terms of included studies.[359–361]

As to micronutrients such as different vitamins, iron, calcium, phosphorus, and magnesium, little evidence to clearly indicate the optimal intake among preterm infants exist:[362] neither the few available vitamin A[363] nor prophylactic enteral iron[364] supplementation trials have shown significant cognitive benefits.

Of course, absence of evidence is not necessarily evidence of absence - many questions about the associations of nutrition and cognitive functioning of preterm infants have not been studied or have only been studied among very small samples that may lack sufficient power to show small or even moderate effects even if they do exist. The effects of neonatal

nutrition on long-term outcomes are not an easy topic to tackle, not least because nutrition forms just one piece of a large puzzle, inevitably intertwined with illness and other early determinants of infant development. In trials, comparisons are usually made between an intervention group and those who receive the standard nutrition in whatever settings the study was conducted in. Surely, providing some "adequate" level of nutrition is the prerequisite of normal neurodevelopment, since providing some adequate level of nutrition is the prerequisite of any development and survival at all, but how to improve the neurodevelopment of a preterm infant by *altering* nutrition remains unclear. Taken together, what these studies suggest is not that nutrition does not matter, but rather, that although observational studies have hinted at long-lasting effects, the nutritional intervention studies that have been conducted so far have seldom looked at long-term neurodevelopmental outcomes, and those that have, have not shown that any specific nutritional interventions would have consistent benefits.

### *2.5.4. Mental health*

#### 2.5.4.1. Mental health among adults born preterm

Preterm-born adults are more likely than term-born adults to have mental disorders, according to large Northern European register studies with partly overlapping data.[284,365–370] For example, one Swedish register study showed that very preterm adults were 2.5, 2.9, and 7.4 times more likely than term-born individuals to be hospitalised because of non-affective psychosis, depressive disorder, and bipolar disorder, respectively.[365] However, the findings from these and other studies are partly conflicting, and the risks may be specific to some outcomes and to certain subgroups of the preterm population.

The range of examined outcomes is wide. Register studies have shown that preterm adults have more mood disorders (including both depression and bipolar disorder),[365,366] autism-spectrum disorder (ASD),[284,367] attention deficit hyperactivity disorder (ADHD),[367,370] stress-related disorders,[366] and eating disorders[365] than controls do. Several studies have indicated an increased rate of psychosis and schizophrenia among preterm individuals,[365,367,368] but confounding parental background factors are likely to explain some of the observed increase.[367,369] These factors also seem to heavily contribute to the increased suicide rate among preterm individuals, however their role in explaining neuropsychiatric disorders seems less important.[367] Smaller clinical studies have also suggested that, based on standardised diagnostic interviews, VLBW[371–373] and ELBW[374]

adults have more anxiety disorders,[371,372] mood disorders,[372,373] somatoform disorders,[372] and ADHD,[371] but no more substance use disorders[372,374] than normal-weight term-born controls do, even when SES-related and some other background factors are taken into account.

VLBW participants also have more internalizing and avoidant personality problems than term-born controls, according to a recent pooled meta-analysis by APIC of 747 VLBW adults and 1512 term-born controls born in Canada, Norway, US, Germany, and Finland, including the VLBW cohort examined in this thesis.[375] On some other self-reported indices of psychosocial adjustment and wellbeing, however, preterm adults seem to do better than term-born peers: the preterm participants of that meta-analysis reported *less* externalizing problems, rule-breaking behaviour, and intrusive and antisocial personality problems than term-born controls.[375] The pattern of findings was similar in the different cohorts, neurosensory impairment or parental education did not account for these differences, and while both preterm men and women reported more internalizing problems than term-born controls did, the pattern of some findings was more pronounced among women.[375]

In line with this meta-analysis and the anxious and shy adult phenotype it suggests, meta-analyses of preterm *children* have suggested an increased risk of internalizing-type problems,[376,377] but also more parent- and teacher-rated externalizing problems.[376,377] It is unclear whether this "change" in the rates of externalizing behaviours represents an actual alleviation of some certain types of problems from childhood to adulthood. Some methodological differences may also contribute, and the parent- and teacher-reported externalizing problems of childhood (such as oppositional behaviour and hyperactivity) could represent a partly different phenomenon than adult-reported externalizing problems (such as delinquent behaviour and substance abuse). Overall, several studies have shown that parents report more mental health and behavioural problems among their preterm offspring than what the preterm individuals themselves report experiencing, both in childhood[378] and in adolescence and young adulthood.[379–381] Of course, when comparing childhood and adult studies (or register and self-report studies, for that matter), individuals with mental health problems may be less likely to actively participate in any voluntary study.

As to actual quality of life, a meta-analysis from 2008 suggested that differences are more pronounced in childhood and attenuate with increasing age, so that preterm and term-born young adults report very similar quality of life despite differences in health.[379] Some

recent adult studies, however, have reported that very preterm and VLBW young adults report poorer health-related quality of life compared with term-born peers, especially in relation to problems in economic and social life.[382,383]

Studies concerning the effects of *late preterm* birth specifically are scarce. The late preterm adults examined in this thesis and their term-born controls had similar rates of mood, substance use, and anxiety disorder based on psychiatric interviews.[384] In another Finnish study, late preterm men had an increased risk of suicide, but otherwise late preterm birth was not associated with substance use, psychotic, mood, anxiety, or personality disorders among a register cohort followed up to old age.[385] In a Norwegian register study, late preterm birth was associated with an increased risk of schizophrenia and disorders of psychological development, behaviour, and emotion (relative risk ratios 1.3 and 1.5, respectively), but not with ASD.[284] In a Swedish register study, late preterm birth was associated with an increased risk of psychotic or bipolar disorder, ASD, and ADHD, whereas the risk of substance use disorders was similar between late-preterm and term-born adults.[367] All these studies took some SES-related factors into account.

Several studies have suggested that within the preterm population, with decreasing gestational age, the risk of psychotic disorders, ASD, ADHD, and mood disorders increases.[365,367] However, quite interestingly and somewhat in line with the findings of self-reported psychological wellbeing, extremely preterm adults may have even *less* substance use disorders and criminal convictions than the general population, while those born moderately or late preterm have a similar or slightly increased risk, compared with term-born adults.[365,367] It is difficult to say why exactly this is: one can hypothesise, for example, that different degrees of prematurity are associated with different underlying risk factors (such as maternal health and behaviour), which also differently affect the risk of mental health disorder in the offspring. It can also be that differences in the nature, timing, and magnitude of early neurodevelopmental insults translate to differences in mental health (for example, some subtle forms of early brain injury could be more important in determining the risk of neuropsychiatric problems or schizophrenia than that of depression or substance use disorders). Further, preterm birth, and especially very preterm birth and the hospitalization and morbidity it entails, could affect early social interactions and susceptibility to parenting effects,[386] as well as peer relations later in childhood,[387] and this could then potentially affect further developmental pathways to adult mental health.

SGA birth may explain the observed association between preterm birth and mental health problems at least in part, but the pattern of findings is not entirely consistent. The Finnish register study of late preterm adults followed into late adulthood suggested that SGA status, but not late preterm birth, was a risk factor for severe mental disorders.[385] A Swedish register study that examined a large population of young adults concluded that preterm birth itself only increased the risk of hospitalization for the combined diagnostic class of child psychiatric disorders and mental retardation, whereas SGA birth was much more closely associated with psychiatric hospitalization both among preterm and term populations, however quite puzzlingly this was mostly observed only among males.[388] Within the preterm group, SGA men were more likely than AGA men to be hospitalised for any psychiatric disorder, psychotic disorder, personality disorder, child psychiatric disorders and mental retardation, and other disorders, but among women the associations were non-significant: the reasons for potential differential susceptibility among men and women remained unclear.[388] Another Swedish-Danish study with partly overlapping data reported that both preterm birth and SGA status increased the risk of mental disorders, however gestational age was not examined independently of SGA status.[368]

In our VLBW adult cohort, the increased risk of depressive[389] and ADHD[390] symptoms was confined to those who were born SGA, after adjustment for several potential confounders, suggesting that IUGR rather than preterm birth *per se* could explain the increased risk of some mental health problems. However, our VLBW participants reported more social interaction related autism-spectrum traits (but less attention to detail),[391] and also had a more pronounced physical stress response (blood pressure elevation) in a psychosocial stress test,[392] compared with controls, and for these outcomes no clear difference between AGA and SGA participants was observed. In the APIC meta-analysis of which our cohort was part, both AGA and SGA preterm adults reported quite similar (increased) rates of internalizing and (decreased) rates of externalizing, compared with term-born peers.[375]

Methodological differences (such as the variation in the populations, outcomes, and statistical models) can contribute to this seemingly inconsistent pattern of findings, but the effects of IUGR may also be outcome-specific, and the underlying mechanisms remain debatable. It is likely that at least in part, early growth restriction in these situations reflects some unmeasured confounders that also assert their influence on child development after birth. Maternal mental disorders, for example, are associated with smoking and other risk behaviours during pregnancy, adverse perinatal outcomes

including SGA birth, and an increased risk of mental disorders in the offspring, which may be (partly) mediated by parenting and home environment factors and also linked with genetic susceptibility.[393] However, animal studies and recent evidence from human models also point towards a more direct causal link, suggesting that the early-life events which cause growth restriction could alter the pathways to adult mental health, for example through epigenetic changes in the early development of the CNS and endocrine systems.[393,394] These explanations or potential mechanisms are by no means mutually exclusive.

Taken together, the studies on adult mental health suggest an increased risk of some mental health problems among preterm individuals. This risk seems at least partly due to intrauterine growth restriction and its underlying factors rather than preterm birth *per se*. Based on the few existing studies, late preterm birth has little independent effect on adult mental health. These findings further supports the hypothesis that the complex mechanisms which underlie the association between preterm birth and the different aspects of neurodevelopment, mental health, and cognitive functioning are outcome-specific.[367]

#### 2.5.4.2. Early growth and nutrition after preterm birth and mental health

Although the role of intrauterine growth restriction in predicting long-term mental health has received an increasing amount of interest, the role of extrauterine growth has not been studied much. This paucity of studies is actually rather surprising, given that the period of EUGR among preterm populations largely coincides with the period of IUGR among term-born populations, but growth during this time is caused by partly different factors: comparisons could thereby shed some light not only on the development of preterm individuals, but also on the association between early growth restriction and mental health problems in general.

Concerning ASD, among our adult VLBW cohort, we reported that faster growth in weight, length, and head circumference from birth to term, but not from term to 12 months CA, was associated with less self-reported autism-spectrum traits in young adulthood, however none of the participants had a diagnosis of ASD.[391] Several pre-, peri- and postnatal factors including parental education, maternal pre-eclampsia and smoking during pregnancy, a range of neonatal complications, developmental disability, or intrauterine growth patterns did not explain this association.[391] Ikejiri and colleagues also reported that the nine VLBW children with diagnosed ASD in their study showed poorer

early weight gain and head growth, compared with the 50 VLBW controls without ASD, however the small number of ASD cases left little room for assessing the role of the other pre- and perinatal characteristics which differed between the two groups.[395] In contrast, Moss and Chugani reported that among VLBW children, those diagnosed with ASD had *faster* head growth from 9 to 24 months, but head size measurements at birth or growth data during the early period before term-age were unavailable in this study.[396] Among the mainly term-born general population, several studies in the early 2000s suggested that ASD may be associated with reduced brain and head size at birth, followed by dramatically accelerated growth in infancy,[397] however more recent studies have suggested that because of methodological problems, these earlier findings may have painted a much simplified picture of the complex associations between early growth and autism.[398–400]

Concerning ADHD, one study reported that growth in head circumference during the first two years of life among ELBW individuals was not associated with parent- or teacher-reported symptoms of ADHD in childhood.[312] As with ASD, the evidence concerning ADHD and early growth among the mainly term-born general population is conflicting, and potentially further complicated by some effects of medication.[401–403] Certainly, one can hypothesise that early growth restriction during a sensitive early period is associated with subtle alterations in brain development which increase the risk of neuropsychiatric disorders, but information from preterm populations is very scarce.[404] Overall, the complex genetic and early environmental origins of both autism-spectrum disorders and traits and ADHD remain, despite intense interest, enigmatic.[405–407]

In terms of more broad behavioural problems, the Chinese study by Huang et al., also discussed in section 2.5.3.3, reported that weight gain between birth and follow-up at 4-7 years was not associated with parent-rated internalizing, externalizing, or other behavioural problems among preterm children (and unlike the findings for IQ which were discussed earlier, these associations were not significant even in the crude model adjusted for sex only).[314] Similarly, a US study discussed in section 2.5.3.3 did not find that weight gain among preterm children (whether AGA or SGA at birth) would be associated with child behavioural problems at 8 years.[303]

Finally, one neonatal glutamine supplementation trial, also discussed in section 2.5.3.5, examined parent- and teacher-reported behavioural problems and found no effects among very preterm or VLBW children at 7.5 years.[352]

## 3. AIMS OF THE CURRENT STUDY

The preterm infant is faced with an increased risk of morbidity, early growth restriction, and neurodevelopmental problems, however the majority of preterm infants grow up to be as healthy and well-functioning as adults as their term-born peers. Faster early growth may predict better neurodevelopmental outcomes, but evidence of whether these effects persist into adulthood are scarce. Moreover, it remains unclear what explains this association: nutrition, morbidity, and prenatal risk factors have been suggested to contribute. Further, intrauterine growth, perhaps even more so than preterm birth itself, may predict mental health in adulthood, but evidence concerning the role of postnatal growth after preterm birth is limited to a few studies on children.

1. *The first aim of this study is to examine whether early growth after preterm birth predicts better cognitive functioning and mental health in adulthood.*

And if so, I wish to seek answer to the following further questions:

2. *Is there evidence of a sensitive period?*
3. *Are associations outcome-specific?*
4. *Is there any indication of mechanisms that underlie the associations?*

Based on the available earlier literature, I hypothesise that those individuals who grow faster after preterm birth have better adult cognitive functioning, compared with those who grow more slowly. I would also expect mental health to be associated with early postnatal growth, although earlier, somewhat conflicting evidence to support this is based mainly on studies of prenatal growth. Any sensitive period is likely to include the first few weeks and months of life and not extend beyond infancy. I also hypothesise that early nutritional intakes are associated with neurodevelopmental outcomes, but based on earlier literature, these associations may not be independent of early morbidity and familial and individual background factors. These questions are addressed in the four publications included in this thesis, with the following focus:

*I.* Early growth and cognitive functioning among VLBW adults
*II.* *a*. Early growth and depressive and ADHD symptoms among VLBW adults
*b*. Early growth and psychosocial adjustment among VLBW adults
*III.* Early growth and cognitive, academic, and mental health outcomes among late preterm adults
*IV.* Early nutrition and cognitive functioning among VLBW adults

# 4. METHODS

## 4.1. Outline of the study

The studies included in this thesis were part of two larger longitudinal follow-up studies, the Helsinki Study of Very-Low-Birth-Weight Adults (HeSVA), which provided the VLBW participants, and the Arvo Ylppö Longitudinal Study (AYLS), which provided the late preterm participants. The role of growth in predicting adult cognitive outcomes and mental health was examined among both cohorts. In the AYLS cohort, I also looked at growth and school outcomes. Because growth was associated with cognitive functioning and detailed data on early nutrition were available in the HeSVA cohort, I further used those data to examine whether early nutritional intakes predict cognitive outcomes.

In both studies, all participants gave their written informed consent. Studies were approved by the Ethics Committee for Children and Adolescents' Diseases and Psychiatry at the Helsinki University Central Hospital (in HeSVA) and the Helsinki and Uusimaa Hospital District Coordinating Ethics Committee (in AYLS). Research staff were unaware of the early medical history or perinatal characteristics of the participants when assessing their adult physical or mental health, cognitive functioning, and wellbeing. Neuropsychological tests were administered and psychiatric interviews conducted by trained master's level psychology students (including myself), who were supervised by experienced clinical psychologists and, in the case of psychiatric interviews, also by an experienced psychiatrist.

## 4.2. The Helsinki Study of Very Low Birth Weight Adults

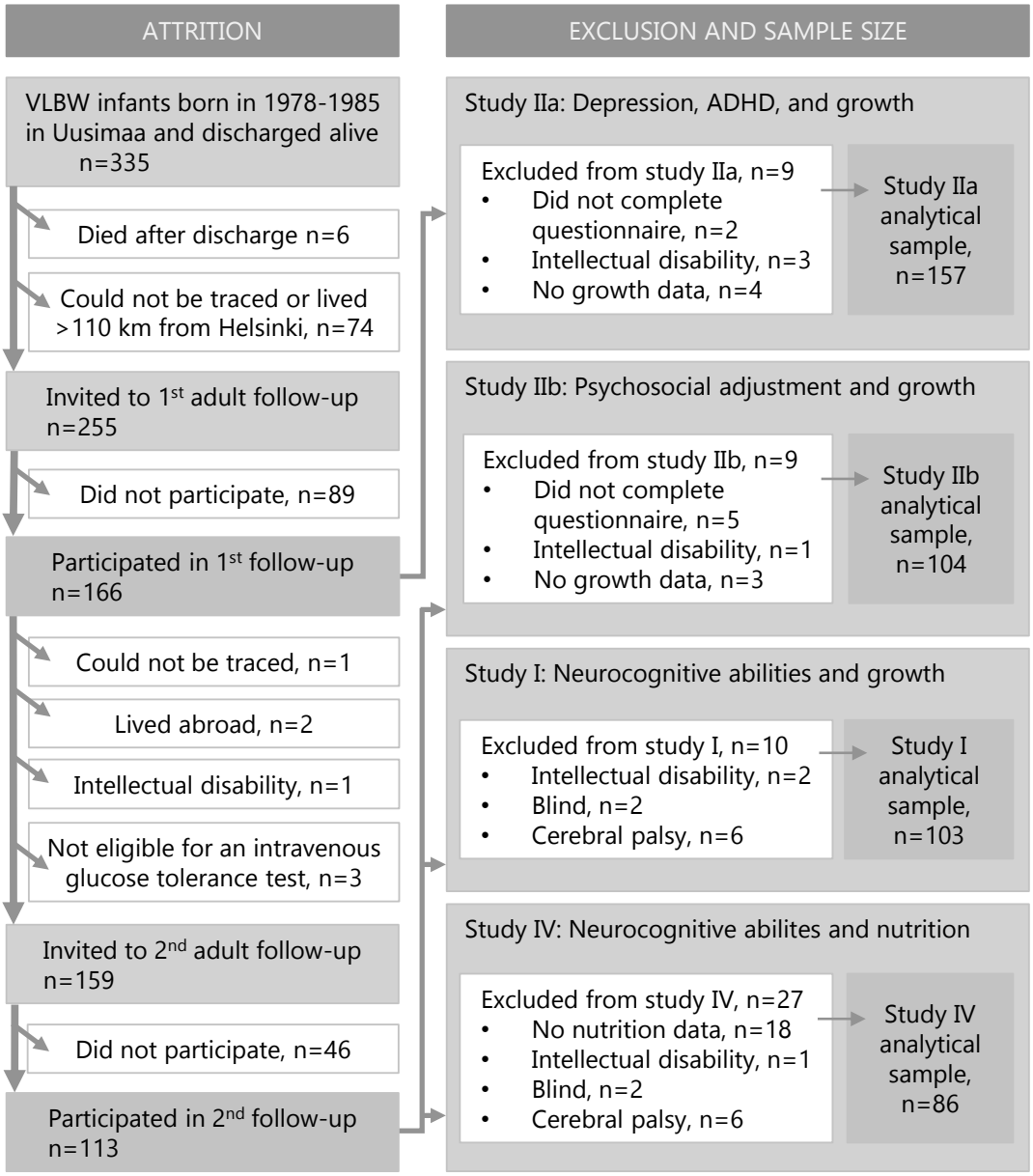
### *4.2.1. Participants*

The HeSVA cohort is a regional cohort of VLBW individuals born between 1978 and 1985 in the province of Uusimaa, Finland. Originally, 474 VLBW infants were born during this time in the five Uusimaa maternity hospitals and admitted to the NICU of the Children's Hospital at the Helsinki University Central Hospital, which serves the entire population of Uusimaa. Of these neonates, 335 (70.7%) survived until discharge, which was comparable to other cohorts born in high-income countries around that time.[408,409]

In 2004-2005, those 255 of these survivors who were still traceable through the Finnish national personal identification number system and living within 110 km of Helsinki were invited to the first clinical follow-up, and 166 participated. During this visit, in addition to an extensive medical check-up, the participants completed several questionnaires

(Study IIa). In 2007-2008, 159 of these 166 participants were invited to a second clinical follow-up, and 113 participated. During this visit, the participants completed more questionnaires and underwent another medical check-up including an intravenous glucose tolerance test and neuropsychological assessment (Studies I, IIb, and IV). Figure 7 shows a flowchart of the formation of the HeSVA study sample.

**Figure 7.** Formation of the Helsinki Study of Very Low Birth Weight sample.



To form a comparison group, for each VLBW infant, the next consecutive singleton same-sex infant who was born AGA at term in the same hospital was invited to participate in HeSVA (172 participated on the first visit, and 105 on the second visit). In this thesis, I focused on differences within the preterm population, not between term-born and preterm populations, and thus did not use the data for the term-born controls.

Characteristics of the HeSVA participants are presented in Table 2.

***Table 2.*** *Characteristics of the Helsinki Study of Very Low Birth Weight participants.*

| | Participants of 1st clinical visit 2004-2005 [a] | | | Participants of 2nd clinical visit 2007-2008 [a] | | |
|---|---|---|---|---|---|---|
| | **M (SD)** | **n (%)** | **N** | **M (SD)** | **n (%)** | **N** |
| **Characteristics at birth** | | | | | | |
| Size at birth | | | | | | |
| Weight, kg | 1.1 (0.2) | | 157 | 1.1 (0.2) | | 103 |
| Length, cm | 37 (2.4) | | 155 | 37 (2.4) | | 102 |
| Head circumference, cm | 26 (2.0) | | 155 | 26 (2.0) | | 100 |
| Small for gestational age | | | | | | |
| Weight ≤-2 SD | | 51 (32) | 157 | | 37 (36) | 103 |
| Length ≤-2 SD | | 49 (32) | 155 | | 29 (28) | 102 |
| Head circumference ≤-2 SD | | 35 (23) | 155 | | 22 (22) | 100 |
| Gestational age, weeks | 29 (2.2) | | 157 | 29 (2.3) | | 103 |
| 24-32 completed weeks (very preterm) | | 139 (89) | 157 | | 89 (86) | 103 |
| 32-33 completed weeks (moderately preterm) | | 12 (8) | 157 | | 10 (10) | 103 |
| 34-35 completed weeks (late preterm) | | 6 (4) | 157 | | 4 (4) | 103 |
| Sex, male | | 66 (42) | 157 | | 43 (42) | 103 |
| Mother smoked during pregnancy | | 28 (19) | 147 | | 17 (18) | 97 |
| **Neonatal complications and illnesses** | | | | | | |
| Duration of ventilator treatment, median days (25th to 75th percentile) | | 4.5 (0 to 14) | 154 | | 4.0 (0 to 14) | 100 |
| Septicaemia | | 12 (8) | 154 | | 9 (9) | 100 |
| Bronchopulmonary dysplasia | | 29 (19) | 152 | | 25 (25) | 99 |
| Received indomethacin | | 44 (28) | 155 | | 33 (33) | 101 |
| Surgery due to patent ductus arteriosus | | 8 (5) | 155 | | 8 (8) | 101 |
| Blood exchange transfusion | | 25 (16) | 155 | | 15 (15) | 100 |
| Intraventricular haemorrhage | | | 111 | | | 78 |
| none | | 90 (81) | | | 64 (82) | |
| grade I or II | | 16 (14) | | | 10 (13) | |
| grade III or IV | | 5 (5) | | | 4 (5) | |

*Table continues on next page*

*Table 2, continued (2/3)*

| | Participants of 1st clinical visit 2004-2005 [a] | | | Participants of 2nd clinical visit 2007-2008 [a] | | |
|---|---|---|---|---|---|---|
| | M (SD) | n (%) | N | M (SD) | n (%) | N |
| **Mean energy intake in infancy, kcal/kg/day** | | | | | | |
| Total, birth to 3 weeks | | | | 94 (17) | | 86 |
| from human milk, birth to 3 weeks | | | | 77 (24) | | 83 |
| Total, 3 to 6 weeks | | | | 119 (15) | | 82 |
| from human milk, 3 to 6 weeks | | | | 108 (22) | | 78 |
| Total, 6 to 9 weeks | | | | 125 (15) | | 79 |
| from human milk, 6 to 9 weeks | | | | 108 (26) | | 75 |
| **Growth during infancy** | | | | | | |
| Weight, birth to term, kg | 1.4 (0.4) | | 157 | 1.4 (0.5) | | 100 |
| Length, birth to term, cm | 9.0 (2.6) | | 148 | 9.0 (2.7) | | 96 |
| Head circumference, birth to term, cm | 7.6 (2.1) | | 147 | 7.5 (2.2) | | 92 |
| Weight, term to 12 months CA, kg | 6.0 (1.0) | | 131 | 6.1 (1.0) | | 84 |
| Length, term to 12 months CA, cm | 27 (2.7) | | 120 | 27 (2.6) | | 79 |
| Head circumference, term to 12 months CA, cm | 12 (1.5) | | 93 | 12 (1.6) | | 58 |
| **Characteristics in adulthood** | | | | | | |
| Age during clinical visit, years | 22 (2.1) | | 157 | 25 (2.1) | | 103 |
| Highest education of a parent | | | 157 | | | 103 |
| basic/primary or less | | 17 (11) | | | 10 (10) | |
| upper secondary | | 34 (22) | | | 20 (19) | |
| lower tertiary | | 62 (39) | | | 40 (39) | |
| upper tertiary | | 44 (28) | | | 33 (32) | |
| Cerebral palsy | | 13 (8) | 157 | | 0 | 103 |
| Blindness | | 2 (1.3) | 157 | | 0 | 103 |
| **Cognitive outcomes** | | | | | | |
| Estimated full intelligence quotient | | | | 102 (15) | | 103 |
| Verbal fluency raw test score, phonetic mean | | | | 12 (4.6) | | 103 |
| Verbal fluency raw test score, categorical mean | | | | 19 (5.1) | | 103 |
| ROCF raw test score, copy task | | | | 34 (3.1) | | 103 |
| ROCF raw test score, immediate recall task | | | | 22 (7.0) | | 103 |
| ROCF raw test score, delayed recall task | | | | 22 (6.8) | | 103 |
| TMT raw score part A, seconds | | | | 38 (15) | | 103 |
| TMT raw score, part B, seconds | | | | 80 (42) | | 103 |
| Stroop raw test score, baseline task, seconds | | | | 78 (19) | | 103 |
| Stroop raw test score, interference task, seconds | | | | 130 (36) | | 102 |
| CPT, number of commission errors | | | | 11 (7.2) | | 101 |
| CPT, hit reaction time, milliseconds | | | | 350 (56) | | 101 |

*Table continues on next page*

*Table 2, continued (3/3)*

| | Participants of 1st clinical visit 2004-2005 [a] | | | Participants of 2nd clinical visit 2007-2008 [a] | | |
|---|---|---|---|---|---|---|
| | **M (SD)** | **n (%)** | **N** | **M (SD)** | **n (%)** | **N** |
| **Mental health outcomes** | | | | | | |
| APQ sum score | 38 (18) | | 157 | | | |
| BDI sum score | 4.5 (5.4) | | 157 | | | |
| CES-D sum score | 9.5 (7.5) | | 157 | | | |
| ASR Total Problems T-score | | | | 49 (10) | | 100 |
| Internalizing Problems T-score | | | | 51 (12) | | 100 |
| Externalizing Problems T-score | | | | 48 (10) | | 100 |

[a] *The first column presents the HeSVA participants from the 1st clinical visit who had mental health data available (Study IIa analytic sample). The second column presents the HeSVA participants from the 2nd clinical visit who had cognitive data available (Study I analytic sample). For more detailed information about the participants in each of the separate studies, please see the publications in the appendix.*

*Abbreviations: APQ: Adult Problem Questionnaire; ASR: Achenbach System of Empirically Based Assessment Adult Self Report; BDI: Beck Depression Inventory; CA: corrected age; CES-D: Center for Epidemiological Studies Depression Scale; CPT: Conners' Continuous Performance Test II; M: mean; N: number of participants with data available; n: number of cases; ROCF: Rey-Osterrieth Complex Figure test; SD: standard deviation; TMT: Trail Making Test; %: percentage of cases in relation to number of participants with data available*

### *4.2.2. Growth*

Weight, length, and head circumference measurements were retrieved from hospital and child welfare clinic records. Size at term was interpolated between true measurements, provided a measurement had been made within 28 days. The median time period between term and the closest true measurement point was one day for weight and four days for length and head circumference. Size at 12 months CA was interpolated if a measurement had been made within 42 days to allow a wider time range to increase sample size, since measurements were made less frequently at this age. The median time period between 12 months CA and the closest true measurement point was 15 days for weight and 16 days for length and head circumference.

Size at birth and at term were converted into *z* scores by sex and gestational/postmenstrual age according to Finnish fetal growth reference charts from approximately the time our study participants were born (as discussed previously in

section 2.4.2).[138] To standardise size at 12 months CA, Finnish infant growth reference charts from approximately the time when the participants were born were used.[139,140] These charts provide *z* scores for length and for head circumference and a percentage score of current weight in relation to expected weight for sex and CA. Therefore, length and head circumference at 12 months CA were converted into *z* scores by sex and age, whereas weight at 12 months was first converted into percentage scores for sex and age and thereafter, to facilitate comparison of effect sizes, into *z* scores within the VLBW cohort. Participants were classified as SGA for weight, length, and head circumference if the measurement in question was at or below -2 SD at birth: others were considered AGA.

### *4.2.3. Nutrition*

Nutritional data during the initial hospital stay came from hospital records and were available for the first nine weeks of life, after which the number of participants with sufficient data was reduced because of hospital discharge. The data were divided into three three-week periods (birth to three, three to six, and six to nine weeks of age). This approach was chosen so that we could examine effects that were specific to the first few weeks of life, when morbidity is especially high (as discussed in section 2.3). Daily mean total energy intakes and energy intakes from protein, fat, and carbohydrates from all enteral and parenteral nutrition, and energy intake from human milk, including donated and maternal milk, per kilogram bodyweight were calculated for each of these three periods. The macronutrient content of the mother's own milk was estimated based on the nutritional composition data published by Anderson et al., who followed the milk content of mothers who delivered preterm.[410] The nutritional composition of banked human milk was based on values published by Rönnholm et al., who analysed macronutrient contents of the banked milk used in the hospital where our study participants were treated.[411,412]

Among these infants, enteral feeding was initiated through a nasogastric tube with human milk on the first or second day of life. Milk intake was then increased to a maximum of 200ml/kg/day according to individual tolerance, and maintained at this level until discharge. All milk was pasteurised. During the 9-week period, of the 86 participants with nutritional and adult outcome data available, 81 (94%) received pooled donor milk, 59 (69%) received maternal milk, and 19 (22%) received formula. If targeted enteral feeding was not possible, intravenous fluids with glucose were initiated, and amino acids and lipids were gradually introduced from the second or third day onwards.

*4.2.4. Cognitive functioning and mental health*

IQ was estimated according to Finnish normative data using four subtests (Vocabulary, Digit span, Similarities, and Block Design) of the Wechsler Adult Intelligence Scale, 3rd edition (WAIS-III), which has good psychometric properties as an assessment tool for general cognitive ability.[413,414] Many short forms of this scale have been used previously, and several four-subtest combinations have been reported to have good, roughly equal accuracy in estimating full-scale IQ: it has been recommended that the combination be chosen based on the clinical characteristics and time limitations of the study in question.[415,416] For the purpose of this study, subtests were chosen to cover both verbal and visuo-spatial ability as well as more crystallised intelligence and, on the other hand, fluid reasoning, within time constraints.

Executive functioning, attention, and visual memory were assessed using five tests. The Trail Making Test (TMT) measures visual-motor speed and tracking, attention, and cognitive flexibility.[417] TMT is one of the most widely used instruments for assessing attention and executive function, and while it is considered to have good sensitivity to neurocognitive deficits and good overall psychometric properties, one could argue its weakness is the lack of specificity when determining the cause of poor performance (which is why it is best used as a screening tool or in combination with other tests, much like other similar tests).[414,418] The Bohnen modification of the Stroop test measures verbal-motor function and flexibility, response inhibition, attention, processing speed, and working memory.[419] The Stroop task is also one of the oldest and most used tests of attention and response inhibition, but like the TMT, it has been criticised for lack of specificity and also for the lack of consistency across the many different versions of the same test.[414] The Verbal fluency task measures verbal ability, executive control, episodic memory, processing speed, and flexibility.[420] It is also a widely used and well-established test, however it has been criticised for tapping into somewhat different cognitive domains in different populations such as different age groups.[414,421] The Rey-Osterrieth Complex Figure test (ROCF) measures visual memory encoding, storage and retrieval, and visual-motor processing.[422] This test has also been used and studied quite extensively, and while generally considered acceptable in its psychometric properties, especially its Copy subtest tends to have a ceiling effect problem.[414] Finally, the computerised Conners' Continuous Performance Test II (CPT) measures sustained attention and response inhibition.[423] In contrast to the four aforementioned tests that are administered face-to-face, the reliability and validity of this computerised test is somewhat less clearly established, although it has currently become one of the most widely used tests of attention and

concentration.[414,424] All of these tests yield several subscale scores. Local normative data were not available for standardization. To reduce the number of related outcomes, principal component analysis with Varimax rotation was used. The first four components were included, because they explained 75% of the variation and only their eigenvalues were greater than 1.0. The components were named Verbal flexibility (on which higher scores reflected better performance especially on the Verbal Fluency and Stroop tasks), Visual memory (higher scores reflect better performance on ROCF), Visual flexibility (higher scores reflect better performance in the TMT), and Impulsivity (higher scores reflect shorter reaction times but also more commission errors in the CPT). The rotated component matrix is presented in the Study I article in the appendix.

Mental health was assessed through widely used self-report questionnaires. During the first clinical visit, the participants completed the Beck Depression Inventory (BDI)[425] and the Center for Epidemiological Studies Depression Scale (CES-D):[426] on these scales, higher scores reflect more symptoms of depression. Both were administered, as BDI focuses more on the severity of symptoms, while CES-D focuses more on the frequency of symptoms: however, both yield similar results with similar reliability and validity.[427] The participants also completed the Adult Problem Questionnaire (APQ),[428] on which higher scores reflect more behavioural symptoms of ADHD. The psychometric properties of this self-rating scale have received little research attention, unfortunately, but within the HeSVA cohort, it showed good internal consistency: the general coefficient of reliability calculated as described by Tarkkonen and Vehkalahti was 0.96.[390,429] During the second clinical visit, the participants completed the clinically validated and standardized Achenbach System of Empirically Based Assessment Adult Self Report (ASR).[430] This questionnaire yields a Total Problems score, on which higher scores reflect lower overall psychosocial adjustment, and two subscores, the Internalizing Problems subscore, which reflects symptoms of anxiety, depression, withdrawal, and somatic complaints, and the Externalizing Problems subscore, which reflects delinquent and aggressive behavioural symptoms.

*4.2.5. Other information*

From initial hospital records, sex, gestational age at birth (based on the mother's last menstrual period and confirmed by a single neonatologist using the Dubovitz examination), maternal smoking during pregnancy (self-reported, yes or no), and maternal pre-eclampsia during pregnancy (using standard blood pressure and proteinuria criteria[431]) were retrieved. Data on neonatal complications and illnesses were

also retrieved from records from the original hospital stay. Septicaemia was diagnosed if the infant showed symptoms and a blood culture was positive. BPD was diagnosed using the Northway criteria (if the infant needed supplementary oxygen at 28 days after birth and a chest x-ray showed typical findings).[60] Surgery or indomethacin treatment due to PDA, and blood exchange transfusion due to hyperbilirubinemia were also recorded. The duration of ventilator treatment was divided into none, less than 8 days, 8-14, 15-28, and over 28 days. Neonatal cerebral ultrasound was being introduced during the study period. IVH was graded as mild (grade I-II) or severe (grade III-IV).[55] None of the participants were diagnosed with necrotizing enterocolitis.

In young adulthood, participants reported the highest education of either parent (divided into basic, secondary, lower tertiary, and upper tertiary education). Information about intellectual disability and neurosensory impairments (cerebral palsy or blindness; none reported severe hearing impairment) was provided by the participant or by a parent and supplemented by information from the early childhood records. Participants with blindness, cerebral palsy, or intellectual developmental disability were excluded because cognitive functioning could not be reliably assessed, except in model I of study II, where those with blindness or cerebral palsy provided mental health data and were included in the first model. Age during the adult assessment (which correlated highly with the year of birth) and the time periods between the closest true measurement point and term or 12 months CA were also considered as covariates.

## 4.3. The Arvo Ylppö Longitudinal Study

### *4.3.1. Participants*

The Arvo Ylppö Longitudinal Study was founded as the Finnish arm of the Bavarian-Finnish Longitudinal Study.[432] Originally, all 1 535 infants who were born between March 15th 1985 and March 14th 1986 in Uusimaa, Finland and admitted to the neonatal wards in obstetric units in the area or transferred to the NICU at the Children's Hospital at the Helsinki University Central Hospital within ten days of birth were included. The reasons for admission ranged from severe illness and prematurity to need for brief inpatient observation. Additionally, for every two of these hospitalised infants, one infant who was not admitted to neonatal wards nor to the NICU was prospectively recruited from the maternal hospitals of the same area, resulting in a non-hospitalised group of 658 infants. Altogether, this cohort of 2 193 infants included 315 late preterm infants. At 5 months CA, 20 months CA, and 56 months, 277, 274, and 227 late preterm individuals, respectively, participated in childhood follow-up examinations.

In 2009–2012, we invited all of the cohort members who could be identified through the Finnish personal identification number system and who were living within southern Finland to participate in an adult follow-up. 270 of the invited were late preterm, and of them, 158 participated in this follow-up. After excluding participants with intellectual disability, congenital malformations, chromosomal abnormalities, or insufficient data, we had an analytic sample of 108 late preterm adults (Study III). Figure 8 shows a flowchart of the formation of the AYLS study sample. Characteristics of the AYLS participants are presented in Table 3.

***Figure 8.*** *Formation of the Arvo Ylppö Longitudinal Study late preterm sample.*

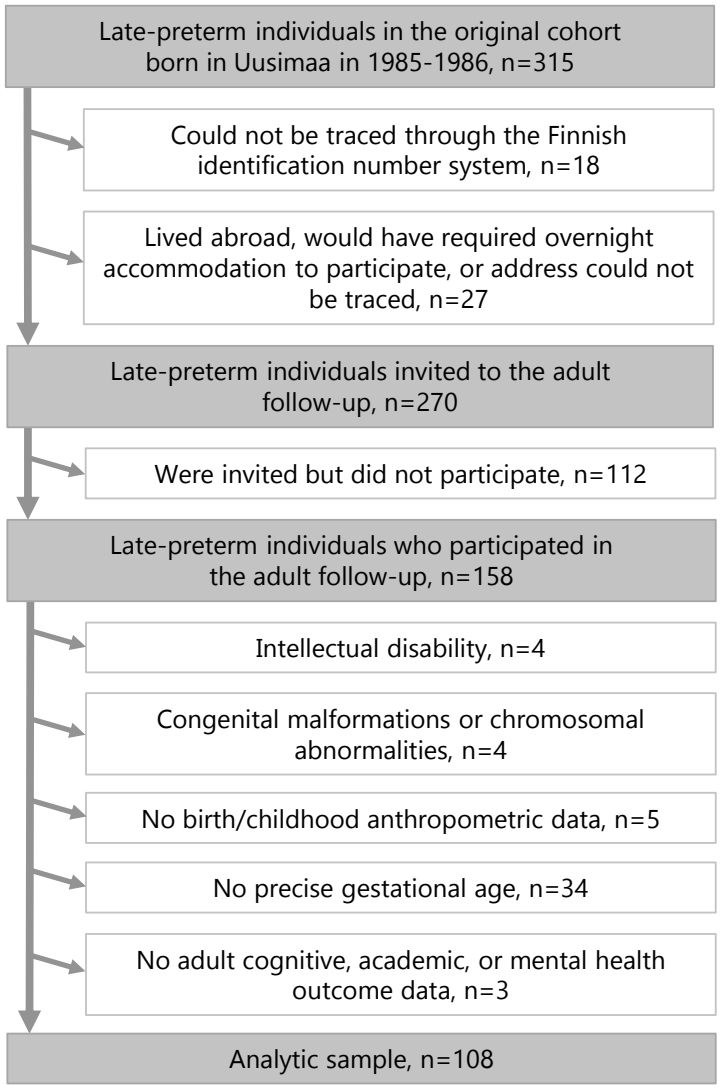


***Table 3.*** *Characteristics of the Arvo Ylppö Longitudinal Study late preterm participants.*

| | M (SD) | n (%) | N |
|---|---|---|---|
| **Characteristics at birth** | | | |
| Size at birth | | | |
| Weight, kg | 2.7 (0.6) | | 108 |
| Length, cm | 47 (2.4) | | 108 |
| Head circumference, cm | 33 (1.6) | | 107 |
| Small for gestational age | | | |
| Weight ≤-2 SD | | 20 (19) | 108 |
| Length ≤-2 SD | | 13 (12) | 108 |
| Head circumference ≤-2 SD | | 5 (5) | 107 |
| Gestational age, days | 250 (6) | | 108 |
| Sex, male | | 62 (57) | 108 |
| Mother smoked during pregnancy | | 20 (19) | 108 |
| **Neonatal complications** | | | |
| Received ventilation treatment | | 8 (7) | 108 |
| Suspected septicaemia | | 18 (17) | 108 |
| Apnoea | | 3 (3) | 108 |
| Convulsions | | 3 (3) | 108 |
| Apgar score below 8 points at five minutes | | 7 (7) | 104 |
| Admitted to a neonatal ward or NICU within 10 days of birth | | 101 (94) | 108 |
| **Breast-feeding status at five months CA** | | | 108 |
| Never breast-fed | | 8 (7) | |
| Breast-feeding discontinued | | 66 (61) | |
| Currently breast-fed | | 34 (31) | |
| **Growth during childhood** | | | |
| Weight, birth to 5 months CA, kg | 4.7 (0.9) | | 108 |
| Length, birth to 5 months CA, cm | 19 (2.3) | | 107 |
| Head circumference, birth to 5 months CA, cm | 10 (1.5) | | 106 |
| Weight, 5 to 20 months CA, kg | 4.5 (0.9) | | 103 |
| Length, 5 to 20 months CA, cm | 19 (2.4) | | 97 |
| Head circumference, 5 to 20 months CA, cm | 5.8 (0.7) | | 100 |
| Weight, 20 months CA to 56 months, kg | 5.9 (1.3) | | 86 |
| Length, 20 months CA to 56 months, cm | 23 (2.4) | | 79 |
| Head circumference, 20 months CA to 56 months, cm | 2.8 (0.6) | | 82 |

*Table continues on next page*

*Table 3, continued (2/2)*

| | M (SD) | n (%) | N |
|---|---|---|---|
| **Characteristics in adulthood** | | | |
| Age during clinical visit, years | 25 (0.6) | | 108 |
| Highest education of a parent | | | 108 |
| basic/primary or less | | 11 (10) | |
| vocational education | | 27 (25) | |
| general upper secondary or lower tertiary | | 37 (34) | |
| higher tertiary | | 33 (31) | |
| Cerebral palsy | | 0 | 108 |
| Blindness | | 0 | 108 |
| Mother had a history of mental disorder [a] | | 14 (17) | 81 |
| **Cognitive and school outcomes** | | | |
| Estimated full intelligence quotient | 108 (10) | | 103 |
| General memory score | 103 (13) | | 105 |
| Verbal fluency raw test score, phonetic mean | 17 (4.6) | | 105 |
| Verbal fluency raw test score, categorical mean | 23 (5.6) | | 105 |
| TMT raw score part A, seconds | 31 (10) | | 104 |
| TMT raw score, part B, seconds | 60 (17) | | 104 |
| Stroop raw test score, baseline task, seconds | 68 (15) | | 102 |
| Stroop raw test score, interference task, seconds | 120 (29) | | 102 |
| Grade point average in comprehensive school, scale of 4 to 10 | 8.2 (0.9) | | 92 |
| Received special education | | 35 (35) | 101 |
| **Mental health outcomes** | | | |
| Diagnosis of mental disorder based on psychiatric interview [b] | | 34 (35) | 98 |
| ASR Total Problems T-score | 44 (11) | | 89 |
| Internalizing Problems T-score | 44 (12) | | 89 |
| Externalizing Problems T-score | 47 (9.0) | | 89 |

[a] *Of the 14 mothers who reported that they themselves had had a mental disorder during their lifetime, 11 reported depression and 3 reported an anxiety disorder; none reported other psychiatric disorders.*

[b] *Of the 34 late-preterm participants diagnosed with at least one mental disorder, 14 were diagnosed with mood disorder, 8 with anxiety disorder, and 25 with substance use disorder.*

*Abbreviations: ASR: Achenbach System of Empirically Based Assessment Adult Self Report; CA: corrected age; M: mean; N: number of participants with data available; n: number of cases; NICU: neonatal intensive care unit; SD: standard deviation; TMT: Trail Making Test; %: percentage of cases in relation to number of participants with data available*

*4.3.2. Growth*

From medical records, weight, length, and head circumference at birth were retrieved and converted into *z* scores by sex and gestational age using Finnish fetal growth reference charts.[138] Experienced research nurses took the corresponding measurements at the 5, 20, and 56 month follow-up visits, and size at these time points was converted into *z* scores by sex and age using the WHO growth standards.[129,130] Age was corrected for prematurity at 5 and 20 months but not at 56 months. Participants were classified as SGA for weight, length, and head circumference, if the measurement in question was at or below -2 SD at birth: others were considered AGA.

*4.3.3. Cognitive functioning, school performance, and mental health*

The neuropsychological assessment protocol was designed to provide estimates of general intelligence and memory functions, as well as provide information about executive functions, attention and processing speed. Seven subtests of the WAIS-III[413] were used to estimate IQ: these were Information, Similarities, Arithmetic, Digit span, Picture completion, Matrix reasoning, and Digit symbol coding. This seven-subtest short form has been shown to have good reliability and validity for estimating full-scale IQ.[433,434] Three subtests of the Wechsler Memory Scale, 3rd edition,[435] were used to estimate General Memory: these were Logical memory, Verbal paired associates, and Faces, as recommended by Axelrod and Woodard.[436] For estimating general intelligence and general memory, local normative data were available.

Participants also completed the Verbal fluency test,[420] the TMT,[417] and the Bohnen version of the Stroop test,[419] which were described in more detail in section 4.2.4. Principal component analysis with Varimax rotation was used to reduce the number of these outcomes. The first component had an eigenvalue of above 1.0 and explained 57% of the total variance, and was named Executive functioning. Higher scores on this component scale reflected better performance in the Fluency, Trail Making, and Stroop tests. The rotated component matrix is presented in the Study III article in the appendix.

Participants reported grade point average (GPA) on their final comprehensive school diploma, which is usually issued the year an individual turns 16 years in Finland. Participants also reported whether they had received remedial or special education in comprehensive school.

To assess mental health, the participants were interviewed using the M-CIDI structured psychiatric interview.[437] This is a valid and reliable instrument and has good concordance

with the structured clinical interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th edition.[438–440] The interview was used to diagnose common mental disorders including mood disorders (major depressive disorder, dysthymia, bipolar disorder), anxiety disorders (general anxiety disorder, social phobia, agoraphobia, panic disorder with agoraphobia, panic disorder without agoraphobia), and alcohol or other substance use dependence or abuse disorders within the past 12 months. The participants also completed the ASR.[430]

*4.3.4. Other information*

Retrieved from medical records, gestational age was based on fetal ultrasound performed before 24 weeks of gestation for 72 participants and on the mother's last menstrual period for 36 participants. Sex was also retrieved from these records. Both pre- and perinatal records were used to establish pregnancy-related factors: these included multiple pregnancy (singleton vs multiple), parity (primiparous vs multiparous), maternal pre-pregnancy BMI ($kg/m^2$), age at delivery (years), and hypertensive disorders (normotension vs hypertensive disorder), diabetes (no diabetes vs gestational or type 1 diabetes; none had type 2 diabetes), and smoking (self-reported, no vs at least one cigarette per day) during pregnancy.

Data on neonatal complications were collected by the paediatricians in the study staff who also worked at the hospital and made daily visits to the wards. These included the Apgar score at five minutes (0-7 vs 8-10 points), suspected septicaemia (based on symptoms), ventilation treatment, convulsions, and apnoea (each no vs yes). Ventilation treatment included continuous positive airway pressure and mechanical ventilation. No participants were diagnosed with intraventricular haemorrhage, necrotising enterocolitis, or blood-culture-positive septicaemia.

The highest education of either parent (basic, vocational, general upper secondary, or tertiary), and child breast-feeding status at 5 months CA (never breast-fed, breast-feeding discontinued by 5 months CA, or currently breast-fed) were recorded based on parental interviews during childhood. Mothers of the participants also completed a background questionnaire and reported history of any mental disorder of their own during the adult follow-up phase. Participants with intellectual developmental disability, congenital malformations or chromosomal abnormalities, and those whose gestational age at birth could not be reliably established were excluded. Information about neurosensory and developmental disabilities and congenital anomalies and malformations came from the initial study records collected at the hospital and during the follow-up visits, and these

data were supplemented by information provided by the participants or by their parents during the adult follow-up.

## 4.4. Statistical analyses

### *4.4.1. Growth and adult outcomes*

As main predictors of cognitive, academic, and mental health outcomes, I used infant growth in weight, length, and head circumference during different time periods. In the HeSVA cohort, I looked at growth from birth to term and from term to 12 months CA. In the AYLS cohort, I looked at growth from birth to 5 months CA, 5 to 20 months CA, and 20 months CA to 56 months.

So that the duration of the growth period or earlier growth would not interfere with the interpretation of results, I used, as growth variables, standardised residual change scores from linear regression models where weight, length, and head circumference *z* scores were regressed on corresponding measures at previous time points, creating uncorrelated residuals that reflect growth conditional on previous history.[441,442]

These growth variables were then used as independent variables in linear and logistic regression models to predict continuous and dichotomised outcomes, respectively. To facilitate comparison of effect sizes, I first square- or square-root-transformed the raw scores if necessary to improve linear model fitting, and then standardised these outcome scores within the sample, as described in more detail in the publications in the appendix. In additional analyses, as reported in the appendix, size *z* scores at different time points were used to predict adult outcomes.

### *4.4.2. Nutrition and adult outcomes*

In study IV, I used linear regression models to test if nutritional intake from birth to three, three to six, and six to nine weeks of age predicted cognitive functioning in adulthood. The different nutritional intake variables included mean daily total energy intake, energy intake from human milk, and protein, fat and carbohydrate intakes.

### *4.4.3. Differences according to sex, gestational age, and birth size*

In additional analyses, I tested if associations between growth or nutrition and adult cognitive, school, or mental health outcomes varied by sex, birth size, or very vs moderately or late preterm status. I first included a product term (continuous independent variable [growth or nutritional intake] *x* continuous or dichotomised

perinatal variable [sex, or standardised birth size, or AGA vs SGA status, or gestational age below vs at least 32 weeks]) into the regression equation followed by the main effects. When statistically significant interactions (p-values <0.05) were observed, the sample was divided into very vs moderately or late preterm participants (study I), AGA vs SGA participants (study II), or into thirds by standardised birth size (study III), and the main effects were assessed separately in each group.

### *4.4.4. Adjustment models*

In each of the studies, different models were presented to show how adjustment for potential confounders affected the results. In the first model, I aimed to show the associations after adjustment for some basic background characteristics. In further models, based on analyses of how the different covariates associated with the independent and dependent variables, on data availability, and on earlier literature and theoretical expectations, I also adjusted for neonatal illnesses and other early-life factors. The details of the adjustments in each of the different models are presented in Table 4.

***Table 4.*** *Covariates that were (+) or were not (-) adjusted for in each of the models.*

| | Study I | | Study II | | Study III | | | | Study IV | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | I | II | I | II | I | II | III | IV | I | II | III |
| Gestational age at birth | + | + | + | + | + | + | + | + | + | + | + |
| Age at child measurement [a] | + | + | + | + | + | + | + | + | - | - | - |
| Age at adult assessment | + | + | + | + | + | + | + | + | + | + | + |
| Sex | + | + | + | + | + | + | + | + | + | + | + |
| Parental education | + | + | + | + | + | + | + | + | - | + | - |
| Maternal mental disorder | - | - | - | - | - | - | - | + | - | - | - |
| Smoking during pregnancy | - | - | - | + | - | + | + | + | - | + | - |
| Other pregnancy-related complications [b] | - | - | - | - | - | + | + | + | - | + | - |
| Breast-feeding at 5 months | - | - | - | - | - | - | + | + | - | - | - |
| Neonatal complications [c] | - | + | - | + | - | - | + | + | - | - | + |

[a] *Age at child measurement refers to the time period between the closest true measurement point and term or 12 months corrected age in the HeSVA study, and to age during the follow-up visit in the AYLS study (corrected age at 5 and 20 months, and chronological age at 56 months). In Study IV, growth measurements were not examined, however birth weight z score at birth was included as a covariate in the analyses.*

[b] *In study III, these included multiple pregnancy, parity, maternal pre-pregnancy BMI, age at delivery, hypertensive disorder, and diabetes, and in study IV, pre-eclampsia.*

[c] *In studies I, II, and IV, these included septicaemia, bronchopulmonary dysplasia, indomethacin treatment and surgery due to patent ductus arteriosus, blood exchange transfusion due to hyperbilirubinemia, duration of ventilator treatment, and intraventricular haemorrhage. In study III, these included low 5-min Apgar score, suspected septicaemia, ventilation treatment, convulsions, and apnoea.*

#### *4.4.5. Missing data*

Participants were included in a specific model only if they had the predictor (growth or nutrition) and outcome data (performance in neuropsychological tests, school outcome, or mental health outcome) in question available. The number of participants for whom data were available are presented in Tables 2 and 3, and detailed in the publications in the appendix.

In the HeSVA cohort, the number of participants with missing data varied according to the model in question. A maximum of 46 participants lacked data on IVH and ten participants lacked data on maternal smoking during pregnancy. These were dummy-coded into separate groups. Two participants who lacked all neonatal complication data were excluded in the analyses which adjusted for these complications. The few participants with some missing complication data were either excluded in the models that adjusted for these complications in studies I and II, or, in study IV, the missing data were individually imputed based on all the available information from the records.

In the AYLS cohort, the four participants without 5-min Apgar scores were included in the "8–10 points" category based on their high 1- and 10-min Apgar scores and clinical descriptions. Eight mothers without mention of blood pressure measurements, hypertension, or pre-eclampsia in any records were included in the "no hypertensive disorder" group. Twenty-seven mothers who did not complete the maternal background questionnaire at all or did not respond to the question about their possible history of mental disorder were considered a separate category when dummy-coding the maternal mental disorder variable.

## 5. RESULTS

### 5.1. Comparison of the participants and non-participants

Within the HeSVA VLBW cohort (n=255, Figure 7), I first compared those participants who had data available from the 1st clinical visit (n=157, Study IIa) with those who were not included in the analytic sample because of non-participation or missing data ("drop-outs", n=92) (*comparison A*). Next, again among VLBW cohort, I compared those participants who had data available from the 2nd clinical visit (n=104, Study I, IV, or IIb) with drop-outs (n=127; among these 127 were the 96 cohort members who were not even invited to the 2nd clinical visit) (*comparison B*). I excluded all those who were known to

have an intellectual disability from these comparisons (n=6). In comparison B, I further excluded those with cerebral palsy (n=16) or blindness (n=2), as the cognitive abilities of these participants could not be reliably assessed and they were thus excluded in studies I and IV. Data on sex, gestational age at birth, birth size, maternal smoking and pre-eclampsia, parental education, and neonatal complications in both the drop-out and analytical groups were available for these comparisons. In comparison B, I also compared mental health questionnaire scores from the 1st visit, and nutrition in infancy, which was retrieved from hospital records for individuals who participated in the 1st visit. The drop-outs were more likely than the analytical sample to have mothers who smoked during pregnancy (32% vs 19% [p-value=0.03] in comparison A, and 29% vs 17% [p-value=0.045] in comparison B), but no other differences between the analytic samples and the drop-outs were observed (p-values>0.11).

Within the AYLS cohort, I compared those late preterm infants who were included in the analytic sample (n=108, Figure 8) with drop-outs (n=188). I excluded those with intellectual developmental disability (n=8) or congenital malformations or chromosomal abnormalities (n=11) from these comparisons. Between the analytic sample and attrition group, I found no differences in sex, gestational age, parental education, or age at childhood follow-ups; weight, length, or head circumference at birth or childhood follow-ups; maternal age, diabetes, hypertensive disorder, or smoking during pregnancy; parity or multiple pregnancy; or infant Apgar scores, ventilation treatment, septicaemia, convulsions, or apnoea (p-values>0.07). Compared with the analytic sample, the attrition group had mothers with a higher pre-pregnancy BMI (mean=23.1 vs 21.8, p-value=0.002) and received less breastfeeding (22%, 48%, 30% vs 7%, 61%, 31% never breast-fed, breast-feeding discontinued by 5 months, and breast-fed at 5 months, respectively, p-value=0.01). Compared with the analytic sample, the adults who participated in the adult follow-up in some way but were excluded because no growth data or data on the outcomes studied in this thesis were available (n=42, Figure 8) were slightly older during the adult follow-up (mean=25.5 vs 25.2 years, p-value=0.048), but I found no differences in cognitive, school, or mental health outcomes or maternal mental disorder (p-values>0.15).

The exact number of drop-outs and participants with data available for these comparisons varied, and more detailed information is presented in the publications in the appendix.

Although recruitment for the HeSVA and AYLS cohorts overlapped geographically and partly in time (year 1985), none of the participants included in any of the studies in this thesis were part of both (HeSVA and AYLS) samples.

### 5.2. Growth, cognitive functioning, and GPA (Studies I and III)

Among both the VLBW and the late preterm participants, faster growth during the first months of life was associated with better cognitive functioning in adulthood.

Among the VLBW individuals (Figure 9), faster growth from birth to term was associated with higher IQ and better visual and verbal flexibility and visual memory scores, but not with impulsivity component scores. Weight, length, and head circumference were all associated with these outcomes, however head growth was most consistently associated with neurodevelopment, especially after adjusting for neonatal complications and illnesses. Growth between term and 12 months CA was not associated with cognitive functioning.

Among late preterm individuals (Figure 10), faster growth from birth to 5 months was associated with better general cognitive ability, executive functioning score, and GPA, but not with the general memory function score. Head growth between 5 and 20 months CA was also associated with better general cognitive ability and GPA. Growth after 20 months CA, or growth in length during any of the examined periods was not associated with the adult outcomes. Adjustment for pregnancy-related and neonatal factors produced only small changes in the regression coefficients. Faster growth from birth to 5 months was also associated with lower odds of receiving special education (OR=0.59 [95% CI 0.36–0.97], and OR=0.49 [95% CI 0.28–0.88], per one SD unit faster weight and head growth, respectively): these effects, too, remained statistically significant and similar in magnitude after adjustment for pregnancy-related and neonatal factors (data shown in more detail in the appendix, Study III).

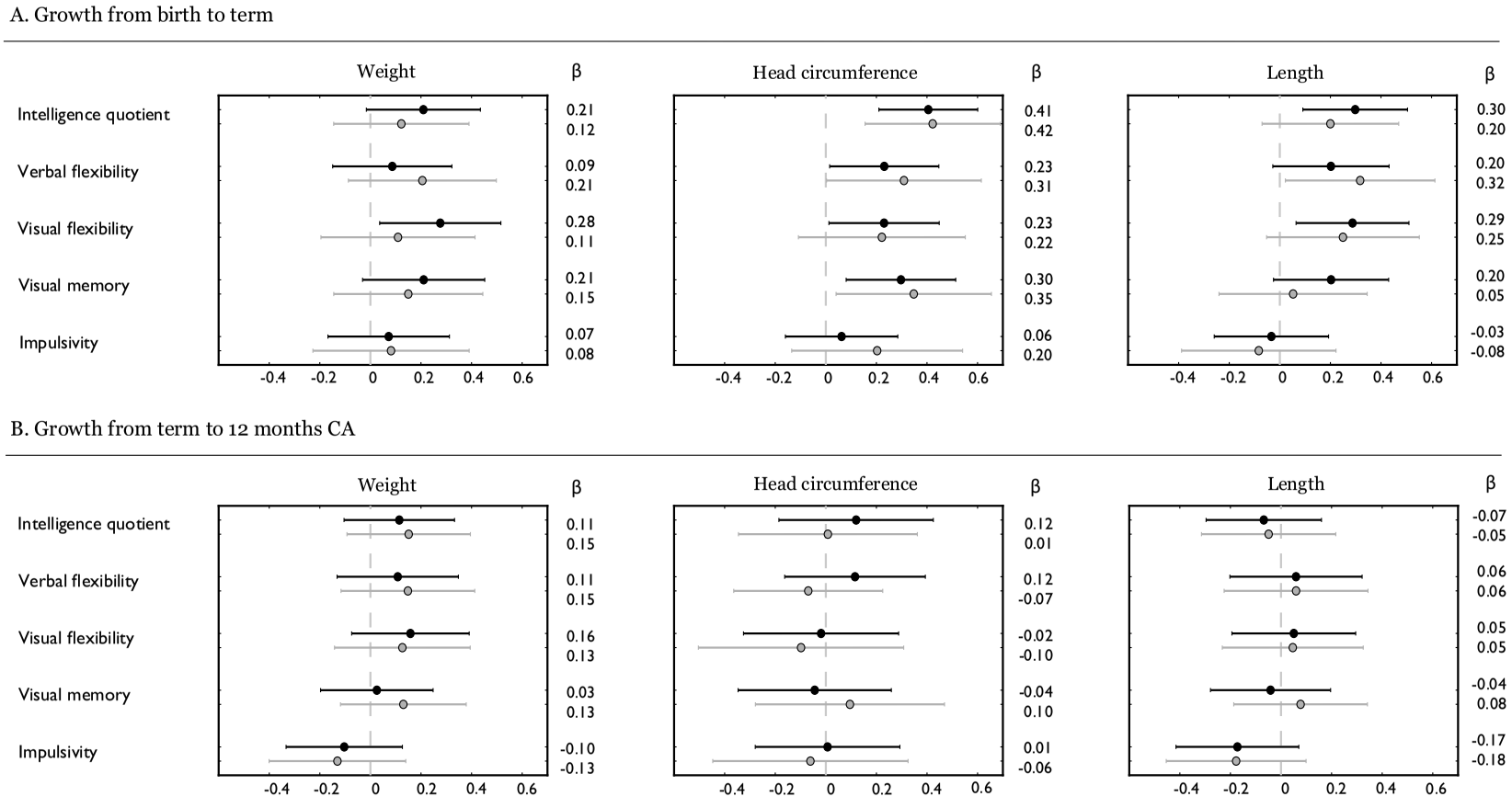
The pattern of findings in the two cohorts was quite similar, including the magnitude and direction of the observed effects, the role of growth soon after birth rather at later time periods, and the persistence of associations after adjustment for neonatal complications. Within the VLBW group, I tentatively also examined whether very preterm birth (n=89) vs moderately or late preterm birth (n=14) and growth interacted in predicting cognitive outcomes, but found no evidence of any consistent differences between the two groups. In the only two cases where interactions were statistically significant (p-values<0.05 in model 1): 1) the main associations between weight gain from birth to term and verbal

flexibility was not statistically significant in either group (p-values>0.21), and 2) the association between length growth from birth to term and IQ was statistically significant among the very preterm (p-value=0.001) but not the moderately/late preterm group (p-value=0.16), however after adjusting for neonatal complications the associations were attenuated to non-significance (p-values>0.06).

The associations between growth and cognitive functioning were not limited to those with poor growth in utero. In the VLBW cohort, AGA/SGA status and growth did not significantly interact in predicting any of the cognitive outcomes (all p-values for AGA/SGA-status x growth interaction >0.05 in model 1). In the late preterm cohort, faster head growth from birth to 5 months CA was associated with higher GPA among those with the *largest* head circumference at birth (effect size 0.56 SD [95% CI 0.08–1.04], n=31, head circumference >0.5 SD), but not among those in the middle third (effect size 0.34 SD [95% CI −0.04–0.73], n=31, head circumference between −0.2 and 0.5 SD) or among those with the smallest head circumference at birth (effect size 0.27 SD [95% CI −0.12–0.67], n=29, head circumference <−0.2 SD) (p-value for interaction 0.023).

The associations between early growth and cognitive functioning were similar among women and men. Within the VLBW cohort, one statistically significant interaction between sex and head growth from term to 12 months in predicting visual memory was observed (p-value for interaction 0.008), however there were no significant main effects of growth during this period on visual memory among males or females (p-values>0.13). Otherwise, I observed no interactions between sex and growth in either cohort (p-values>0.05, model 1).

***Figure 9.*** *Growth in weight, head circumference, and length from birth to term (panel A), and from term to 12 months corrected age (panel B), and neurocognitive abilities in adulthood among VLBW participants.*



*The figure shows change in neurocognitive scores in SD units per one SD faster growth in weight, head circumference, and length during each time period. Effect sizes and 95% confidence intervals are shown graphically, and effect sizes (β) are also given numerically on the right.*

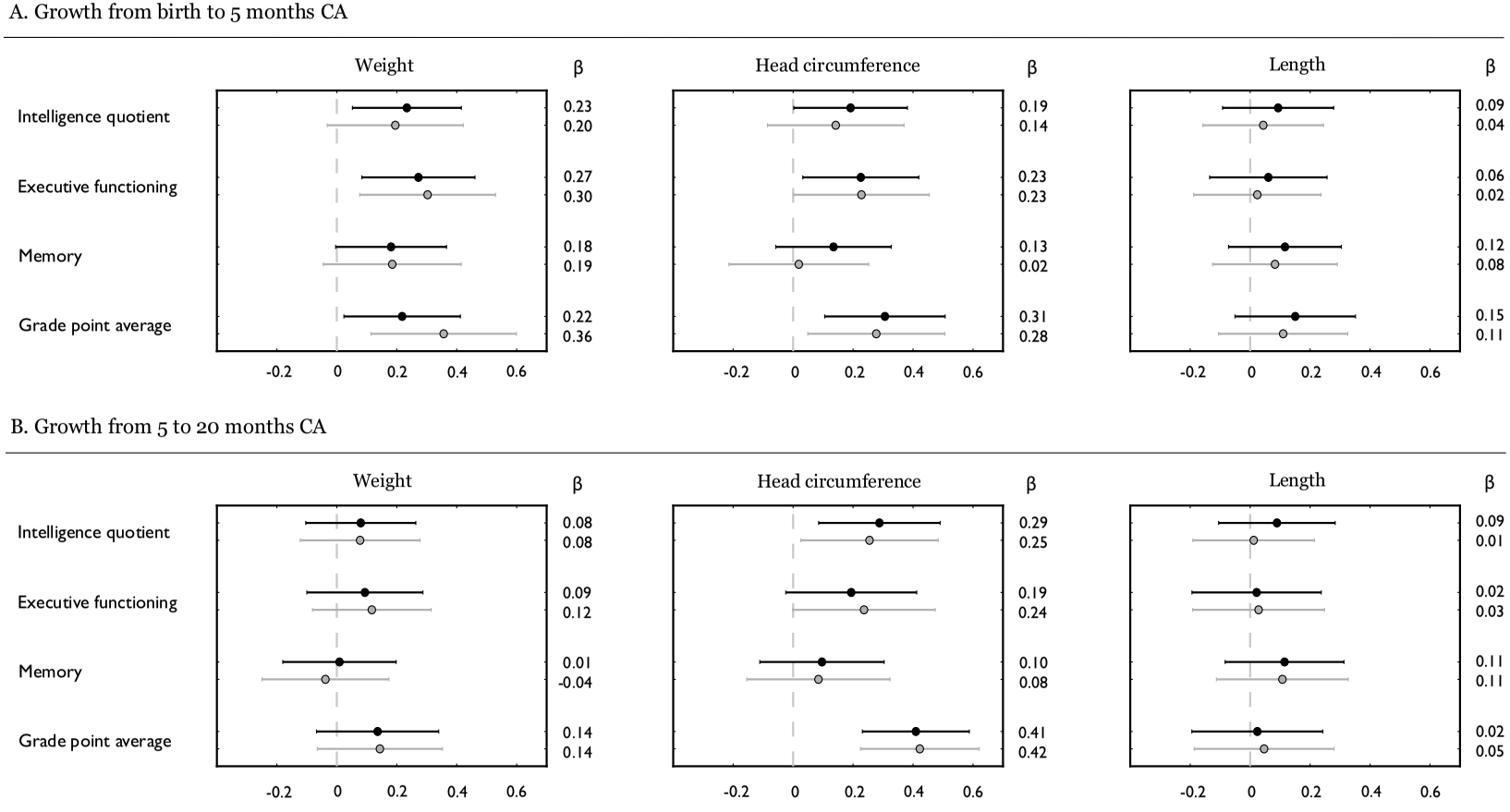


*Associations adjusted for gestational age, sex, time period between closest true measurement point and term or 12 months CA, age at neurocognitive testing, and highest education of a parent (Model I in Study I).*

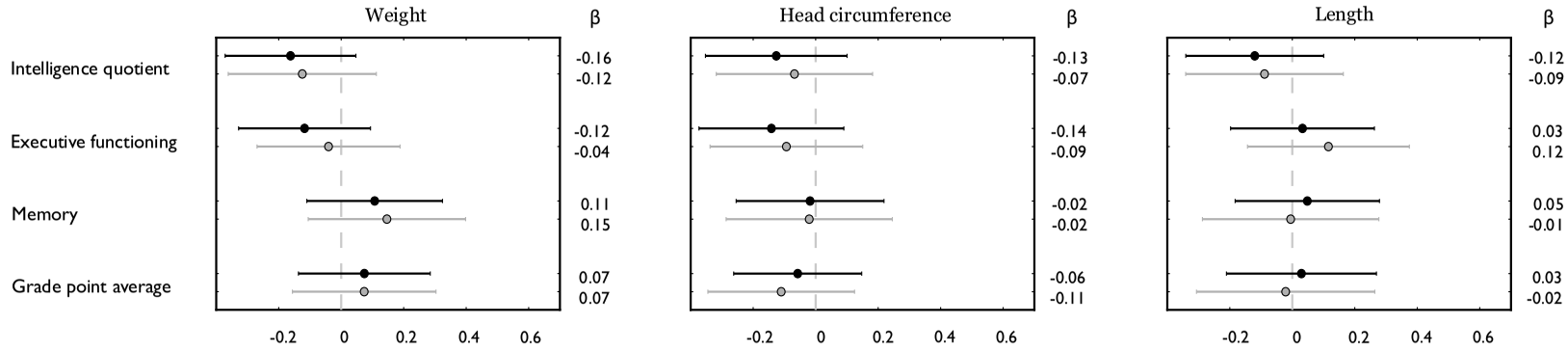


*Associations adjusted for gestational age, sex, time period between closest true measurement point and term or 12 months CA, age at neurocognitive testing, highest education of a parent, and neonatal complications and illnesses (septicaemia, bronchopulmonary dysplasia, indomethacin treatment and surgery because of patent ductus arteriosus, blood exchange transfusion due to hyperbilirubinemia, intraventricular haemorrhage, and duration of ventilator treatment) (Model II in Study I).*

***Figure 10.*** *Growth in weight, head circumference, and length from birth to 5 months (panel A), 5 to 20 months CA (panel B), and 20 months CA to 56 months (panel C), and neurocognitive abilities and grade point average in adulthood among late preterm participants.*



C. Growth from 20 months CA to 56 months






*The figure shows change in neurocognitive scores and grade point average in SD units per one SD faster growth in weight, head circumference, and length during each time period. Effect sizes and 95% confidence intervals are shown graphically, and effect sizes (β) are also given numerically on the right.*

*Associations adjusted for gestational age, sex, age at follow-up visits, and highest education of a parent (Model I in Study III).*

*Associations adjusted for gestational age, sex, age at follow-up visits, highest education of a parent, pregnancy-related factors, breast-feeding status at 5 months, and neonatal complications and illnesses (low Apgar score, apnoea, convulsions, suspected septicaemia, and ventilation treatment) (Model III in Study III).*

### 5.3. Growth and mental health (studies II and III)

Early growth was not consistently associated with mental health outcomes in either of the cohorts. Table 5 presents associations between growth and mental health outcomes in both cohorts. Only one statistically significant effect was observed among the large number of analyses, perhaps reflecting chance: among the late preterm cohort, faster head growth between 20 and 56 months was associated with less total and internalizing problems on the ASR scale, even after adjusting for neonatal and pregnancy factors and maternal mental health (effect sizes -0.30 and -0.33, respectively, 95% CI -0.66 to -0.004).

***Table 5.*** *Growth in weight, head circumference, and length in early childhood and mental health outcomes in young adulthood among VBLW and late preterm adults.*

| | **Weight** | | | **Head circumference** | | | **Length** | | |
|---|---|---|---|---|---|---|---|---|---|
| | *OR* | *β* | *(95 % CI)* | *OR* | *β* | *(95 % CI)* | *OR* | *β* | *(95 % CI)* |
| **VLBW cohort** | | | | | | | | | |
| *Birth to term* | | | | | | | | | |
| ASR Total Problems | | -0.05 | (-0.28, 0.17) | | -0.03 | (-0.24, 0.18) | | -0.06 | (-0.28, 0.17) |
| BDI sum score | | 0.01 | (-0.19, 0.20) | | -0.06 | (-0.23, 0.11) | | 0.03 | (-0.16, 0.21) |
| CES-D sum score | | 0.05 | (-0.14, 0.24) | | 0.04 | (-0.14, 0.22) | | 0.08 | (-0.10, 0.27) |
| APQ sum score | | -0.07 | (-0.26, 0.12) | | -0.02 | (-0.19, 0.16) | | 0.05 | (-0.12, 0.23) |
| *Term to 12 months* | | | | | | | | | |
| ASR Total Problems | | -0.02 | (-0.26, 0.22) | | -0.18 | (-0.48, 0.13) | | 0.02 | (-0.25, 0.30) |
| BDI sum score | | -0.08 | (-0.26, 0.10) | | -0.11 | (-0.33, 0.11) | | 0.07 | (-0.12, 0.26) |
| CES-D sum score | | 0.00 | (-0.18, 0.18) | | 0.03 | (-0.19, 0.25) | | 0.04 | (-0.15, 0.24) |
| APQ sum score | | 0.13 | (-0.06, 0.31) | | 0.07 | (-0.18, 0.31) | | 0.10 | (-0.10, 0.29) |
| **Late preterm cohort** | | | | | | | | | |
| *Birth to 5 months* | | | | | | | | | |
| ASR Total Problems | | 0.09 | (-0.13, 0.32) | | -0.02 | (-0.25, 0.20) | | 0.08 | (-0.14, 0.29) |
| Mental disorder | 0.75 | | (0.47, 1.19) | 0.76 | | (0.47, 1.24) | 0.81 | | (0.52, 1.28) |
| *5 to 20 months* | | | | | | | | | |
| ASR Total Problems | | 0.02 | (-0.21, 0.25) | | -0.10 | (-0.34, 0.15) | | 0.08 | (-0.16, 0.33) |
| Mental disorder | 0.92 | | (0.58, 1.46) | 0.63 | | (0.37, 1.08) | 0.93 | | (0.56, 1.52) |
| *20 to 56 months* | | | | | | | | | |
| ASR Total Problems | | -0.14 | (-0.38, 0.10) | | -0.28 | (-0.54, -0.02) | | 0.12 | (-0.12, 0.37) |
| Mental disorder | 0.87 | | (0.50, 1.53) | 0.92 | | (0.53, 1.59) | 1.31 | | (0.71, 2.40) |

*The table shows change in mental health questionnaire scores in standard deviation units and the odds ratio for receiving a diagnosis of a at least one common mental disorder (mood, anxiety, or substance disorder) based on a psychiatric interview, per one standard deviation faster growth in weight, head circumference, and length during each time period. Associations are adjusted for*

*gestational age, sex, age at follow-up visits, and highest education of a parent (Model I in Studies I and III). Age was corrected for prematurity at 5, 12, and 20 months.*

*Abbreviations: APQ: Adult Problem Questionnaire; ASR Total Problems: Achenbach System of Empirically Based Assessment Adult Self Report Total Problems Score; BDI: Beck Depression Inventory; CES-D: Center for Epidemiological Studies Depression Scale; CI: confidence interval; OR: odds ratio; VLBW: very low birth weight*

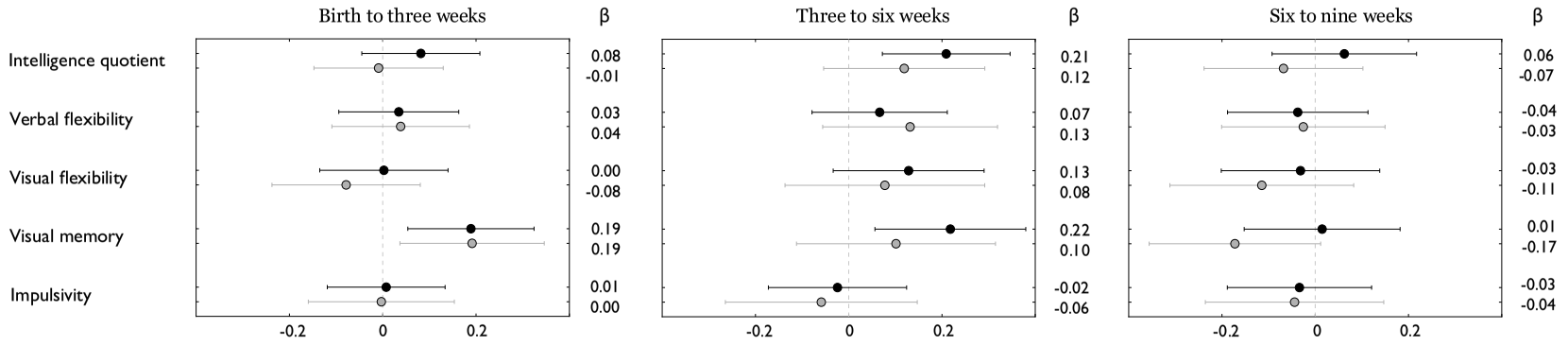
I found no evidence that faster growth would offer any mental health benefits specifically after prenatal growth restriction. In the VLBW cohort, faster head growth from birth to term was associated with *more* frequent depressive symptoms (CES-D scores increased by 0.61 SD units per one SD faster head growth [95% CI 0.13 to 1.09]) among those born SGA for head circumference, but not among those whose head circumference was above -0.2 SD (p-value=0.16) (p-value for interaction 0.001); a similar interaction (p=0.047), but no statistically significant main effects were observed for BDI scores. Otherwise, I observed no statistically significant interactions between birth size and any measure of postnatal growth in predicting mental health outcomes (p-values>0.05).

### 5.4. Nutrition and cognitive functioning (study IV)

Among the VLBW participants, higher energy intake during the initial hospital stay was associated with higher IQ and better Visual memory (Figure 11). For example, 10 kcal more energy per kilogram of bodyweight per day at age 3 to 6 weeks was associated with 0.21 SD higher IQ at 25 years (Figure 11). Details concerning the source of energy can be found in the appendix: while the associations between energy intake at 3 to 6 weeks and cognitive functioning appeared to be due to energy from carbohydrates and fat and human milk, protein intake seemed to predict neurodevelopment slightly earlier, during the first three weeks of life.

However, after adjusting for neonatal complications, there were no independent associations between nutrition and adult IQ (Figure 11). The only remaining statistically significant association was that between higher energy intake during the first three weeks and higher Visual memory, but any speculations based on this single association among the several that were tested seems ill-advised. Overall, IVH seemed to be the main down-driver of the effect sizes, associated with both lower energy intakes during each of the studied periods and with poorer IQ (p-values <0.04). Those with longer ventilator treatment, BPD, blood exchange transfusion, and PDA also had lower total energy intakes, but although mean IQ's were slightly lower in those with these complications, compared with those without the complications, the differences were not statistically

***Figure 11.*** *Mean daily energy intake during the first nine weeks after birth and neurocognitive abilities in adulthood among VLBW participants.*






*The figure shows change in neurocognitive scores in SD units per 10 kcal higher daily mean energy intake during three three-week periods after birth. Effect sizes and 95% confidence intervals are shown graphically, and effect sizes (β) are also given numerically on the right.*

*Associations adjusted for gestational age, sex, birth weight standard deviation score, and age at follow-up (Model I in Study IV).*

*Associations adjusted for gestational age, sex, birth weight standard deviation score, age at follow-up, and neonatal complications and illnesses (septicaemia, bronchopulmonary dysplasia, indomethacin treatment and surgery because of patent ductus arteriosus, blood exchange transfusion due to hyperbilirubinemia, intraventricular haemorrhage, and duration of ventilator treatment) (Model III in Study IV).*

significant (p-values>0.12). Associations between total energy, human milk, carbohydrate, protein, or fat intakes and IQ did not vary according to birth weight SD scores or to sex (p-values for interactions >0.06).

# 6. DISCUSSION

## 6.1. Strengths and limitations of the study

### *6.1.2. Strengths*

The main strengths of the study include the long follow-up of VLBW and late preterm individuals to adulthood and validated and extensive outcome data. The detailed data on prenatal and background factors, early growth, nutrition, and health are exceptional for such a long follow-up. The similarity of the results among both VLBW and late preterm individuals provide mutual support, suggesting that the findings represent true associations rather than chance.

Individual performance on different neuropsychological tests is quite highly correlated and, many would argue, heavily influenced by general cognitive ability - this means that, for example, the estimates of IQ and of executive functioning that were used in this thesis are hardly separate from each other. In situations where the studied associations or outcomes are not independent, but rather reflect different aspects of the same phenomena, there is no consensus over the optimal method of formally adjusting for the number of statistical tests, and one can argue that correction for multiple testing is overly cautious and may hide true associations. Thus, I chose to boil down the outcomes to some key components and show the regression coefficients with 95% confidence intervals, to give the reader the best possible opportunity to evaluate the pattern of findings.

Unlike the majority of previous studies, I used the standardised residual approach to model growth,[441,442] and feel this is a study strength. The conditional growth variables used in this study represent infants' deviation from their expected body size, based on their own previous measures, in relation to the growth of the other individuals of the cohort. This approach enabled me to look at growth as the change in body size that could not be explained by earlier growth, and thus to address the concern that any results could have been altered or explained by the background effects of earlier growth patterns.

### *6.1.2. Limitations*

Although not exceptional for long-term follow-up studies that require active participation,[443] the rate of attrition is in my opinion the main limitation of this study. Those whom I could not include because of non-participation or missing data differed from the analytic samples in some ways: in the HeSVA, but not in the AYLS cohort, the mothers of the drop-outs were more likely to have smoked during pregnancy, whereas in the AYLS cohort, the mothers of the drop-outs had higher pre-pregnancy BMI and were less likely to have breast-fed their child, compared with those in the analytic samples. Although the drop-outs and the analytic samples did not differ from each other based on any other available data, loss of follow-up may cause selection bias and impact the generalizability of the results, perhaps most likely to the less healthy and more disadvantaged individuals. Further, the number of participants may hinder the detection of small-scale effects, and did not allow me to study many potentially interesting subgroup-specific effects, such as the effects of postnatal growth among participants with specific prenatal or postnatal complications, or the possible mediating effects of nutrition within the most severely ill of the VLBW individuals.

Moreover, although mental health data included well-validated self-report questionnaires in both cohorts and structured diagnostic interviews in the late preterm cohort, these do not provide a window into all aspects of mental health, whose underlying mechanisms seem to vary according to the outcome in question. Less common psychiatric problems and illnesses such as schizophrenia or other psychotic disorders, for example, were entirely outside the scope of this study. Although our findings suggested a link between growth and ASD related traits and performance in tests of executive functioning, but not between growth and self-reported ADHD-related symptoms or impulsivity, diagnosed neuropsychiatric disorders could not be assessed.

As always, the risk of residual confounding remains, and one must also be cautious when generalizing the results of adult follow-up studies to current neonates. Our participants, born in 1978-1986, may not be representative of preterm infants born in high-income settings today, where pre- and postnatal care have improved. For example, in the VLBW cohort, the nutritional intakes of the participants fell well below currently recommended levels especially during the first few weeks of life, and the participants showed considerable variation in early growth - also something of a study strength. Further, I was not able to evaluate the potential effects of corticosteroid administration, which would have been interesting since this treatment, which gained acceptance in the 1980s and 1990s, may influence both growth, neurodevelopment, and neonatal morbidity.

Conclusions cannot be drawn regarding the term-born fetus or child, either: any discrepancies or similarities between the preterm and term-born populations were beyond the scope of this study.

Although the volumes of maternal milk intake were recorded in detail, we did not have data available on any individual variation in milk composition, and thus had to estimate the nutrient content of the milk based on previous research on lactating mothers of preterm infants. Further, some data were only available in one of the two cohorts: for example, size at term was unavailable and could not be reliably interpolated for the AYLS participants.

In the HeSVA cohort, only one non-verbal subtest of the WAIS-III, Block design, was used: the estimate of performance IQ may be less reliable than that of verbal IQ, but the other test data support the interpretation that performance on both verbal and non-verbal tests is associated with early growth. The possible effects of parental cognitive ability on the studied associations were not addressed directly: parental education was used as a proxy of socioeconomic background.

In an era when neonatal cerebral ultrasound was just being introduced, over 70% of our VLBW participants underwent the scan: a strength for an adult follow-up, yet a limitation in comparison to modern-day cohorts where cerebral ultrasound has widely become routine practice. Further, imaging techniques today are much more sophisticated than during the time when these preterm adults were born, and severe forms of IVH are rare, whereas more subtle signs of brain damage are worryingly common.[293] Future studies may be able to link neonatal cerebral abnormalities with adult outcomes much more precisely than what is now possible.

I did not test mediation in models where growth would mediate the effects of nutrition or where nutrition would mediate the effects of neonatal illnesses, on adult outcomes, for theoretical and practical reasons. In our data, there was the problem of temporal overlap that makes statistical assessment of mediation especially problematic: nutritional intakes were recorded simultaneously with the growth measures that were associated with cognitive functioning, and neonatal illnesses are also concentrated in those early weeks. Growth can certainly reflect nutrition, but it can also, in a sense, affect nutrition, since nutritional targets are determined based on the size of the infant. Further, both nutrition and growth can be affected by morbidity, and the rarity of these morbidities makes building complicated mediation models in small study samples difficult.

## 6.2. Implications of the findings

In this study, faster growth soon after preterm birth was associated with better cognitive functioning in adulthood. The pattern on findings, including the size and direction of the effects was similar in both the VLBW and the late preterm cohorts. Head growth, in particular, seemed important in predicting adult cognitive functioning. In the late preterm cohort, those who grew faster also received less special education and had better grades in their comprehensive school leaving certificate, compared with those who grew more slowly.

I did not find that just one specific aspect of cognitive functioning would be affected. Rather, early growth was reflected on performance across a number of neuropsychological tests that measure general cognitive ability, verbal and non-verbal reasoning, visuo-motor performance, executive control, and working memory. Further, the associations were not limited to performance in tests that require participants to adhere to strict time limits and perform quickly, suggesting that the associations were not explained by just differences in processing speed. However, in the VLBW cohort, it appeared that growth was associated with performance in tasks that rely on visuo-spatial processing and memory, while in the late preterm cohort the memory index score was not as clearly associated with growth. Further, it seemed based on the VLBW data that measures of impulse control and selective and sustained attention, unlike many other aspects of cognitive ability, were not associated with early growth. It is possible that these findings are explained by some subtle, uneven pattern of cognitive deficits associated with poor growth. It would be tempting to hypothesise that these differences reflect sensitivity periods for the developing brain: attention and impulse control in particular are closely related to the late-maturing prefrontal cortex, and differences between the late preterm and VLBW cohorts might reflect differential vulnerability during different time periods. Furthermore, differences observed between the two cohorts could relate to the methods we used to assess cognitive functioning. Even if memory functions were intact, problems in visuo-motor functioning could cause slow-growing VLBW infants to perform poorly in tasks that measure both visual memory and visuo-motor performance, whereas the memory index score that was calculated for the late preterm participants was based on tests that are more strictly focused on memory functions. However, these remain speculations. I feel that based on these findings and the previous studies discussed in the literature review, there is not enough evidence to say that early growth would be associated with some specific aspects of cognitive ability, and not others.

In contrast to cognitive and school outcomes, the effect size, direction, or confidence intervals of the associations between growth and mental health outcomes did not suggest any systematic associations in either cohort. In this thesis, I examined growth in relation to self-reported depressive and ADHD symptoms, diagnosis of depression, anxiety disorder, or substance use disorder, and overall psychosocial adjustment. These results support the hypothesis that the mechanisms underlying preterm birth and cognitive vulnerability are at least partly different from those that underlie preterm birth and the risk of common mental health problems.[367] However, poor early growth was associated with some autism-spectrum traits in this cohort,[391] suggesting that some mental health-related neurobehavioural outcomes may be susceptible to the early insults that affect general cognitive ability. Further, the findings on mental health outcomes are interesting in light of the earlier, somewhat conflicting evidence regarding the associations between fetal growth restriction and mental disorders. They further encourage researchers to examine the early outcome-specific underlying mechanisms behind differential vulnerability to neurodevelopmental and psychiatric morbidity, while taking carefully into account potential confounders such as maternal characteristics.

Of course, these follow-up data can only hint at potential causal pathways between early growth and adult cognitive functioning. Our results highlight the importance of an early vulnerable period after preterm birth, when the interruption of development in the normal protective intrauterine environment may alter brain maturation and growth through an interplay of early morbidity, nutrition, care, and individual susceptibility. In this study, higher nutritional intakes during the first weeks of life were associated with better performance during neuropsychological assessment, however these associations seemed to be largely intertwined with neonatal morbidities, which can affect both growth, nutrition, and neurodevelopment. Clinical recommendations concerning neonatal nutrition cannot be made based on these results. The results are in line with the many nutritional intervention studies that have had little lasting impact on neurodevelopment, and support the hypothesis that early differences in energy, human milk, and macronutrient intakes at the NICU may mediate the effects of neonatal morbidity on neurodevelopment, rather than independently alter its course.

However, the neonatal morbidities I examined did not entirely explain the associations between growth and neurodevelopment, suggesting that other factors also underlie the connection. Gestational age, the most important determinant of morbidity among the preterm participants did not explain the associations, nor did manifest intellectual disability or neurosensory impairment, as participants with these conditions were

excluded. The effects were no more pronounced among those who were born small for gestational age, indicating that environmental factors during the growth period, rather than catch-up growth after previous growth restriction underlay the associations. Moreover, adjustment for a multitude of background factors, such as pregnancy-related factors and parental education produced only small changes in the results, further suggesting that a multitude of environmental factors during the early postnatal period, rather than just prenatal adversity, could alter both growth and long-term neurodevelopment. What these factors are remains unknown.

Preterm birth, and the risk of hospitalisation and complications that follow, can form a stressful starting point not only for the life of the preterm infant him- or herself, but also for the family. In addition to any subsequent illness or nutritional regime, the disruption of early interaction with parents, as well as the noise, pain and other exceptional environmental stimuli that come with NICU life may alter both growth and neurodevelopment. One observational study among VLBW adults found that even after taking into account a number of potential confounders including SES, a good parent-infant relationship was associated with a 5-point increase in adult IQ.[289] In line, an increasing number of interventions are used to improve the interaction between the parent and the preterm infant and to reduce early stress. For example, these include sensitising the parent to the infant's cues, reduction of noise at the NICU, and increasing skin-to-skin contact, and despite methodological problems such as large heterogeneity between interventions and difficulties in randomization, the beneficial effects of these interventions seem to extend beyond infancy and into school-age.[444] It is not that the mothers of preterm children would be less sensitive or responsive towards their children (they are not, as a recent meta-analysis reported),[445] but rather that all infants - including preterm ones[446] - benefit from interactions with parents that are positive, warm, and sensitive, and promoting these interactions could help compensate for early adversity. It will certainly be interesting to see whether these interventions could offer a persisting benefit for adult cognitive outcomes.

It has been suggested that biological factors such as neonatal complications have an important role in explaining early and severe cognitive impairments, while the importance of the family and social environment is more pronounced when looking at more subtle differences in childhood, adolescence, and adulthood. However, the environment and the genetic build-up of the individual are inescapably intertwined and distinguishing "biological" effects from "social" or indeed "environmental" ones is a daunting task and, even more importantly, probably less fruitful than studying the

interactions between the two. In this study, I was unable to look at potential genetic and epigenetic factors which could affect the phenotype of these individuals, including growth trajectories, neurodevelopment, or even preterm birth and early morbidity, but these would be interesting to examine.

Some have argued that increasing the rate of early growth after preterm birth presents a trade-off between improved neurodevelopment and poorer cardio-metabolic health, but I have not found convincing evidence for such a trade-off, based on the current or previous research. There is no clear evidence that faster growth during early infancy among a population of whom the majority experience at least some degree of growth failure would have significant detrimental effects on adult cardio-metabolic health, when the confounding effects of immaturity and IUGR are taken into account, however it would seem that faster growth is associated with neurodevelopmental benefits. In contrast, rapid weight gain and particularly the accumulation of fat in disproportion to other measures of growth later on in childhood and in adolescence may increase the risk of cardio-metabolic morbidity and are unlikely to offer neurodevelopmental advantages in return, however studies on these phenomena among preterm adults specifically are scarce.[447] Of course, adult outcomes can only be examined among populations who were born much before the current standard of care. As infants, these individuals received, arguably, less adequate levels of nutrition, were more prone to several severe neonatal illnesses, and experienced high rates of early growth restriction compared with the preterm infants in today's high-income settings. Those of our cohort members who grew faster may have been the ones healthy enough to come close to today's recommended rates, but it is hardly plausible that accelerating early growth indefinitely beyond fetal growth rates would be beneficial.

### 6.3. Conclusion

Faster growth during the first weeks and months of life after preterm birth is associated with better cognitive functioning, and these associations persist into adulthood. While these findings suggest that early environmental factors could alter long-term neurodevelopment, the mechanisms explaining these associations are unclear, and seem outcome-specific. Early intakes of nutrients may reflect or possibly even mediate the effects of neonatal morbidity on neurodevelopment, however the neonatal morbidities commonly associated with preterm birth that were evaluated in this thesis do not wholly account for the associations between early growth and cognitive functioning in adulthood. Further studies are warranted to unravel why some preterm individuals are

vulnerable to subtle neurodevelopmental deficits and mental health problems while others remain resilient - and whether new kinds of targeted interventions during this critical early time period could compensate for the long-lasting risks associated with preterm birth.

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**Appendix:**

**Original publications**

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