Developmental origins of psychological vulnerability factors for mental disorders

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ABSTRACT

Premature birth and associated small body size are known to affect health over the life course. Moreover, compelling evidence suggests that birth size throughout its whole range of variation is inversely associated with risk for cardiovascular disease and type 2 diabetes in subsequent life. To explain these findings, the Developmental Origins of Health and Disease (DOHaD) model has been introduced. Within this framework, restricted physical growth is, to a large extent, considered either a product of harmful environmental influences, such as suboptimal nutrition and alterations in the foetal hormonal milieu, or an adaptive reaction to the environment. Whether inverse associations exist between body size at birth and psychological vulnerability factors for mental disorders is poorly known. Thus, the aim of this thesis was to study in three large prospective cohorts whether prenatal and postnatal physical growth, across the whole range of variation, is associated with subsequent temperament/personality traits and psychological symptoms that are considered vulnerability factors for mental disorders.

Weight and length at birth in full term infants showed quadratic associations with the temperamental trait of harm avoidance (Study I). The highest scores were characteristic of the smallest individuals, followed by the heaviest/longest. Linear associations between birth size and psychological outcomes were found such that lower weight and thinness at birth predicted more pronounced trait anxiety in late adulthood (Study II); lower birth weight, placental size, and head circumference at 12 months predicted a more pronounced positive schitzotypal trait in women (Study III); and thinness and smaller head circumference at birth associated with symptoms of attention-deficit hyperactivity disorder (ADHD) in children who were born at term (Study IV). These associations occured across the whole variation in birth size and after adjusting for several confounders. With respect to growth after birth, individuals with high trait anxiety scores in late adulthood were lighter in weight and thinner in infancy, and gained weight more rapidly between 7 and 11 years of age, but weighed less and were shorter in late adulthood in relation to weight and height measured at 11 years of age (Study II).

These results suggest that a suboptimal prenatal environment reflected in smaller birth size may affect a variety of psychological vulnerability factors for mental disorders, such as the temperamental trait of harm avoidance, trait anxiety, schizotypal traits, and symptoms of ADHD. The smaller the birth size across the whole range of variation, the more pronounced were these psychological vulnerability factors. Moreover, some of these outcomes, such as trait anxiety, were also predicted by patterns of growth after birth. The findings are concordant with the DOHaD model, and emphasise the importance of prenatal factors in the aetiology of not only mental disorders but also their psychological vulnerability factors.

TIIVISTELMÄ

Keskosuus ja siihen liittyvä pieni syntymäkoko on jo pitkään liitetty useisiin terveydellisiin ongelmiin eri vaiheissa elämänkaarta. On myös laajalti osoitettu, että syntymämitat ennustavat myöhempää tyypin 2 diabetes- ja sydäntautiriskiä niin, että riski kasvaa syntymäkoon pienentyessä myös täysaikaisina ja –kokoisina syntyneillä. Näitä yhteyksiä selittämään on kehitetty Developmental Origins of Health and Disease (DOHaD) –malli. Sen mukaan pieni syntymäkoko johtuu suurelta osin joko haitallisista ympäristötekijöistä, kuten epäoptimaalisesta ravitsemuksesta tai muutoksista sikiön hormonialtistuksessa, tai on sopeutumisreaktio ympäristötekijöille. Sitä, ennustavatko täysaikaisina syntyneiden syntymämitat tai myöhempi fyysinen kasvu mielenterveyden häiriöitä tai niille altistavia psykologisia piirteitä, tunnetaan vielä huonosti. Tämän tutkimuksen tarkoituksena oli selvittää kolmessa laajassa kohortissa, joissa on seuranta-asetelma, miten syntymämitat ja myöhempi fyysinen kasvu ennustavat sellaisia temperamentti- ja persoonallisuuspiirteitä ja käyttäytymisoireita, jotka kasvattavat psykiatristen sairauksien riskiä.

Syntymäpaino ja –pituus ennustivat ”vahingollisuuden välttäminen”-temperamenttipiirrettä niin, että tätä piirrettä esiintyi eniten kaikkein kevyimpien/lyhyimpien joukossa ja seuraavaksi eniten kaikkein painavimpien/pisimpien keskuudessa (Tutkimus I). Pieni syntymäpaino ja -hoikkuus ennustivat myös voimakkaampaa piirreahdistuneisuutta myöhäisellä aikuisiällä (Tutkimus II). Pienen syntymäpainon, istukan koon ja päänympäryksen todettiin olevan yhteydessä psykoosipiirteisiin naisilla (Tutkimus III). Näiden yhteyksien lisäksi vastasyntyneen hoikkuus ja pieni päänympärys ennustivat myös tarkkaavaisuus- ja yliaktiivisuushäiriön (ADHD) oireita lapsuudessa (Tutkimus IV). Nämä yhteydet eivät rajoittuneet vain kaikkein pienikokoisimpina syntyneisiin, vaan löydettiin läpi koko syntymämittojen vaihtelun, useiden kontrollimuutujien vakioimisenkin jälkeen. Syntymänjälkeistä kasvua tutkittaessa osoitettiin, että voimakas piirreahdistuneisuus myöhäisellä aikuisiällä oli yhteydessä pienempään fyysiseen kokoon aina kaksivuotiaaksi asti. Voimakkaan piirreahdistuneisuuden omaavilla henkilöillä paino kasvoi nopeammin seitsemän ja 11 vuoden välillä, painon ja pituuden kasvun kuitenkin hidastuessa 11 vuoden ja aikuisiän välillä (Tutkimus II).

Tämän tutkimuksen tulokset osoittavat, että pienempi syntymäkoko, joka heijastelee epäoptimaalista ravitsemusta tai hormonaalista altistumista raskauden aikana, on yhteydessä laaja-alaisesti erilaisiin mielenterveyden häiriöihin altistaviin käyttäytymispiirteisiin, kuten vahingollisuuden välttämiseen, piirreahdistuneisuuteen, psykoosipiirteisiin ja ADHD-oireisiin. Nämä yhteydet eivät rajoitu vain kaikkein pienimpinä syntyneisiin, vaan kuvaavat myös täysaikaisina ja –kokoisina syntyneitä. Piirreahdistuneisuuteen oli yhteydessä myös syntymänjälkeinen kasvu. Tämän tutkimuksen tulokset ovat DOHaD-mallin mukaisia ja osoittavat, että mielenterveyden häiriöille altistavat käyttäytymisen piirteet voivat ohjelmoitua jo ennen syntymää.

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II **Lahti, J**., Räikkönen, K., Pesonen, A-K., Heinonen, K., Kajantie, E., Forsén, T., Osmond, C., Barker, D.J.P. & Eriksson, J.G. (in press). Body size at birth, growth, and trait anxiety in adulthood. *Acta Psychiatrica Scandinavica*.

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IV **Lahti, J**., Räikkönen, K., Kajantie, E., Heinonen, K., Pesonen, A-K., Järvenpää, A-L. & Strandberg, T. (2006). Small body size at birth and behavioural symptoms of ADHD in children aged five to six years. *Journal of Child Psychology & Psychiatry*, 47:11, 1167-74.

ABBREVIATIONS

11βHSD2	Hydroxysteroid (11-beta) Dehydrogenase 2
ADHD	Attention-Deficit Hyperactivity Disorder
AGA	Appropriate for Gestational Age
β	Standardised beta coefficient
B	Unstandardised beta coefficient
BMI	Body Mass Index (kg/m^2)
CI	Confidence Interval
CNS	Central Nervous System
DNA	Deoxyribonucleic Acid
DOHaD	Developmental Origins of Health and Disease
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders (3^{rd} edition, revised)
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (4^{th} edition)
ELBW	Extremely Low Birth Weigh (< 1000 g)
FTT	Failure to Thrive
GH	Growth Hormone
HA	Harm Avoidance
HADS	Hospital Anxiety and Depression Scale
HDR	Hospital Discharge Register
HPAA	Hypothalamic-Pituitary-Adrenal Axis
HPG	Hypothalamic-Pituitary-Gonadal
HPT	Hypothalamic-Pituitary-Thyroid
IC	Infancy-Childhood
ICP	Infancy, Childhood, and Puberty
IGF	Insulin-like Growth Factor
IUGR	Intrauterine Growth Restriction
LBW	Low Birth Weight (< 2500 g)
M	Mean
MDD	Major Depressive Disorder

neg-STAI-T	Negatively worded trait items of the Spielberger State Trait Anxiety Inventory
NS	Novelty Seeking
p	Probability
PAS	Perceptual Aberration Scale
PhAS	Physical Anhedonia Scale
r	Correlation
STAI-T	Trait items of Spielberger State Trait Anxiety Inventory
RD	Reward Dependence
SD	Standard Deviation
SGA	Small for Gestational Age
SES	Socioeconomic Status
pos-STAI-T	Positively worded trait items of the Spielberger State Trait Anxiety Inventory
WHO	World Health Organization
VLBW	Very Low Birth Weigh (< 1500 g)

1. INTRODUCTION

> "The history of man for nine months preceding his birth would, probably, be far more interesting, and contain events of greater moment than all three score and ten years that follow it."
> *Samuel Taylor Coleridge* (1772-1834) NOTES ON SIR THOMAS BROWN'S 'RELIGIO MEDICI'. 1802.

It is well known that premature birth and associated small body size at birth affect health not only in the immediate peri- and neonatal periods, but also over the life course. Compelling evidence suggests that associations between birth size and health in later life also exist across the whole range of variation of body size at birth, particularly with respect to cardiovascular disease and type 2 diabetes (reviewed in Barker (2004a)). Some evidence suggests that this may also be the case with mental disorders and their psychological vulnerability factors, such as negative affectivity (Pesonen, Räikkönen, Strandberg & Järvenpää, 2006b; Pesonen, Räikkönen, Heinonen, Kajantie, Strandberg & Järvenpää, 2006a), hostility (Räikkönen, Pesonen, Heinonen, Lahti, Kajantie, Forsen et al., 2008), depressive symptoms (Thompson, Syddall, Rodin, Osmond & Barker, 2001; Räikkönen, Pesonen, Heinonen, Kajantie, Hovi, Järvenpää et al., 2008), schizophrenia (Wahlbeck, Forsen, Osmond, Barker & Eriksson, 2001), and hyperactivity (Kelly, Nazroo, McMunn, Boreham & Marmot, 2001). Moreover, physical growth after birth has been associated with various comparable outcomes (e.g., Wolke, Skuse & Mathisen, 1990; Spencer, Biederman & Wilens, 1998; Wahlbeck, Forsen, Osmond, Barker & Eriksson, 2001; Bjerkeset, Romundstad, Evans & Gunnell, 2008).

To explain these findings, Barker and his colleagues (1993) introduced the concept of foetal programming, which has evolved into the Developmental Origins of Health and Disease (DOHaD) framework. Within this developmental programming framework, restricted physical growth is considered either a product of harmful environmental influences, such as suboptimal materno-foetal nutrition and alterations in the foetal hormonal milieu, or an adaptive reaction to the environment. During the past few decades, this area of research has evoked extensive efforts, and even molecular mechanisms that may exert early environmental influences on later health outcomes

have been introduced. Compared to somatic health outcomes, however, the extent to which physical size at birth and later on predict subsequent mental disorders and their psychological vulnerability factors is less known, and the nuances of the findings have been mixed.

The aim of this thesis is to elucidate the associations of prenatal physical growth with temperament/personality traits and psychological symptoms that have been shown to be vulnerability factors for mental disorders. Moreover, associations between physical growth after birth and trait anxiety will be explored. Knowledge of these associations may, in the future, aid in preventive actions. The introduction of this summary consists of three parts. The reader is first introduced to the basic concepts related to physical growth, such as measuring physical size and growth, peaks in physical growth, and factors influencing physical growth in the prenatal period and after birth; then to theoretical models and mechanisms explaining how and why variation in physical growth predicts health and behaviour in later life; and finally, to the existing empirical work on associations between physical growth and somatic diseases, mental disorders, and psychological vulnerability factors for mental disorders.

1.1. Physical size and growth: measurements, peaks and determinants

Physical growth can be defined as a "quantitative increase in size or mass" (Bogin, 1999b). Physical growth comprises cell growth and proliferation, migration, and interaction as well as apoptosis. Studying human physical growth is confounded by several factors. Physical size and growth can be measured in a variety of ways, for growth velocity tends to vary according to age-period and is affected by a number of factors. These topics will be introduced first.

1.1.1. Measuring physical size and growth

Physical size can be measured in a variety of ways, and these measures differ only slightly with newborns or older people. Most commonly reported anthropometric measures of physical size at birth are weight, length, and head circumference. Although birth weight reflects only one dimension of prenatal growth, it has advantages. It is easy

to measure, the figures are reliable, and it has already been measured systematically already for decades. The World Health Organization (WHO) has issued guidelines on restricted and typical weight at birth (WHO Expert Commitee on Physical Status, 1995), and many studies report birth weight as their primary indicator of prenatal growth. According to WHO guidelines, low birth weight (LBW) is defined as < 2500 g, very low birth weight (VLBW) as < 1500 g, and extremely low birth weight (ELBW) as < 1000 g (WHO Expert Commitee on Physical Status, 1995). Measuring birth length is more difficult than measuring birth weight and provides less reliable estimates (Johnson, Engstrom & Gelhar, 1997). Another limitation to the use of birth length instead of birth weight in research is smaller variation. Head circumference has not been reported in early studies on the effects of prenatal growth, but the measure is as reliable as birth weight (Johnson et al., 1997), and its role as an indicator of brain growth has been recently emphasised (Bartholomeusz, Courchesne & Karns, 2002). Furthermore, since nutrients obtained by the foetus are transferred through the placenta, changes in placental permeability impact foetal size. Therefore, placental size and weight are typically measured immediately after birth and many studies report placental parameters as additional indicators of prenatal growth. Moreover, several ratios can be calculated from these direct measurements, such as ponderal index (kg/m^3), an equivalent to BMI (kg/m^2) in adults, which indicates thinness at birth and the ratio of head circumference at birth to weight or length at birth, which indicates the relative size of the head. Although birth weight has been the most widely studied anthropometric measure, recent studies also encourage the use of other indicators of body size at birth, such as ponderal index (Gillman, 2002).

Indicators of intrauterine growth restriction (IUGR), a failure of the foetus to achieve its intrinsic growth potential, which take into account the gestational age of the newborn have been proposed. A typically growth-restricted infant has been defined as one belonging to the lowest 10^{th} percentile for gestational age in birth weight (SGA; small for gestational age), although other cut-off points have also been used (WHO Expert Commitee on Physical Status, 1995). Those with a higher birth weight for gestational age are considered appropriate for gestational age (AGA). It is important, however, to acknowledge that SGA and IUGR are not strictly synonymous, since some SGA infants (e.g., those born to small parents) may represent merely the lower extreme of the normal

fetal growth distribution, whereas other infants who meet the criteria for AGA may actually have been exposed to one or more growth-inhibiting factors.

Evidently, measurements of birth size overlap and are related to each other; weight encompasses two important aspects of body size: linear (skeletal) growth (i.e., length), and the growth of soft tissues, which is commonly measured with ponderal index. Therefore, attempts aim to characterise birth size by a small number of composite measures (e.g. factor scores)(Joglekar, Fall, Deshpande, Joshi, Bhalerao, Solat et al., 2007).

Physical size after birth and growth can also be measured in a wide variety of ways. In epidemiological studies, typical measures of physical size after birth include weight, height, and BMI. Moreover, restricted growth after birth can be defined in several ways. In infancy, failure to thrive (FTT) has been defined as low weight (e.g., 5^{th} percentile for age) or poor weight gain (e.g., weight deceleration crossing more than two major centile lines), but definitions vary (Olsen, Petersen, Skovgaard, Weile, Jorgensen & Wright, 2007).

1.1.2. Peaks in physical growth

Insults affecting physical growth may have the greatest effect on development during periods of rapid growth. The first human growth velocity peak, or 'Initial peak' (Tanner, 1986), occurs during the foetal and early postnatal period (Figure 1) (Bogin, 1999a). Estimates indicate that the foetus undergoes some 42 mitotic divisions in progressing from a fertilised ovum to a term infant, and only five more divisions to achieve adult size (Milner, 1989). Another, although much smaller, peak occurs during puberty and is called the 'Adolescent peak' (Tanner, 1986). During the Initial peak, organs and nuclei have different periods of maximal development. For example, brain mass continues to grow until around five years with the Initial peak growth lasting until the end of the second postnatal year (Leigh, 2004). In addition to the 'Initial peak' and 'Adolescent peak', a third peak, namely a mid-childhood growth spurt, has been found to occur at the end of the early childhood stage or in the beginning of the juvenile stage (Figure 2) (e.g., Bogin (1999a)). Interestingly, this peak in velocity of linear growth overlaps with an increase in body mass index (BMI) after a nadir during the period around six years of

age (Rolland-Cachera, Deheeger, Bellisle, Sempe, Guilloud-Bataille & Patois, 1984). This pattern of growth in BMI is called adiposity rebound.

Several models describe human physical growth after birth. The Infancy, Childhood, and Puberty (ICP) growth model is based on the analysis of growth parameters and divides human linear growth into three additive and partly superimposed components that reflect the endocrine control mechanisms of the growth process (Karlberg et al., 1987a; Karlberg et al., 1987b). The ICP model has been shown to predict adult height fairly accurately (Limony, Zadik, Pic & Leiberman, 1993). Linear growth during the first two to three years of life is rapid and is represented by a combination of a sharply decelerating infancy component and a slowly decelerating childhood component. The infancy component has been suggested to begin at mid-gestation and to tail off at the age of two to three years, representing the postnatal extension of foetal growth, whereas the childhood component acts from the second half of the first postnatal year. The childhood growth phase is characterised by a steadier growth rate, and is followed by the pubertal growth spurt, which continues until linear growth ceases.

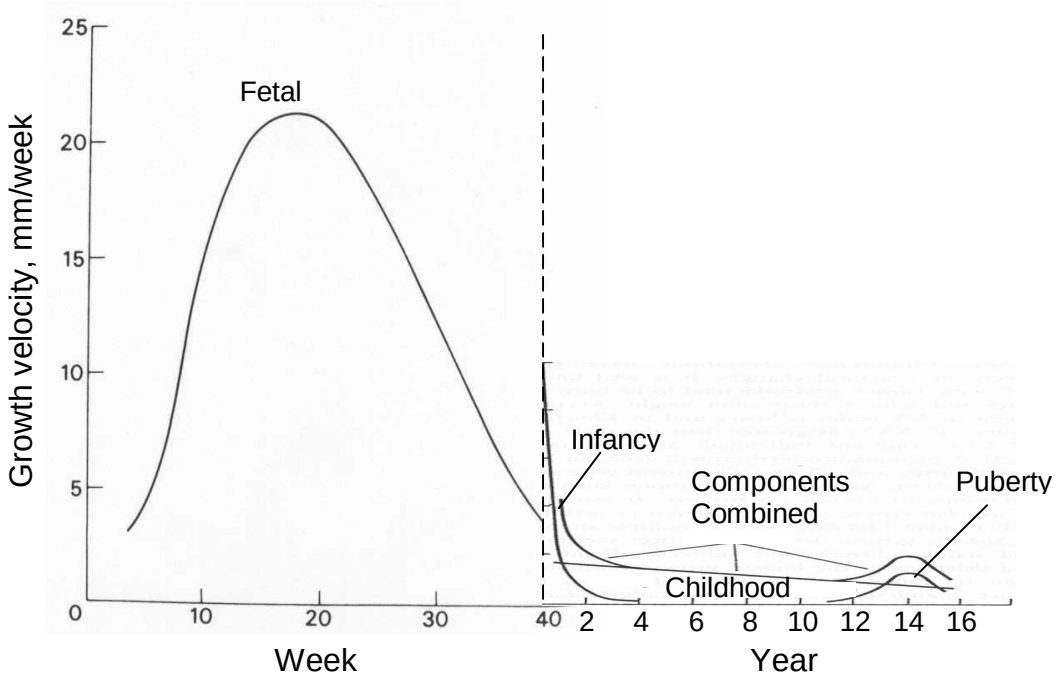

Figure 1. Growth velocity throughout the human growth period. Combined from Dattani & Preece (1998) and the infancy-childhood-puberty model by Karlberg et al. (1987). The scale of the Y axis is the same for both parts of the figure, illustrating the high growth rate during the fetal period compared with postnatal life. Adapted from Kajantie (2003).

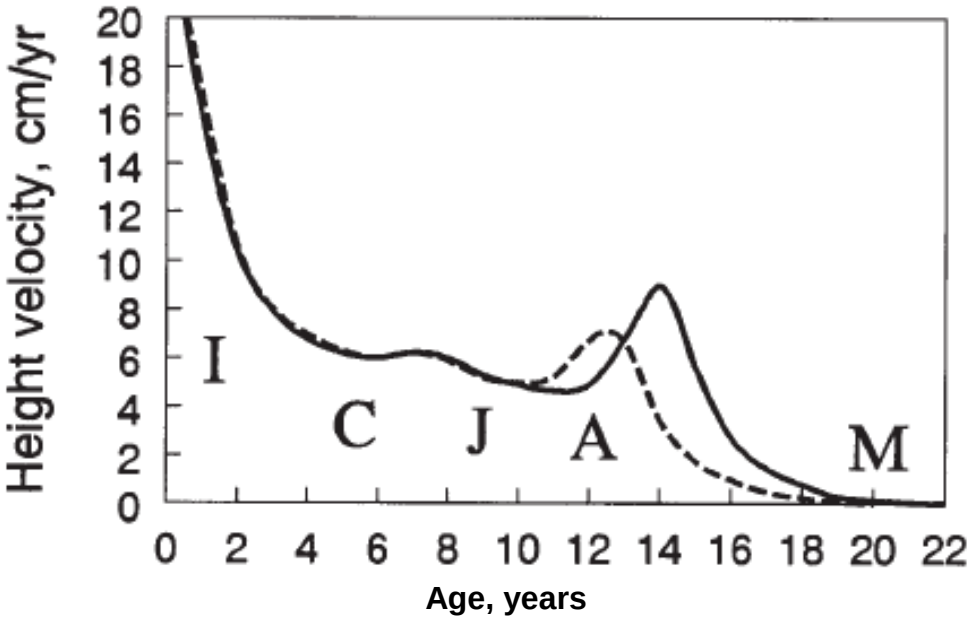

Figure 2. Mean velocity curves of growth in height for healthy girls (*dashed lines*) and boys (*solid lines*) showing the postnatal stages of the pattern of human growth. The stages of human postnatal growth are abbreviated as follows: **I**, infancy; **C**, childhood; **J**, juvenile; **A**, adolescence; **M**, mature adult. Adapted from Bogin (1999a).

1.1.3. Factors influencing prenatal physical growth

> "The size attained *in utero* depends on the services which the mother is able to supply. These are mainly food and accommodation" *(McCance, 1962)*

Prenatal growth is affected by genetic and environmental factors (Figure 3). Heritability ratings of birth weight, derived from the difference between the correlation of monozygotic and dizygotic twins, vary greatly. Some have reported low heritability (i.e. 11-17% in Hur, Luciano et al. (2005)), and others, high heritability (more than 50% in Magnus (1984)), but the bulk of studies conducted in Western cultures have shown moderate heritability suggesting that the genetic component accounts for around 30% of the variation in birth weight (Little & Sing, 1987; Clausson, Lichtenstein & Cnattingius, 2000; Lunde, Melve, Gjessing, Skjaerven & Irgens, 2007).

Length of gestation is a major determinant of body size at birth. In addition, a wide range of foetal, placental, and parental factors have been linked to foetal growth restriction (reviewed in Bernstein & Divon (1997) and Robinson, Moore, Owens & McMillen (2000)). Foetal factors include genetic conditions and congenital anomalies. Placental factors include structural anomalies that alter the permeability of the placenta, such as a single umbilical artery, bilobate placenta, placental abruption, and placental hemangiomas. Parental factors include maternal macronutrient or micronutrient intake (Moore, Davies, Willson, Worsley & Robinson, 2004; Yajnik, 2006), maternal prepregnancy body size and weight gain during pregnancy, paternal height, numerous infectious diseases, maternal medical conditions such as hypertension, renal disease, and collagen vascular diseases, maternal smoking, alcohol consumption, and illicit drug use during pregnancy, as well as demographics such as maternal age, parity, and ethnicity. In addition, low family socioeconomic status (SES) may increase the risk for low birth weight even after adjusting for several confounders, such as maternal age and parity (Gisselmann, 2006) or weight gain during pregnancy, ethnicity, maternal smoking and alcohol use during pregnancy (Finch, 2003). Furthermore, multiple pregnancy, prenatal psychosocial stress (Wadhwa, 2005), and chronic hypoxia, for example, due to a high altitude environment (Jensen & Moore, 1997) may contribute to variation in body size at birth.

However, disentangling genetic and environmental effects is difficult since a genetic component may exist in factors typically considered environmental, such as maternal size and parity (Ounsted, Scott & Moar, 1988). In turn, genetic effects may be moderated by environmental factors (Lahti, Räikkönen, Ekelund, Peltonen, Raitakari & Keltikangas-Järvinen, 2005).

Besides the nature of the environmental insult, such as a famine or traumatic event, the timing of the insult may also affect birth size. Since the foetus undergoes its maximum growth in length at mid-gestation and in weight during the third trimester (Falkner, Holzgreve & Schloo, 1994), the timing of any environmental insult during pregnancy is thought to have different effects on various measures of body size at birth. Proportionately growth-retarded infants have a normal ponderal index, but their weight, length, and/or head circumference at birth are small. Proportional growth retardation can be a sign of a genetically regulated growth pattern or arise from undernutrition or adverse insults in early pregnancy or throughout the pregnancy (Villar & Belizan, 1982). Low ponderal index, by contrast, is a sign of disproportionate growth retardation, which is thought to originate from undernutrition or insults incurred during late pregnancy. These adversities are believed to lead to a reduced amount of muscle and/or fat and, consequently, a relatively normal length and head circumference, but to low body weight and ponderal index (Stein, Zybert, van de & Lumey, 2004). Although recent studies have questioned this "timing hypothesis" (Lampl & Jeanty, 2003), it is worth noting that the balance of the diet, such as the rate of carbohydrate over protein intake in late pregnancy, has been associated with low ponderal index in the offspring (Moore et al., 2004).

1.1.4. Factors influencing physical growth after birth

Dynamic control of physical growth after birth is endowed by a complex interplay of sex- and age-dependent hormonal, genetic, environmental, nutritional, socioeconomic, developmental, behavioural, and metabolic factors (Figure 3). It is plausible that genes affect growth after birth more than prenatal growth, since heritability ratings of weight are lowest at birth and increase with age (Pietiläinen, Kaprio, Räsänen, Rissanen & Rose, 2002). An exhaustive description of factors and processes influencing growth after birth is beyond the scope of this thesis, but because one of the studies considers

growth after birth, some of these factors will be briefly described from the perspective of the ICP model (Karlberg et al., 1987a; Karlberg et al., 1987b).

Within the ICP model of human physical growth, the infancy component is regarded as largely nutrition dependent. The model proposes a period of infancy-childhood transition (IC transition) whereby the initiation of the childhood growth phase overlaps with the infancy growth phase and the infantile period. The IC growth transition, an index of stunting growth, represents the age at which growth hormone (GH) begins to regulate growth significantly and reflects the control of growth by the growth hormone/insulin-like growth factor-I (GH-IGF-I) endocrine axis and target cell responsiveness (Low, Tam, Kwan, Tsang & Karlberg, 2001; Karlberg & Albertsson-Wikland, 1988). IC growth transition occurs in parallel with a rise in the serum levels of GH-dependent IGF-I and IGF-binding protein-3 during the second half of the first year of life, and children with a delayed IC growth transition show a delay in the 6- to 12-month rise of IGF-I levels (Wang & Chard, 1992; Leger, Oury, Noel, Baron, Benali, Blot et al., 1996). Environmental factors associated with delayed IC transition have been related to the family's general economic situation, such as a smaller number of rooms in the household, and the child's nutritional practice, such as a shorter duration of breastfeeding (Liu, Jalil & Karlberg, 1998). Moreover, several illnesses or syndromes such as Turner syndrome (Davenport, Punyasavatsut, Stewart, Gunther, Savendahl & Sybert, 2002), congenital hypothyroidism (Heyerdahl, Ilicki, Karlberg, Kase & Larsson, 1997), and diarrhoeal diseases (Liu et al., 1998) were found to be particularly important factors associated with a delayed onset of childhood linear growth and, thus, plausibly to reduced adult height. The ICP model also proposes that during the pubertal growth spurt, gonadal hormones play a central role in growth directly or by altering the effects of growth hormone (Karlberg et al., 1987b).

In some instances, physical growth may also be predicted by the preceding physical growth. A period of restricted growth is often followed by accelerated growth, beyond the normal rate for the age in question (Kay's & Hindmarsh, 2006). This rapid, compensatory growth during rehabilitation from prior nutritional deficits or illness is called catch-up growth (WHO Expert Commitee on Physical Status, 1995).

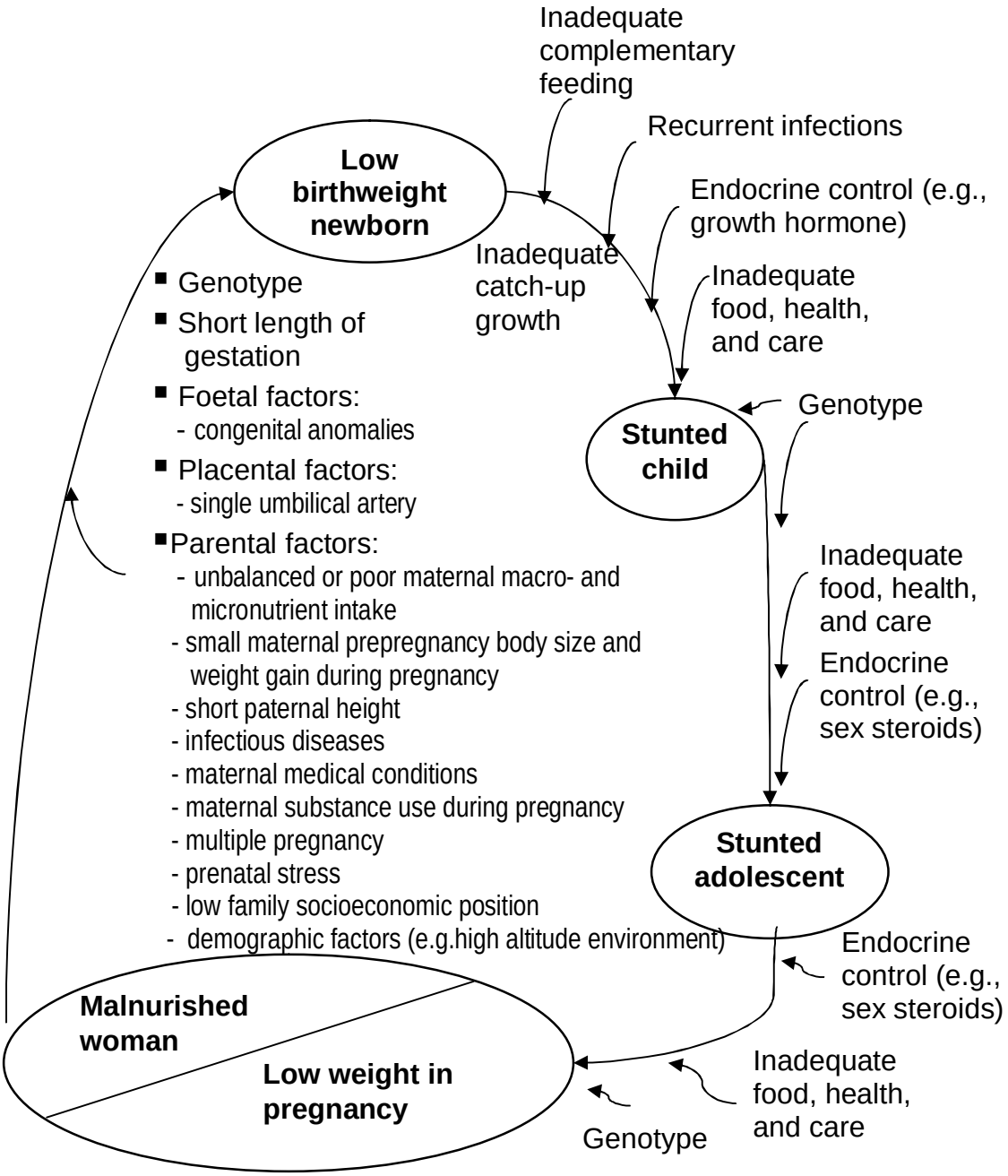

Figure 3. Poor physical growth cycle. Modified from Branca & Ferrari (2002).

1.2. Variation in physical growth and health: theoretical perspectives

It has long been evident that severe prematurity (and very low birth weight), which is followed by a period of immaturity-associated illness, and severe intrauterine growth restriction (frequently a consequence of severe placental dysfunction) or both, may indicate damage to the physiological system of the individual and compromise somatic or mental health immediately after birth or later on. However, the extent to which the findings from studies focusing on only the smallest at birth can be generalised to the general population is unknown. Only recently has the focus been extended from the smallest at birth to include the whole variation in birth size and gestational age. While some studies suggest that the health of only the smallest born is affected (Gale & Martyn, 2004; Räikkönen, Pesonen, Kajantie, Heinonen, Forsen, Phillips et al., 2007), a growing number of studies also show linear effects throughout the whole variation in birth size (Barker et al., 1993; Barker, 1997; Sorensen, Sabroe, Olsen, Rothman, Gillman & Fischer, 1997; Wahlbeck et al., 2001; Thompson et al., 2001; van Os, Wichers, Danckaerts, Van Gestel, Derom & Vlietinck, 2001; Richards, Hardy, Kuh & Wadsworth, 2001; Barker, Osmond, Forsen, Kajantie & Eriksson, 2005).

1.2.1. Developmental Origins of Health and Disease (DOHaD)

To explain the associations between body size at birth and subsequent morbidity, the concept of "foetal programming" was introduced (Lucas, 1991; Barker et al., 1993) and later refined as the Developmental Origins of Health and Disease (DOHaD) framework (Gillman, 2005). According to this developmental programming framework, adverse influences during sensitive periods of development change or program the structure and function of the cells and organs – and, consequently, the function of the organism – that persist throughout the lifespan (Barker, 1997). It has been suggested that a sensitive period occurs *in utero*, when the cells for most organs and systems proliferate rapidly. Although the initial model of foetal programming focused mainly on the associations between prenatal growth and diseases in later life, the DOHaD framework extends the focus to include growth after birth also. An outline of the mechanisms and outcomes of developmental programming appears in Figure 4.

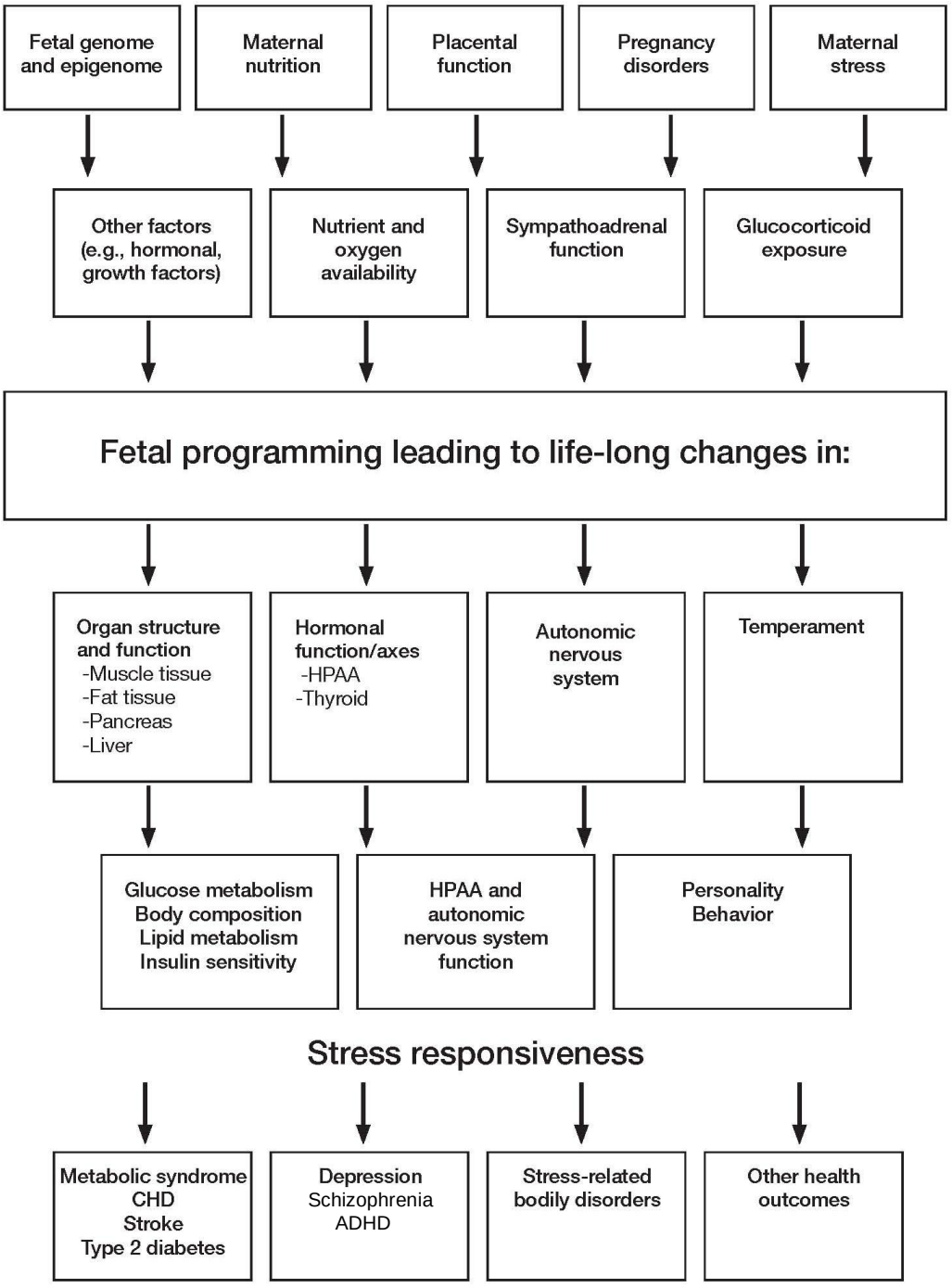

Figure 4. Schematic presentation of key mechanisms of fetal programming of adult health and disease. Modified from Räikkönen, Kajantie, Rautanen & Eriksson (2008).

The developmental programming of adverse health outcomes in animals has been induced with diverse interventions, such as modification of the maternal diet, prenatal administration of glucocorticoid hormones, various prenatal stress paradigms, ligation of the uterine artery, and experimentally induced anemia (McMillen & Robinson, 2005). Within the DOHaD framework, these perturbations have been proposed to result in the adverse development of organs directly (e.g., as a result of physical or chemical constraint or exposure disrupting developmental processes) or in adaptive responses that may be beneficial in the short term, but deleterious in the long term (Bateson, Barker, Clutton-Brock, Deb, D'Udine, Foley et al., 2004; Gillman, 2005).

Several mechanisms associating small birth size with later health and disease have been proposed (reviewed in Jaddoe & Witteman, 2006). First, pleiotropic genetic effects may influence physical growth and health outcomes (Hattersley & Tooke, 1999). Second, sub-optimal foetal nutrition, may lead to developmental adaptations in the structure, physiology, and metabolism of the foetus (Barker et al., 1993). Finally, increased cortisol exposure due to the altered function of placental 11βHSD2 enzyme, which converts maternal cortisol to inactive cortisone (Edwards, Benediktsson, Lindsay & Seckl, 1993), or due to other developmental alterations in the hypothalamic-pituitary-adrenal axis (HPAA) (Clark, 1998), may exlain the association. Furthermore, yet unmeasured factors may also account for this association. Such factors may relate to environmental influences that are risk factors for both small birth size and compromised mental health in later life. For example, recent studies involving data from mothers as well as from exposed and unexposed siblings showed that although prenatal exposure to alcohol or smoking was associated with externalising problems in the offspring, these associations were not causal (D'Onofrio, Van Hulle, Waldman, Rodgers, Rathouz & Lahey, 2007; D'Onofrio, Van Hulle, Waldman, Rodgers, Harden, Rathouz et al., 2008). The authors suggested that these associations were caused by unmeasured environmental influences that vary between families and confound the association between maternal alcohol use and smoking during pregnancy and offspring externalisation behaviors.

All these mechanisms may render those who are small at birth vulnerable to later adversities by reducing the number of cells in key organs in those with smaller birth size or by setting their hormones and metabolism (Barker, 2004b). Most studies linking

small birth size with pathophysiological outcomes have focused on alterations in internal organs (e.g., the number of nephrons in the kidney). In addition, it has been suggested that among the organs, the brain would be the last to show alterations. This 'brain sparing effect' occurs due to the fact that if constrained, the blood circulation of the foetus is redistributed for the benefit of the brain and at the cost of the other organs. However, Roza, Steegers et al. (2008) recently showed that brain sparing can only partly compensate for the effects of placental insufficiency or environmental insults. It is therefore plausible that physiological processes mediating the associations between birth size and somatic health outcomes in later life are applicable to the brain and to the mental health outcomes emerging from the brain as well. Indeed, evidence suggests that small body size at birth and suboptimal prenatal environments are also linked to various structural and functional alterations in the brain and in key metabolic axes. For example, recent human studies link LBW to increased lateral ventricular volume (a sign of smaller total brain volume) in adulthood (Allin, Henderson, Suckling, Nosarti, Rushe, Fearon et al., 2004) and preterm birth to a smaller hippocampus (Nosarti, Al Asady, Frangou, Stewart, Rifkin & Murray, 2002; Lodygensky, Seghier, Warfield, Tolsa, Sizonenko, Lazeyras et al., 2008). Moreover, intrauterine growth retardation has been associated with metabolic disturbances in brain serotonin synthesis in infants (Manjarrez, Cisneros, Herrera, Vazquez, Robles & Hernandez, 2005), and small birth weight in rats was associated with reduced serotonin transporter density in the frontal cortex in adulthood (Himpel, Bartels, Zimdars, Huether, Adler, Dawirs et al., 2006). Furthermore, experimental studies in animals have shown that the administering of synthetic glucocorticoids or inducing stress during pregnancy – interventions known to reduce the birth weight of the offspring – lead to alterations in serotonin (Slotkin, Kreider, Tate & Seidler, 2006), dopamine, and noradrenalin neurotransmission (Muneoka, Mikuni, Ogawa, Kitera, Kamei, Takigawa et al., 1997; Bowman, MacLusky, Sarmiento, Frankfurt, Gordon & Luine, 2004). In addition, a large body of evidence suggests that lower birth weight predicts alterations in major metabolic axes, such as the HPAA (Kajantie, 2006), the growth hormone-insulin-like growth factor (GH-IGF) axis (Holt, 2002), the hypothalamic-pituitary-gonadal (HPG) axis (Rhind, Rae & Brooks, 2001), and the hypothalamic-pituitary-thyroid (HPT) axis (Fisher, 2008) as well as in sympathetic nervous system activity (for a review, see Kajantie (2006)). How the effects

of the prenatal environment affect late adulthood on a molecular level remain poorly understood. However, Weaver, Cervoni et al., (2004) have shown that the early postnatal environment has long-term effects on the functioning of the HPAA that operates through deoxyribonucleic acid (DNA) methylation or histone acetylation. Moreover, an altered DNA methylation is a plausible mechanism for the developmental programming of gene expression and organ function (Meaney, Szyf & Seckl, 2007).

In line with hypotheses that the effects of developmental programming are mediated through altered exposure to hormones, such as glucocorticoids, during the prenatal period, studies have shown that exposure to a particular hormone imprints the response to the same hormone later on (Waterland & Garza, 1999).

1.2.2. Environmental influences after birth

In addition to prenatal processes, postnatal environmental factors may contribute in a number of ways to associations between small birth size and subsequent mental health. While some have proposed that these associations are best explained by postnatal factors, others have emphasised the interactive effects of prenatal processes and postnatal environment on health. As an example of the former, Singhal & Lucas (2004) have suggested that associations between small birth size and health in later life may be explained by accelerated physical growth after birth (catch-up growth), which is often preceded by small birth size. In addition, differences in parenting between those born small and those born larger may also contribute to these associations. Although the literature about the effects of prematurity on parenting is inconsistent (see review by Miles & Holditch-Davis, 1997), parents of VLBW children may be more protective than those of term-born children (Indredavik, Vik, Heyerdahl, Romundstad & Brubakk, 2005). Overprotective parenting, in turn, may associate with compromised mental health in later life (Heider et al., 2006; Heider et al., 2008).

As an example of the interplay of prenatal processes and postnatal environment, Barker (2004b) proposed that the altered physiology or reduced number of cells in the key organs may render those of smaller birth size more vulnerable to adverse environmental influences in later life. In addition, the postnatal environment may also be beneficial and protect from or compensate for the consequences of prenatal adversities. For example, individualised infant- or parent-focused interventions that aim

to fascilitate parent-infant interactions, the early stimulation of infants, or both, have been found beneficial in terms of neurocognitive skills and educational achievement in those born LBW and VLBW (Als, Lawhon, Duffy, McAnulty, Gibes-Grossman & Blickman, 1994; McCormick, Brooks-Gunn, Buka, Goldman, Yu, Salganik et al., 2006). Moreover, responsive parenting may be particularly important in terms of language and social development in early childhood for those born VLBW with more severe medical complications (Landry, Smith, Swank, Assel & Vellet, 2001), although later on, when children are in the school environment, the extent to which an early responsive parenting environment can support the most biologically fragile children to demonstrate better outcomes seems limited (Smith, Landry & Swank, 2006). Yet cohort studies with a wide variation in birth size have seldom explored the interactive effects of birth size and postnatal environment on mental health. Kelly et al. (2001) found a stronger inverse association between birth weight and behavioural problems in the children of families whose head of household worked at skilled non-manual and manual occupations (Social Class III) than in those from a higher or lower social class. Their findings remain speculative, however, as tests for statistical interactions between birthweight and social class were insignificant.

1.2.3. Adaptive nature of variation in growth: developmental plasticity

> "…we do not always bear in mind, that, though food may be now superabundant, it is not so at all seasons of each recurring year… A large number of eggs is of some importance to those species which depend on a fluctuating amount of food, for it allows them rapidly to increase in number."*(Darwin, 1859)*

Evolutionary view may offer insights on the interaction between prenatal and postnatal environments. Initially within developmental programming framework, restricted growth was mainly considered a consequence of adverse environmental insults and has often served to conceptualise the development of pathologies (Lucas, 1991; Barker et al., 1993; Barker, 1997). Clearly some responses of the foetus (e.g., response to environmental teratogens) to its environment are developmentally disruptive with no adaptive value. However, as postulated in the contemporary DOHaD framework alterations in growth can also be viewed from an evolutionary perspective as an

adaptation to the environment (Bateson et al., 2004; Gillman, 2005). The foetus has homeostatic and homeorhetic mechanisms that confer immediate survival advantage (e.g., alterations in regional blood flows and organ growth when nutrients or the oxygen supply are reduced) even in the face of subsequent costs after birth. Furthermore, studies on the interplay between the developing organism and the circumstances in which it finds itself have suggested that a given genotype can give rise to different phenotypes, depending on environmental conditions (Gilbert, 2001). Such developmental plasticity or predictive adaptive response to the environment enables the production of phenotypes that are better matched to their environment than would be possible if the same phenotype were produced in all environments (West-Eberhard, 1989; Bateson, 2001; Bateson et al., 2004; Gluckman & Hanson, 2004). These adaptive responses can include short-term changes in physiology and behaviour, as well as long-term adjustments to conditions predicted by the state of the environment when the organism is in its very early stages of growth. Thus, if a mother is faced with nutritional or psychosocial stress during pregnancy, the foetus may respond with adaptations such as reduced body size and altered metabolism, which will help it to survive in a harsh environment. However, if this "weather forecast" is inaccurate and the effects of prenatal conditions produce a mismatch with conditions after birth, developmental plasticity may have an adverse effect on survival and reproductive success (Bateson et al., 2004). For example, insulin resistance, a "thrifty" way of handling glucose, is more often found in those who have been born VLBW (Hovi, Andersson, Eriksson, Järvenpää, Strang-Karlsson, Mäkitie et al., 2007). It may pose an advantage in survival in situations of malnutrition, whereas it becomes maladaptive if undernutrition in the womb is followed by nutritional excess in later life due to its associations with increasing blood glucose and type 2 diabetes (Hales, Desai & Ozanne, 1997). Conversely, individuals with large bodies at birth may be particularly at risk in harsh environments, such as during a famine (Bateson, 2001).

1.3. Physical growth and health: empirical evidence

Subsequent chapters will present empirical results on how prenatal growth and growth after birth have been associated with behaviour and risk for disease. Studies relating to

somatic diseases will be briefly presented, after which studies on psychiatric outcomes and vulnerability factors for mental disorders will be discussed more thoroughly. The results of some selected studies focusing on extremes of prenatal growth (e.g., those born VLBW) will be presented, but cohort studies concerning the full range of the birth sizes will be focused on more systematically.

1.3.1. Developmental origins of somatic diseases

It has long been suggested that those born prematurely and very small are at increased risk for compromised somatic health later in life. In addition, a large body of evidence from the Helsinki Birth Cohort and other cohorts shows that lower birth weight, thinness, or shortness at birth predict coronary heart disease (Barker et al., 2005), stroke (Barker, 1997), hypertension, type 2 diabetes (Barker et al., 1993), and various risk factors associated with these and other non-communicable diseases. These relationships are inverse, linear, and are found even with body sizes within a normal range in at-term births.

Existing data from the Helsinki Birth Cohort also suggest that not only prenatal growth, but also growth during infancy and childhood influence disease risk in subsequent life. Children who developed coronary heart disease in adulthood were shorter in length and thinner in infancy up to two years of age, but gained weight more rapidly thereafter (Barker et al., 2005). Accordingly, lower birth weight coupled with a higher BMI in childhood or adulthood appears to be associated with increased risk for insulin resistance in children at the age of eight (Bavdekar, Yajnik, Fall, Bapat, Pandit, Deshpande et al., 1999), high blood pressure in adolescence (Adair & Cole, 2003), and metabolic syndrome in adulthood (Valdez, Athens, Thompson, Bradshaw & Stern, 1994).

1.3.2. Developmental origins of mental disorders

Very short gestational age, LBW, and severe IUGR have each been associated with increased risk for a variety of mental disorders (Cannon, Jones & Murray, 2002; Mick, Biederman, Prince, Fischer & Faraone, 2002; Gustafsson, Josefsson, Selling & Sydsjö, 2009). Although the predictive value of birth size has been less extensively investigated

in epidemiological cohort studies with respect to mental disorders, some evidence suggests inverse linear effects between birth size in full gestational range and several mental disorders and their psychological vulnerability factors (Kelly et al., 2001; Thompson et al., 2001; Wahlbeck et al., 2001). Moreover, some studies suggest that body size at birth may not necessarily extend to linear effects on psychiatric outcomes; rather such effects may be curvilinear, with those born either small or large being at higher risk for adversities (Nilsson, Nyberg & Ostergren, 2001).

1.3.2.1. Anxiety disorders and major depressive disorder (MDD)

Higher risk for anxiety disorders (Botting, Powls, Cooke & Marlow, 1997; Indredavik, Vik, Heyerdahl, Kulseng, Fayers & Brubakk, 2004) and MDD (Räikkönen et al., 2008) have been reported in those born VLBW. Moreover, those with MDD weighed less at birth than did controls (Preti, Cardascia, Zen, Pellizzari, Marchetti, Favaretto et al., 2000). Cohort studies have shown that being born at term, but SGA predicted increased risk for anxiety and adjustment disorder diagnosis derived from the hospital discharge register (HDR) in young adults (Gustafsson et al., 2009), and that LBW predicted MDD in girls even after adjusting for a wide range of plausible confounding factors (Costello, Worthman, Erkanli & Angold, 2007). However, not all studies have confirmed associations between being born small and the diagnosis of anxiety disorders (Breslau, Brown, DelDotto, Kumar, Ezhuthachan, Andreski et al., 1996) or MDD (Osler, Nordentoft & Andersen, 2005; Vasiliadis, Gilman & Buka, 2008).

Physical growth after birth has shown inconsistent associations with respect to anxiety disorders. Longitudinal studies of anxiety disorders in adulthood have shown no associations between anxiety and obesity measured in 9- to 16-year old children annually for eight years (Mustillo, Worthman, Erkanli, Keeler, Angold & Costello, 2003) or annual change in BMI from 14 to 33 years (Anderson, Cohen, Naumova & Must, 2006). However, some cross sectional studies have shown that obesity or higher BMI are associated with increased risk for anxiety disorders (Becker, Margraf, Turke, Soeder & Neumer, 2001; Anderson et al., 2006; Bjerkeset et al., 2008; Simon, Von Korff, Saunders, Miglioretti, Crane, van Belle et al., 2006), whereas other studies have failed to confirm such association (Lamertz, Jacobi, Yassouridis, Arnold & Henkel, 2002; Mustillo et al., 2003; John, Meyer, Rumpf & Hapke, 2005).

1.3.2.2. Schizophrenia

Case-control and cohort studies have shown that those with LBW are at increased risk for subsequent schizophrenia (Jones, Rantakallio, Hartikainen, Isohanni & Sipila, 1998; Cannon et al., 2002). In addition, people with schizophrenia tend to have lower birth weight and/or smaller head circumference at birth than do matched controls (Rifkin, Lewis, Jones, Toone & Murray, 1994; Kunugi, Takei, Murray, Saito & Nanko, 1996; Willinger, Heiden, Meszaros, Formann & Aschauer, 2001). Furthermore, birth weight, length at birth, and placental weight across the entire spectrum inversely predicted a risk for schizophrenia diagnosis derived from the HDR in a Helsinki Birth Cohort 1924–1933 (Wahlbeck et al., 2001). In that study, every 1-kg decrease in birth weight, 1-cm decrease in length at birth, and 100-g decrease in placental weight associated with 1.48, 1.12, and 1.22 times higher odds for schizophrenia, respectively. Finally, studies of twins discordant for schizophrenia have replicated these findings and have showed that foetal growth restriction in terms of birth weight and head circumference was associated with a risk for schizophrenia independently of familial factors (Nilsson, Stalberg, Lichtenstein, Cnattingius, Olausson & Hultman, 2005). However, not all studies have found an association between birth weight and later schizophrenia. For example, a large Swedish HDR study of 720 000 partcipants found no evidence of an association between either birthweight or ponderal index and schizophrenia (Gunnell et al., 2005). Rather, they found that short birth length was associated with an increased risk for schizophrenia.

Reduced physical growth after birth may also be linked to a risk for schizophrenia. Reduced linear growth from birth to 2.5 years was reported in women with schizophrenia in adulthood (Perrin et al., 2007), and Wahlbeck et al. (2001) reported that those who developed schizophrenia as adults were leaner throughout their childhood. In another study, shorter stature and smaller BMI in males at the age of 18 years were associated with increased risk for schizophrenia some years later (Gunnell et al., 2005).

1.3.2.3. Attention-Deficit Hyperactivity Disorder (ADHD)

A few case-control studies have linked VLBW or LBW with increased risk for diagnosis of ADHD (Breslau et al., 1996; Botting et al., 1997; Mick et al., 2002). Mick et al., (2002) concluded that if this association was causal, 13.8% of all ADHD cases could be attributed to LBW, and that after adjusting for confounders, ADHD cases were three times more likely to have been born LBW than were non-ADHD controls. Associations of birth weight with ADHD have also been found within twin-pairs, suggesting that the effect is independent of genetic influences (Hultman, Torrang, Tuvblad, Cnattingius, Larsson & Lichtenstein, 2007). Moreover, growth after birth has also been linked to ADHD. Spencer et al., (1998) found that ADHD may be associated with temporary deficits in height gain through mid-adolescence that may normalise by late adolescence.

1.3.3. Developmental origins of psychological vulnerability factors for mental disorders

In some cases, full-scale mental disorders such as MDD, anxiety disorders, schizophrenia, and ADHD can be predicted by temperamental/personality traits or subclinical psychological symptoms. For example, self-reported psychotic symptoms (Poulton, Caspi, Moffitt, Cannon, Murray & Harrington, 2000) as well as schizotypal traits (Chapman, Chapman, Kwapil, Eckblad & Zinser, 1994; Gooding, Tallent & Matts, 2005) predicted subsequent psychotic illness (Chapman et al., 1994; Poulton et al., 2000; Gooding et al., 2005) and MDD (Gooding et al., 2005). It has also been shown that these symptoms are relatively common. In a general population sample of 7076 men and women, 17.5% of the participants reported experiences resembling the clinical psychosis concept (van Os, Hanssen, Bijl & Ravelli, 2000). Some have therefore suggested that psychotic symptoms may have predictive value and lie on a continuum with schizophrenia-spectrum disorder at one end (reviewed in van Os, Linscott, Myin-Germeys, Delespaul & Krabbendam, 2009). In a similar manner, higher levels of behavioural dispositions that are normally distributed in the general population, such as trait anxiety (Chambers, Power & Durham, 2004; Weems, Pina, Costa, Watts, Taylor & Cannon, 2007) and the temperamental trait of harm avoidance

(Ono, Ando, Onoda, Yoshimura, Momose, Hirano et al., 2002; Cloninger, Svrakic & Przybeck, 2006), may predict anxiety disorders (Chambers et al., 2004; Weems et al., 2007) or depression (Ono et al., 2002; Cloninger et al., 2006) in later life. Likewise, dimensional measures of inattentiveness and hyperactivity-impulsivity have been shown to predict ADHD diagnosis (Power, Doherty, Panichelli-Mindel, Karustis, Eiraldi, Anastopoulos et al., 1998) and subsequent disruptive behaviours (Fergusson & Horwood, 1995). Furthermore, diagnostic systems have been critisized on the basis of arbitrary thresholds above which the clinical manifestations should be regarded as disorders (Maj, 1998).

Therefore, it seems important not only to study physical growth as an aetiological factor of somatic and mental disorders, but also as a determinant of psychological vulnerability factors for mental disorders. This is especially important since twin studies have shown that the consequences of developmental programming are not be limited to disorders, but may extend to a wide range of temperamental or behavioural dispositions independently of genetic effects (van Os et al., 2001). Thus the next chapters will present associations between physical growth and psychological vulnerability factors for mental disorders such as temperaments, personality traits, and psychological symptoms.

1.3.3.1. Temperament/personality

Several studies examining the associations between being born extremely small and subsequent temperament/personality have been conducted. A recent Helsinki Study of VLBW adults has shown that in young adulthood, those born VLBW scored significantly higher in conscientiousness and agreeableness, but lower in openness to experience (Pesonen et al., 2008) and behavioural activation system-related fun seeking (Pyhälä, Räikkönen, Pesonen, Heinonen, Hovi, Eriksson et al., 2009). In line with these findings, VLBW adults reported lower scores on measures of risk-taking and antisocial behaviour than those of a matched control group (Hack, Flannery, Schluchter, Cartar, Borawski & Klein, 2002). Similarly, Schmidt, Miskovic et al. (2008) recently showed that ELBW adults were more cautious, shy, and risk aversive and less extraverted than their normal birth weight counterparts. Moreover, Allin, Rooney et al. (2006) found that

adults born very preterm reported significantly higher scores on neuroticism and lie (i.e., social desirability) scales, but lower extraversion scores.

Only a few cohort studies with birth sizes across the whole range of variation have explored how prenatal growth associates with temperament and/or personality in later life. In such studies, findings have pointed to a pattern similar to that in studies with extremes in birth size. Those Finnish children of the GLAKU project who were born SGA showed more pronounced negative reactivity in infancy (Pesonen et al., 2006b). In the same cohort, birth size was inversely linearly associated with characteristics of negative affectivity in children aged five to six years (Pesonen et al., 2006a). Pesonen et al. (2006a) showed that every one-standard deviation decrease in the ponderal index associated with a 0.14 standard deviation increase in negative affectivity. A comparable association was also reported in children five years of age (Hawdon, Hey, Kolvin & Fundudis, 1990). Moreover, smaller birth size predicted lower effortful control at the age of seven to nine years (Schlotz, Jones, Godfrey & Phillips, 2008). Since none of these studies assessed personality/temperament in adults, whether such associations extend to older populations remains unknown.

Empirical evidence examining whether prenatal growth is linked to variation in schizotypal personality traits is almost non-existent. In one study of patients with schizophrenia or affective psychosis an inverse association was reported between birth weight and retrospectively reported schizoid and schizotypal personality traits in childhood and adolescence (Foerster, Lewis, Owen & Murray, 1991).

Physical growth after birth may also associate with temperament. Some studies have suggested that failure-to-thrive infants are often rated as temperamentally more difficult than healthy control infants (Bithoney & Newberger, 1987; Wolke et al., 1990). Moreover, Darlington & Wright (2006) recently showed in 75 eight-week-old infants that fearful temperament, defined as a rejection of new objects or people, was predicted by slow weight gain from birth to eight weeks, whereas distress to limitations, which refers to irritable behaviour in situations in which an infant might have to wait for food or be placed in a confining place, was related to fast weight gain.

1.3.3.2. Symptoms of anxiety or depression

Some studies have suggested that ELBW, VLBW, and prematurity combined with SGA associate with more pronounced parental-reported internalising problems in girls (Hack, Youngstrom, Cartar, Schluchter, Taylor, Flannery et al., 2004), symptoms of anxiety/withdrawal at the age of seven to eight (Horwood, Mogridge & Darlow, 1998), symptoms of depression in adolescence (Saigal, Pinelli, Hoult, Kim & Boyle, 2003), and symptoms of depression in Finnish young adults participating in the Helsinki Study of VLBW adults (Räikkönen et al., 2008). However, not all studies have confirmed associations between being born small and symptoms of anxiety (Saigal et al., 2003) or depression (Elgen, Sommerfelt & Markestad, 2002; Cooke, 2004).

Some cohort studies with full variation of birth sizes have investigated the association between body size at birth and subsequent symptoms of anxiety. Berle, Mykletun et al. (2006) reported, in a cohort of 7806 Norwegians, that being born small for gestational age (i.e., below the 10^{th} percentile in birth weight for gestational age) increased the risk for scoring high on the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS) at the age of 25. In line with these findings, Gustafsson et al., (2009) recently showed that those born SGA were hospitalised more often before age 23 due to anxiety disorders than were those born AGA. Moreover, in a cohort of 3344 Chinese children, LBW predicted elevated levels of anxious/depressed symptoms between the ages of 6 and 16 (Liu, Sun, Neiderhiser, Uchiyama & Okawa, 2001). However, in a sample of 580 adults aged 18 to 25 years, Mallen, Mottram et al. (2008) found that HADS anxiety scores were no higher in those born LBW than in those born with normal birth weight. No studies have shown whether such associations between birth size and anxiety persist into late adulthood, neither have studies examined whether birth size linearly predicts anxiety in later life.

Several cohort studies have, however, investigated linear associations between birth size and symptoms of depression. Some of these studies have shown linear associations between smaller birth weight and symptoms of depression in men and women (Cheung, Khoo, Karlberg & Machin, 2002; Gale & Martyn, 2004), in men (Thompson et al., 2001), or in women (Alati, Lawlor, Mamun, Williams, Najman, O'Callaghan et al., 2007). Thompson et al. (2001) demonstrated that those born below 3 kg, between 3.0 and 3.4 kg, or 3.4 and 3.9 kg were, respectively, at a 3.5, 3.2, and 2.8 times higher risk

for depression, as defined by the Geriatric Depression Scale or Geriatric Mental State interview at the age of 68, than were men born > 3.9 kg. Not all studies have confirmed this association, however. For example, among the Helsinki Birth Cohort 1934-1944, no linear associations were found between birth weight and symptoms of depression, although those born LBW exhibited significantly more symptoms of depression than did the rest of the sample (Räikkönen et al., 2007). And a recent study by Herva, Pouta et al. (2008) showed more depressive symptoms in women with high birth weight or ponderal index.

Furthermore, the study found that not only smaller birth weight, but also smaller weight gain before age 7 predicted psychological distress at the age of 42 (Cheung et al., 2002). The results also suggest that the impact of smaller size at birth is partly compensated by a higher weight gain in childhood (catch-up growth). It is difficult, however, to draw conclusions on studies associating physical growth after birth with symptoms of anxiety due to variations in methodology and inconsistencies in results. Failure to thrive in infancy was not predictive of symptoms of anxiety at the age of 12 (Drewett, Corbett & Wright, 2006). However, cross-sectional community-based studies have shown that obesity in adulthood was related to low levels of anxiety symptoms (Crisp & McGuiness, 1976; Crisp et al., 1980), and that shorter stature (Bjerkeset et al., 2008) and smaller weight for height (Stewart & Brook, 1983) in adulthood were related to high levels of anxiety symptoms.

1.3.3.3. Inattentiveness and hyperactivity

Several previous studies focusing on highly selected groups at the small extreme of the birth size continuum have associated small birth size with symptoms of ADHD (Horwood et al., 1998; Saigal et al., 2003) and attention problems in childhood (Elgen et al., 2002), adolescence (O'Keeffe, O'Callaghan, Williams, Najman & Bor, 2003; Indredavik et al., 2004) and in young adulthood (Liu et al., 2001; Hack, 2004). One population-based cohort study examined associations between the whole range of birth size and symptoms of ADHD. In that study, 5181 English children aged 4-15 years showed a linear association between lower birth weight and hyperactivity in boys (Kelly et al., 2001). In their study, every one-kilogram decrease in birth weight associated with 1.25 times higher odds for high scores on the hyperactivity subscale in the Strengths and

Difficulties Questionnaire in boys. Whether the effects of small birth size on ADHD persist into adulthood remains unclear, but Strang-Karlsson, Räikkönen et al., (2008) have shown that this may be the case at least in the SGA subgroup of those born VLBW.

Not all the studies have confirmed associations between being born small and symptoms of ADHD. For example, Sommerfelt, Andersson et al. (2001) reported that SGA and AGA groups showed no differences at the age of five in a wide range of behavioural problems, including inattentiveness and hyperactivity.

To conclude, the majority of – but not all – studies focusing on the low extreme of the birth size continuum have shown that being born small increased the risk for mental disorders and for their psychological vulnerability factors later in life. Whether these associations exist in the full range of birth size remains uncertain. Whether growth after birth associates with mental disorders and their psychological vulnerability factors have also been investigated to some extent, but these studies show inconsistent results.

1.4. Aims of the present study

The general aim of this thesis was to study whether prenatal physical growth and physical growth after birth across the full variation was associated with subsequent psychological vulnerability factors for mental disorders at various developmental stages. To achieve this aim, the following research questions were addressed in the four separate studies constituting this thesis.

i) Whether smaller body size at birth in those born full-term is associated with temperamental characteristics in late adulthood? (Study I)

ii) Whether smaller body size at birth and in later life predicts higher levels of trait anxiety in late adulthood? (Study II)

iii) Whether smaller body size at birth, small placental size, or both predict more pronounced schizotypal traits in adulthood? (Study III)

iv) Whether smaller body size at birth predicts more pronounced symptoms of ADHD in children aged five to six years who were born healthy and full-term? (Study IV)

Based on the previous literature, we hypothesised that birth size across the full variation would inversely linearly predict psychological vulnerability factors for mental disorders in later life.

2. METHODS

2.1. Outline of the study and samples

This thesis consists of four studies conducted using three datasets:

1) The Helsinki Birth Cohort 1934-1944 (Study I and Study II),

2) Northern Finland Birth Cohort 1966 (Study III), and

3) The Glaku project (Study IV).

All these samples contain comparable measures of neonatal characteristics. These characteristics are presented first, followed by other details of these epidemiological samples.

2.2. Neonatal characteristics

In all samples, data on each newborn's date of birth, weight (g), length (cm), placental weight (g), and head circumference (cm) were extracted from the birth records. Ponderal index (kg/m^3) and BMI (kg/m^2), measures of thinness, and head circumference-to-length ratio were calculated from these measurements. Length of gestation was estimated based on either the date of the mother's last menstrual period (Studies I, II, and III) or on the foetal ultrasound before 20 weeks of gestation (Study IV).

2.3. Helsinki Birth Cohort 1934-1944 (Study I and Study II)

2.3.1. Participants

The cohort comprised men and women who were born at the Helsinki University Central Hospital between 1934 and 1944, attended child welfare clinics in the city of Helsinki, and were still resident in Finland in 1971. Altogether 10 519 men and women with birth and child welfare records were identified. Of these, 8760 (83%) were alive and living in Finland in 1971, when a unique personal identification number was

allocated to all persons living in Finland. Between 2001 and 2004, at an average age of 61.5 years (standard deviation [SD] = 2.9, range: 56.7-69.8), a random sample of 2003 women (n = 1075) and men (n = 928) participated in a clinical examination. In 2004, at an average age of 63.4 years (SD = 2.9, range: 59.7-70.7), a psychological survey questionnaire was mailed to those in the random sample who were still traceable (n = 1975). Of these, a total of 1704 women (n = 951) and men (n = 753) returned the questionnaires. Of these, 1369 women (n = 755) and men (n = 614) were born full term (between 37 and 42 weeks of gestation) and had valid data in the temperament questionnaire embedded in the psychological survey. This group formed the sample of Study I (see Table 1 for representativeness of the sample).

The sample of Study II was drawn from those 1698 women (n = 949) and men (n = 749) who returned the psychological survey questionnaires and completed the questionnaire pertaining to trait anxiety (see Table 1 for representativeness of the sample).

Table 1. Sample sizes and representativeness of the final samples.

	Study cohort	Representative cohort	Final sample	Representativeness of the final samples
Study I	Helsinki Birth Cohort 1934-1944	N=2003	n=1369 (68.3%)	More often women and better educated. No differences in terms of body size at birth, length of gestation, childhood SES, age, or BMI in adulthood or in maternal age or BMI in late pregnancy.
Study II	Helsinki Birth Cohort 1934-1944	N=2003	n=1698 (84.8%)	More often women, better educated, and taller. No differences in terms of body size at birth, length of gestation, childhood SES, age, or BMI in adulthood, or in maternal age or BMI in late pregnancy.
Study III	Northern Finland Birth Cohort 1966	N=8463	n=4976 (58.8%)	More often women, higher family SES in early life, pregnancy more often desired, mothers smoked more seldom and were less depressed during pregnancy, had a higher gestational age, were longer and heavier at birth, and had a greater head circumference at 12 months.
Study IV	Glaku project	N=1049	n=267 (25.5%)	Mothers were older, had longer pregnancies, smoked less frequently, and had better incomes. No differences in terms of maternal pre-pregnancy BMI, placental weight, the infant's gender, one-minute Apgar score, weight, length, ponderal index, head circumference, and head circumference-to-length ratio at birth.

2.3.2. Measures of temperament and trait anxiety

Adult temperament, for Study I, was measured with the 98-item Tridimensional Personality Questionnaire (TPQ; Cloninger, 1987), which is based on Cloninger's psychobiological model of temperament. The TPQ is a self-reporting instrument with a bivariate response model (true/false) that measures the traits of novelty seeking (NS), harm avoidance (HA), or reward dependence (RD) (Cloninger, 1987; Cloninger, Przybeck & Svrakic, 1991). The internal consistency (Cronbach's alpha) of the scales in this study ranged from 0.70 to 0.89. The scales were intercorrelated as follows: NS correlated negatively with HA (Pearson $r = -0.22$, $p < 0.001$) and positively with RD

(Pearson r = 0.17, p < 0.001), and HA correlated negatively with RD (Pearson r = -0.08, p < 0.003). NS, HA, and RD each comprise four subscales (Cloninger, 1987).

Trait anxiety, for Study II, was assessed with trait items of the Spielberger State Trait Anxiety Inventory (STAI-T; Spielberger, Gorsuch, Lushene, Vagg & Jacobs (1983)). The STAI-T consists of 20 items touching on propensity to experience anxiety and is among the most widely-used self-reporting anxiety questionnaires. Previous studies of the STAI-T have demonstrated high internal consistency (Spielberger et al., 1983) and predictive validity (Chambers et al., 2004; Weems et al., 2007). Each item of the STAI-T is rated on a four-point intensity scale. Half of the items are negatively worded (sample item: 'I feel nervous and restless') and half are positively worded (sample item: 'I feel happy'). Although the STAI-T scale was developed as a unidimensional measure, several factor analytic studies have found an underlying two-factor structure with positively and negatively worded items loading on separate factors (Vagg, Spielberger & Hearn, 1980; Kabacoff, Segal, Hersen & Van Hasselt, 1997). For an anxiety sum score (STAI-T total score), positively worded items were reversed, and all items were summed. Moreover, subscales from negatively worded items (neg-STAI-T) and positively worded items (pos-STAI-T) were designed to respect this two-dimensionality. High scores on the STAI-T total score and the neg-STAI-T, and low scores on the pos-STAI-T, indicate elevated trait anxiety. In this study, internal consistency (Cronbach's alpha) for the scales ranged from 0.81 to 0.90.

2.3.3. Other measures

For Study I and Study II, adult height (cm), weight (kg), educational attainment (23% reported having a university degree, 27% a high school diploma, 19% vocational school training, and 31% an elementary school education or less), and history of cardiovascular disease (i.e., self-reported physician-diagnosed coronary heart disease, stroke, and/or use of medication for cardiovascular disease; positive history: 8.9%) were measured in conjunction with a clinical examination.

The participants' SES in childhood was defined by the father's occupational status. Data were derived from the participants' school records and, in the case of missing values (7.0 %), were derived from child welfare clinic or birth records. The fathers'

occupations were classified into three groups according to the Classification of Socio-Economic Groups (1989): upper-level employees (e.g., physicians, priests, bank managers)(high SES), lower-level employees (e.g., civil servants, foremen, policeofficers)(intermediate SES), and manual workers (e.g., industrial or construction workers, waiters, and cleaners)(low SES). On this basis, 12%, 23%, and 65% of the participants belonged to the category of upper- and lower-level employees and manual labourers, respectively. Students and pensioners and, owing to the heterogeneity of the category, employers and the self-employed (n = 50), were removed from the analyses.

For Study II, data on weight (kg) and height (cm) at ages 1 month to 11 years were estimated from child welfare clinic and school records as previously described (Barker et al., 2005), and BMI was calculated. Moreover, data on breastfeeding (yes: 83.9%, no: 16.1%) were extracted from child welfare clinic records.

2.4. Northern Finland Birth Cohort 1966 (Study III)

2.4.1. Participants

Births with deliveries in 1966 in Northern Finland were eligible (n = 12 058 live births) (Rantakallio, 1988). Women were recruited through maternity health centres, and about 80% visited these centres for the first time by the 16th gestational week. In 1997, members of the original cohort living in the original target or Helsinki area were invited to a clinical examination (n = 8463 eligible; 72.7% of those living). Questionnaires were given to those participating in the examination (N = 6033). Of those participating in the clinical examination, 84.7% (N = 5112) returned the questionnaire on schizotypal traits.

The analytic sample of this study comprises 4976 (58.8% of those eligible: 2233 males and 2743 females; mean age: 31.2 years; SD: 0.36) participants who provided adequate data on schizotypal traits, were not diagnosed with schizophrenia according to DSM-III-R criteria after re-checking all psychiatric diagnoses appearing in the National Finnish Hospital Discharge Register (Isohanni, Mäkikyrö, Moring, Räsänen, Hakko, Partanen et al., 1997), and scored below three on the validity scale (the Infrequency Scale by Chapman, Chapman & Raulin (1976)), which was incorporated into the questionnaire (see Table 1 for representativeness of the sample).

2.4.2. Measures of schizotypal traits

In conjunction with the 31-year follow-up examination, the participants received a questionnaire on schizotypal traits. Positive schizotypal traits were measured with the Perceptual Aberration Scale (PAS; Chapman, Chapman & Raulin (1978)) as suggested in the literature (Vollema & Van den Bosch, 1995). The PAS explores the distorted perception of one's body or of other objects with 35 items such as 'I have sometimes felt that some parts of my body no longer belong to me' and 'Sometimes when I look at things like tables and chairs, they seem strange'. The PAS has successfully identified individuals who report psychotic-like experiences, schizotypal symptoms, and social withdrawal during structured diagnostic interviews (Chapman, Edell & Chapman, 1980), and, together with the Magical Ideation scale, predicted increased risk for DSM III-R psychoses, schizotypal symptoms, and psychotic-like experiences in a ten-year follow-up (Chapman et al., 1994), as well as diagnoses of depression in a five-year follow-up (Gooding et al., 2005). The internal consistency of the PAS in this study was high (Cronbach's alpha: 0.83).

Anhedonia, a decreased capacity to experience pleasure, was measured with revised versions of the 61-item Physical Anhedonia Scale (PhAS) and the 40-item Social Anhedonia Scale (SAS; Chapman et al., (1976); Revised version by Eckblad, Chapman, Chapman & Mishlove (1982)) which reflect negative schizotypal traits (Vollema & Van den Bosch, 1995). These true-false self-reporting measures provide indices of the pleasure derived from physical (sample item of the PhAS: 'One food tastes as good as another to me') and social-interpersonal sources (sample item of the SAS: 'I attach very little importance to having close friends'), respectively. Previous studies have shown that people with schizophrenia score higher on the PhAS and SAS scales than do control subjects (Chapman et al., 1976). Furthermore, subjects scoring exceedingly high on the PhAS exhibit more schizotypal symptoms, greater social isolation, and lower heterosexual interest and activity than do control subjects (Chapman et al., 1980). Moreover, three longitudinal studies have shown that higher SAS scores among college students have been associated with increased risk for psychosis, more pronounced schizotypal personality, diagnoses of schizophrenia-spectrum disorder or any combination of these (Chapman et al., 1994; Kwapil, 1998; Gooding et al., 2005). The

internal consistency of the PhAS and the SAS in this study was high (Cronbach's alphas: 0.84 and 0.82, respectively).

2.4.3. Other measures

The course of pregnancy was prospectively recorded in maternity records and transferred by midwives onto the study forms (for a detailed description of the procedures, see Rantakallio (1988)). Mothers reported their smoking during pregnancy (yes/no), mood (normal/depressed), place of residence (urban/rural), birth order, and desirability of pregnancy (yes/no/pregnancy wanted later) by answering a questionnaire during their 24^{th} to 28^{th} gestational week at the maternity health centres. Moreover, childhood family SES was defined as mother-reported the spouse's occupation (and mother's own occupation in single mothers), which was classified into four groups: SES class I; upper-level employees/employers (highest prestige and usually requiring an academic education (e.g., dentists, teachers)), SES class II; lower-level employees (professionals with moderate prestige and usually requiring less education than in class I (e.g., clerks and stewards)), SES classes III+IV; no occupation or manual laborers (skilled and unskilled workers (e.g., night watchmen and office boys)), and farmers. Data were missing for 3.0% of the subjects (n = 150), so the mother's occupation was used instead.

Data on birth (99% occurred in hospitals) and on the newborn at the time of delivery were obtained from the hospital records. Children were considered to have incurred perinatal brain damage if they had an Apgar score of zero at one minute or of less than five at 15 min after birth, convulsions during the neonatal period, or a diagnosis of asphyxia, brain injury, or intraventricular haemorrhage, but showed no central nervous system (CNS) malformation, chromosomal aberrations, or hereditary CNS degeneration (for more details, see Jones et al., (1998)). The season of birth was classified into four groups: Summer birth (June to August), Autumn birth (September to November), Winter birth (December to February), and Spring birth (March to May). Head circumference (cm) was measured at the welfare centres at one year of age, and data on CNS viral infections up to the age of 14 were collected mainly from the admissions records of four children's hospitals, the National Finnish Hospital Discharge Register,

and the records of neurological outpatient clinics (for more details, see Rantakallio, Jones, Moring & Von Wendt (1997)).

Adulthood data from the 31-year follow-up were collected with a questionnaire in 1997. Each participant's SES was based on occupation and occupational status in 1997 with the following categorisation: upper white collar, lower white collar, entrepreneurs, manual labourers, farmers, students/pensioners/ungrouped SES, and the long-term unemployed. Adulthood BMI (kg/m^2) was calculated and categorised (< 18.5 low weight; 18.5-25: normal weight; > 25: overweight).

2.5. The Glaku project (Study IV)

2.5.1. Participants

The initial sample formed a consecutive series of mothers and their singleton infants who were born healthy in one of the main maternity hospitals in the Helsinki area between March and November 1998 (N = 1049).

A psychological follow-up survey was sent to the sample in 2003; 906 participants' addresses were traceable through the Finnish Population Register Centre. Of those contacted, 447 mothers and 273 fathers returned the follow-up questionnaire. Ratings of symptoms of ADHD were simultaneously available for 267 biological mother-father-child triads. These triads formed the sample analysed in this study (see Table 1 for representativeness of the sample).

The children were born healthy at term (Mean [M] = 39.8 weeks, SD = 1.2, range = 37-42), and at the time of the follow-up were aged 5.5 years on average (M = 65.8 months, SD = 2.9, range = 60-72); 54% of the participants were girls.

2.5.2. Measure of symptoms of ADHD

Symptoms of ADHD were rated by the mother and the father of the child on the ADHD Rating Scale (DuPaul, 1991) at the age of five to six years. The scale consists of 14 items directly adapted from the ADHD symptoms list in the Diagnostic and Statistical Manual of Mental Disorders (3^{rd} edition, revised [DSM-III-R] (American Psychiatric Association, 1987). Each item is rated on a four-point scale ranging from 'Does not

describe my child at all' (0) to 'Describes my child very well' (3). The items are then summed, with a higher total score indicating that ADHD symptoms are more descriptive of the child's behaviour. A more recent version of the scale corresponding to the Diagnostic and Statistical Manual of Mental Disorders (4th edition) [DSM-IV] does exist (ADHD-IV Rating Scale) (Dupaul, Anastopoulos, Power, Reid, Ikeda & McGoey, 1998), but this version contains several items pertaining to behaviour at school. Because the obligatory school age in Finland is seven, school-related questions related to children aged five to six are inapplicable, so the DSM-III-R -based scale was used to retain comparability of the reliability and validity with other studies.

Previous studies using exploratory factor analysis have revealed two factors, namely Inattention-hyperactivity and Impulsivity-hyperactivity (DuPaul, 1991), which correspond to the DSM-IV categorisation into two subtypes of ADHD (American Psychiatric Association, 1994). Therefore, in addition to the total score, two subscale scores representing these two factors were calculated. Previous studies have demonstrated adequate levels of test-retest reliability, internal consistency, and criterion validity for the two subscales as well as for the total rating score (DuPaul, 1991). In the current study, the reliabilities (Cronbach's alpha) for the total score and for the two subscales were 0.90, 0.85, and 0.82 for the mothers, and 0.89, 0.85, and 0.84 for the fathers, respectively. Intra-class correlations between the mothers and the fathers, and ratings for the total score as well as for the Inattention-hyperactivity and Impulsivity-hyperactivity subscale scores were 0.72, 0.69, and 0.72, respectively.

2.5.3. Other measures

Data on maternal alcohol use (M = 0.25 standard alcohol units/week, SD = 0.5, Median, 25, and 75 percentiles = 0.00 standard alcohol units/week, range 0-3) and tobacco use (yes/no; 9% reported smoking during pregnancy), maternal pre-pregnancy BMI (M = 22.8 kg/m^2, SD = 3.5, Range = 16.5-35.6), the mother's age at the time of delivery (M = 30.4 years, SD = 4.6, Range = 19-43), parity (60% were nulliparous), and, as an index of SES of the family, the monthly gross income of the family (22.1% ≤ 3000 €/month; 40.4% 3001 to 5000 €/month; 37.2% > 5000 €/month) were collected via a questionnaire administered to the mothers while still in the maternity ward. In conjunction with the psychological survey conducted in 2003, maternal reports of the

weight (kg) and length (cm) of their children,as well as their children's BMI (M = 15.5 kg/m^2, SD = 1.5, Range = 11.3-23.0) were calculated.

2.6. Statistical analyses

Multiple linear regression analyses were used to test whether body size at birth or growth after birth associates with temperament (Study I), trait anxiety (Study II), schizotypal traits (Study III), and symptoms of ADHD (Study IV). In all studies, measures of birth size and growth after birth served as continuous variables to test for linear associations. Moreover, in some studies, additional analyses were conducted.

In addition, in Study I, curvilinear associations between birth size and temperamental traits were explored. Curvilinear effects were tested in a model, which included the squared term of the variable centred around the grand mean, together with a non-squared, linear, variable. To test whether the associations are particularly characteristic of those born with low birth weight (≤ 2.5 kg), individuals belonging to this group were contrasted with the rest of the sample (> 2.5 g). Since there are no generally accepted cut-offs for short stature and small head circumference at birth, those who belonged to the smallest 5^{th} percentile in length (≤ 47.5 cm) and head circumference (< 33 cm) at birth were contrasted with the rest of the sample (> 47.5 cm in length or ≥ 33 cm in head circumference).

Study I also tested whether SES in childhood modified any potential linear or curvilinear associations between body size at birth (treated as continuous variables) with NS, HA, and RD. The main effects and the cross-product terms of childhood SES × body size at birth variables were entered into regression equations with continuous variables centred around the grand mean in order to account for multicollinearity.

In Study II, the primary analyses of associations between birth size and trait anxiety were expanded by forming uncorrelated composite measures (components) derived through factor analysis to characterise the prenatal pattern of growth. Two principal components, namely 'overall body size at birth and gestational age' and 'thinness at birth', were derived. These principal components resemble those found by Joglekar et al., (2007) and served as predictors of trait anxiety in adulthood in linear regression models.

In addition to the neonatal characteristics, Study II examined whether growth after birth up to 11 years of age and in adulthood is linked with trait anxiety. For the analyses of growth after birth, the focus was on measurements of weight, height, and BMI conducted at six months, 1, 2, 7, 11 and 63 years to represent periods of infancy (to 2 years), childhood (to 11 years) and adulthood (to 63 years). Linear regression was applied to test the association between size at different ages ("unconditional growth") and trait anxiety. Moreover, growth was analysed with respect to previous body size ("conditional growth"). Conditional growth variables were standardised residuals from linear regression models of height, weight and BMI (in separate models). Body size at each time point was regressed on corresponding measures at all earlier time points, creating completely uncorrelated residuals reflecting growth conditional on previous history (Barker et al., 2005).

In Study III, the primary analyses of testing associations between birth size and schizotypal traits were extended by analysing with multiple linear regression analyses whether placental size was predictive. In addition, we tested whether the associations were different between men and women and whether excluding premature participants influenced the associations.

Furthermore, in all the studies, we tested whether the associations between birth size and behavioural traits were explained by some other factors in early life or adulthood. In Study I, the full model was adjusted for gender, age, and length of gestation, as well as for adulthood BMI and education. Furthermore, in order to account for the potential confounding effect of depression on the associations studied, the analyses were re-run by controlling for physician-diagnosed depression as self-reported in the clinical examination. In Study II, the models were adjusted for gender, age at testing, socioeconomic position in childhood and in adulthood (father's occupation in childhood and level of education attained in adulthood), mother's age at delivery, parity, and breastfeeding (in the analyses concerning neonatal characteristics, breastfeeding was excluded). Moreover, adult body size (adult BMI in the analyses of weight and BMI, and adult height in the analyses of length/height) and history of cardiovascular disease was taken into account. In Study III, models controlled for gestational age, birth order, twin birth, season of birth, perinatal brain damage, maternal smoking during pregnancy, maternal antenatal depression, desirability of pregnancy, place of residence, family SES

in early childhood, and CNS viral infections in childhood as well as SES and BMI in adulthood. Finally, in Study IV, length of gestation, maternal alcohol and tobacco use during pregnancy, maternal pre-pregnancy BMI, the mother's age at the time of delivery, parity, the family's monthly gross income, the child's BMI at five to six years of age and gender were statistically controlled for in the analyses.

3. RESULTS

3.1. Is smaller body size at birth in those born full-term associated with temperamental characteristics in late adulthood? (Study I)

Multiple linear regression analyses showed that there were no statistically significant linear associations between body size at birth and novelty seeking (NS), harm avoidance (HA), or reward dependence (RD) after adjusting for gender, age, and length of gestation (p-values > 0.38). As illustrated in Figure 5, curvilinear, reverse J-shaped associations were found between weight (unstandardised beta coefficient [B] = 0.08, $p < 0.01$) and length (B = 0.06, $p < 0.05$) at birth and HA in adulthood. The highest HA scores were characteristic of those with low birth weight (≤ 2.5 kg; B = 3.3; 95% confidence interval [CI] = 0.9 to 5.7; P = 0.007) or of those who belonged to the smallest 5^{th} percentile in length at birth (≤ 47.5 cm; B = 2.5; 95% CI = 1.0 to 3.9; P = 0.001). The subscales of HA revealed that these associations were largely attributable to high scores in fear of uncertainty (weight: B = 0.55, 95 % CI = 0.25 to 0.84, $p < 0.001$; length: B = 0.02, 95% CI = 0.01 to 0.04, $p < 0.01$) and in shyness with strangers (weight: B = 0.44, 95% CI = 0.08 to 0.80, p = 0.02). Further, those who belonged to the smallest 5^{th} percentile in head circumference (< 33 cm) at birth scored higher in HA in late adulthood than did those who had greater head circumferences at birth (B = 2.5; 95% CI = 0.55 to 4.3; p = 0.01).

Next, we tested whether any of the hypothesised associations between smaller body size at birth with adulthood NS, HA, and RD were confined to lower childhood SES groups. The results showed that curvilinear associations between measures of body size at birth and HA were not moderated by childhood SES (p-values for interactions >

0.26), whereas interactions between childhood SES and weight and length at birth were significant when the latter were treated as linear, continuous variables (childhood SES × birth weight: B = -1.1, 95% CI = -2.2 to -0.03, p = 0.04; childhood SES × birth length: B = -0.34, 95% CI = -0.63 to -0.05, p = 0.02). Moreover, those participants belonging to the lowest SES group in childhood had higher HA scores regardless of body size at birth ($P < 0.05$). HA scores were just as high among those belonging to the high SES group in childhood if their body size at birth was small. In this group, HA scores inversely correlated with body size at birth, with the lowest HA scores characterising those heavier at birth (birth weight: B = -2.6, 95% CI = -4.8 to -0.34, p = 0.02; birth length: B = -0.81, 95% CI = -1.4 to -0.20, p = 0.009). In other words, larger body size at birth did not protect from higher HA scores among those who belonged to the lowest SES group. Neither was high SES sufficient to protect from higher HA scores if the body size at birth was small. These findings were not confounded by gender, length of gestation, age, adulthood BMI, education, or self-reported physician-diagnosed depression.

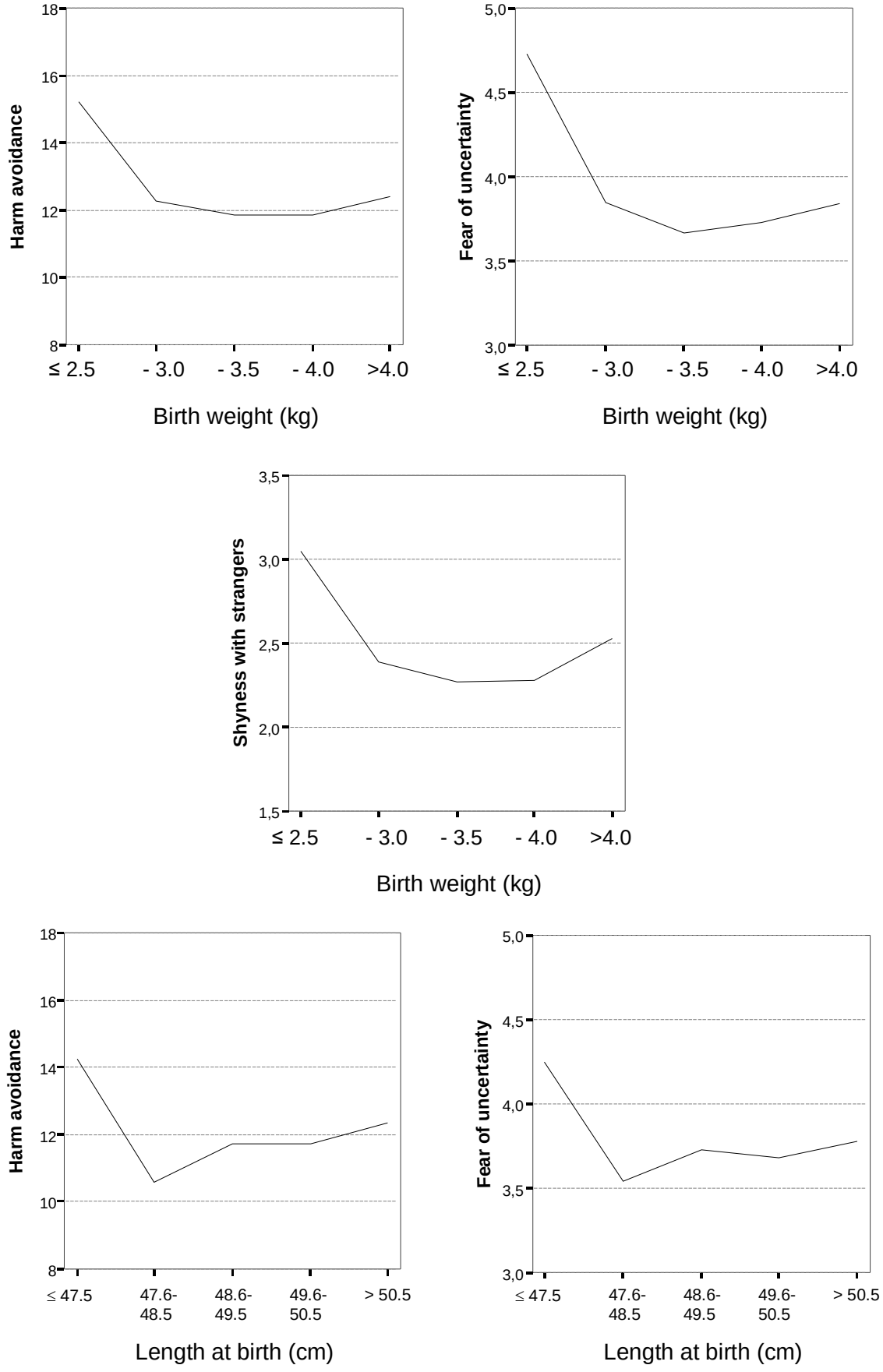

Figure 5. Harm avoidance total score and its subscales 'fear of uncertainty' and 'shyness with strangers' in late adulthood according to birth weight and birth length after adjusting for gender, age, and length of gestation.

3.2. Does smaller body size at birth or in later life predict trait anxiety in late adulthood (Study II)?

Table 2 shows that after adjusting for confounders (sex, age at testing, socioeconomic position in childhood and in adulthood, mother's age at delivery, and parity), STAI-T total scores increased by decreasing birth weight ($p < 0.02$), and by decreasing BMI at birth ($p < 0.02$). Every one-kilogram decrease in birth weight increased STAI-T total score by 2.7% and every one-unit decrease in BMI at birth increased STAI-T total score by 1.1%. Moreover, lower scores on the positively worded items of the STAI-T were predicted by lower birth weight and BMI at birth (standardised beta coefficients [*β's*] = 0.06, 95% CI's 0.01 to 0.11, p's = 0.02). Table 2 also shows the associations between the two-factor analytically derived components of prenatal growth and trait anxiety. Smaller overall body size at birth and gestational age (principal component 1) was characteristic of those with higher STAI-T total scores after adjusting for confounders ($p < 0.03$). Moreover, lower scores on the positively worded items of the STAI-T were predicted by smaller overall body size at birth and gestational age (principal component 1) ($\beta = 0.05$, 95% CI 0.00 to 0.10, $p = 0.04$). The thinness component (principal component 2) was not associated with trait anxiety (p's > 0.07). In addition, smaller head circumference predicted lower scores in the positively worded items of the STAI-T in the non-adjusted model as well as after adjusting for confounders ($\beta = 0.06$, 95% CI 0.01 to 0.11, $p = 0.03$).

With respect to growth after birth, Table 2 further shows that after adjusting for confounders, a higher STAI-T total score was predicted by lower weight and BMI from six months to two years and lower weight and shorter height in adulthood (p's < 0.03). Higher scores on the negatively worded items of the STAI-T were predicted by lower weight from six months to two years (*β's* < -0.05, 95% CI's -0.10 to 0.00, p's < 0.03), by lower BMI at one and two years (*β's* < -0.05, 95% CI's -0.10 to -0.01, p's < 0.03), and by shorter adult height (*β's* < -0.06, 95% CI's -0.11 to -0.01, p's < 0.01). Lower scores on the positively worded items of the STAI-T were predicted by lower BMI at one and two years (*β's* < 0.05, 95% CI's 0.00 to 0.09, p's < 0.05).

Furthermore, we tested whether growth conditional on history predicted trait anxiety in adulthood. We found that trait anxiety was predicted by a faster growth in weight from 7 to 11 years (neg-STAI-T: β = 0.05, 95% CI 0.00 to 0.10, p = 0.04), and a slower growth in weight from 11 to 63 years (STAI-T total score: β = -0.05, 95% CI -0.10 to -0.01, p = 0.03; neg-STAI-T: β = -0.06, 95% CI -0.11 to -0.01, p = 0.01) and in height from 11 to 63 years (STAI-T total score: β = -0.08, 95% CI -0.13 to -0.03, p = 0.001; neg-STAI-T: β = -0.07, 95% CI -0.12 to -0.02, p = 0.008, and pos-STAI-T: β = 0.08; 95% CI 0.03 to 0.13; p = 0.002). These associations remained significant after adjusting for confounders.

All the significant associations tested changed only slightly after further controlling for adult body size or history of cardiovascular disease.

Table 2. Standard deviation (SD) change in the total STAI-T score per SD change in weight, length/height, and BMI at different ages as well as in composite measures (components) that characterise the prenatal pattern of growth. The models are adjusted for sex, age at testing, socioeconomic position in childhood and in adulthood, mother's age at delivery, parity, and breastfeeding (in the models pertaining to body size at birth, breastfeeding was excluded).

	β	95% CI		p
Weight				
Birth	-0.06	-0.11	-0.01	**0.02**
6 months	-0.06	-0.10	-0.01	**0.02**
1 year	-0.05	-0.10	0.00	**0.03**
2 years	-0.05	-0.10	0.00	**0.04**
7 years	-0.03	-0.08	0.02	0.25
11 years	-0.01	-0.06	0.04	0.81
Adult	-0.05	-0.10	-0.01	**0.03**
Length/Height				
Birth	-0.03	-0.08	0.01	0.17
6 months	-0.03	-0.07	0.02	0.28
1 year	-0.02	-0.06	0.03	0.54
2 years	-0.01	-0.06	0.04	0.68
7 years	-0.01	-0.06	0.04	0.74
11 years	0.00	-0.05	0.05	0.86
Adult	-0.06	-0.11	-0.01	**0.02**
BMI				
Birth	-0.06	-0.11	-0.01	**0.01**
6 months	-0.05	-0.10	0.00	**0.03**
1 year	-0.06	-0.11	-0.01	**0.01**
2 years	-0.06	-0.11	-0.01	**0.01**
7 years	-0.03	-0.08	0.01	0.17
11 years	-0.01	-0.06	0.04	0.80
Adult	-0.03	-0.08	0.02	0.21
Principal components				
1: Overall body size at birth and gestational age	-0.05	-0.10	-0.01	**0.03**
2: Thinness at birth	-0.04	-0.09	0.01	0.09

Notes: *β*: standardised regression coefficient derived from linear regression analyses; 95% CI : 95% confidence interval

3.3. Does smaller body size at birth, small placental size, or both predict more pronounced schizotypal traits in adulthood? (Study III)

In women, a higher score on the Perceptual Aberration Scale (PAS) at age 31 was predicted by lower birth weight (B = -0.09, 95% CI: -0.17 to -0.00, p < 0.04), lighter placental weight (B = -0.04, 95% CI: -0.07 to -0.01, p < 0.01), and smaller head circumference at 12 months of age (B = -0.04, 95% CI: -0.07 to -0.01, p < 0.01) after adjusting for gestational age. For every 1-kg increase in birth weight, 100-g increase in placental weight, and 1-cm increase in head circumference at 12 months, the PAS decreased by 0.09, 0.04, and 0.04 standard deviations, respectively. Birth weight, placental weight, and head circumference at 12 months remained significant predictors of the PAS in women after further adjusting for maternal smoking during pregnancy, maternal antenatal depression, season of birth, perinatal brain damage, desirability of pregnancy, birth order, twin birth, CNS viral infections in childhood, place of residence, family SES in early childhood, and SES and BMI in adulthood. In men, body or placental size at birth were not significantly associated with schizotypal traits at the age of 31 (p-values > .28).

By excluding 114 subjects who were born preterm (4.4% of the study population) and by conducting the analyses among a substratum of subjects who were born full-term (37 + 0 to 42 + 0 weeks of gestation), all significant inverse associations between birth weight, placental weight, and head circumference at 12 months with the PAS remained so. Furthermore, shorter birth length in women predicted higher scores on the PAS after adjusting for gestational age (B = -0.02; 95% CI: -0.04 to -0.00; p = 0.02) and all other early life factors (B = -0.02; 95% CI: -0.04 to -0.00; p = 0.04).

3.4. Does smaller birth size predict symptoms of ADHD in children? (Study IV)

A higher total score on the ADHD rating scale was predicted by a lower ponderal index (standardised β = -0.12; p = 0.04) and a smaller head circumference-to-length ratio (standardised β = -0.13; p = 0.03) at birth. Moreover, a higher score on the Inattention-

hyperactivity subscale was predicted by a lower ponderal index (standardised β = -0.12; p < 0.05), smaller head circumference (standardised β = -0.12; p < 0.05), and a smaller head circumference-to-length ratio (standardised β = -0.14; p= 0.02) at birth. Figure 6 illustrates the graded nature of some of these associations. When the analyses were repeated with the child's gender, the gross income of the family, and the age of the mother serving as significant covariates in the regression equation, the associations remained significant. Further controls for length of gestation, maternal alcohol and tobacco use during pregnancy, maternal pre-pregnancy BMI, parity and the child's BMI at the age of five to six did not change the significance levels, with two exceptions: both the association between the ponderal index or head circumference-to-length ratio at birth and the total score on the ADHD rating scale became marginally significant (p-value = 0.06). Neither weight nor length at birth predicted total or subscale scores of symptoms of ADHD (p-values > 0.29).

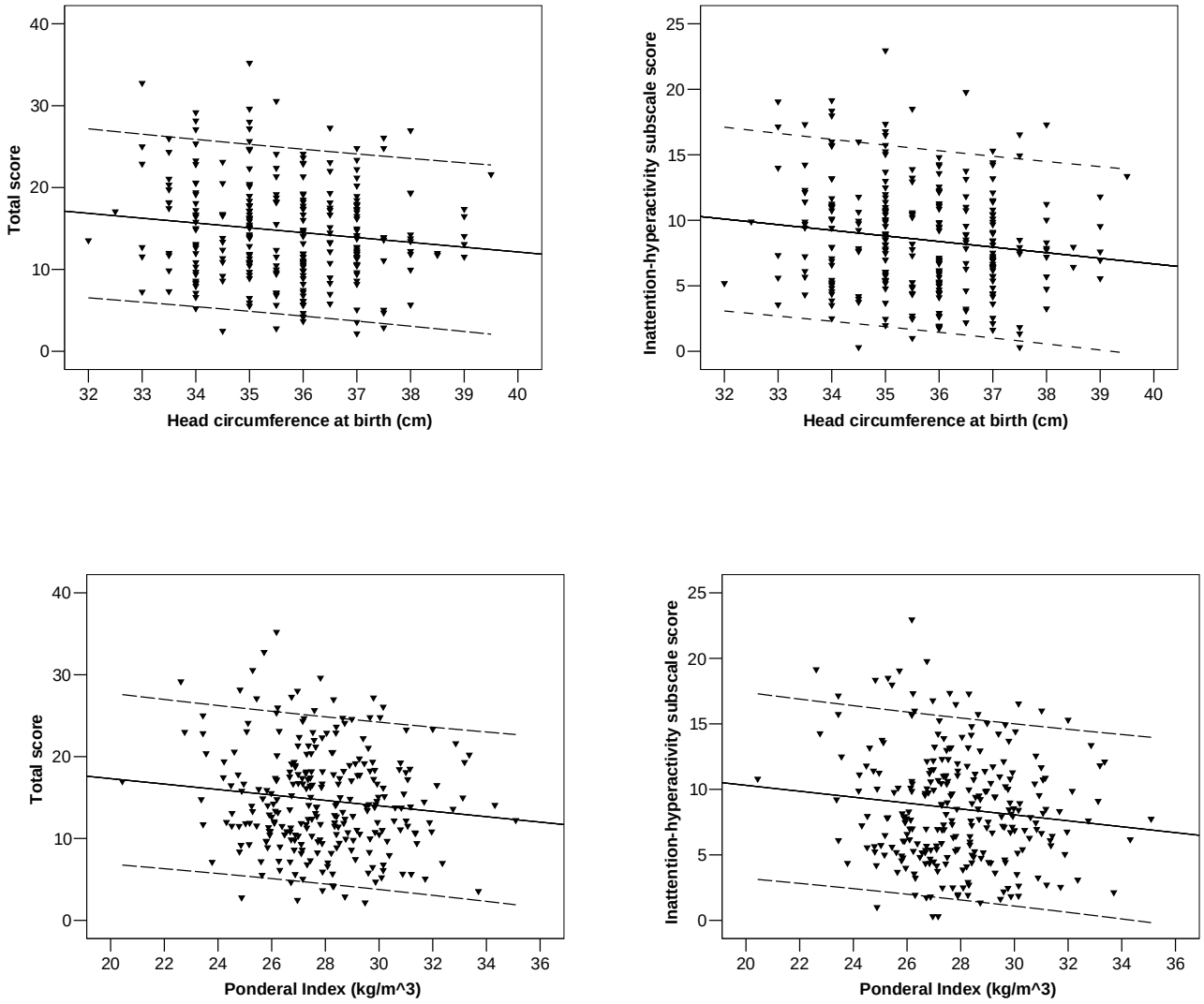

Figure 6. Regression lines and 95% confidence intervals representing associations between the head circumference (upper figures) or ponderal index (lower figures) and the total score on the ADHD rating scale (left), and the Inattention-hyperactivity subscale (right) in children aged five to six years. (Note: the rating scale scores were adjusted for the child's gender, gross family income, and the mother's age).

4. DISCUSSION

4.1. General conclusions

As hypothesised, small body size at birth predicted psychological vulnerability factors for mental disorders in later life. We found that temperamental/personality traits and psychological symptoms that increase the risk for MDD, anxiety disorders, schizophrenia-spectrum disorders, and ADHD were associated with smaller birth size in cohorts with wide variation in birth size.

With respect to temperament, however, instead of inverse linear associations, curvilinear reverse J-shaped associations were found between the temperamental trait of harm avoidance in adulthood and weight and length at birth. The highest harm avoidance scores were characteristic of those with the smallest birth weight and of those who were shortest at birth. These findings are in line with previous studies of much younger age groups than those studied in this thesis. These previous studies have shown that characteristics of negative affectivity characterise children who were smaller in body size at birth (Hawdon et al., 1990; Pesonen et al., 2006a). These traits closely resemble harm avoidance. Furthermore, those who belonged to low SES families in childhood showed more pronounced harm avoidance. It was also found that childhood SES moderated the associations between birth size and harm avoidance in adulthood such that birth size was inversely associated with harm avoidance in those with high childhood SES. To our knowledge, this is the first investigation of the interplay of birth size and postnatal environment on later personality in the context of a cohort study with a wide variation in birth size. Our finding underscores the need to account for childhood environment in the analyses of birth size and subsequent mental health.

In addition, smaller weight and BMI at birth were found to predict more pronounced trait anxiety in late adulthood. Moreover, a lower ponderal index, smaller head circumference-to-length ratio, and smaller head circumference at birth were associated with symptoms of ADHD in children. These associations were found in both men and women across the whole variation in birth size. Furthermore, lower birth weight and smaller placental size and head circumference at 12 months predicted more pronounced positive schitzotypal traits in women.

These associations were not explained by a wide variety of other factors that have been shown to influence body size at birth, mental health, or both.

The results concerning trait anxiety, schizotypal traits, and symptoms of ADHD show that these characteristics are inversely and linearly associated with birth size. These findings are consistent with most of the existing literature, which has shown that being born at the extreme end of the birth weight continuum (i.e., SGA, VLBW, or LBW) increases the risk for subsequent internalising behaviours (Horwood, Mogridge & Darlow, 1999; Liu et al., 2001; Elgen et al., 2002; Hack et al., 2004), anxiety (Botting et al., 1997; Indredavik et al., 2004; Berle et al., 2006; Gustafsson et al., 2009), schizophrenia (Jones et al., 1998; Cannon et al., 2002), and ADHD (Breslau et al., 1996; Botting et al., 1997; Mick et al., 2002; Saigal et al., 2003; Hack et al., 2004; O'Keeffe et al., 2003). Although literature on associations between small size at birth and schizophrenia or ADHD is relatively consistent, not all the previous studies have found a link between birth size and subsequent anxiety (Breslau et al., 1996; Saigal et al., 2003; Mallen et al., 2008). The findings of this thesis lend support to the DOHaD model and add to this literature by suggesting that slower intrauterine growth plays a role in predisposing to higher trait anxiety, symptoms of ADHD, and schizotypal characteristics, and that these associations are not restricted to the extreme low end of the distribution in birth weight, but also exist within normal variation in body size at birth.

These studies were the first to show an inverse linear association between birth size and trait anxiety or schizotypal traits in adulthood. The results are in line with those of previous research in adults, showing that smaller birth size linearly predicts increased risk for conditions comorbid with trait anxiety and schizotypal traits, such as depression (Cheung et al., 2002; Gale & Martyn, 2004) and schizophrenia (Wahlbeck et al., 2001). Moreover, our findings showing that birth size inversely linearly predicted symptoms of ADHD in childhood correspond to Kelly et al. (2001) results showing comparable association between birth weight and hyperactivity in boys. Variety in the mental health outcomes associated with small body size at birth suggests a non-specific effect of suboptimal prenatal environment on psychological vulnerability factors and mental disorders.

The gender-specific findings on associations between birth size and schizotypal traits suggest that women may be more sensitive to the effects of lower birth weight. Indeed, some animal studies have suggested increased susceptibility to prenatal stress exposure in female

offspring (McCormick, Smythe, Sharma & Meaney, 1995). However, previous gender-spesific findings of the associations between birth size and mental health outcomes have been mixed. Some studies have reported stronger inverse associations between birth weight and emotional or attentional problems in women than in men (Lagerström et al., 1990; O'Keeffe et al., 2003; Hack et al., 2004; Alati et al., 2007; Rice, Jones & Thapar, 2007), while studies also exist showing links between low birth weight and depression or motor activity in men but not in women (Kelly et al., 2001; Thompson et al., 2001; Wiles, Peters, Leon & Lewis, 2005; Schlotz et al., 2007). It is also possible that other gender differences in the etiology or nature of schizophrenia-spectrum disorders, such as in the age of onset of disorder or in the symptom profiles, may influence the findings of this thesis.

The magnitude of the associations in the studies of this thesis is similar to the well established associations between size at birth and many adulthood outcomes, such as blood pressure (Huxley, Shiell & Law, 2000) and glucose tolerance (Lithell, McKeigue, Berglund, Mohsen, Lithell & Leon, 1996). Although the effect of birth size on any outcome has been modest at best, the fact that small birth size appears to be a non-specific precursor of a variety of health outcomes and vulnerability factors emphasises its value. Moreover, even a relatively small effect size can be important on the population level.

Furthermore, it was investigated whether physical growth after birth associated with trait anxiety in later life. Individuals who remained lighter in weight and were thinner throughout infancy scored higher in trait anxiety in late adulthood. Moreover, rapid increase in weight between the ages of 7 and 11, and weighting less and being shorter in late adulthood in relation to weight and height measured at 11 years of age linked with higher trait anxiety. To our knowledge, no prior studies on early childhood growth and trait anxiety exist. However, previous studies have found no link between symptoms of anxiety or anxiety disorders and failure to thrive in infancy (Drewett et al., 2006) or physical growth in childhood or in early adulthood (Mustillo et al., 2003; Anderson et al., 2006). Yet, findings showing that lower weight and shorter stature in adulthood are associated with high trait anxiety are in line with some of the previous cross-sectional community-based studies that focused mainly on symptoms of anxiety (Crisp & McGuiness, 1976; Crisp et al., 1980; Bjerkeset et al., 2008; Stewart & Brook, 1983). However, some studies show that BMI and anxiety disorders are not linked (Lamertz et al., 2002; Mustillo et al., 2003; John et al., 2005), and that obesity or higher

BMI are associated with increased risk for anxiety disorders (Becker et al., 2001; Anderson et al., 2006; Bjerkeset et al., 2008; Simon et al., 2006). These inconsistencies in findings may partly stem from differences in the outcomes studied, or differences in sample characteristics. Most studies using anxiety disorders as an outcome have found no association or have found a positive association, whereas inverse associations between physical size after birth and anxiety have been found in most studies focusing on symptoms of anxiety.

4.1.1. Possible mechanisms linking physical size with health outcomes

Although birth size effects may reflect genetic actions (i.e., pleiotropy) such that the same genes that affect variation in body size at birth also affect health outcomes (Hattersley & Tooke, 1999), several lines of evidence point to a major role for environmental factors as well. Research in twins suggests that most of the variance in birth weight is attributable to environmental factors (Little & Sing, 1987; Clausson et al., 2000; Lunde et al., 2007). Moreover, twin studies have shown that decreased birth weight is associated with increased risk for hypertension (Bergvall, Iliadou, Johansson, de Faire, Kramer, Pawitan et al., 2007), schizophrenia (Nilsson et al., 2005), ADHD (Hultman et al., 2007; Lehn, Derks, Hudziak, Heutink, van Beijsterveldt & Boomsma, 2007), and childhood behavioural problems (van Os et al., 2001) independently of genetic factors. Since the pattern of fetal growth and birth outcomes in twins is not representative of singleton pregnancies, it is noteworthy that also associations between manipulations of the early-life environmentand and subsequent physiology and disease risk in isogenic rodent models strongly implicate a major role for environmental factors (Meaney et al., 2007). Although it remains possible that restricted intrauterine growth is a first expression of a genotype that is expressed as a behavioural phenotype in later life, there also seems to be a strong environmental influence explaining the associations between birth size and psychological factors.

Other explanations, as proposed in the DOHaD framework (Barker, 1997), for the link between birth size and subsequent health outcomes pertain to adverse environmental influences during pregnancy. These influences may at least relate to prenatal cortisol exposure or to suboptimal nutrition or both (Barker et al., 1993; Edwards et al., 1993; Clark, 1998; Jaddoe & Witteman, 2006). Due to the large number of environmental factors influencing

birth size (Figure 3), it is difficult to know which specific factor(s) mediated by birth size affect mental disorders and their psychological vulnerability factors in later life. However, a recent review by Huizink, Mulder et al. (2004) concluded that prenatal stress, through increased cortisol exposure, probably results in a general susceptibility to psychopathology. The same authors concluded that in animal studies, prenatal stress has been associated with a wide range of alterations in hormonal axes and in serotonergic, dopaminergic, noradrenergic and cholinergic neurotransmission in the offspring. In humans, anxiety and stress during pregnancy have been linked not only to several behavioural alterations including poorer attention regulation, more difficult infant temperament (Huizink, de Medina, Mulder, Visser & Buitelaar, 2002; Austin, Hadzi-Pavlovic, Leader, Saint & Parker, 2005) and behavioural/emotional problems in middle childhood (O'Connor, Heron, Golding & Glover, 2003), but also to more advanced motor development in the offspring (DiPietro, Novak, Costigan, Atella & Reusing, 2006). Moreover, several psychosocial (e.g., loss of a spouse or exposure to a traumatic event) or nutritional (e.g., famine) stressors, when they occur during pregnancy, have been shown to increase the risk for distress to novelty (Brand et al., 2006), personality disorders (Hoek et al., 1996), affective disorders (Brown et al., 1995), and schizophrenia (Huttunen & Niskanen, 1978; Susser & Lin, 1992; Susser et al., 1996; St Clair et al., 2005) in the offspring. Furthermore, prenatal exposure to synthetic glucocorticoids has been associated with impulsivity (Pesonen, Raikkonen, Lano, Peltoniemi, Hallman & Kari, 2009) and attention problems at the age of two years (Crowther, Doyle, Haslam, Hiller, Harding & Robinson, 2007), and with hyperactivity in childhood (French, Hagan, Evans, Mullan & Newnham, 2004), although some studies have found no such effects (Dalziel, Lim, Lambert, McCarthy, Parag, Rodgers et al., 2005).

As a more specific mechanism, Barker (2004b) proposed that the association between small birth size and subsequent health outcomes results from a smaller number of cells in key organs. The current knowledge of alterations in brain structure and function that are linked to small birth size is scarce. The findings of this thesis may provide indirect insight into the structural or functional alterations in the brain that are associated with small birth size. On the one hand, variation in human serotonin neurotransmission may relate to harm avoidance (Hennig, Toll, Schonlau, Rohrmann & Netter, 2000; Bond, 2001; Moresco, Dieci, Vita, Messa, Gobbo, Galli et al., 2002; Munafo, Clark & Flint, 2005) and trait anxiety (Reimold,

Batra, Knobel, Smolka, Zimmer, Mann et al., 2008). Moreover, trait anxiety has been associated with indicators of reduced hippocampal volume (Gallinat, Strohle, Lang, Bajbouj, Kalus, Montag et al., 2005). On the other hand, the pathophysiology of ADHD (Castellanos, 1997; Davids, Zhang, Tarazi & Baldessarini, 2003) has been suggested to involve prefrontal and striatal dysfunctional dopaminergic and noradrenaline neurotransmission, and alterations in the brain structure involve smaller total volume (Krain & Castellanos, 2006) as well as a larger hippocampus than those of healthy controls (Plessen, Bansal, Zhu, Whiteman, Amat, Quackenbush et al., 2006). Likewise, psychotic-like symptoms of schizotypal personality disorder have been linked to increased dopaminergic function, as measured by the dopamine metabolite homovanillic acid content in cerebrospinal fluid or plasma, whereas deficit-like symptoms were related to reduced dopamine function (Siever & Davis, 2004). In addition, a recent study found women with schizotypal personality disorder to have smaller hippocampal size (Dickey, McCarley, Xu, Seidman, Voglmaier, Niznikiewicz et al., 2007). Moreover, schizophrenia has typically been linked to dopaminergic alterations (Murray, Lappin & Di Forti, 2008), enlarged ventricular volume and decreased hippocampal size (Steen, Mull, McClure, Hamer & Lieberman, 2006). Thus, the findings of this thesis suggest that rather than exerting an effect on a specific neurotransmitter system or nucleus, smaller birth size may be linked with a variety of changes in brain neurotransmission (e.g., alterations in serotonin and dopamine system) and structures (e.g. reduced hippocampal and total brain volume). This view is supported by animal research showing alterations in serotonin (Slotkin et al., 2006), dopamine, and noradrenalin neurotransmission (Muneoka et al., 1997; Bowman et al., 2004) after the prenatal administration of synthetic glucocorticoids or inducing stress during pregnancy. Furthermore, this view is supported by human studies linking LBW to increased lateral ventricular volume in adulthood (Allin et al., 2004), preterm birth to a smaller hippocampus (Nosarti et al., 2002; Lodygensky et al., 2008), and IUGR to metabolic disturbances in brain serotonin synthesis in infants (Manjarrez et al., 2005). Consequently, the brain is likely not spared from prenatal insults, but rather the effects of factors operating early in life that reduce birth size exert their effects on health and other developmental outcomes in several ways.

Some have proposed that the setting of hormones and metabolism may account for the association between birth size and subsequent health outcomes (Barker, 2004b). This

suggestion parallels that of Waterland & Garza's (1999) 'hormonal imprinting' hypothesis, which proposes that prenatal exposure to a hormone may increase the response to the same hormone later in life. Indeed, alterations in HPAA activity in adulthood have been associated not only with lower birth weight (Kajantie, 2006), prenatal exposure to synthetic glucocorticoids (Matthews, 2000) and psychosocial stress (Gutteling, de Weerth & Buitelaar, 2004; Gutteling, de Weerth & Buitelaar, 2005), but also to harm avoidance (Gerra, Zaimovic, Timpano, Zambelli, Delsignore & Brambilla, 2000), trait anxiety (van Eck, Berkhof, Nicolson & Sulon, 1996; Takahashi, Ikeda, Ishikawa, Kitamura, Tsukasaki, Nakama et al., 2005), schizotypal personality disorder (Weinstein, Diforio, Schiffman, Walker & Bonsall, 1999), and ADHD (Kariyawasam, Zaw & Handley, 2002). Furthermore, some evidence suggests that variation in the prenatal hormonal milieu related to the HPT, HPG, and GH-IGF axis may account for some associations between birth size and subsequent health or neurodevelopment. Maternal hypothyroidism during pregnancy has been linked to smaller birth size, altered HPT axis function (Blazer, Moreh-Waterman, Miller-Lotan, Tamir & Hochberg, 2003), delay in both mental and motor development (Pop, Brouwers, Vader, Vulsma, van Baar & de Vijlder, 2003), and impaired neurocognitive development (Haddow, Palomaki, Allan, Williams, Knight, Gagnon et al., 1999) in the offspring. Moreover, exposure to high levels of maternal testosterone (Carlsen, Jacobsen & Romundstad, 2006), low levels of maternal estrogens (Nagata, Iwasa, Shiraki & Shimizu, 2006) and reduced maternal IGF-1 (Murphy, Smith, Giles & Clifton, 2006) during pregnancy have been associated with lower birth weight. Interestingly, high levels of maternal testosterone during pregnancy have been linked to more masculine gender role behaviour in the offspring (Hines, Golombok, Rust, Johnston & Golding, 2002), and GH-IGF function has been proposed to underlie the associations between LBW and schizophrenia (Gunnell & Holly, 2004).

Others have also suggested that associations between birth size and subsequent health outcomes pertain to accelerated growth after birth in infancy (Singhal & Lucas, 2004). This explanation was not supported by the data since conditional physical growth from birth to six months failed to predict trait anxiety in adulthood. With respect to failure to thrive (FTT) in infancy, the findings emphasise the importance of its exact definition. If FTT is defined as poor weight gain in infancy, the findings lend no support to a major role for FTT in the development of trait anxiety, whereas if it is defined as low weight in infancy, FTT may play a

role. However, since growth after birth was studied only with respect to a certain time period and trait anxiety, some association may have been missed.

Finally, yet unmeasured factors could account for the association. For example, overprotective or responsive parenting could partly explain the associations between birth size and subsequent mental health. However, the magnitude of this effect in a general population is difficult to estimate since, to our knowledge, previous studies on the consequences of birth size on parenting have been limited to those born prematurely.

According to the ICP model, postnatal human physical growth is largely dependent on nutrition up to the age of 6 to 12 months, after which the GH-IGF-I endocrine axis, followed by sex steroids during puberty, begin to regulate growth (Karlberg et al., 1987a; Karlberg et al., 1987b). This suggests that the association between high trait anxiety and lower weight and thinness from birth up to the age of two may be mediated by suboptimal prenatal or early postnatal nutrition, whereas the regulation of the GH-IGF-I endocrine axis in infancy may be relatively unimportant with respect to later trait anxiety. The association between increased physical growth in mid-childhood and trait anxiety may reflect a more active GH-IGF-I endocrine axis during that period or earlier activation of the HPG axis or both. In line with the suggestion that gonadal hormones may mediate the association of faster growth in childhood with anxiety, a recent review concluded that earlier pubertal timing is associated with higher anxiety scores in girls (Reardon, Leen-Feldner & Hayward, 2009). However, since the ICP model is focused on explaining skeletal growth, it may not be applicable with respect to growth in weight or BMI. Increased growth in childhood may also reflect an earlier adiposity rebound in BMI, which has been associated with increased risk for obesity in adulthood (Rolland-Cachera et al., 1984) and type II diabetes (Wadsworth, Butterworth, Marmot, Ecob & Hardy, 2005). However, no studies have explored associations between the age of adiposity rebound and later mental health, thus making these conclusions preliminary. Furthermore, the association between increased physical growth in mid-childhood and trait anxiety may be explained by parental practices or adverse experiences in childhood. Indeed, low parental care and high maternal overprotection along with traumas and abuse in childhood have been associated with increased risk of overweight (Turner, Rose & Cooper, 2005; Gunstad, Paul, Spitznagel, Cohen, Williams, Kohn et al., 2006; Noll, Zeller, Trickett & Putnam, 2007) as well as increased trait anxiety later in life (Daugherty, 1998; Mancini, Van Ameringen &

MacMillan, 1995; Seibel & Johnson, 2001). Furthermore, some have proposed that a relative deficiency in growth hormone may mediate associations between small adult stature and anxiety symptoms (Uhde, 1994).

The DOHaD hypothesis also proposes that the consequences of insults are influenced by their timing (Barker, 1997). The finding that symptoms of ADHD were predicted by thinness at birth may point towards the importance of late pregnancy adversities in the development of attention networks (Villar & Belizan, 1982). In line with this, animal models of induced hypoxia during pregnancy have shown that acute insults in late gestation result in neuronal death in, for example, the dopamine-rich striatal areas (Rees & Inder, 2005). The finding that lower birth weight (but not ponderal index or BMI) predicted positive schizotypal trait in women may point towards adversities in early pregnancy or throughout the pregnancy (Villar & Belizan, 1982). This is again consistent with studies of induced gestational hypoxia, which have shown that acute insults in early gestation have detrimental effects on the hippocampus, cerebellum, and cortical neurons, whereas chronic insults typically result in reduced axonal myelination, compromised synaptogenesis, and reduced brain weight (Rees & Inder, 2005). Thus, sensitive periods in brain development may provide clues to understand the findings of this thesis. The effects of timing are under debate, however, due to the small number of studies showing consistent findings and to multiple factors that influence birth size.

4.1.2. Altered behaviour as adaptation to the environment

One can only speculate whether the associations between smaller birth size and increased harm avoidance, trait anxiety, symptoms of ADHD, and schizotypal traits reflect developmental plasticity or predictive adaptive responses. It is advantageous not only to adapt by altering energy metabolism (Hales et al., 1997), but also by basing behaviour (Bateson et al., 2004) on cues received from the environment. One can speculate that behavioural traits, such as harm avoidance, trait anxiety, and impulsivity, may offer survival or adaptive benefits in certain environments. Indeed, some have suggested an adaptive function for dysthymic temperamental traits, which correlate strongly with harm avoidance. These traits may promote bonding as well as enhance protection of the pregnancy and the offspring (Akiskal & Akiskal, 2005). Trait anxiety may offer survival benefits in dangerous environments, and indeed, high

trait anxiety in adolescence has been shown to predict fewer accidents and accidental death in early adulthood (Lee, Wadsworth & Hotopf, 2006). Jensen, Mrazek, Knapp, Steinberg, Pfeffer, Schowalter et al. (1997) suggested that characteristics of ADHD (i.e., hyperactivity, inattention, and impulsivity) may offer adaptive benefits to the individual, social group or to the kin in certain environments, and thus evolutionary theories can explain the persistence of ADHD traits in some individuals. Increased motor activity (hyperactivity) conveys benefits due to enhanced exploration of the environment for threats and opportunities; attentional processes such as continuous scanning (i.e., 'inattention' to a single repetitive stimuli) and rapidly shifting attention may be adaptive in high-threat or highly novel environments. Finally, quick response to environmental cues (i.e., impulsivity) may be beneficial in dangerous and resource-scarce environments. Jensen et al. (1997) also labelled hypervigilant, rapid-scanning, quick to pounce or flee, and motorically hyperactive persons as "response-ready" who would likely have been advantaged under brutal or harsh circumstances. Alternatively, other researchers have proposed that these disadvantageous traits may be by-products in the evolution of complex human skills. Although most researchers view schizophrenia as costly trade-offs in the evolution of complex social cognition while having no adaptive advantage of its own (Burns, 2004; Nichols, 2009), some have suggested that certain characteristics related to schizophrenia-spectrum disorders, such as habituation deficits and behavioural disinhibition, may have had adaptive value in an ancient environment (Reser, 2007). To sum up the evolutionary view on the association between birth size and later behaviours, the foetus may be equipped for taxing and dangerous environments, signalled via increased maternal HPAA activity, with altered temperament and behavioural dispositions that may, during the course of human evolution, have offered survival or adaptive benefits in dangerous environments, but that in modern society may prove disadvantageous. Interestingly, some have proposed that adaptive responses to a threat or danger include freeze, flight, fight, and fright behaviours (Gray, 1988). Of these responses, freeze (hypervigilance) and flight (low threshold of avoidance behaviours) resemble harm avoidance and trait anxiety, whereas the fight response may include characteristics of impulsivity and increased motor activity.

4.2. Methodological considerations

The crudeness of the birth size measures poses a challenge in developmental origins epidemiology. Body size at birth, although a convenient indicator in epidemiological studies, is a crude indicator of the intrauterine environment. For example, the wartime famine in Holland produced lifelong consequences for those who were *in utero* at the time, but caused little alteration in birth weight (Ravelli, van der Meulen, Michels, Osmond, Barker, Hales et al., 1998), and the prenatal glucocorticoid programming of blood pressure has been reported with no alterations in birth weight (Huh, Andrew, Rich-Edwards, Kleinman, Seckl & Gillman, 2008). However, this limitation would only be expected to reduce rather than to strengthen our ability to detect associations. Therefore, even modest associations between birth size and subsequent outcomes are generally considered strongly suggestive of a relationship between the intrauterine environment and the outcome in question. Nevertheless, large epidemiological cohorts, such as those in this thesis, are usually needed to link body size at birth to subsequent outcomes. In these cohorts, birth size usually provides the most accurate available indicator for estimating the magnitude of the effects of suboptimal environment, though it is likely to underestimate them. Furthermore, it is important that anthropometric variables be either prospectively measured or derived from the registers, as in this thesis, instead of recalled retrospectively.

Developmental origins epidemiology has been criticised for inappropriate adjustments of potential confounders (Schluchter, 2003). The importance of accounting for potential confounders was illustrated in a recent large Dutch study, which showed that even though those infants who were smaller at birth showed higher activity levels and prolonged duration of orienting at six months, these effects disappeared after adjusting for national origin, maternal education level, and maternal age and height (Roza, van Lier, Jaddoe, Steegers, Moll, Mackenbach et al., 2008). In highly multiethnic societies, one plausible confounder of associations between birth size and subsequent health is ethnical background. This makes ethnically relatively homogenous societies, such as Finland, optimal populations in which to study moderate effect sizes in large cohorts.

Studies on the developmental origins of health and disease should also account for concurrent body size and SES, and some have suggested that these factors should be treated as

moderators instead of merely confounders (Kramer & Joseph, 1996; Gillman, 2002). Therefore, multiple measurements of weight, height, and SES throughout the lifecourse would be optimal for distinguishing prenatal influences from influences occurring at various points in later life (Gillman, 2002). In each of the studies in this thesis, concomitant body size was adjusted for. Moreover, with respect to trait anxiety, growth after birth, measured at multiple ages, was an important focus. Concurrent SES was also controlled for in each of the studies and, as recommended by Kramer & Joseph (1996), family SES at birth was also adjusted for with respect to trait anxiety and schizotypal traits. In addition, as recommended by Gillman (2002), the interplay of prenatal growth and family SES in childhood was investigated with respect to temperament in late adulthood. However, SES can be measured in several ways. In comparison with income, occupational status, which was used as a proxy for SES in two of the studies, was shown to be poorer predictor of mental disorders (Fryers, Melzer & Jenkins, 2003). Thus, part of the association between physical size and psychological vulnerability factors for mental disorders may be explained by effects of SES that has not been measured in these studies (i.e. residual confounding).

Developmental origins epidemiology has also been criticised for inconsistencies in the results (Kramer & Joseph, 1996). Studies have reported associations of different indicators of prenatal growth with a comparable outcome. One possible solution would be the use of composite measures of body size at birth. Therefore, an attempt was made to use a factor analytical method to aggregate different birth size measures and to test the predictive value of these indices with respect to trait anxiety. Another explanation for inconsistencies in the results is the use of somewhat similar, but still different, outcome measures. Therefore, the use of well-validated outcome measures is vital. In addition, studies associating physical growth with mental health outcomes have been criticized for not taking account for relatively great number of statistical tests conducted. This may lead to false positive findings (type I error). However, correction for multiple testing increases the possibility for false negative findings (type II error), and should be used with caution in studies with hypothesis-driven analyses (Perenger, 1998).

Thus, the obvious strengths of the studies in this thesis include large samples of ethnically homogenous participants derived from the general population, prospective and registry-based study designs, the possibility to take into account a wide variety of confounding factors that

could contribute to either smaller birth size or studied outcomes, thus confounding the associations, and the use of well-validated scales to measure the outcomes. In addition, the fact that the results are derived from three separate cohorts should increase the reliability of the findings.

There are, however, some general and sample-specific limitations to these studies. There are important general limitations relating to the fact that small body size at birth is a marker of processes that affect health outcomes in later life. First, one can question whether associations between restricted foetal growth and subsequent outcomes can be considered causal or are they merely epiphenomena of something else (Kramer, 2000). Whatever the final answer is, it has been emphasised that the public health "use value" of research findings in regard to prediction and intervention is, to a large extent, independent of explicit causal claims (Lipton & Odegaard, 2005). However, future studies should explore these associations with more complex designs (e.g. quasi-experimental designs applying data on parental and exposed vs. non-exposed siblings or a children-of-twins design) that can provide stronger arguments about causation. The second issue relates to the fact that although the slowing of foetal growth may be a response to a suboptimal environment, the same body size at birth can be attained in many different ways, and each is likely to be accompanied by gene-environment interactions (Harding, 2001). The third issue relates to the fact that the intrinsic growth potential of an individual is unknown. It is, therefore, challenging to know whether and to what extent someone is growth restricted or merely small by constitution. In this thesis, we assumed that the probability of growth restriction increases with smaller physical size. Furthermore, our studies failed to take into account the effects of parenting on associations between birth size and psychological vulnerability factors for mental disorders. Thus, future studies should investigate the extent to which parenting moderates or mediates the effects of birth size across the entire spectrum of mental health later on.

Some specific limitations apply to the Helsinki Birth Cohort 1934-1944 (Study I and Study II). Subjects who died before 1971 were excluded from the cohort. Loss to follow-up across decades is inevitable, although over 86% of the randomly selected, still traceable cohort members were available for the psychological survey. Careful consideration of the possible effects of attrition is essential since, as Kramer & Joseph (1996) points out, the results of some studies of the foetal origins of disease have been based only on a tiny fraction of the original

birth cohort. A higher proportion of women than men agreed to participate in the study. Participation in the follow-up, however, was unrelated to any of the neonatal or maternal characteristics, nor was participation related to childhood SES. However, it is not known whether participation was related to psychological outcomes. In addition, uncontrolled childhood factors, such as a overcontrolling and undercaring parenting as well as childhood traumas and abuse, that have been shown to affect subsequent body size (Turner et al., 2005; Gunstad et al., 2006; Noll et al., 2007) and mental health (Mancini et al., 1995; Daugherty, 1998; Seibel & Johnson, 2001) may mediate the associations found between growth after birth and trait anxiety in adulthood.

Study III (Northern Finland Birth Cohort 1966) also has its limitations. Compared to the original cohort, the sample more often comprised women from more affluent families and with larger body size at birth. However, these differences should only diminish the associations between early-life factors and schizotypal traits in adulthood. Future studies should take into account other factors that may be relevant to the epidemiology of schizotypy, such as breastfeeding (McCreadie, 1997), maternal influenza during pregnancy (Venables, 1996), and trauma/maltreatment (Berenbaum, Valera & Kerns, 2003) or low parental affection or nurturing and aversive parenting behaviour (Johnson, Cohen, Chen, Kasen & Brook, 2006) during childhood.

The results of Study IV (The Glaku project) must also be evaluated in light of the methodological limitations raised by a relatively small number of participants against those of the original cohort and the use of the parent-reported dimensional ADHD symptom scale. Although behaviour-problem scales yield no psychiatric diagnoses, and parental reports of child behaviour may be questioned, the utility of dimensional measures in terms of clinical correlates and prognosis has recently been emphasised (Jensen & Watanabe, 1999). Moreover, parental reports of ADHD have been found to closely associate with teacher ratings (Biederman, Faraone, Milberger & Doyle, 1993) and to incorporate sensitivity to change in ADHD symptoms in drug treatment trials to a similar level as in the teacher reports (Biederman, Faraone, Monuteaux & Grossbard, 2004). However, in order to reduce possible bias in evaluations of child behaviour, the mean ratings of the mother and the father were used. This study was based on a subsample of the original cohort for which both maternal and paternal reports were available. This would be expected to introduce a bias only if the

associations between body size at birth and ADHD symptoms of the responders differed from those of the non-responders.

4.3. Implications of the study

The studies presented in this thesis provide several implications for further research and for promoting public health (Table 3). The findings of this thesis emphasise the importance of prenatal factors in the aetiology not only of mental disorders, but also of psychological vulnerability factors for them. These results are in line with those of the DOHaD model. However, only a few studies have examined whether birth size across its whole variation predicts vulnerability factors for compromised mental health or mental health as such. Thus, further studies are needed. These studies should take into account possible gender differences in the associations between birth size and subsequent health outcomes. Furthermore, future studies in developmental origins epidemiology should take into account the interplay of genes and the environment in affecting health outcomes by for example testing whether the associations of small size at birth and mental disorders are moderated by certain genotypes. Moreover, future studies should investigate the role of certain genotypes as mediators of the association between birth size and health outcomes. Nevertheless, the results of this thesis suggest that the risk for MDD, anxiety disorders, schizophrenia-spectrum disorders, and ADHD, for example, may increase linearly with decreasing birth size even within the normal variation of birth size. The findings of this thesis also suggest that some of the factors that directly cause restricted growth *in utero* (e.g., adverse nutritional or hormonal environment) may exert effects linearly. Studies of the effects of these factors should also examine the extent to which their effect on health is mediated by small birth size, and whether the timing of the insult affects the outcome. Since some of the factors affecting birth size are modifiable (e.g., psychosocial stress, nutrition, and infections), it will be important to examine within a study whether alterations in these conditions will impact birth size as well as subsequent physical growth and health. The studies of this thesis also suggest that the interplay of prenatal physical growth with SES and physical growth after birth should be studied more intensely, and that in addition to prenatal physical growth, determinants and consequences of physical

growth after birth, especially during the mid-childhood years between the ages of seven and 11, should also be investigated more thoroughly.

The findings of the studies in this thesis may also have implications for the promotion of public health. From that perspective, the findings of this thesis provide clues for identifying the early signs of vulnerability characteristics related to MDD, anxiety disorders, schizophrenia-spectrum disorders, and ADHD. Although this early identification of individuals at increased risk for mental disorders should be carried out with caution because of the limited magnitude of an association between birth size and mental health outcomes and because of the possible stigma and stress it may cause, early identification may help in future preventive actions. Should the proposed mechanisms linking small physical size and subsequent health prove tenable, these actions may relate to the improvement of conditions among pregnant women by, for example, reinforcing balanced nutrition, attenuating psychosocial stressors, and promoting coping skills throughout pregnancy. Although the impact of these interventions should be studied further, the potential benefit of improving the situation on a community level with respect to any precursor of compromised health is greater if that factor is a non-specific marker, such as birth size, of several health outcomes (Jones & Tarrant, 2000). Furthermore, at least two intervention programmes have shown in controlled trials that individually tailored early stimulation for those born LBW (McCormick et al., 2006) or VLBW (Als et al., 1994) may have neurodevelopmental and neurocognitive benefits that endure until at least young adulthood. Based on the results of this thesis, it may be possible that not only those of the lowest birth size, but also larger-sized newborns could benefit from these interventionsas.

In sum, findings presented in this thesis show that vulnerability factors for mental disorders, such as harm avoidance, trait anxiety, schizotypal characteristics, and symptoms of ADHD, may have their origins in the suboptimal early environment, even when the size of the newborn is within the normal range.

Table 3. Key findings and implications of the study.

Key findings:

- Birth size across its whole variation was associated inversely and linearly with variety of psychological vulnerability factors for mental disorders even after adjusting for several confounders.
- Weight and length at birth showed quadratic associations with the temperamental trait of harm avoidance, which may increase the risk for depression. The highest scores were characteristic of the smallest individuals, followed by the heaviest/longest.
- Lower weight and thinness at birth predicted higher trait anxiety, which may predispose to anxiety disorders. High trait anxiety was also predicted by lower weight and thinness throughout infancy as well as more pronounced growth in weight between the ages of seven and 11 years and decreased growth in weight and height between age 11 and late adulthood.
- In women, smaller birth weight, placental size, and head circumference at 12 months predicted more pronounced positive schitzotypal traits, which may increase the risk for schizophrenia.
- Thinness and smaller head circumference at birth predicted symptoms of ADHD in children. These symptoms are a vulnerability factor for a clinical dignosis of ADHD and are a necessary component of the clinical diagnosis.

Implications:

- The results emphasise the prenatal aetiology of psychological vulnerability factors for mental disorders.
- The risk for depression, anxiety disorders, schizophrenia-spectrum disorders, and ADHD may increase linearly with decreasing birth size, even within normal variations in birth size.
- The results also emphasise the importance of links of physical growth after birth with trait anxiety. The identification of critical periods of growth for other vulnerability factors and disorders should be elucidated.
- The results underline the interplay between prenatal factors and physical growth or the developmental environment (such as SES) after birth in the aetiology of psychological vulnerability factors for mental disorders.
- A better understanding of the associations between early physical growth and psychological vulnerability factors for mental disorders enables health promotion actions to protect wellbeing of pregnant women and their babies by more accurate identification of those at risk for mental disorders.

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