Early growth, infant feeding and childhood cardiovascular risk factors

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Early growth, infant feeding and childhood cardiovascular risk factors

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door

Marieke de Beer

geboren te Hoorn

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	prof.dr. C.H.D. Fall

Leef hard en goed en schoon en wild. Kijk goed, voel beter. Wees niet bang. Kies voor wat u blij maakt, wat het ook moge zijn. Durf proberen wat te lastig lijkt. Leg de lat hoog genoeg. Koester en laat u koesteren. Geef anderen wat ze verdienen, en uzelf minstens ook. Blijf hopen, willen, dromen, wensen.

— *Griet Op de Beeck, Vele hemels boven de zevende*

TABLE OF CONTENTS

General introduction

Adapted from:
Early growth patterns and cardiometabolic function at the age of 5 in a multi-ethnic birth cohort: the ABCD study

Marieke de Beer, Manon van Eijsden, Tanja GM Vrijkotte, Reinoud JBJ Gemke

BMC Pediatrics 2009; 9:23

1

Cardiovascular risk factors

Cardiovascular diseases (CVDs) are a group of disorders of the heart and blood vessels including coronary heart disease and cerebrovascular disease.(1) CVDs are the number one cause of death globally.(1) Intermediate risk factors for developing CVDs are raised blood pressure (BP), raised blood glucose, raised blood lipids and overweight and obesity and indicate an increased risk of developing a heart attack, stroke, heart failure and other complications.(1) Data from diverse populations have in turn shown that BP, levels of blood insulin (one of the glucose homeostasis hormones), lipids and body mass index (BMI), track from childhood to adulthood, with average reported correlation coefficients around 0.3-0.4(2), 0.2-0.4(3), 0.4-0.7(4-6) and 0.2-0.5(7) respectively.

Developmental Origins of Health and Disease

Although it is clear that genetic factors and adult lifestyle contribute to the propensity towards obesity and associated conditions, recent findings have pointed out that CVDs may originate from periconceptional and perinatal environmental factors.(8,9) The 'Developmental Origins of Health and Disease' (DOHaD) hypothesis postulates that several chronic diseases in adulthood originate from adaptation to the (compromised) nutritional environment during early (antenatal or postnatal) life.(10) These adaptations, which appear to be mediated by certain epigenetic processes, may result in vascular, metabolic or endocrine changes in the structure and function of the body in adult life.(11) One adverse antenatal factor that is potentially associated with fetal adaptation (reprogramming) is maternal hypertension.

Developmental Origins of Health and Disease: Associations of early growth with cardiovascular risk factors

As maternal hypertension is one of the factors associated with placental dysfunction(12), resulting in restricted maternoplacental delivery of nutrients and oxygen to the fetus, the offspring of mothers with hypertension are expected to have a higher risk of retarded fetal growth.(13-18) A reduction of fetal growth then potentially constitutes a surrogate marker of fetal adaptation to a compromised intrauterine environment. A series of epidemiological studies in several countries have documented that subjects with fetal growth restriction have a higher risk of developing hypertension(19,20), type 2 diabetes (T2DM)(21,22) and coronary heart disease(23) in later life. In addition, prematurity has been demonstrated as an independent risk factor for high BP in later life.(24) Evolving evidence suggests an independent role of faster postnatal growth (also referred to as "catch-up growth") on CVDs in later life (the so called accelerated growth hypothesis).(25-35) Faster growth in postnatal life may be driven by the aim to compensate for antenatal growth retardation or prematurity which may subsequently increase the adverse effect on CVD risk in later life. However, the occurrence of faster postnatal growth is not limited to babies born growth retarded or premature, it also occurs in full term, normal birth weight infants, with comparable adverse associations with cardiovascular risk factors in later life.(36) Although faster postnatal growth also occurs in normal birth weight infants, it may still be the consequence of a fetal response to a compromised

intrauterine environment, such as maternal hypertension during pregnancy.(9) It is unknown whether maternal hypertension is related to faster postnatal growth in the offspring, independent from birth weight and pregnancy duration.

In order to examine whether some periods of postnatal growth are more important for the development of CVDs in later life than other periods, in most studies, a distinction is made between infancy and post-infancy (childhood) growth. Studies addressing the relationship of growth in infancy with BP and glucose and lipid biomarkers in later life have shown mixed results. There is therefore confusion about what constitutes optimal infant growth for future cardiovascular health. Furthermore, some studies suggest that it is weight gain in early infancy that is most important.(28,30,32,34) The Amsterdam Born Children and their Development (ABCD) study was unusual in collecting growth measures at frequent intervals in infancy. In contrast, there is consistent evidence for an association between faster weight gain in infancy and faster weight gain in childhood (*after* infancy) and subsequent risk of overweight in later life.(27,30,31,37,38) In addition, greater weight gain in childhood has been consistently associated with a higher BP(32,33,39-41), insulin resistance (IR), T2DM and an adverse lipid profile in later life in numerous studies.(42-45) It is not clear however, whether the relationship of weight gain to later life cardiovascular risk factors comes from the component of weight gain that is due to linear (skeletal) growth or to weight gain due to soft tissue (lean and fat) growth. Knowing this may provide insight into the mechanisms linking postnatal growth and later life CVDs. The Amsterdam Born Children and their Development (ABCD) study has measurements of both weight and height. We used conditional regression analysis (a statistical method that is described in the methods and design section of this general introduction) enabling us to separate the associations of cardiovascular risk factors with relative weight gain (weight gain independent of height) from those with linear growth.

Developmental Origins of Health and Disease: Associations of infant feeding with cardiovascular risk factors

Early feeding is associated with early growth(46,47), and therefore is an example of potential modifiable factors for the prevention of obesity, and other CVDs in later life. Furthermore, infant feeding may have direct programming effects on later life CVDs, for example due to differences in sodium intake(48,49), differences in long-chain polyunsaturated fatty acids (LCPUFAs)(49-51), epigenetic effects(52), a different distribution of body fat(53), differences in endocrine responses(54), anti-inflammatory effects(51) and nutritional programming of cholesterol synthesis.(55)

The associations of breastfeeding with later life BP, overweight, type 2 diabetes and raised blood lipids have received considerably more attention than the associations of timing of introduction of complementary feeding and these outcomes. A longer duration of breastfeeding has been associated with lower childhood BP in some studies(56,57), while in others this was not confirmed.(58-61) It has been associated with a reduced prevalence of later life overweight(62-65), a reduced risk of T2DM(55) and with lower cholesterol concentrations(55) in later life when compared to formula

feeding. While recent findings from the Generation R study group showed that later introduction of complementary feeding was associated with lower childhood BP(66), no clear associations with childhood obesity or glucose and lipid metabolism were found.(67,68)

The aims of this thesis were: 1) to determine the putative independent role of maternal hypertension on the offspring's growth and 2) to examine the associations of early growth and infant feeding with childhood cardiovascular risk factors. The associations investigated in this thesis are presented in figure 1.1.

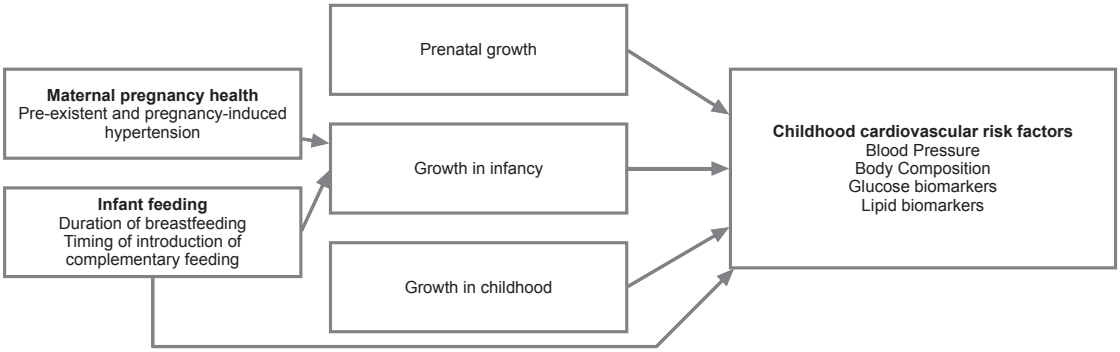

Figure 1.1. The associations investigated in this thesis

Methods and design

This study was nested in the Amsterdam Born Children and their Development (ABCD) study. The ABCD study is a prospective cohort study, a collaborative effort of the Municipal Health Service (GGD), all hospitals and midwife practices in Amsterdam and a research group hosted at the GGD/Amsterdam Medical Centre (AMC)/VU university medical centre Amsterdam (VUmc), www.abcd-study.nl.(69) One of the main objectives of the study is to investigate early-life conditions and the extent to which these conditions explain children's health in later life. The sampling procedure of the study is depicted in figure 1.2.

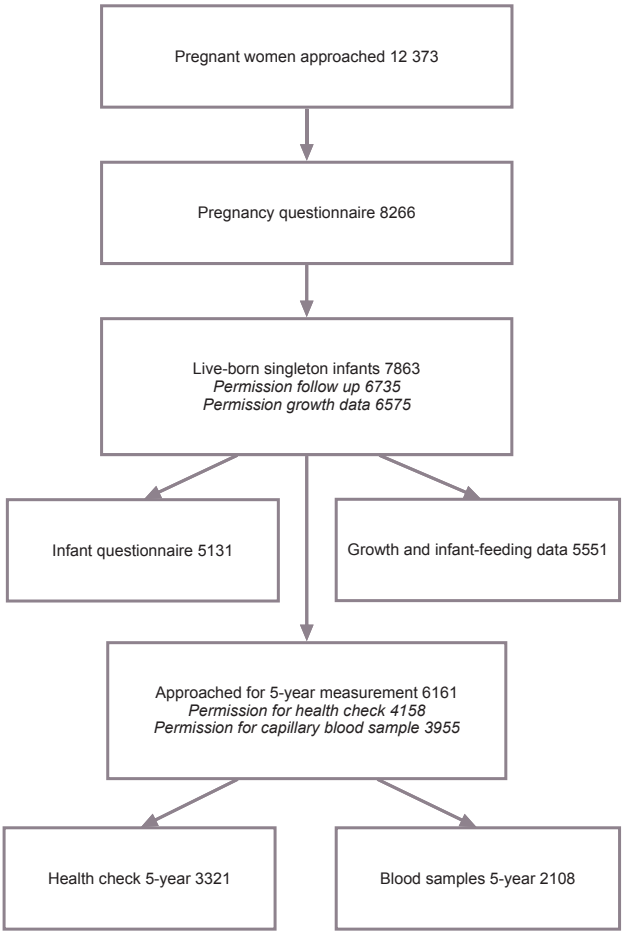

Figure 1.2. Sampling procedure

Between January 2003 and March 2004, all pregnant women living in Amsterdam were invited to participate in this study at their first visit (12–14th week of pregnancy) to an obstetric caregiver. A questionnaire, including sociodemographic data, obstetric history and lifestyle, was sent to the pregnant woman's home address.

Questionnaires were returned by 8266 women (response rate 67%). From this group 7863 gave birth to a viable singleton infant. Pregnancy duration, gender and birth weight were obtained from Youth Health Care (YHC) centres, which perform neonatal screening for congenital inborn errors of metabolism in all Dutch newborns. Supplementary information concerning complications during pregnancy and neonatal outcomes was obtained by probabilistic medical record linkage with The Netherlands Perinatal Registry (www.perinatreg.nl).

Three months after birth, another questionnaire, which included information about hypertension during pregnancy, was sent to the mothers who had given permission for follow-up (n=6735, 86%). With 5131 women returning the questionnaire, the response rate was 76%.

The YHC centres routinely invite parents and child from birth onwards for regular health evaluations at set ages: 8 times between birth and 12 months of age: around 1, 2, 3, 4, 6, 7.5, 9 and 11 months. During these check-ups weight and supine height were measured and feeding patterns (duration of breastfeeding and timing of introduction of complementary feeding) were registered. When measuring height, the parent was asked to hold the infant's head in contact with a fixed board, and the YHC health worker stretched the infant out to its maximum length and then brought a moving board into contact with the heels. Growth- and infant feeding data were collected for a total of 5551 children. Using these measures of size, we derived measures of growth (i.e. change in size). Disentangling the consequences of relative weight gain and linear growth at different ages requires statistical methods to address the high correlation of weight with height, and of repeated measurements in the same individual over time. Our "conditional" size measures were standardised residuals derived from regressing current size on all prior size measures. (32,33,41,70-73) Conditional relative weight was current weight accounting for current height and all prior weight and height measures. Conditional height was current height accounting for prior height and weight measures (but not current weight). Current weight was not accounted for in constructing conditional height because it does not contribute to current height. In contrast, we accounted for current height in constructing conditional weight because it does contribute to current weight. For example, conditional relative weight 6-12 months was derived from regressing 12-month weight on 12-month height, weights and heights at 1, 3 and 6 months, and birth weight. Conditional variables represent children's deviation from expected size, based on their own previous size and the growth of the other children in the study population, and can be interpreted as representing faster or slower relative weight gain or linear growth. Conditional regression analysis is designed to assess growth over distinct age periods and to eliminate collinearity problems caused by repeated measures.(73)

When the children reached the age of 5 years, the addresses of 6161 mothers were retrieved from the YHC registry. The mothers received an informed consent sheet for a health check of their child, for which 4158 (67%) women gave permission; 3955 (64%) women gave permission for a capillary blood sample. The health check included anthropometric measurements (height, weight), body composition (fat-free mass (FFM), fat mass (FM)) using bioelectrical impedance analysis (BIA) and BP (systolic BP, diastolic BP), and was carried out by trained research assistants in 3321 children aged 5 years; the fasting capillary blood sample glucose, total cholesterol (TC), high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides (TG) and C-Peptide(74) were assessed in 2108 children (2008-2010).

RESEARCH QUESTIONS

The following research questions will be addressed in this thesis:

Maternal pregnancy health and the offspring's early growth

1. What is the association of maternal hypertension during pregnancy with infant growth in the offspring (weight and height)? (chapter 2)

Validation of assessment of body composition, one of the outcome measures

2. What is the validity of assessment of body composition by bioelectrical impedance analysis (BIA) in (pre)school children? (chapter 3)

Associations of early growth and infant feeding with childhood cardiovascular risk factors

3. What is the association of birth weight, relative weight gain and linear growth during different periods in infancy (0-1y) and childhood (1-5y), and infant feeding with childhood BP? (chapter 4)
4. What is the association of birth weight, relative weight gain and linear growth during different periods in infancy (0-1y), and infant feeding with childhood body composition? (chapter 5)
5. What are the associations of birth weight, relative weight gain and linear growth during different periods in infancy (0-1y) and childhood (1-5y), and infant feeding with childhood glucose and lipid biomarkers? (chapter 6)
6. If infant feeding is associated with childhood BP, childhood body composition or childhood glucose and lipid biomarkers, does growth in infancy have a mediating role? (chapters 4, 5 and 6)

In the general discussion (chapter 7) the answers to the abovementioned research questions are summarised and discussed in the broader perspective of the current literature. Furthermore, methodological considerations and recommendations for practice and future research are discussed.

Relation of maternal hypertension with infant growth in a prospective birth cohort: the ABCD study

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2

ABSTRACT

The aim of this study was to investigate the hypothesised positive association of pre-existing and pregnancy-induced hypertension with the offspring's weight and height gain in the first 14 months of life. We studied 3994 pregnant women and their offspring in a prospective community-based cohort study, starting between 2003 and 2004 (Amsterdam Born Children and their Development, ABCD study). Questionnaires obtaining information about hypertension during pregnancy were completed, and this was complemented with additional information from the obstetric caregiver. Anthropometry of the offspring was followed during the first 14 months of life. Main outcome measures were presence or absence of growth acceleration in weight or height (normal: ΔSDS ≤0.67 vs. growth acceleration: ΔSDS >0.67). The relation between hypertension during pregnancy and offspring's weight and height gain was assessed by logistic regression analyses. We found that pre-existing hypertension was related to growth acceleration in weight and height. After correction for birth weight and pregnancy duration, the effect remained significant for growth acceleration in weight (OR 1.89; 95% CI 1.21–2.97; P<0.01). Pregnancy-induced hypertension showed similar results, although correction for birth weight and pregnancy duration rendered the associations non-significant. In conclusion, infants of women with pre-existing hypertension during pregnancy more frequently have growth acceleration in weight and height, and yet the mechanisms acting on postnatal growth appear to be different.

INTRODUCTION

The 'Developmental Origins of Health and Disease' hypothesis postulates that several chronic diseases in adulthood originate from adaptation to the (compromised) nutritional environment during early (antenatal or postnatal) life.(75) These adaptations, which appear to be mediated by certain epigenetic processes, may result in vascular, metabolic or endocrine changes in the structure and function of the body in adult life.(9)

An array of epidemiological studies in several countries have provided evidence supporting this hypothesis. They have documented that subjects with fetal growth retardation due to intrauterine malnutrition have a higher risk of developing hypertension, obesity, diabetes and coronary heart disease in later life.(43,76-82) In addition to fetal growth retardation, prematurity has been identified as an independent risk factor for high blood pressure and cardiovascular risk in later life.(24)

Moreover, evolving evidence suggests an independent role of rapid infant growth (also referred to as 'catch-up growth') on cardiovascular disease in later life (the accelerated growth hypothesis). Rapid growth in early postnatal life may be driven particularly by an aim to compensate for intrauterine growth retardation or prematurity, which consequently may increase the adverse effect on cardiovascular disease risk in later life.(25,76,78,80,83,84) Although rapid postnatal growth also occurs in normal birth weight infants, it may still be the consequence of a fetal response to a compromised intrauterine environment.(9)

One adverse antenatal factor that is potentially associated with fetal adaptation (reprogramming) is maternal hypertension. As maternal hypertension is one of the factors associated with placental dysfunction(12), resulting in restricted maternoplacental delivery of nutrients and oxygen to the fetus, the offspring of mothers with hypertension are expected to have a higher risk of retarded fetal growth and preterm birth. This may however be restricted to those with severe hypertension.(13-18) It is unknown whether maternal hypertension is related to postnatal growth acceleration in the offspring, independent from birth weight and pregnancy duration.

The aim of this study was to determine the putative independent role of maternal hypertension (pre-existing and pregnancy-induced hypertension) on the offspring's growth. We hypothesised that maternal pre-existing hypertension and pregnancy-induced hypertension are independent determinants of the offspring's growth acceleration, in addition to birth weight, pregnancy duration and potential confounding variables. When confirmed, these hypotheses provide novel insights into the role of the potential determinants of cardiovascular diseases in later life.

METHODS

Study population

Data from the Amsterdam Born Children and their Development (ABCD) study were used.(85-88) The ABCD study is a prospective cohort study that focuses on the explanatory role of dietary and lifestyle habits during pregnancy on birth outcomes and the future health of the child with specific attention to ethnicity (www.abcd-study.nl). Between January 2003 and March 2004, all pregnant women living in Amsterdam were invited to participate in this study at their first visit to an obstetric caregiver (Figure 2.1). A questionnaire covering sociodemographic data, obstetric history and lifestyle was sent to the pregnant woman's home address. This was around the 12th to 14th week of pregnancy. Questionnaires were returned by 8266 women (response rate: 67%). From this group, 7809 women gave birth to a live-born singleton infant with information on birth weight, gender and pregnancy duration. Mothers with diabetes or with missing information on pre-existing and pregnancy-induced hypertension were excluded from the analysis, leaving us with a group of 7163 mothers. Three months after birth, another questionnaire was sent to the mothers who had given permission for follow-up of their health status during pregnancy and of their child after being born (n=6693, 86%). These questions concerned the course of pregnancy and delivery, and maternal lifestyle during and after pregnancy. With 5131 women returning the questionnaire, the response rate was 77%. The height and weight of these children were collected at the Youth Health Care (YHC) registration of the Municipal Health Service in Amsterdam. The YHC registration is an organization which is represented all over the Netherlands. It offers regular consults during infancy and childhood at which vaccinations are administered and development is monitored. Height and weight measurements took place during regular follow-up moments and were performed by well-trained nurses. Since these data were not digitised at the time, we had to collect them afterwards. Up until now, we have managed to retrieve and digitize the growth data of 3994 of these children. Weight and height at a median age of 4 weeks (range 1–7 weeks) as well as a median of 14 months (range 10-18 months) were used. The reason for using anthropometric data at 4 weeks instead of birth data is that length is not always measured unequivocally at birth in the Netherlands.

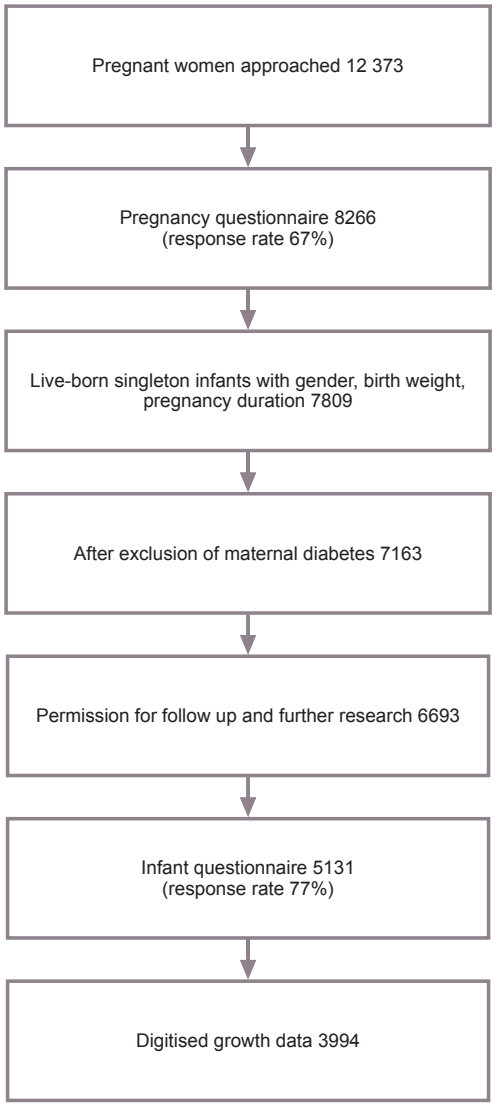


Figure 2.1. Flowchart

Measurements

Antenatal risk

Pre-existing hypertension

The pregnancy questionnaire contained questions concerning pre-existing hypertension, pregnancy-induced hypertension and use of anti-hypertensive medication. If a woman reported hypertension or used anti-hypertensive medication before the 20th week of pregnancy, this was classified as pre-existing hypertension. In addition, information from obstetric care, and Dutch perinatal registration, containing information concerning possible complications of the pregnancy (e.g. by pre-existing hypertension) were available for all women to complement this classification.(89) In case of discrepancies between both sources, we chose to use data from the questionnaires because this information was more complete.

Pregnancy-induced hypertension

The infant questionnaire addressed pregnancy-induced hypertension. If a woman reported hypertension that was not reported in the preceding pregnancy questionnaire, this was regarded as pregnancy-induced hypertension. In addition, data from the perinatal registration were available to complement the presence of pregnancy-induced hypertension. In case of discrepancies between diagnoses of both sources, we chose to use data from the questionnaires because this information was more complete.

Outcome

Infant growth acceleration (weight and height) in the first 14 months

Infant weight and height were expressed as standard deviation scores (SDS), using Dutch reference standards.(90) Infant growth acceleration (i.e. change in standardised weight or height gain) was expressed as a change in SDS (ΔSDS) and was calculated by subtracting SDS at 4 weeks from SDS at 14 months. Growth acceleration was defined as ΔSDS >0.67 between 4 weeks and 14 months. SDS 0.67 represents the width of each percentile band on standard growth charts (that is P2–P9, P9–P25, P25–P50, etc.). Crossing of centiles is the most commonly used indicator of clinically significant accelerated growth.(38,84)

Covariables

Pregnancy duration and birth weight

Pregnancy duration, gender and birth weight were obtained from YHC centers, which perform neonatal screening on congenital inborn errors of metabolism in all Dutch newborns. A standardised birth weight was calculated using the most recent Dutch reference values obtained from the Dutch perinatal registration (www.perinatreg.nl). Measured birth weight was divided by the mean birth weight of a reference group (alike in gender, pregnancy duration and parity) and expressed as a ratio. It was interpreted as an expression of intrauterine growth.

Breastfeeding

Information on feeding practices was obtained from the YHC registration of the Municipal Health Service in Amsterdam. Duration of exclusive breastfeeding was divided into five categories: not started, <1 month, 1–3 months, 4–6 months, >6 months.

Other confounding variables

The pregnancy questionnaire contained questions concerning maternal age in years (continuous), height in meters (continuous), pre-pregnancy body mass index (BMI)=maternal weight/height^2 (continuous), parity (0, 1, >2 children), maternal education (<5, 5–10, >10 years after primary school), ethnicity (based on mother's place of birth: Dutch, Surinamese, Turkish, Moroccan, other), paternal height in meters (continuous), cohabitant status (living together, single), smoking (yes, no) and use of alcohol during pregnancy (yes, no). We considered all amounts of smoking, and drinking more than once a day to be relevant.(91-93)

Statistics

Differences between participants with and without available growth data (total group=7163) were analysed using Chi-square analysis and independent sample t-tests. Differences between women without hypertension, pre-existing hypertension and pregnancy-induced hypertension were addressed using Chi-square analysis and ANOVA. Logistic regression was used to determine the relation between maternal hypertension and infant growth acceleration. After univariate analysis, possible confounding factors that appeared to be different between the three groups, women without hypertension, pre-existing hypertension and pregnancy-induced hypertension were added to the first model, forced entry. Standardised birth weight (as resultant from fetal growth) and pregnancy duration, as a linear term and as a quadratic term, were added to the final model to adjust for their acknowledged independent impact on infant weight gain and to explore their potential intermediating role. Furthermore, to assess whether the use of antihypertensive medication affected the relation between maternal hypertension and the outcome variables studied, sensitivity analyses were conducted excluding mothers who used antihypertensive hypertension.

All analyses were conducted using SPSS statistical software (version 15).

RESULTS

Data sources for hypertension

Data regarding hypertension were available for all women in this subgroup (they were not available for 32 women of the total group of 8266 who initially participated). Pre-existing hypertension was reported by 141 mothers. This was supported eight times by information from the perinatal registration. In addition, in two cases, the perinatal registration classified a mother as having both pre-existing and pregnancy-induced hypertension. These mothers reported pregnancy-induced hypertension. Furthermore, in one case, the mother reported pregnancy-induced hypertension, whereas the perinatal registration reported pre-existing hypertension. All three cases

were classified as pregnancy-induced hypertension, which was reported by 294 mothers. This was supported 122 times by information from the perinatal registration. In addition, 59 cases were identified by information from the perinatal registration.

Background variables

In the group with no available growth data (n=3169), the prevalence of maternal pre-existing hypertension was higher compared to the group with growth data (n=3994; 4.9% vs. 3.5%; P<0.01), whereas the prevalence of pregnancy-induced hypertension was lower (7.1% vs. 8.8%; P<0.01). Furthermore, in the group without growth data, more infants were born preterm (9.1% vs. 4.1%; P<0.001), maternal pre-pregnancy BMI was lower (22.9 kg/mt^2 vs. 23.1 kg/mt^2; P<0.05), nulliparity was greater (59.0% vs. 53.7%; P<0.001) and more women of Dutch and Surinamese origin were present (65.9% resp. 5.3% vs. 64.2% resp. 4.5%; P<0.001). Importantly, the educational level was not significantly different in participants with and without growth data.

Relevant sociodemographic background variables are shown in Table 2.1. Higher maternal BMI, older age, lower educational level, multiparity and shorter pregnancy duration were positively associated with pre-existing hypertension. Furthermore, among these women, breastfeeding was started less frequently.

Table 2.1. Background variables in three groups[a]

	No hypertension	Pre-existing hypertension	Pregnancy-induced hypertension		
	Mean (SD) or %	Mean (SD) or %	Mean (SD) or %		
	n=3500 (88%)	n=141 (3%)	n=353 (9%)		
Maternal factors					
Age (years)	30.9 (5.2)	32.0 (5.8)	31.4 (5.0)	*	b
Height (mt)	1.68 (0.07)	1.68 (0.07)	1.69 (0.08)	ns	
Height partner (mt)	1.81 (0.11)	1.81 (0.08)	1.82 (0.09)	ns	
Pre-pregnancy BMI (kg/mt²)	22.9 (3.9)	26.3 (6.0)	23.9 (3.9)	***	b,c
Parity				***	b,c
0 (%)	52.7	34.8	72.0		
1 (%)	33.7	42.6	20.1		
≥2 (%)	13.6	22.7	7.9		
Smoking during pregnancy (%)	10.7	6.4	8.2	ns	
Use of alcohol (%)	22.7	17.7	19.8	ns	
Use of antihypertensive drugs(%)	0	19.1	8.2	**	b,c
Maternal education				***	b,c
<5 years (%)	22.8	34.0	16.7		
5-10 years (%)	37.0	37.6	39.7		
>10 years (%)	40.2	28.4	43.6		
Two parent family (%)	87.3	82.3	90.9	*	c
Ethnicity				***	c
Dutch (%)	63.3	59.6	75.6		
Surinamese (%)	4.3	8.5	4.5		
Turkish (%)	4.8	3.5	2.5		
Moroccan (%)	7.3	9.2	4.2		
Other (%)	20.3	19.1	13.0		
Intrauterine and child factors					
Birth weight (g)	3473 (503)	3482 (615)	3357 (585)	***	c
Standardised birth weight ratio	1.00 (0.12)	1.03 (0.20)	0.98 (0.14)	**	c
IUGR (%<P10 standardised birth weight)	12.0	16.3	17.6	**	c
Pregnancy duration (weeks)	39.9 (1.5)	39.4 (1.7)	39.7 (1.5)	***	b
Preterm (%)	4.0	5.7	4.5	ns	
Male gender (% boy)	50.2	48.2	48.7	ns	
Duration of breast feeding				***	b,c
Not initiated (%)	28.8	45.0	37.4		
<1 month (%)	9.5	6.4	9.1		
1-3 months (%)	19.4	16.4	16.3		
4-6 months (%)	21.9	10.7	18.6		
>6 months (%)	20.5	21.4	18.6		
Weight SDS 4 weeks	0.18 (1.2)	0.18 (1.3)	-0.14 (1.3)	***	c
Weight SDS 14 months	-0.09 (1.0)	0.11 (1.0)	-0.16 (1.0)	*	b
ΔSDS weight	-0.27 (1.2)	-0.08 (1.3)	0.02 (1.3)	***	c
Accelerated growth weight (%)	18.0	29.8	24.1	***	b,c
Height SDS 4 weeks	0.09 (1.0)	-0.10 (1.1)	-0.05 (1.2)	*	c
Height SDS 14 months	-0.11 (1.0)	-0.05 (1.0)	-0.18 (1.1)	ns	
ΔSDS height	-0.19 (1.0)	0.04 (1.1)	-0.12 (1.2)	*	b
Accelerated growth height (%)	17.7	27.6	22.2	**	b,c

BMI=body mass index; IUGR=intrauterine growth retardation; SD=standard deviation; SDS=standard deviation score; ΔSDS=change in standard deviation score

* P<0.05, ** P<0.01, *** P<0.001

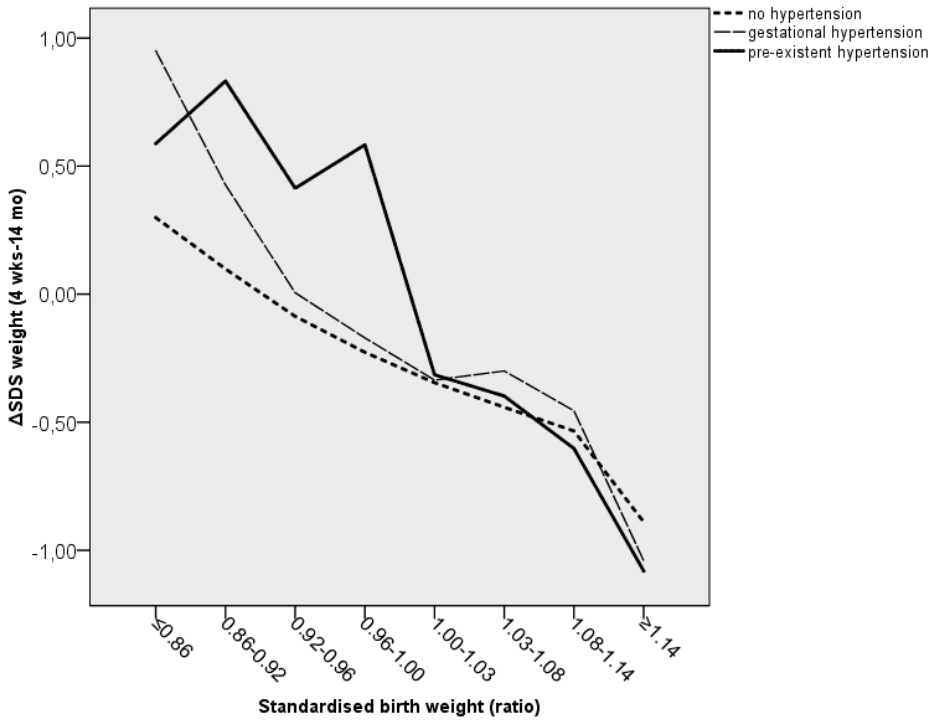
[a] Chi-square analysis and ANOVA were used

[b] difference between pre-existing hypertension and controls

[c] difference between pregnancy-induced hypertension and controls.

Infant growth acceleration in weight

For all three groups, the mean ΔSDS for weight (growth acceleration in weight as a continuous variable) are presented for eight different strata of standardised birth weight (Figure 2.2). This figure demonstrates the modifying effect of standardised birth weight on the association between maternal hypertension and accelerated growth in weight: only in the below average birth weight group a synergistic effect of maternal hypertension on accelerated weight gain was present.



ΔSDS = change in Standard Deviation Score

Figure 2.2. Accelerated growth in weight. Standardised birth weight (ratio) is measured birth weight divided by the mean birth weight of a reference group (alike in gender, pregnancy duration and parity)

After adjustment for confounding variables, pre-existing and pregnancy-induced hypertension were independent determinants of growth acceleration in weight. After correction for standardised birth weight and pregnancy duration, the relation between pre-existing hypertension and growth acceleration in weight remained significant (OR 1.89; 95% CI 1.21–2.97; P<0.01); however, the relation of pregnancy-induced hypertension with growth acceleration lost significance (Table 2.2). Furthermore, we did a sensitivity analysis excluding women who used antihypertensive drugs (n=116), leaving us with a group of 25 subjects. The relation between pre-existing hypertension and growth acceleration in weight was stronger, but it was no longer significant (OR 1.93; 95% CI 0.67–5.61; P=0.22).

Table 2.2. Relation of maternal hypertension with the offspring's growth acceleration in weight[a]

	Univariate effects OR (95%CI)	Multivariate effects Model 1 OR (95%CI)	Multivariate effects Final model OR (95%CI)
Maternal factors			
Pre-existing hypertension	1.93 (1.33-2.80)**	1.93 (1.30-2.86)**	1.89 (1.21-2.97)**
Pregnancy-induced hypertension	1.44 (1.11-1.87)**	1.38 (1.05-1.81)*	1.10 (0.81-1.50)
Age	0.96 (0.95-0.98)***	0.99 (0.97-1.01)	0.99 (0.98-1.01)
Pre-pregnancy BMI (kg/mt²)	1.01 (0.99-1.03)	0.99 (0.97-1.01)	1.02 (1.00-1.04)
Parity			
0 (ref)	-	-	-
1	0.61 (0.51-0.73)***	0.66 (0.54-0.80)***	0.54 (0.43-0.67)***
≥2	0.73 (0.57-0.94)*	0.67 (0.51-0.90)**	0.54 (0.39-0.74)***
Maternal education			
<5 years (ref)	-	-	-
5-10 years	0.71 (0.59-0.87)**	0.85 (0.68-1.07)	0.91 (0.71-1.17)
> 10 years	0.56 (0.46-0.69)***	0.83 (0.64-1.07)	0.93 (0.70-1.25)
Cohabitant status (living together)	0.67 (0.54-0.84)***	0.87 (0.68-1.11)	0.88 (0.67-1.15)
Ethnicity			
Dutch (ref)	-	-	-
Surinamese	1.85 (1.32-2.61)***	1.53 (1.06-2.22)*	0.98 (0.65-1.48)
Turkish	1.38 (0.96-1.98)	1.46 (0.98-2.18)	1.37 (0.88-2.14)
Moroccan	1.75 (1.32-2.33)***	1.77 (1.28-2.43)**	1.95 (1.37-2.77)***
Other	1.10 (0.90-1.36)	1.13 (0.90-1.41)	0.99 (0.77-1.27)
Intrauterine and child factors			
Standardised birth weight	0.01 (0.00-0.01)***	Not entered	0.00 (0.00-0.01)***
Linear term of pregnancy duration (weeks)	0.19 (0.03-1.32)	Not entered	0.06 (0.01-0.47)**
Quadratic term of pregnancy duration (weeks²)	1.01 (0.99-1.04)	Not entered	1.03 (1.00-1.06)*
Duration of breast feeding			
Not initiated	3.38 (2.60-4.38)***	3.14 (2.40-4.12)***	2.38 (1.77-3.20)***
<1 month	3.05 (2.20-4.23)***	2.86 (2.05-4.00)***	2.83 (1.96-4.08)***
1-3 months	2.13 (1.59-2.85)***	2.13 (1.58-2.87)***	2.09 (1.52-2.89)***
4-6 months	1.15 (0.84-1.57)	1.19 (0.87-1.64)	1.15 (0.82-1.63)
>6 months (ref)	-	-	-

BMI=body mass index. * P<0.05, ** P<0.01, *** P<0.001. [a]Logistic regression analysis was used. Model 1: adjusted for maternal age, pre-pregnancy BMI, parity, educational level, cohabitant status, ethnicity and duration of breastfeeding. Final model: adjusted for maternal age, pre-pregnancy BMI, parity, educational level, cohabitant status, ethnicity, duration of breastfeeding, standardised birth weight and pregnancy duration as a linear and as a quadratic term.

In subsequent analyses including standardised birth weight as a dichotomous variable (below vs. above average standardised birth weight), a significant interaction was found between pre-existing hypertension and standardised birth weight (OR 3.17; 95% CI; 1.20–8.38; P<0.05). Therefore, we performed a stratified analysis in two birth weight subgroups. In the below average birth weight subgroup, a larger effect size was found for the association between pre-existing hypertension and growth acceleration in weight (OR 2.64; 95% CI 1.48–4.71; P<0.01). This relation was not significant in the above average birth weight group (Table 2.3). Furthermore, we excluded women who used antihypertensive drugs (n=553), leaving us with a group of 11 subjects. The relation between pre-existing hypertension and growth acceleration in the below average birth weight subgroup was stronger, though of borderline significance (OR 3.53; 95% CI 0.98–12.71; P=0.05).

Table 2.3. Relation of maternal hypertension with the offspring's growth acceleration in weight after stratifying for standardised birth weight below vs. above average[a]

	Univariate effects OR (95%CI)	Multivariate effects Model 1 OR (95%CI)	Multivariate effects Final model OR (95%CI)
Logistic regression weight			
Birth weight ≤ average			
Pre-existing hypertension	3.07 (1.86-5.07)***	2.95 (1.72-5.04)***	2.64 (1.48-4.71)**
Pregnancy-induced hypertension	1.71 (1.23-2.37)**	1.60 (1.13-2.26)**	1.13 (0.77-1.67)
Birth weight > average			
Pre-existing hypertension	1.09 (0.55-2.14)	1.04 (0.51-2.13)	1.09 (0.48-2.44)
Pregnancy-induced hypertension	1.03 (0.65-1.65)	0.91 (0.56-1.48)	1.06 (0.63-1.80)

BMI=body mass index
* P<0.05, ** P<0.01, *** P<0.001
[a]Logistic regression analysis was used
Model 1: adjusted for maternal age, pre-pregnancy BMI, parity, educational level, cohabitant status, ethnicity and duration of breastfeeding.
Final model: adjusted for maternal age, pre-pregnancy BMI, parity, educational level, cohabitant status, ethnicity, duration of breastfeeding, standardised birth weight and pregnancy duration as a linear and as a quadratic term.

Infant growth acceleration in height

In univariate analysis, as well as after adjustments for the confounding variables, both pre-existing and pregnancy-induced hypertension were significantly associated with infant growth acceleration in height. However, after adjustments for standardised birth weight and pregnancy duration, the associations lost significance (Table 2.4). In subsequent analyses including standardised birth weight as a dichotomous variable (below vs. above average birth weight), no significant interactions were found between pre-existing or pregnancy-induced hypertension and standardised birth weight.

Table 2.4. Relation of maternal hypertension with the offspring's growth acceleration in height[a]

	Univariate effects OR (95%CI)	Multivariate effects Model 1 OR (95%CI)	Multivariate effects Final model OR (95%CI)
Maternal factors			
Pre-existing hypertension	1.77 (1.19-2.63)**	1.82 (1.19-2.79)**	1.58 (0.99-2.51)
Pregnancy-induced hypertension	1.32 (1.01-1.74)*	1.39 (1.04-1.85)*	1.17 (0.85-1.60)
Age (years)	0.95 (0.93-0.96)***	0.98 (0.96-0.99)**	0.98 (0.96-1.00)*
Pre-pregnancy BMI (kg/mt²)	1.00 (0.98-1.02)	0.97 (0.95-0.99)*	0.99 (0.97-1.02)
Parity			
0 (ref)	-	-	-
1	0.70 (0.58-0.85)***	0.76 (0.62-0.93)**	0.68 (0.55-0.85)**
≥2	0.84 (0.65-1.08)	0.82 (0.61-1.10)	0.74 (0.54-1.02)
Maternal education			
<5 years (ref)	-	-	-
5-10 years	0.68 (0.55-0.83)***	0.84 (0.67-1.06)	0.88 (0.68-1.12)
>10 years	0.45 (0.37-0.56)***	0.70 (0.54-0.92)*	0.73 (0.55-0.98)*
Cohabitant status (living together)	0.56 (0.45-0.71)***	0.75 (0.59-0.96)*	0.74 (0.57-0.97)*
Ethnicity			
Dutch (ref)	-	-	-
Surinamese	2.05 (1.41-2.99)***	1.57 (1.05-2.35)*	1.05 (0.68-1.63)
Turkish	1.96 (1.37-2.79)***	1.85 (1.24-2.75)**	1.68 (1.10-2.56)*
Moroccan	1.63 (1.20-2.21)**	1.45 (1.03-2.05)*	1.49 (1.04-2.14)*
Other	1.49 (1.21-1.84)***	1.49 (1.20-1.86)***	1.36 (1.07-1.73)*
Intrauterine and child factors			
Standardised birth weight	0.03 (0.01-0.06)***	Not entered	0.02 (0.01-0.04)***
Linear term of pregnancy duration (w)	0.10 (0.01-0.88)*	Not entered	0.02 (0.00-0.20)***
Quadratic term of pregnancy duration (w²)	1.02 (1.00-1.05)	Not entered	1.04 (1.01-1.07)**
Duration of breast feeding			
Not initiated	3.22 (2.45-4.22)***	3.06 (2.31-4.06)***	2.35 (1.74-3.16)***
<1 month	2.78 (1.97-3.92)***	2.66 (1.87-3.79)***	2.49 (1.71-3.62)***
1-3 months	1.87 (1.37-2.53)***	1.93 (1.41-2.64)***	1.84 (1.32-2.55)***
4-6 months	1.45 (1.06-1.98)*	1.59 (1.15-2.18)**	1.54 (1.10-2.15)*
>6 months (ref)	-	-	-

BMI=body mass index. * P<0.05, ** P<0.01, *** P<0.001. [a]Logistic regression analysis was used. Model 1: adjusted for maternal age, pre-pregnancy BMI, parity, educational level, cohabitant status, ethnicity and duration of breastfeeding. Final model: adjusted for maternal age, pre-pregnancy BMI, parity, educational level, cohabitant status, ethnicity, duration of breastfeeding, standardised birth weight and pregnancy duration as a linear and as a quadratic term.

DISCUSSION

The results of this study show that the offspring of women with pre-existing hypertension are 1.9 times more likely to have growth acceleration in weight during the first 14 months of life. Interestingly, this association appears to be only significant in infants with a below average birth weight, with an even 2.6 times higher odds for growth acceleration in weight. Neither fetal growth retardation nor shorter duration of pregnancy is solely responsible for these findings, but these factors partly act as intermediating variables. It should be mentioned, however, that these secondary analyses were relying on small numbers, and should therefore be interpreted with some caution. Furthermore, we found some indication for a possible attenuating effect of the use of antihypertensive drugs on offspring's accelerated growth in weight. This suggests a better condition of women who are prescribed anti-hypertensive drugs with a resultant better offspring.

Furthermore, in contrast to growth acceleration in weight, the association of maternal pre-existing hypertension with growth acceleration in height was mainly mediated by birth weight and pregnancy duration.

A significant relation between pregnancy-induced hypertension and offspring's growth acceleration (both weight and height) was found. However, the association of pregnancy-induced hypertension with growth acceleration was mainly mediated by reduced birth weight and shorter pregnancy duration. There may be numerous differences in the causes and consequences of pre-existing and pregnancy-induced hypertension, respectively, explaining this incongruence. For instance, in contrast with pregnancy-induced hypertension, pre-existing hypertension probably has its effect in early pregnancy. This period of organogenesis seems especially sensitive to permanent alterations in physiological and metabolic homeostatic set points.(94) Furthermore, pre-existing hypertension is one of the risk factors for pre-eclampsia, which in turn is associated with preterm birth and intrauterine growth retardation (and potentially subsequent accelerated postnatal growth).(16,95) If hypertension was reported before the 20th week of pregnancy, we classified this as pre-existing hypertension, which in a proportion of cases might progress to superimposed pre-eclampsia. It is conceivable that the combination of these two conditions is mainly associated with accelerated postnatal growth.

To our knowledge, few studies have specifically addressed the relation between maternal hypertension and accelerated infant growth. Part of the demonstrated associations seem to work through a reduction in birth weight and shorter pregnancy duration. Moreover, there appears to be additional weight gain in the offspring of mothers with pre-existing hypertension. As proposed in the recent literature, a reduction of fetal growth constitutes a surrogate marker of a coordinated fetal response to a restricted intrauterine environment. Growth acceleration is than mainly related to this fetal response.(9) When translating this to our findings, a reduction in birth weight may be a sign for permanent alterations in the constitution of an infant, with growth acceleration in weight as a result.

This study has a number of strengths. First, we studied a community-based sample with a substantial number of subjects. Second, we collected possible confounding variables known to be related to maternal hypertension and potentially also to infant growth acceleration, for which we could adjust. Third, we assessed growth

acceleration not only in weight but also in height. The latter is sparsely used in analyses of growth acceleration, while it is likely to provide an interesting extra dimension of growth. Finally, we used multiple resources to determine the presence of hypertension: two questionnaires assessed at different moments, and in addition information from the obstetric care provider. A number of limitations to the study should be considered. First, there was a substantial amount of missing data because we were not able to retrieve growth data for all participants. Regarding some background variables, the group that we used for the analysis was different from the rest of the original cohort (for which we did not have growth data). However, the prevalence of both determinants was comparable to the rates reported in a recent review, which are in agreement with the representativeness of our sample.(96) This review reported a prevalence of 3% for pre-existing hypertension and 6% for pregnancy-induced hypertension, compared to 3% and 9%, respectively, in our group.(96) Moreover, in subjects with growth data, some growth acceleration associated factors had a lower prevalence. Therefore, there should be some prudence regarding the external validity of our findings. Second, we used participant self-reporting of pre-existing and pregnancy-induced hypertension, which could affect the accuracy. However, in a recent study comparing self-report questionnaires and medical record data, Okura et al. reported reliable agreement for hypertension.(97) Another study, which also addressed the reliability of self-report data on hypertension, suggested that this method may also lead to underestimated prevalence estimates.(98) However, the validity of self-reported information on hypertension in this study is not unequivocal. Third, blood pressure in women was not quantified. This would have enabled us to assess a possible effect of severity of hypertension on the infants' growth more accurately. Moreover, it would have shed light on whether well-managed hypertension would have the same effect on offspring growth patterns. Fourth, birth weight was used as a proxy for intrauterine growth. This is a rather crude measure for fetal growth restriction as there may be appropriate for gestational age children who suffered from intrauterine growth restriction. In contrast, there are small for gestational age children who are constitutionally small but not growth retarded. Finally, in the pregnancy-induced hypertension group, no differentiation was made between women with gestational hypertension and the different phenotypes of pre-eclampsia. These conditions are likely to differ in their pathophysiological impact regarding endothelial function, maternal organ development, placentation, placental function and subsequent fetal growth and fetal organ programming.(99) However, as stated earlier, a proportion of the women with pre-existing hypertension may develop pre-eclampsia. Preliminary analyses in a subset of primiparous women showed that pre-eclampsia was related to growth acceleration in weight and height, whereas this was not the case in pregnancy-induced hypertension. The relation seems to be intermediated by birth weight and pregnancy duration (data not shown).

In conclusion, we have shown that maternal hypertension during pregnancy is an important risk factor for accelerated growth in offspring. Yet the mechanisms which act on postnatal growth in weight and height appear to be different. In contrast to pre-existing hypertension, the association between pregnancy-induced hypertension and accelerated growth appears to work entirely through a reduction in birth weight and pregnancy duration. Future studies should further explore the role of maternal hypertension on the offspring's growth. If our findings are confirmed, growth of hypertensive mothers' offspring should be monitored more attentively.

Validation of total body water analysis by bioelectrical impedance analysis with deuterium dilution in (pre)school children

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3

ABSTRACT

Background and aims Accurate field methods to assess body composition in young children are scarce. The aim of this study was to validate bioelectrical impedance analysis with deuterium based total body water analysis in (pre)school children.

Methods We examined fifty-six 4-7 year old children, 36% boys. Total body water estimated with standardised single frequency bioelectrical impedance analysis was compared with deuterium dilution technique. An established equation (Kushner) was tested, recalibrated and subsequently cross-validated in an independent sample.

Results Compared to deuterium dilution (mean total body water 12.66 kg, n=56), bioelectrical impedance analysis underestimated total body water by 0.51 kg (P=0.002) and this varied across the range of total body water (r=0.41; P=0.002). Recalibration of the equation yielded: total body water (kg) = 0.439 height^2 (cm^2)/resistance (Ω) + 0.027 weight (kg) + 4.014 (R^2=0.74, SEE=0.96 kg). Application of this equation in the independent sample (n=20) showed a non-significant bias in total body water (mean bias -0.30 kg, P=0.17).

Conclusions These data indicate that BIA underestimates total body water by 0.51 kg in (pre)school children, when using the Kushner equation. Recalibration and cross-validation enables enhanced assessment of body composition in (pre)school children for use in epidemiological field studies.

INTRODUCTION

Field methods that accurately assess body composition in children are scarce. Currently, body mass index (BMI=weight/height^2) is the most commonly used routine measure that gives an indication of relative weight. International BMI-for-age cut offs have been proposed to classify overweight as well as undernutrition.(100) However, BMI levels among children should be interpreted with caution. Although high BMI-for-age is a good indicator of excess fat mass (FM), BMI differences among thinner children can be largely due to fat-free mass (FFM).(101) Following this, to identify the need for intervention in case of suspected overweight or undernutrition, more information is needed about whole body FM and whole body FFM which is reflected in body composition.

Body composition is best addressed by applying a multi-component model, in which measurements of different body properties are combined.(102) The three-component (3C) model for instance is based on the measure of weight, total body water (TBW) and body volume (BV). It distinguishes FM, water and fat-free dry mass. Although highly accurate, these methods are relatively expensive, sometimes rather invasive and therefore not suitable in routine (field) applications.

Bioelectrical Impedance Analysis (BIA) is potentially more suitable for survey and outpatient clinical use, particularly in pre-school and school aged children. BIA estimates FFM (and indirectly FM) by measuring the resistance (*R*) of body tissue to a weak imperceptible current. The measured resistance is first of all used to estimate TBW.(103) For the estimation of TBW in children, a large number of BIA equations are available. An important practical concern is that the prediction equations are population specific. Therefore, it is recommended to validate equations in the population or sample in which they are used, by comparing BIA to a reference method, such as hydrometry.(104)

In the next step, FFM is calculated from TBW using the percentage of hydration of FFM (hydration constant). Because chemical composition of FFM changes during childhood and is different in boys and girls age- and sex-specific constants for hydration of FFM are recommended.(105-107) Finally, FM can be calculated by subtracting FFM from total weight.

The aim of the present study was to assess the validity and reliability of an established BIA equation for 4-7 year old children. Furthermore, to derive a recalibrated equation when this BIA equation differed significantly from hydrometry.

MATERIALS AND METHODS

For the recalibration sample, a total of thirty-six healthy children were recruited from four local primary schools in Amsterdam, the Netherlands. The measurements were performed in September and October of 2009. Participants were visited at school in the morning for baseline urine collection and the administration of deuterium water (^2H_2O). In the afternoon they visited the Nutritional Assessment Laboratory of the Hogeschool van Amsterdam, University of Applied Sciences, accompanied by a parent for a second urine collection and a 1 hour measurement session. A second independent sample of 20 children, referred as the external cross-validation sample, was recruited. They were participants of a large prospective cohort study in

Amsterdam and were of the same age as the recalibration sample children (www.abcd-study.nl).(87) Permission was granted by the institutional review board of the VU University Medical Centre. All parents gave written informed consent.

Anthropometrics

Height (ht) was measured to the nearest millimeter using a Leicester portable height measure (Seca, Hamburg, Germany) and weight (wt) to the nearest 100 g using the electronic weighing scale that is part of the Bod Pod® (validation group) or to the nearest 100 g using a Marsden weighing scale, model MS-4102 (Marsden weighing group, Oxfordshire, UK) (cross-validation group).

BIA

After the child had emptied his/her bladder, arm-to-leg BIA was measured using the Bodystat 1500MDD system (Bodystat Inc., Douglas, UK). The BIA measurement was performed after 2 minutes in supine position with the legs abducted to 45°. A pair of electrodes was attached at the right wrist/hand and the right ankle/foot and a 50 kHz alternating current (800 mA) was passed through the body. The voltage drop was measured and the *R* calculated. The procedure was repeated and the average of the 2 measurements was used for further calculations. We chose to use the Kushner et al.(103) formula for the calculation of TBW, because it was based on population based samples of an age range comparable to our sample and because it is incorporated into the Bodystat software.

- TBW (kg) = 0.59 ht^2 (cm^2)/*R* (Ω) + 0.065 wt (kg) + 0.04

Total body water, measured by deuterium dilution

Total body water (TBW) was determined by ^2H_2O dilution with a dose equivalent to 0.05 g per kg body weight. Doses were sweetened by lemonade. After drinking the ^2H_2O dose the dose container was rinsed with 20 mL of tap water and given to the participants to drink, in order to ensure complete ingestion of the total dose. Urine samples were collected pre-dose and 4 h post-dose using a urine collection system. These were stored in special glass vials at -20°C, and then analysed using isotope-ratio mass spectrometry (IRMS).(108) For calculating TBW, it was assumed that ^2H_2O dilution space overestimated TBW by a factor of 1.04, therefore TBW was divided by 1.04.(109)

Statistics

Validation of the Kushner equation

Paired sample t-tests were used to compare TBW calculated with BIA and obtained from ^2H_2O. For assessment of TBW agreement between BIA and ^2H_2O the statistical graphic approach proposed by Bland and Altman was used.(110) Pearson's correlation analysis was performed of the variables generated on the x and y axes of the Bland-Altman plot. This was used to report whether the bias between techniques varied in relation to the amount of TBW.

Recalibration of the prediction equation for TBW and cross-validation

Linear regression analysis was used to recalibrate the relationship between ht^2/R incorporating weight in the regression model and TBW from ^2H_2O. The standard error of the estimate (SEE) was calculated, in order to indicate accuracy of body composition estimates in individuals. The regression equation was then used to predict TBW in the cross-validation group. The same analyses were applied as described for the validation of the existing equation. All analyses were conducted using SPSS statistical software (version 16.0).

RESULTS

Characteristics of subjects

Figure 3.1 shows the flowchart of the study procedure.

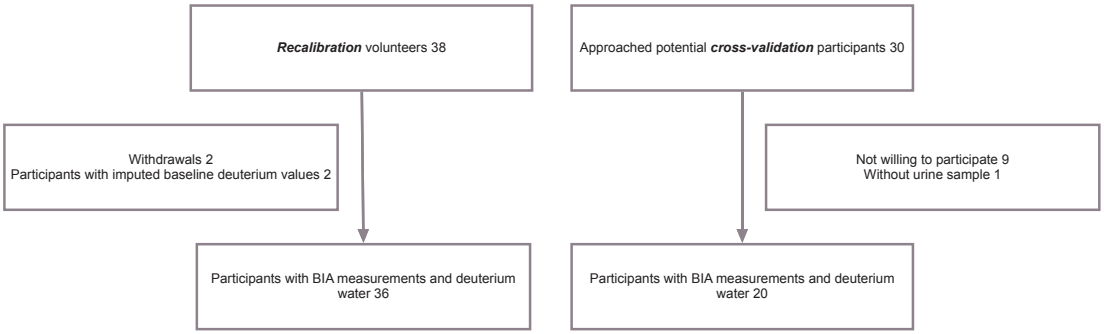

Figure 3.1. Flowchart of participants in the study

Two girls from the recalibration group showed higher than expected baseline measurement levels of deuterium. We imputated these values with average values of baseline measurement. Furthermore, one child of the cross-validation group was excluded because we administered deuterium dilution twice (with an interval of 1 week) because she did not show up at the first measurement session. Therefore, the second baseline measurement showed too high a level of deuterium. Table 3.1 shows a description of the characteristics of the recalibration and the cross-validation sample, stratified by gender.

Table 3.1. Description of the sample

	Recalibration sample (n=36)				*Cross-validation sample (n=20)*			
	Boys (n=14)		**Girls (n=22)**		**Boys (n=6)**		**Girls (n=14)**	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	5.9	0.9	5.6	1.0	5.5	0.2	5.6	0.2
Weight (kg)	21.0	2.8	23.5	7.9	22.7	3.3	20.5	2.4
Height (mt)	113.6	5,8	114.7	8.7	118.0	4.3	113.9	5.8
BMI (kg/mt^2)	16.3	1.7	17.4	3.3	16.2	1.5	15.8	1.0
R_{BIA} (Ω)	712.8	54.7	741.0	72.0	694.6	80.0	775.3	68.4
TBW_{DEU} (kg)	12.8	1.3	12.4	2.1	13.7	1.6	12.4	1.5

BMI, body mass index; R_{BIA} (Ω), resistance; TBW_{DEU}, total body water.

Validation of Kushner BIA equation

We found an underestimation in TBW of 0.51 kg (P=0.002) using the Kushner equation in BIA when compared to deuterium water. This bias varied across the range of TBW with a correlation of 0.41 (P=0.002) with a smaller difference between the techniques at a higher amount of TBW (Figure 3.2).

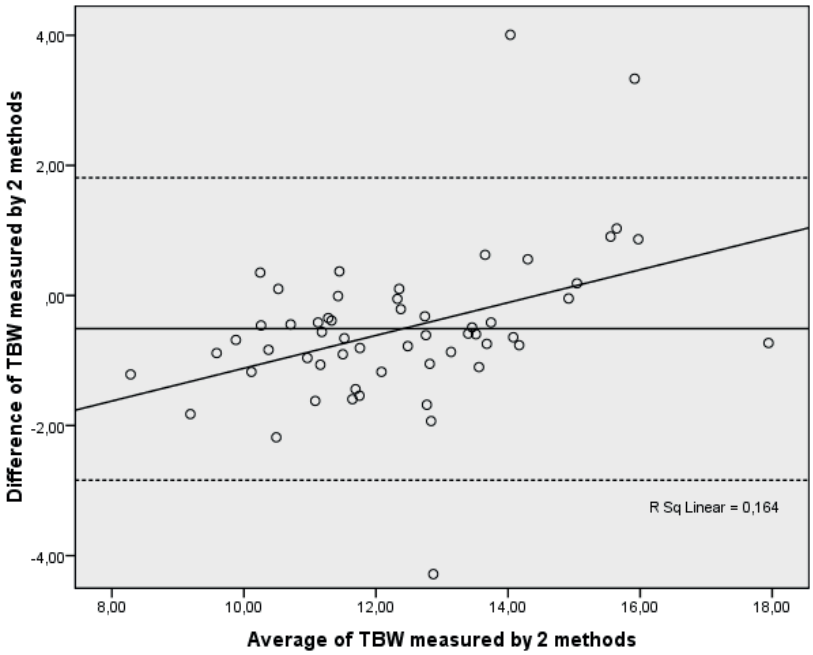

Figure 3.2. Bland-Altman plot showing the agreement between the differences (BIA existing equation - Deuterium dilution) and mean (BIA existing equation + Deuterium dilution) of TBW (r=0.41; P=0.002) (recalibraton and cross-validation sample, n=56)

Recalibration of the prediction equation and cross validation

The correlation between ht^2/R and TBW_{DEU} was 0.84 (P<0.001). We recalibrated the existing equation: TBW = 0.439 (ht^2/R) + 0.027 wt + 4.014, with R^2 of 0.74, standard error of the estimate (SEE) of 0.96 kg.

Using the recalibrated formula, we found a non-significant underestimation of TBW in the cross-validation sample of -0.30 kg (P=0.17). This bias did not vary across the range of TBW with a correlation of -0.11 (P=0.65) (Figure 3.3).

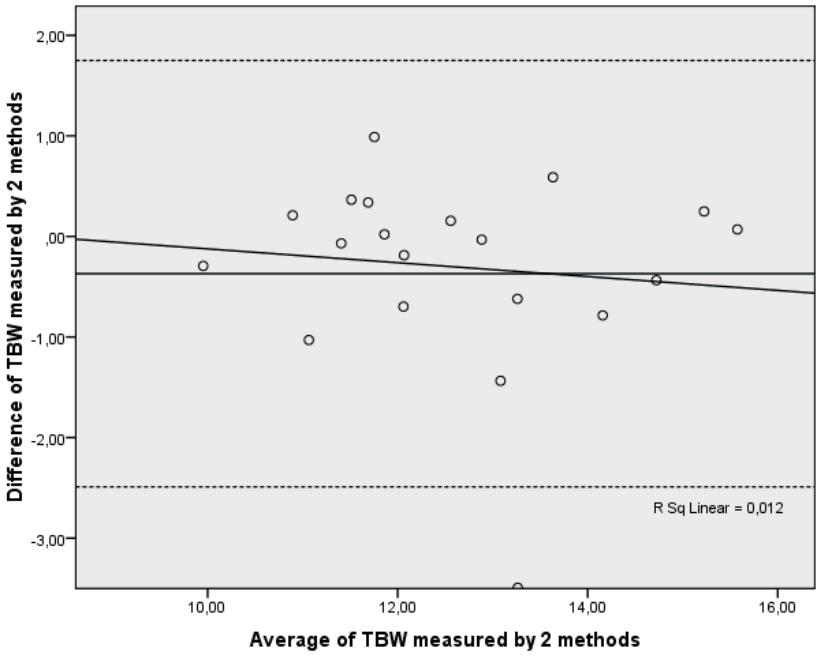

Figure 3.3. Bland-Altman plot showing the agreement between the differences (BIA recalibrated equation – Deuterium dilution) and mean (BIA recalibrated equation + Deuterium dilution) of TBW (r=-0.11; p=0.65) (cross-validation sample, n=20)

DISCUSSION

Analysis of body composition in children becomes increasingly important in light of the expanding prevalence of overweight and obesity and is also suitable for use in children with undernutrition. BIA represents one of the few potentially applicable methods for this purpose in field settings. There are several available BIA-equations for the prediction of TBW in children. The Kushner equation incorporated in the Bodystat system is based on a sample of 24 children (4.8-9.8 years). The equation was cross-validated in 13 children (6.4-9.9 years).(103) These reference groups are comparable with the current study group of 4.4-7.5 years respectively 5.1-5.9 years. Previous BIA validation studies in adults and children have reported that equations generated in one population do not always transfer successfully to others.(111-113) The present study shows that the Kushner BIA equation for school age children, when compared to the Deuterium dilution method underestimated TBW and therefore FFM. This underestimation is non-systematic which means values cannot simply be converted to get an accurate value of TBW. Recalibration of the equation yielded: TBW = 0.439 (height^2/resistance) + 0.027 weight + 4.014. Application of this equation showed a small non-significant bias. Importantly this bias was systematic, thereby allowing more robust assessment of body composition in (pre)school aged children for use in epidemiological field studies.

This study has several strengths. First, we used a larger recalibration and cross validation group with a more homogenous age range than was previously used. Second, because we cross-validated the recalibrated equation in a different sample, we were not only able to assess a potential bias, but we could also examine whether this bias was systematic and therefore whether it is possible to correct for a potential bias.

There are some limitations of the present study. First, children were allowed to eat and drink during the 4 hour equilibration period. We did not adjust for dilution of the dose by water intake during the 4 hour equilibration period. This could have resulted in an over-estimation of TBW. Secondly, although the cross-validation is a strength, it is possible that the bias did not reach significance due to the smaller sample size. However, the small underestimation seems to be systematic which means values can be converted to get an accurate value of TBW.

In this study, we were not able to address the issue whether BIA is also an accurate method for children with a body composition in the more extreme ranges, like obesity. In this group, limitations could be due to a difference in hydration constants. According to Wells et al.(107) hydration is higher in higher-BMI SDS individuals. Therefore they conclude that, when high levels of accuracy are required, 2-component techniques like BIA are inherently limited in this group because of their assumption of constant values for lean tissue composition.(107) Whether BIA is suitable for clinical use for the follow up of body composition in individual children, particularly in the more extreme ranges of BMI, therefore remains to be established and should be further addressed in future research.

In conclusion BIA appears a feasible, reasonably accurate and affordable tool for epidemiologic studies of body composition of school-aged children.

Associations of infant feeding and timing of weight gain and linear growth during early life with childhood blood pressure: findings from a prospective population based cohort study

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4

ABSTRACT

Objective Small birth size and rapid postnatal growth have been associated with higher future blood pressure. The timing of these effects, the relative importance of weight gain and linear growth, and the role of infant feeding need to be clarified.

Methods We assessed how blood pressure relates to birth weight, infant and childhood growth and infant feeding (duration of exclusive breastfeeding and timing of introduction of complementary feeding) in 2227 children aged 5 years from a prospective cohort study (Amsterdam Born Children and their Development). Postnatal growth was represented by statistically independent measures of relative weight gain (weight gain independent of height) and linear growth in four age periods during infancy (0-1 month; 1-3 months; 3-6 months; 6-12 months) and from 12 months to 5 years.

Results Lower birth weight was associated with higher childhood diastolic blood pressure (-0.38 mm Hg.SD^{-1}; P=0.007). Faster relative weight gain and linear growth after 1 month were positively associated with systolic and diastolic blood pressure. Associations of linear growth with systolic blood pressure ranged from 0.47 to 1.49 mm Hg.SD^{-1}; P<0.01 for all. Coefficients were similar for different periods of infancy and also for relative weight gain and linear growth. Compared to breastfeeding <1 month, breastfeeding >3 months was associated with lower blood pressure (e.g. >6 months -1.70 mm Hg systolic blood pressure; P=0.001). Compared to >6 months, introduction of complementary feeding <6 months was associated with higher blood pressure (e.g. 4-6 months 0.91 mm Hg systolic blood pressure; P=0.004).

Conclusions After the age of one month faster growth in either weight or height is associated with higher childhood blood pressure. It is unknown whether faster weight gain and linear growth carry the same risk for adult hypertension and cardiovascular morbidity. Longer breastfeeding and delayed introduction of complementary feeding may be associated with lower adult blood pressure.

INTRODUCTION

The World Health Organization has attributed 13% of deaths worldwide to raised blood pressure (BP), making it one of the most important modifiable cardiovascular risk factors globally.(114) Data from diverse populations have shown that blood pressure tracks from childhood to adulthood, with average correlation coefficients around 0.3-0.4.(2) Fetal growth restriction has been identified as a risk factor for raised BP in later life.(19,20) Studies addressing the relationship of weight gain in infancy to later life BP have shown mixed results. The Helsinki Birth Cohort study showed an inverse association between infant weight gain and later life BP.(39) Some studies, including the Hertfordshire, Brompton, Hong Kong and Northern Finland Birth cohorts, showed no association.(40,71,115,116) The Barry Caerphilly Growth, COMPASS, Pelotas birth cohort and ALSPAC studies showed a positive association between infant weight gain and later life BP.(28,29,32,33) Two of these studies suggested that it is weight gain in early infancy (the first 5-6 months of life) that is most important.(28,32) There is therefore confusion about what constitutes optimal infant weight gain for future cardiovascular health.

Greater weight gain in childhood (*after* infancy) has been associated with higher later life BP in numerous studies.(32,33,39-41) It is not clear, however, whether the relationship of weight gain to later life BP comes from the component of weight gain that is due to linear (skeletal) growth or to soft tissue (lean and fat) growth. Knowing this may provide insight into the mechanisms linking postnatal growth and later life BP. The Amsterdam Born Children and their Development (ABCD) study has measurements of both weight and height, and was unusual in collecting these at frequent intervals in infancy.

In the ABCD study we found that longer duration of breastfeeding and later introduction of complementary feeding were associated with slower growth in infancy(117) which was in accordance with other studies.(46,47) Early feeding may therefore be related to later life BP. Furthermore, infant feeding may have direct programming effects on later life BP, for example due to differences in sodium intake(48,49), long-chain polyunsaturated fatty acids (LCPUFAs)(49,50) or epigenetic effects.(52) Breastfed compared with formula-fed infants have been shown to have lower adult BP in some(56,57), but not all studies.(59-61)

The role of complementary feeding has received little attention until now. In two cohort studies, no association was found between timing of introduction of complementary feeding and childhood BP.(59,118) However, recent findings from the Generation R study group showed that later introduction of complementary feeding was associated with lower childhood BP.(66)

The aims of our study were to answer the following questions in a population based cohort: 1) Does growth in either weight or height during infancy have significant positive or negative associations with BP at age 5 years?; 2) If so, are there ages and periods in infancy when the associations are stronger?; 3) Is the association of childhood weight gain with BP related to linear growth or soft tissue growth?; 4) Are duration of breastfeeding and timing of introduction of complementary feeding associated with BP at 5 years?; 5) If so, does growth in infancy have a mediating role?

METHODS

The present study is part of the Amsterdam Born Children and their Development (ABCD) study, a population based prospective, longitudinal pregnancy cohort.(69)

Study population

Between January 2003 and March 2004, all pregnant women living in Amsterdam were invited to participate in this study at their first visit (12–14th week of pregnancy) to an obstetric caregiver (figure 4.1). A questionnaire, including sociodemographic data, obstetric history and lifestyle, was sent to the pregnant woman's home address. Questionnaires were returned by 8266 women (response rate 67%). From this group 7863 gave birth to a viable singleton infant. Pregnancy duration, gender and birth weight were obtained from Youth Health Care (YHC) centres, which perform neonatal screening for congenital inborn errors of metabolism in all Dutch newborns. The YHC centres routinely invite them from birth onwards for regular health evaluations at set ages: 8 times between birth and 12 months of age: around 1, 2, 3, 4, 6, 7.5, 9 and 11 months. During these check-ups weight and supine height were measured and feeding patterns (duration of breastfeeding and timing of introduction of complementary feeding) were registered. When measuring height, the parent was asked to hold the infant’s head in contact with a fixed board, and the YHC health worker stretched the infant out to its maximum length and then brought a moving board into contact with the heels. Growth- and infant feeding data were collected for a total of 5551 children. When the children reached the age of 5 years, the addresses of 6161 mothers were retrieved from the YHC registry. The mothers received an informed consent sheet for a health check of their child, for which 4158 (67%) women gave permission. The health check included measurements by trained research assistants, including anthropometry and BP, and was carried out in 3321 children aged 5 years (2008-2010).(87) The current study population included children whose birth weight and growth and infant feeding data were available, as well as anthropometry and BP at age 5 years (n=2533). Babies born preterm (pregnancy duration less than 37 weeks, n=249) and babies of mothers with pre-existing or gestational diabetes mellitus (n=57) were excluded, leaving 2227 children for analysis.

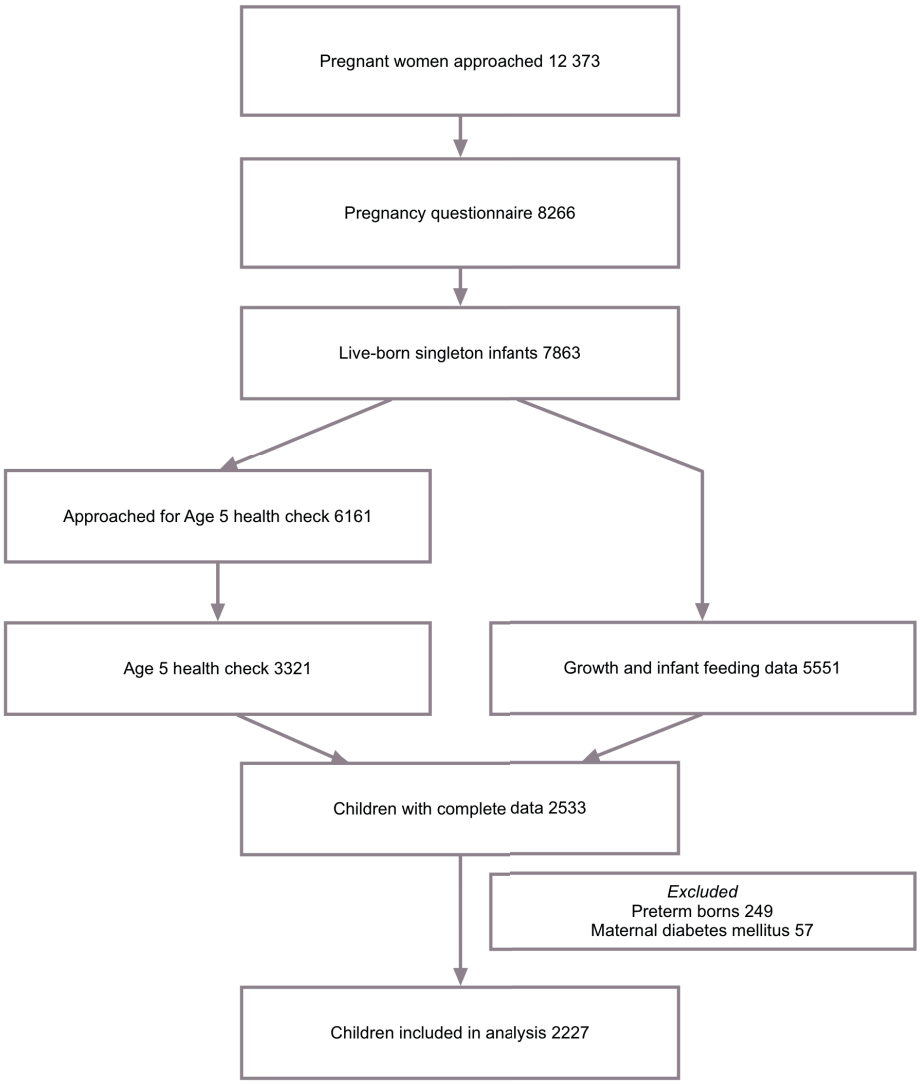

Figure 4.1. Sampling procedure

Exposure variables: birth weight, postnatal growth and infant feeding

We used birth weight (birth height is not routinely measured in the Netherlands) and subsequent weight and height at 1, 3, 6, and 12 months and 5 years of age. Using the maximum number of measurements available at all time points, sex-specific internal z scores were generated. If a measurement was not recorded at the exact age, we derived this value by interpolating between the nearest measurements. Because children without birth weight or 5-year measurements were excluded we did not need to extrapolate these measures. The age ranges accepted for interpolation

at 1, 3, 6 and 12 months were 0-2 months, 2-4 months, 4-8 months and 9-15 months respectively. 95% of measurements were made within 0.3, 0.3, 0.4, and 0.9 months respectively from the exact age.

Using these measures of size, we derived measures of growth (i.e. change in size). Disentangling the consequences of relative weight gain and linear growth at different ages requires statistical methods to address the high correlation of weight with height, and of repeated measurements in the same individual over time. Our "conditional" size measures were standardised residuals derived from regressing current size on all prior size measures.(32,33,41,70-73) Conditional relative weight was current weight accounting for current height and all prior weight and height measures. Conditional height was current height accounting for prior height and weight measures (but not current weight). Current weight was not accounted for in constructing conditional height because it does not contribute to current height. In contrast, we accounted for current height in constructing conditional weight because it does contribute to current weight. For example, childhood conditional relative weight was derived from regressing 5-year weight on 5-year height, weights and heights at 1, 3, 6 and 12 months, and birth weight. Conditional variables represent children's deviation from expected size, based on their own previous size and the growth of the other children in the study population, and can be interpreted as representing faster or slower relative weight gain or linear growth. Conditional regression analysis is designed to assess growth over distinct age periods and to eliminate collinearity problems caused by repeated measures.(73) Although the age intervals chosen increased in length, the correlations between measurements at the beginning and end of each interval were similar, as the child's growth stabilised. This justified the selection of shorter intervals at younger ages.

Duration of exclusive breastfeeding (excluding any other form of nutrition including formula feeding and complementary feeding) was categorised into 4 subgroups: no exclusive breastfeeding or <1 month, 1-3 months, 3-6 months and >6 months. Timing of introduction of complementary feeding (defined as any food other than breastfeeding or formula feeding) was divided into 3 subgroups: <4 months, between 4-6 months and >6 months.

Outcome measures

Outcome measures were systolic BP and diastolic BP at age 5 years. BP in the right arm was measured three times after five minutes rest in the supine position using an Omron 705 IT (Omron Healthcare Inc., Bannockburn, IL, USA) with an age appropriate cuff. The first measurement was discarded and the last two measurements were averaged for the analysis.

Confounding variables

Potential confounding variables that we considered were: the child's sex (male, female) and exact age (continuous, years) at the 5-year health check, and the following maternal characteristics: age (continuous, years), pre-pregnancy body mass index (BMI, continuous, kg/mt^2), height (continuous, cm), educational level (years of education after primary school, continuous), primiparity (yes, no), use of alcohol during pregnancy (yes, no), smoking during pregnancy (no, 1-5 cigarettes/day, ≥ 6 cigarettes/day), hypertension (none, pre-existing hypertension,

pregnancy-induced hypertension), ethnicity (based on mother's country of birth: Dutch, Surinamese, Turkish, Moroccan, other) and pregnancy duration (continuous, weeks).(87)

Statistical analyses

We used multivariable linear regression to estimate associations of birth weight, conditional relative weight and conditional height 0-1, 1-3, 3-6, 6-12 months (infancy) and 12 months-5 years (childhood) with BP at age 5 years, adjusting for all the above-mentioned potential confounding variables. We examined the association of infant feeding with BP using the same approach, further adjusting for birth weight. When looking at timing of introduction of complementary feeding as the exposure variable we adjusted for duration of full breastfeeding (defined as no formula feeding). To examine the potential mediating role of growth in infancy in the relation of infant feeding and childhood BP, we further adjusted for conditional relative weight and conditional height in infancy (all variables representing conditional relative weight and conditional height 0-1, 1-3, 3-6 and 6-12 months were additionally included in the model). Both exclusive breastfeeding and timing of introduction of complementary feeding were treated as categorical variables. Statistical analysis was carried out using IBM SPSS for Mac (version 20.0.0).

Ethics committee approval

Approval was obtained from the VU University medical center medical ethical committee, Academic Medical Center medical ethical committee, and the Registration Committee of Amsterdam. All participants gave written informed consent for themselves and their children.

RESULTS

Descriptives

Compared to the cohort members who were not studied (n=3324), the study group (n=2227) mothers were older (mean 32.2 vs. 30.2 years, P<0.001), had a lower pre-pregnancy BMI (22.9 vs. 23.2 kg/mt^2, P=0.003) and taller stature (mean 1.70 vs. 1.68 mt, P<0.001). They were less likely to smoke during pregnancy (5.8 vs. 7.3%, P=0.015), more likely to drink alcohol during pregnancy (28.3 vs. 18.8%, P<0.001), more likely to be of Dutch origin (43.2 vs. 22.1%, P<0.001), less likely to have pre-existing hypertension (2.4 vs. 4.5%, P<0.001), had a longer pregnancy duration (40.1 vs. 39.6 weeks, P<0.001), were more likely to initiate exclusive breastfeeding (77 vs. 71%, P<0.001) and tended to breastfeed for longer (e.g. 14.3 vs. 12.1%, P=0.01 continued for >6 months). The offspring had a higher birth weight (mean z score 0.08 vs. -0.06, P<0.001) and slower relative weight gain between 1-3 months (-0.05 vs. 0.05, P=0.001) and 3-6 months (-0.03 vs. 0.03, P=0.04). They had faster linear growth between 0-1 month (mean z scores 0.03 vs. -0.03, P=0.039) and slower linear growth between 1-3 months (-0.04 vs. 0.03, P=0.017) and 3-6 months (-0.06 vs. 0.05, P<0.001). These differences between responders and non-responders were similar for people of Dutch and non-Dutch origin. The characteristics of the study sample are shown in Table 4.1. Using the WHO growth standards (www.who.int) mean weights and heights at the different time points in the first year varied between 0 and 0.5 SD. Mean weight and height at 5 years were around 1 and 1.5 SD respectively (Table 4.2).

Table 4.1. Maternal and child characteristics by sex (N=2227)

Measurement	Boys (n=1146)		Girls (n=1081)	
	Mean	SD	Mean	SD
Mother				
Age (y)	32.2	4.4	32.2	4.3
Pre-pregnancy BMI (kg/mt^2)	22.9	3.7	22.9	3.6
Height (mt)	1.70	0.07	1.69	0.07
Education after primary school (y)	10.0	3.7	10.0	3.5
Primiparous (% yes)	55.3		54.4	
Alcohol (% yes)	28.4		28.1	
Smoking				
Non-smoking (%)	94.2		94.2	
1-5 cigarettes/day (%)	3.6		3.1	
≥6 cigarettes/day (%)	2.3		2.8	
Ethnicity				
Dutch (%)	78.0		77.7	
Surinamese (%)	2.8		2.0	
Turkish (%)	2.1		1.9	
Moroccan (%)	5.4		3.3	
Other (%)	11.7		15.0	
Hypertension				
Pre-existing hypertension (%)	2.4		2.4	
Gestational hypertension (%)	8.1		9.1	
Child – At birth				
Pregnancy duration (weeks)	40.2	1.2	40.1	1.2
Birth weight (kg)	3.61	0.50	3.47	0.46
Small for gestational age (<P10) (%)(119)	8.9		7.9	
Large for gestational age (>P90) (%)(119)	11.1		10.4	
Child – 1-12 months measurements				
Weight (kg)				
1 month	4.57	0.54	4.28	0.49
3 months	6.40	0.68	5.83	0.62
6 months	8.09	0.82	7.45	0.76
12 months	10.21	1.01	9.53	0.99
Height (cm)				
1 month	55.2	2.0	54.1	2.0
3 months	62.0	2.0	60.4	1.9
6 months	68.4	2.1	66.6	2.0
12 months	76.5	2.4	74.9	2.3

Measurement	Boys (n=1146)		Girls (n=1081)	
	Mean	SD	Mean	SD
Duration of exclusive breastfeeding (months)				
<1 month (%)	22.6		23.7	
1-3 months (%)	28.0		26.9	
3-6 months (%)	34.0		35.3	
>6 months (%)	15.0		13.5	
Age at introduction of complementary feeding (months)				
<4 months (%)	5.9		5.2	
4-6 months (%)	37.6		37.2	
>6 months (%)	56.5		57.6	
Child – At age 5 health check				
Age (y)	5.8	0.5	5.8	0.5
Weight (kg)	21.2	3.0	21.0	3.5
Height (cm)	116.9	5.6	116.2	5.7
BMI (kg/mt^2)	15.5	1.3	15.5	1.6
Systolic BP (mm Hg)	99.0	7.0	99.0	7.1
Diastolic BP (mm Hg)	56.0	5.7	57.8	6.0

BP − blood pressure; P10 - 10th percentile of the Dutch reference(119); P90 – 90th percentile of the Dutch reference(119).

Table 4.2. Weight and height z scores at the different time points using the WHO growth standards (www.who.int)

	Boys (n=1146)		Girls (n=1081)	
	Mean	Z score	Mean	Z score
Child - measurements				
Weight (kg)				
0 months	3.6	0.50	3.5	0.52
1 month	4.6	0.21	4.3	0.19
3 months	6.4	0.04	5.8	-0.01
6 months	8.1	0.17	7.5	0.17
12 months	10.2	0.51	9.3	0.51
5 years	21.2	1.03	21.0	0.94
Height (cm)				
1 month	55.2	0.28	54.1	0.24
3 months	62.0	0.29	60.4	0.30
6 months	68.4	0.35	66.6	0.37
12 months	76.5	0.32	74.9	0.35
5 years	116,9	1.50	116.2	1.43

Confounding variables

The associations of confounding variables with size and growth, BP and infant feeding are presented in tables 4.3, 4.4, 4.5 and 4.6. To summarise these data briefly, lower birth weight was associated with the following maternal characteristics: younger age, lower pre-pregnancy BMI, shorter stature, lower educational level, smoking during pregnancy, non-use of alcohol, primiparity, non-Dutch ethnicity, gestational hypertension and shorter pregnancy duration (Table 4.3). Faster relative weight gain and linear growth tended to be associated with younger maternal age, higher pre-pregnancy BMI, lower educational level, smoking during pregnancy, non-use of alcohol and pre-existing hypertension (Table 4.3). Faster linear growth was additionally associated with taller maternal stature and shorter pregnancy duration (Table 4.3). Exceptions to the above were that faster linear growth during 0-1 months was associated with lower maternal BMI, higher educational level, not smoking during pregnancy and longer pregnancy duration (Table 4.3). There were significant differences in growth between ethnic groups (Table 4.3).

Younger maternal age, higher pre-pregnancy BMI, lower educational level, pre-existing hypertension, smoking during pregnancy and non-use of alcohol were associated with higher childhood BP in the offspring (Table 4.4).

Women who exclusively breastfed for 3-6 months were thinner (P=0.006), taller (P=0.02) better-educated (P<0.001), had longer pregnancies (P<0.001) and consumed more alcohol during pregnancy (P=0.04) than women who breastfed for <1 month (Table 4.5). They were less often primiparous (P=0.004), less likely to smoke (P=0.03 and <0.001), have pre-existing hypertension during pregnancy (P=0.04) and be of Surinamese (P=0.001) or Moroccan (P<0.001) origin, than women who breastfed for <1 month (Table 4.5). Their offspring's birth weight was higher (P<0.001) than that of women who breastfed for <1 month. Findings for women who breastfed for >6 months were similar regarding maternal height, educational level, primiparity, smoking, pregnancy duration and offspring birth weight. In addition, these women were older and were more likely to be of other origin than women who breastfed for <1 month (Table 4.5).

Women who introduced complementary feeding >6 months were older (P=0.01), thinner (P=0.01) and better-educated (P<0.001). They were less likely to smoke (P=0.003-0.05), to have hypertension during pregnancy (P=0.01) and to be of Surinamese origin (P=0.003) than women who introduced complementary feeding <6 months (Table 4.6).

Table 4.3. Relation of confounding variables with birth weight, relative weight gain and linear growth (in standard deviation scores)

	Birth weight		Relative weight gain (z scores)									
			0-1 m		1-3 m		3-6 m		6-12 m		12 m-5 y	
	B	P	B	P	B	P	B	P	B	P	B	P
Mother												
Age (y)	0.02	<.001	-0.02	.001	-0.02	<.001	-0.02	.001	0.00	.77	-0.02	.001
BMI (kg/mt^2)	0.03	<.001	0.01	.18	0.02	<.001	0.01	.03	0.00	.95	0.05	<.001
Height (mt)	3.11	<.001	-0.33	.28	-0.55	.07	-0.18	.56	-0.57	.06	-1.96	<.001
Education (y)	0.03	<.001	-0.01	.08	-0.03	<.001	-0.01	.02	0.01	.04	-0.03	<.001
Smoking												
No (ref)	-	-	-	-	-	-	-	-	-	-	-	-
1-5 cigarettes/day	-0.33	.006	0.22	.06	0.20	.09	0.20	.09	-0.09	.47	0.14	.23
≥6 cigarettes/day	-0.56	<.001	0.04	.78	0.28	.04	0.33	.01	0.06	.69	0.26	.06
Alcohol, yes	0.12	.01	-0.10	.04	-0.11	.02	0.01	.85	0.06	.17	-0.09	.06
Primiparity, yes	-0.27	<.001	-0.15	<.001	0.08	.06	0.05	.24	0.01	.85	-0.01	.80
Ethnicity												
Dutch (ref)	-	-	-	-	-	-	-	-	-	-	-	-
Surinamese	-0.46	.001	0.08	.55	0.29	.03	0.07	.62	-0.41	.003	0.26	.06
Turkish	-0.38	.01	0.50	.001	0.40	.008	0.09	.53	0.11	.47	0.38	.01
Moroccan	-0.20	.06	0.23	.03	0.54	<.001	0.47	<.001	0.09	.37	0.35	.001
Other	-0.22	<.001	0.10	.11	0.19	.002	-0.05	.39	-0.12	.06	0.09	.15
Hypertension												
None (ref)	-	-	-	-	-	-	-	-	-	-	-	-
Pre-existing	-0.11	.43	0.04	.78	0.37	.008	0.03	.86	-0.14	.32	0.07	.60
Gestational	-0.30	<.001	-0.08	.27	0.09	.23	0.06	.41	0.03	.67	0.18	.02
Child - At birth												
Pregnancy duration (w)	0.34	<.001	-0.01	.61	-0.11	<.001	0.00	.86	-0.02	.16	0.02	.26

Table 4.3 continued. Relation of confounding variables with birth weight, relative weight gain and linear growth (in standard deviation scores)

	Linear growth (z scores)									
	0-1 m		1-3 m		3-6 m		6-12 m		12 m-5 y	
	B	P	B	P	B	P	B	P	B	P
Mother										
Age (y)	0.00	.36	0.00	.88	-0.02	<.001	-0.01	.21	0.01	.07
BMI (kg/mt^2)	-0.02	.003	0.00	.49	0.01	.11	0.01	.22	0.01	.02
Height (mt)	2.67	<.001	1.90	<.001	1.02	.001	1.30	<.001	3.25	<.001
Education (y)	0.02	.005	-0.01	.11	-0.03	<.001	-0.02	.001	0.01	.18
Smoking										
No (ref)	-	-	-	-	-	-	-	-	-	-
1-5 cigarettes/day	-0.13	.28	0.11	.34	0.25	.04	0.35	.003	-0.17	.15
≥6 cigarettes/day	-0.54	<.001	-0.05	.73	0.20	.14	0.22	.11	0.13	.34
Alcohol, yes	-0.03	.56	0.00	.94	-0.12	.01	-0.07	.15	0.01	.83
Primiparity, yes	0.21	<.001	0.15	<.001	0.00	1.00	0.00	.96	0.05	.21
Ethnicity										
Dutch (ref)	-	-	-	-	-	-	-	-	-	-
Surinamese	-0.17	.21	-0.14	.31	0.44	.001	0.06	.65	0.13	.34
Turkish	-0.06	.69	0.06	.68	0.34	.02	0.02	.88	-0.64	<.001
Moroccan	-0.28	.006	-0.24	.02	0.26	.01	0.17	.10	-0.27	.009
Other	-0.07	.24	0.07	.24	0.06	.36	-0.02	.71	-0.18	.005
Hypertension										
None (ref)	-	-	-	-	-	-	-	-	-	-
Pre-existing	0.06	.66	-0.03	.84	-0.13	.36	0.15	.29	0.30	.03
Gestational	0.05	.50	0.01	.92	-0.03	.70	0.09	.22	0.04	.64
Child - At birth										
Pregnancy duration (w)	0.16	<.001	-0.01	.48	-0.07	<.001	-0.06	.001	-0.05	0.03

B values are linear regression coefficients indicating the relative weight gain and linear growth (in standard deviation scores) per unit change in the confounding variable (if a continuous variable) or between each category of the confounding variable and the reference category (if a categorical variable).

Table 4.4. Relation of confounding variables with childhood blood pressure

	Systolic BP (mm Hg)		Diastolic BP (mm Hg)	
	B	P	B	P
Mother				
Age (y)	-0.08	.02	-0.09	.002
BMI (kg/mt^2)	0.21	<.001	0.16	<.001
Height (mt)	3.78	.10	-1.94	.31
Education (y)	-0.15	.002	-0.15	<.001
Primiparous, yes	0.16	.60	0.29	.24
Alcohol, yes	-0.16	.63	-0.66	.02
Smoking				
No (ref)	-	-	-	-
1-5 cigarettes/day	1.65	.05	0.71	.30
≥6 cigarettes/day	0.93	.32	1.10	.13
Hypertension				
None (ref)	-	-	-	-
Pre-existing	2.74	.005	2.05	.01
Gestational	0.92	.08	0.82	.06
Child - At birth				
Pregnancy duration (w)	-0.11	.35	-0.17	.09

B values are linear regression coefficients indicating the change in BP (in mm Hg) per unit change in the confounding variable (if a continuous variable) or between each category of the confounding variable and its reference category (if a categorical variable) adjusting for the child's age and sex and maternal ethnicity.
BP−blood pressure.

Table 4.5. Confounding variables by duration of exclusive breastfeeding

	Duration of exclusive breastfeeding (N=2217)							
	<1 m (reference) (n=515, 23.1%)		1-3 m (n=612, 27.5%)		3-6 m (n=772, 34.7%)		>6 m (n=318, 14.3%)	
Mother	**(Mean, SD)**		**(Mean, SD)**	**B**	**(Mean, SD)**	**B**	**(Mean, SD)**	**B**
Age (y)	(32.0, 4.8)	-	(32.0, 4.4)	0.03	(32.4, 3.9)	0.47	(32.8, 4.6)	0.83 **
BMI (kg/mt^2)	(23.2, 3.8)	-	(22.8, 3.7)	-0.41	(22.6, 3.5)	-0.57 **	(22.9, 3.7)	-0.34
Height (mt)	(1.69, 0.07)	-	(1.70, 0.07)	0.01	(1.70, 0.07)	0.01 *	(1.70, 0.07)	0.01 *
Education (y)	(9.1, 3.8)	-	(9.6, 3.4)	0.52 *	(10.7, 3.2)	1.69 ***	(10.4, 3.7)	1.32 ***
Mother	**Col %**		**Col %**	**OR**	**Col %**	**OR**	**Col %**	**OR**
Primiparous, yes	62.1	-	54.4	0.72 **	54.0	0.72 **	46.2	0.52 ***
Alcohol, yes	24.1	-	33.5	1.59 **	29.3	1.31 *	22.3	0.91
Smoking								
No (reference)	89.5	-	94.0	-	96.1	-	97.5	-
1-5 cigarettes/day	5.0	-	3.6	0.76	2.7	0.56 *	1.3	0.27 *
≥6 cigarettes/day	5.4	-	2.5	0.63	1.2	0.26 ***	1.3	0.34 *
Hypertension								
None (reference)	85.2	-	90.6	-	91.1	-	87.4	-
Pre-existing	3.1	-	3.1	1.09	1.6	0.48 *	1.9	0.66
Gestational	11.7	-	6.2	0.63	7.4	0.73	10.7	1.24
Mother	**Row %**		**Row %**	**OR**	**Row %**	**OR**	**Row %**	**OR**
Ethnicity								
Dutch (reference)	22.9	-	27.7	-	35.7	-	13.7	-
Surinamese	37.0	-	38.9	1.19	14.8	0.26 **	9.3	0.53
Turkish	15.9	-	34.1	1.18	43.2	1.33	6.8	0.47
Moroccan	31.3	-	31.3	1.03	18.8	0.36 ***	18.8	1.15
Other	21.0	-	22.7	0.86	37.3	1.19	19.0	1.51 *
Child - At birth	**(Mean, SD)**		**(Mean, SD)**	**B**	**(Mean, SD)**	**B**	**(Mean, SD)**	**B**
Pregnancy duration (w)	(40.1, 1.3)	-	(40.0, 1.2)	0.03	(40.3, 1.2)	0.27 ***	(40.2, 1.3)	0.17 *
Birth weight (kg)	(3.47, 0.53)	-	(3.54, 0.47)	0.07 *	(3.59, 0.46)	0.12 ***	(3.57, 0.48)	0.10 **

B values are linear regression coefficients indicating the change in the confounding variable (if a continuous variable) for each category of the breastfeeding variable compared with the reference category. OR is the corresponding odds ratio (if a categorical variable). *P<0.05, **P<0.01, ***P<0.001.

Table 4.6. Confounding variables by timing of introduction of complementary feeding

	Timing of introduction of complementary feeding (N=2203)					
	<4 m (n=117, 5.3%)		4-6 m (n=826, 37.5%)		>6 m (reference) (n=1260, 57.2%)	
Mother	**(Mean, SD)**	**B**	**(Mean, SD)**	**B**	**(Mean, SD)**	
Age (y)	(32.2, 5.1)	-0.21	(31.9, 4.4)	-0.48 *	(32.4, 4.3)	-
BMI (kg/mt^2)	(23.6, 4.0)	0.87 *	(23.0, 3.8)	0.24	(22.7, 3.5)	-
Height (mt)	(1.69, 0.07)	-0.01	(1.70, 0.07)	-0.00	(1.70, 0.07)	-
Education (y)	(8.7, 3.5)	-1.43 ***	(9.9, 3.6)	-0.27	(10.1, 3.6)	-
Mother	**Col %**	**OR**	**Col %**	**OR**	**Col %**	
Primiparous, yes	47.9	0.76	55.7	1.04	54.8	-
Alcohol, yes	25.6	0.93	29.8	1.14	27.2	-
Smoking						
No (reference)	86.3	-	93.1	-	95.6	-
1-5 cigarettes/day	7.7	3.25 **	3.8	1.47	2.6	-
≥6 cigarettes/day	6.0	3.63 **	3.1	1.77 *	1.8	-
Hypertension						
None (reference)	84.5	-	90.0	-	88.9	-
Pre-existing	6.0	2.95 *	2.2	1.00	2.1	-
Gestational	9.5	1.11	7.8	0.85	9.0	-
Mother	**Row %**	**OR**	**Row %**	**OR**	**Row %**	
Ethnicity						
Dutch (reference)	5.3	-	37.3	-	57.3	-
Surinamese	14.8	3.45 **	38.9	1.29	46.3	-
Turkish	4.4	0.90	42.2	1.22	53.3	-
Moroccan	7.1	1.57	43.9	1.38	49.0	-
Other	3.1	0.53	35.3	0.88	61.7	-
Child - At birth	**(Mean, SD)**	**B**	**(Mean, SD)**	**B**	**(Mean, SD)**	
Pregnancy duration (w)	(39.9, 1.2)	-0.22	(40.1, 1.2)	-0.04	(40.1, 1.2)	-
Birth weight (kg)	(3.49, 0.51)	-0.06	(3.56, 0.49)	0.02	(3.54, 0.48)	-

B values are linear regression coefficients indicating the change in the confounding variable (if a continuous variable) for each category of the complementary feeding variable compared with the reference category. OR is the corresponding odds ratio (if a categorical variable). *P<0.05, **P<0.01, ***P<0.001.

Relationships of birth weight, relative weight gain and linear growth in infancy and childhood with childhood blood pressure

Lower birth weight was associated with higher childhood diastolic BP (Table 4.7). Being small for gestational age or large for gestational age did not modify this association (not shown). Faster relative weight gain after the first month (i.e. 1-3, 3-6 6-12 months and 12 months-5 years) was associated with higher systolic and diastolic BP in childhood (Table 4.7). Similar associations were found for linear growth after 1-3 months. The strength of the associations was comparable for the different age intervals in infancy, while the associations of growth from 12 months-5 years with BP were 2-3 times stronger than those of infant growth. Associations for relative weight gain were comparable to those for linear growth. Having a BMI >2 SD at age 5 years according to WHO growth standards (www.who.int) did not modify the associations found (not shown).

Table 4.7. Relationships of birth weight, relative weight gain and linear growth (all expressed in z scores) with childhood systolic blood pressure (mm Hg) and diastolic blood pressure (mm Hg)

	Systolic BP (mm Hg)			Diastolic BP (mm Hg)		
	B	95% CI		B	95% CI	
Birth weight	-0.18	-0.50	0.14	-0.38	-0.66	-0.11
Relative weight gain 0-1 m	0.09	-0.19	0.36	0.03	-0.21	0.26
Relative weight gain 1-3 m	0.73	0.45	1.01	0.27	0.02	0.51
Relative weight gain 3-6 m	0.86	0.59	1.14	0.46	0.23	0.70
Relative weight gain 6-12 m	0.71	0.44	0.98	0.26	0.02	0.49
Relative weight gain 12 m-5 y	1.36	1.08	1.63	0.92	0.68	1.16
Linear growth 0-1 m	0.20	-0.08	0.49	0.00	-0.25	0.24
Linear growth 1-3 m	0.47	0.20	0.75	0.11	-0.13	0.35
Linear growth 3-6 m	0.65	0.37	0.93	0.34	0.10	0.59
Linear growth 6-12 m	0.53	0.25	0.80	0.29	0.05	0.53
Linear growth 12 m-5 y	1.49	1.21	1.77	0.51	0.27	0.76

B values are linear regression coefficients indicating the change in BP (in mm Hg) per standard deviation change in the exposure. The analyses were adjusted for the child's age and sex and maternal age, pre-pregnancy BMI, height, educational level, primiparity, ethnicity, smoking, use of alcohol, hypertension and pregnancy duration. BP−blood pressure.

Relationship of feeding type with childhood blood pressure

Compared with breastfeeding for <1 month, exclusive breastfeeding for >3 months and for 3-6 months were associated with lower systolic and diastolic BP respectively (Table 4.8).

Compared with the introduction of complementary feeding >6 months, their introduction <4 months tended to be associated with higher systolic (P=0.09) and diastolic BP (P=0.03). Introduction of complementary feeding between 4-6 months was associated with higher systolic (P=0.004) and diastolic (P=0.08) BP (Table 4.8). Adjusting for growth in infancy attenuated these associations, indicating a possible mediating role of growth in infancy. Having a BMI >2 SD at age 5 years according to WHO growth standards (www.who.int) did not modify the associations found (not shown).

Table 4.8. Relationships of duration of exclusive breastfeeding and timing of introduction of complementary feeding with childhood blood pressure (mm Hg)

	Systolic BP (mm Hg)							Diastolic BP (mm Hg)						
		Model 1			Model 2				Model 1			Model 2		
	(mean, SD)	B	95% CI		B	95% CI		(mean, SD)	B	95% CI		B	95% CI	
Duration of exclusive breast feeding														
<1 m (n=515) ref	(99.9, 7.3)	-	-	-	-	-	-	(57.5, 5.9)	-	-	-	-	-	-
1-3 m (n=612)	(99.2, 7.4)	-0.58	-1.40	0.23	-0.44	-1.25	0.36	(57.2, 6.5)	-0.06	-0.73	0.62	-0.02	-0.70	0.66
3-6 m (n=772)	(98.7, 6.7)	-0.81	-1.60	-0.02	-0.24	-1.05	0.56	(56.3, 5.4)	-0.85	-1.51	-0.19	-0.63	-1.31	0.06
>6 m (n=318)	(97.9, 6.5)	-1.70	-2.68	-0.71	-0.72	-1.72	0.29	(56.6, 5.8)	-0.59	-1.41	0.23	-0.16	-1.01	0.69
Timing of introduction of complementary feeding														
<4 m (n=117)	(100.4, 7.5)	1.16	-0.19	2.50	0.76	-0.56	2.07	(58.2, 5.5)	1.21	0.10	2.33	1.04	-0.08	2.15
4-6 m (n=826)	(99.6, 7.3)	0.91	0.29	1.53	0.72	0.11	1.33	(57.2, 6.1)	0.47	-0.05	0.98	0.38	-0.14	0.89
>6 m (n=1260) ref	(98.5, 6.8)	-	-	-	-	-	-	(56.6, 5.8)	-	-	-	-	-	-

B values are linear regression coefficients indicating the change in BP (in mm Hg) for each category of the feeding variables compared with the reference category. (Model 1) Adjusting for the child's birth weight, age and sex and maternal age, pre-pregnancy BMI, height, educational level, primiparity, ethnicity, smoking, use of alcohol, hypertension and pregnancy duration; (Model 2) as in model 1 but with the addition of relative weight gain and linear growth for all age periods of infancy. BP−blood pressure.

DISCUSSION

This study showed that faster relative weight gain and faster linear growth after 1-3 postnatal months were associated with higher systolic and diastolic BP at age 5 years. In contrast, growth during the first postnatal month was unrelated to BP. Coefficients were similar for growth during the different periods of infancy (after 1-3 months), and were stronger for growth between 1 and 5 years. They were similar for relative weight gain and linear growth. Exclusive breastfeeding for longer than 3 months and introduction of complementary feeding after 6 months were associated with lower childhood BP, and these associations appeared to be partly mediated through growth in infancy.

Conditional relative weight gain and linear growth are, by construction, uncorrelated, enabling us to separate the associations of BP with relative weight gain from those with linear growth. By expressing them in SD units, we were able to compare the size of their effects, and compare effects at different ages. Weight gain is a result of both soft tissue gain and linear growth; our relative weight gain variables represent soft tissue growth distinct from skeletal growth and therefore give more information than weight gain alone, which is correlated with height gain.

A 1 SD increase in relative weight in infancy was associated with a 0.71 to 0.86 mm Hg higher childhood systolic BP. This is higher than the associations found in the UK ALSPAC study (+1 SD increase in weight-for-height in infancy was associated with a 0.25 to 0.4 mm Hg higher adolescent systolic BP)(33) and lower than those found in the UK Barry Caerphilly Growth study, the COMPASS study in Sweden and the Pelotas birth cohort study in Brazil (+1 SD increase in weight in infancy was associated with a 1 to 1.79 mm Hg higher adolescent/adult systolic BP).(28,29,32) The associations of infant growth with childhood diastolic BP in our study were also weaker than associations found in the Barry Caerphilly study (0.26 to 0.46 mm Hg . SD^{-1} vs. 0.74 mm Hg . SD^{-1}).(28) The other cohort studies either did not find associations with diastolic BP(33) or did not have diastolic BP as an outcome measure.(29,32) The Barry Caerphilly study and Pelotas birth cohort study suggested that weight gain in *early* infancy (5-6 months) is most important(28,32), however they did not look at separate age intervals within this period. We found that relative weight gain and linear growth in the first month were unrelated to childhood BP. Only one other study that we are aware of looked at separate age intervals in the first postnatal months.(33) Similar to our findings, this study showed that relative weight gain between 2.9 weeks and 1.6 months, and linear growth in the first 2 months were unrelated to adolescent BP.(33) We are unable to explain the mechanism(s) by which growth in the first postnatal month may have different associations with later BP.

Associations of childhood relative weight gain and linear growth with childhood BP were equal in strength, a finding that is consistent with 3 other large cohort studies.(33,39,41) In contrast, in the Pelotas birth cohort study, childhood weight gain, but not linear growth was associated with adolescent BP.(32) Another large birth cohort study in Hong Kong showed that higher BMI gain between 3-7 years and greater linear growth between 7-11 years predicted higher adolescent BP.(40) The positive association between relative weight gain and childhood BP may be related to the same mechanisms which are thought to cause adiposity-related higher BP, namely activation of the sympathetic nervous system, primary sodium retention, increased

renin activity, increased levels of angiotensinogen and aldosterone, insulin resistance and inflammation.(120) However, relative weight gain comprises both fat and lean tissue gain. Gain in lean mass is regulated by insulin-like growth factor-1 during infancy, and by growth hormone after infancy(121), these hormones have been associated with changes in blood vessel structure and later higher BP.(61) We were not able, in our study, to distinguish between fat and lean tissue gain in our infants and children. It has been suggested that the positive relationship between height and systolic BP may represent a physiological adaptation by which the cardiovascular system accommodates to the relative length of the arterial tree by a commensurate variation in perfusion pressure.(122,123) It is not clear whether this has pathological consequences, but the evidence suggests not; taller people actually have a lower risk of cardiovascular disease, despite higher BP.(124,125)

Compared with exclusive breastfeeding for less than 1 month, exclusive breastfeeding for longer than 3 months was associated with a 0.81 to 1.70 mm Hg lower childhood systolic BP. The associations appeared to be partly mediated through growth in infancy, however no formal tests were performed to prove mediation. This is consistent with findings from a meta-analysis in 2005, which showed that initiation of breastfeeding was associated with a 0.6 mm Hg lower later life systolic BP.(57) A follow-up study at age 13–16 years of preterm infants, randomised to breast milk or preterm formula showed that the proportion of human milk in the neonatal period was inversely related to later mean arterial BP.(56) However, the findings differ from those of the PROBIT study, a large randomised controlled trial (RCT) of breastfeeding promotion.(58) There were no differences in systolic or diastolic blood pressure between children in the intervention and control groups at 6.5 years.(58) RCTs in general yield a higher level of evidence than observational studies, but the difference in duration of breastfeeding between the intervention and control groups in PROBIT (72.7% vs. 60% of mothers were still breastfeeding at 3 months) may have been too small to produce a detectable difference in BP.(58)

The introduction of complementary feeding before 4 months and between 4-6 months was associated with a 1.21 mm Hg higher diastolic and a 0.91 mm Hg higher systolic BP respectively when compared with the introduction of complementary feeding after 6 months. This is consistent with recent findings from the Generation R study group showing that introduction of complementary feeding before compared with after 5 months was associated with a 0.86 mm Hg higher diastolic and a 0.94 mm Hg higher systolic BP.(66) In our study, the association appeared to be partly mediated by growth in infancy, however no formal tests were performed to prove mediation. Higher sodium intake due to earlier introduction of complementary feeding may be another factor.(48,49) Although an association with childhood overweight may partially explain our findings(117), controlling for 5-year BMI and height hardly altered the effect estimates (our data; not shown).

Strengths and limitations

Strengths of our study were that it was a large community based cohort study with extensive prospective data on confounding factors. In contrast to some other large studies, anthropometry was carried out by professional health workers, as was the collection of information about infant feeding, and childhood BP was measured by trained research assistants. Measurements were made in the Youth Health Care

centres at slightly varying ages, but always within days or weeks of the selected ages, and so interpolation is likely to have had only modest effects on the results. Only two other studies that we are aware of have frequent serial measures of growth between birth and 12 months(28,33), and our data were highly complete, enabling conditional regression analysis. Using the WHO growth standards, children of our study group had faster mean weight gain and faster mean linear growth between 1 and 5 years. However, we cannot say whether the associations that we found were due to the higher prevalence of faster growth in our population. We had detailed information about duration of exclusive breastfeeding and timing of introduction of complementary feeding.

A limitation was that, despite considerable effort, there was substantial loss to follow up (we were able to analyse 2227 children with complete growth data out of 5551 children in the original cohort). The analysis sample differed from the original cohort in several characteristics, which could bias our results if associations differed between those who did and did not take part in the study. Because length at birth is not always measured in the Netherlands we were not able to explore associations between birth length and childhood BP, and had to use birth weight as the anchor for our conditional measures. However, Adair et al.(41) compared results with and without the inclusion of birth length, and found that associations of subsequent relative weight gain and linear growth with later life BP were similar. Due to the observational nature of our study it is not possible to attribute causality or to exclude the possibility that the demonstrated associations might be due to residual confounding. There is very little data on the relationship between childhood BP and later ‘hard’ disease outcomes like coronary heart disease and stroke. However, two studies have shown positive associations between adolescent blood pressure and either coronary artery disease(126) or coronary artery calcification (an indicator of atherosclerosis).(127) Finally, we studied a large number of associations, and some significant findings may have arisen by chance. This may be more of a concern with the infant feeding associations than with the growth associations, which were highly consistent.

Conclusions

Faster growth after the age of one month and up to 5 years, in either weight or height is associated with higher childhood BP. While it would not seem advisable (nor probably feasible) to limit infant linear growth, it seems reasonable to recommend avoiding consistent upward crossing of centiles for body weight in infancy and childhood. There is still uncertainty about whether the association between breastfeeding and lower BP in later life is causal in nature. However, in light of other known health benefits(128), we think that promotion of a longer duration of breastfeeding is an important public health recommendation. Further studies are needed, particularly in populations with different infant feeding practices and other patterns of confounding factors, to assess the long-term effect of exclusive breastfeeding and timing and nature of the weaning diet.

Associations of infant feeding and timing of linear growth and relative weight gain during early life with childhood body composition

5

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ABSTRACT

Background Growth and feeding during infancy have been associated with later life body mass index. However, the associations of infant feeding, linear growth and weight gain relative to linear growth with separate components of body composition remain unclear.

Methods Of 5551 children with collected growth- and infant feeding data in a prospective cohort study (Amsterdam Born Children and their Development), body composition measured using bioelectrical impedance analysis at age 5-6 years was available for 2227 children. We assessed how feeding (duration of full breastfeeding and timing of introduction of complementary feeding), and conditional variables representing linear growth and relative weight gain were associated with childhood fat-free mass (FFM) and fat mass (FM).

Results Birth weight was positively associated with both FFM and FM in childhood, and more strongly with FFM than FM. Faster linear growth and faster relative weight gain at all ages in infancy were positively associated with childhood FFM and FM. The associations with FM were stronger for relative weight gain than for linear growth (FM z score: β coefficient 0.23 (95% CI 0.19 to 0.26), P<0.001 and 0.14 (0.11 to 0.17), P<0.001 per SD change in relative weight gain and linear growth between 1-3 months respectively). Compared to full breastfeeding <1 month, full breastfeeding >6 months was associated with lower FM (FM z score: -0.17 (-0.28 to -0.05), P=0.005) and lower FFM (FFM z score: -0.13 (-0.23 to -0.03), P=0.015), as was the introduction of complementary feeding >6 months (FM z score: -0.22 (-0.38 to -0.07), P=0.004), compared with <4 months.

Conclusions Faster infant weight gain is associated with a healthier childhood body composition when it is caused by faster linear growth. Full breastfeeding >6 months and introduction of complementary feeding >6 months are associated with lower childhood FM.

INTRODUCTION

Both the prenatal period and the first year of life have been identified as critical periods for the development of body composition.(129) In line with this, two recently published meta-analyses reported that high birth weight is associated with increased risk for later life overweight.(130,131) Furthermore, four systematic reviews and one meta-analysis found consistent evidence for an association between faster infant weight gain and subsequent risk of overweight in later life.(27,31,37,38,129) Slower infant growth has been associated with longer duration of breastfeeding and later introduction of complementary feeding.(46,47) However, while a longer duration of breastfeeding has been associated with a reduced prevalence of later life overweight(62-65), a recent systematic review showed that the timing of introduction of complementary feeding has no clear association with childhood obesity.(67)

Most studies were based on infant weight gain, while weight gain is a result of linear growth and soft tissue gain. Therefore, the relative importance of infant linear growth vs. weight gain relative to linear growth needs to be further established. Also, the definitions of overweight and obesity in most studies were based on BMI or weight-for-height criteria, lacking the potential to disentangle the associations of infant feeding and early growth with the separate components of body composition (fat-free mass (FFM) and fat mass (FM)).

The objectives of our study were to examine in a population based pregnancy cohort 1) the associations of birth weight, linear growth and weight gain relative to linear growth during different time intervals in infancy with childhood body composition (height, BMI, FFM and FM); 2) the association of infant feeding (duration of full breastfeeding and timing of introduction of complementary feeding) with childhood body composition and, if associated, to explore whether growth in infancy has an explanatory role.

METHODS

The present study is part of the Amsterdam Born Children and their Development (ABCD) study, a multi-ethnic population based prospective, longitudinal pregnancy cohort.(69) Approval was obtained from the research ethics committees of all participating hospitals and the Registration Committee of Amsterdam. All participants gave written informed consent for themselves and their children.

Study population

Between January 2003 and March 2004, all pregnant women living in Amsterdam were invited to participate in this study at their first visit (12–14th week of pregnancy) to an obstetric caregiver. A questionnaire, including sociodemographic data, obstetric history and lifestyle, was sent to the pregnant woman's home address. Questionnaires were returned by 8266 women (response rate 67%). From this group 7863 gave birth to a viable singleton infant. Pregnancy duration, gender and birth weight were obtained from Youth Health Care (YHC) centres, which perform neonatal screening on congenital inborn errors of metabolism in all Dutch newborns. Furthermore, the YHC centres routinely invite them from birth onwards for regular health evaluations at set ages: 8 times between birth and 12 months of age: around 1, 2, 3, 4, 6, 7.5, 9 and 11 months. During these check-ups growth (weight and supine height) and feeding patterns (duration of breastfeeding and timing of introduction of complementary feeding) were registered. When measuring height, the parent was asked to hold the infant’s head in contact with a fixed board, and the YHC health worker stretched the infant out to its maximum length and then brought a moving board into contact with the heels. Growth- and infant feeding data were collected for a total of 5551 children. When the children reached the age of 5 years, the addresses of 6161 mothers were retrieved from the YHC registry; the attrition in follow-up was largely due to untraceable changes in address or migration. The mothers received a questionnaire, including an informed consent sheet for a health check of their child, for which 4158 (67%) women gave permission. The health check included measurements by trained research assistants, including anthropometrics, and was carried out in 3321 children aged 5-6 years (2008-2010).(87) The current study population included children whose birth weight and growth data in the first year of life were available as well as anthropometric measurements at age 5-6 (n=2533). Prematurely born babies (with a pregnancy duration less than 37 weeks, n=249) and babies of mothers with pre-existing or gestational diabetes mellitus (n=57) were excluded. Following these criteria, 2227 children were included in the analysis.

Exposure variables: birth weight, postnatal growth and infant feeding.

We used birth weight (birth height is not routinely measured in the Netherlands) and subsequent weight and height at 1, 3, 6 and 12 months of age. These time points were chosen because we were specifically interested in testing the accelerated early growth hypothesis.(132) The measurements were standardised using internal sex-specific z scores to allow comparisons across ages. If a certain measurement did not take place at the exact time we derived this value by interpolating between the nearest measurements. Because children without birth weight or 5-6 year measurements were excluded we did not need to extrapolate these measures. The allowed age ranges for the interpolation at 1, 3, 6 and 12 months were

respectively 0-2 months, 2-4 months, 4-8 months and 9-15 months. 95% of measurements were made within respectively 0.3, 0.3, 0.4 and 0.9 months from the exact age. Using these measures of size, we derived measures of growth (i.e. change in size). Disentangling the consequences of linear growth and relative weight gain at different ages requires statistical methods to address the high correlation of weight with height, and of repeated measurements in the same individual over time. Our "conditional" size measures were standardised residuals derived from regressing current size on all prior size measures.(33,41,70-72) Conditional height was current height accounting for prior height and weight measures (but not current weight). Conditional relative weight was current weight accounting for current height and all prior weight and height measures. For example, conditional relative weight 6-12 months was derived from regressing 12-month weight on 12-month height, weights and heights at 1, 3 and 6 months, and birth weight. Conditional variables represent children's deviation from the expected size on the basis of their own previous measures and the growth of the other children in the study population, and can be interpreted as representing faster or slower linear growth or relative weight gain. Conditional regression analysis as an approach to assess growth over distinct age periods has been shown to be one of the methods least prone to collinearity problems caused by repeated measures, as was recently discussed by Tu et al.(73) Duration of full breastfeeding (defined as no formula feeding) was categorised into 4 subgroups: no breastfeeding or < 1 month, 1-3 months, 3-6 months and > 6 months. Timing of introduction of complementary feeding was divided into 3 subgroups: < 4 months, between 4-6 months and > 6 months.

Outcome variables

Outcome measures were height, BMI, FFM and FM at age 5-6. Height was measured to the nearest millimeter using a Leicester portable height measure (Seca, Hamburg, Germany) and weight to the nearest 100 gram using a calibrated weighing scale (Marsden, Oxfordshire, UK, model MS-4102). We calculated BMI as weight in kilograms divided by the square of height in meters. After the child had emptied his/her bladder, arm-to-leg bioelectrical impedance analysis (BIA) was measured using the Bodystat 1500MDD system (Bodystat Inc., Douglas, UK). The BIA measurement was performed after 2 minutes in the supine position with the legs abducted to 45 degrees. A pair of electrodes was attached at the right wrist/hand and the right ankle/foot and a 50 kHz alternating current (800 mA) was passed through the body. The voltage drop was measured and the resistance calculated. The procedure was repeated and the average of the 2 measurements was used for further calculations. We used the recalibrated Kushner et al. formula(103) for calculating total body water, which has been cross-validated in our cohort and provided superior estimates of total body water.(133)

(1) total body water (l) = 0.439 (height^2 (cm^2))/Resistance (Ω) + 0.027 weight (kg) + 4.014

We used hydration constants recently provided by Wells et al.(107) to calculate FFM and subsequent FM.

(2) FFM (kg) = c * total body water (l)
(3) FM (kg) = weight (kg) - FFM (kg)

in which c is 100/76.5, 100/76.3, 100/76.7, and 100/76.1 for boys < 6 years, boys ≥ 6 years, girls < 6 years and girls ≥ 6 years, respectively.

All measures were standardised using internal sex-specific z scores to allow comparisons across outcome measures.

Potential confounding variables

Potential confounding variables we considered were: the child's sex (male, female) and exact age (continuous) at age 5 health check, and the following maternal characteristics: maternal age (continuous), pre-pregnancy BMI (continuous), height (continuous), educational level (years of education after primary school, continuous), ethnicity (based on mother's country of birth: Dutch, Surinamese, Turkish, Moroccan, other), smoking during pregnancy (none, 1-5 cigarettes a day, ≥ 6 cigarettes a day), use of alcohol during pregnancy (yes, no), hypertension (pre-existing hypertension, pregnancy-induced hypertension) and pregnancy duration (continuous).(87)

Statistical analyses

Adjusting for all potential confounding variables, we used linear regression to estimate associations of birth weight, conditional height and conditional relative weight for each of the 4 infant time periods with the outcome variables. When looking at childhood FFM and FM as outcome measures we further adjusted for childhood conditional height (12 months – 5-6 years). The adjustments for childhood conditional height in calculations with FFM and FM were intended to produce measures of FFM and FM that were independent of height. In view of the nature of conditional growth variables, we could assess independent associations of birth weight, conditional height and conditional relative weight with subsequent childhood FFM and FM, without concern about statistical issues such as the reversal paradox.(134) We chose not to use %fat, which can be high either because FM is high or FFM is low, and we anticipated that these two components may be related differently to early growth. We explored the relation of infant feeding with conditional height and conditional relative weight in infancy using linear regression analysis, adjusting for maternal characteristics and mutually adjusting for feeding types. Finally, we examined the association of infant feeding with height, BMI, FFM and FM at age 5-6 years, using linear regression analysis. We adjusted for all potential confounding variables and mutually adjusted for feeding types and for childhood conditional height (12 months – 5-6 years) in calculations with FFM and FM. To examine the potential explanatory role of growth in infancy in the relation of infant feeding and childhood height, BMI, FFM and FM, we further adjusted for conditional height and conditional relative weight in all periods of infancy. Both full breastfeeding and timing of introduction of complementary feeding were treated as categorical variables. Statistical analysis was carried out using IBM SPSS for Mac (version 20.0.0).

RESULTS

Descriptives

Compared to the group without age 5 health check data (n=3324), in the group with available growth- and age 5 health check data (n=2227), mothers were older (mean 32.2 vs. 30.2 years, P<0.001), had a lower BMI (22.9 vs. 23.2 kg/mt^2, P=0.003) and taller stature (mean 1.70 vs. 1.68 mt, P<0.001), were less likely to smoke during pregnancy (5.8 vs. 7.3%, P=0.015), were more likely to drink alcohol during pregnancy (28.3 vs. 18.8%, P<0.001), were less often of non-Dutch origin (22.1 vs. 43.2%, P<0.001), less often had pre-existing hypertension (2.4 vs. 4.5%, P<0.001) and the pregnancy duration was longer (40.1 vs. 39.6 weeks, P<0.001). The offspring had a higher birth weight (mean z score 0.08 vs. -0.06, P<0.001) and had faster linear growth between 0-1 month (mean z score 0.03 vs. -0.03, P=0.039). They had slower linear growth between 1-3 months (-0.04 vs. 0.03, P=0.017) and 3-6 months (-0.06 vs. 0.05, P<0.001). Furthermore, they had slower relative weight gain between 1-3 months (-0.05 vs. 0.05, P=0.001) and 3-6 months (-0.03 vs. 0.03, P=0.04). These differences between responders and non-responders were largely the same for people of Dutch origin and non-Dutch origin. The characteristics of the study sample are shown in Table 5.1.

Table 5.1. Maternal and child characteristics by sex (N=2227)

Measurement	Boys (n=1146)		Girls (n=1081)	
	Mean	SD	Mean	SD
Mother				
Age (y)	32.2	4.4	32.2	4.3
Pre-pregnancy BMI (kg/mt^2)	22.9	3.7	22.9	3.6
Height (mt)	1.70	0.07	1.69	0.07
Education after primary school (y)	10.0	3.7	10.0	3.5
Primiparous (% yes)	55.3		54.4	
Alcohol (% yes)	28.4		28.1	
Smoking				
Non-smoking (%)	94.2		94.2	
1-5 cigarettes/day (%)	3.6		3.1	
≥ 6 cigarettes/day (%)	2.3		2.8	
Ethnicity				
Dutch (%)	78.0		77.7	
Surinamese (%)	2.8		2.0	
Turkish (%)	2.1		1.9	
Moroccan (%)	5.4		3.3	
Other (%)	11.7		15.0	
Hypertension				
Pre-existing hypertension (%)	2.4		2.4	
Gestational hypertension (%)	8.1		9.1	

Measurement	Boys (n=1146)		Girls (n=1081)	
	Mean	SD	Mean	SD
Child – At birth				
Pregnancy duration (weeks)	40.2	1.2	40.1	1.2
Birth weight (kg)	3.61	0.50	3.47	0.46
Small for gestational age (%)(119)	8.9		7.9	
Large for gestational age (%)(119)	11.1		10.4	
Child – 1-12 months measurements				
Height (cm)				
1 month	55.2	2.0	54.1	2.0
3 months	62.0	2.0	60.4	1.9
6 months	68.4	2.1	66.6	2.0
12 months	76.5	2.4	74.9	2.3
Weight (kg)				
1 month	4.57	0.54	4.28	0.49
3 months	6.40	0.68	5.83	0.62
6 months	8.09	0.82	7.45	0.76
12 months	10.21	1.01	9.53	0.99
Duration of full breastfeeding (months)				
< 1 month (%)	22.6		24.2	
1-3 months (%)	27.6		25.6	
3-6 months (%)	30.5		32.3	
> 6 months (%)	19.3		17.9	
Age at introduction of complementary feeding (months)				
< 4 months (%)	5.9		5.2	
4-6 months (%)	37.6		37.2	
> 6 months (%)	56.5		57.6	
Child – At age 5 health check				
Age (y)	5.8	0.5	5.8	0.5
Height (cm)	116.9	5.6	116.2	5.7
Weight (kg)	21.2	3.0	21.0	3.5
BMI (kg/mt^2)	15.5	1.3	15.5	1.6
FFM (kg)	17.1	1.8	16.4	1.7
FM (kg)	4.2	1.8	4.6	2.3

Abbreviations: BMI-body mass index, FM-fat mass, FFM-fat-free mass.

Confounding variables

For associations between confounding variables and exposure variables we refer to Table 5.2.

Table 5.2. Association of confounding variables with conditional relative weight and conditional height (in standard deviation scores) and duration of full breastfeeding and timing of introduction of complementary feeding (continuous variables)

	Conditional relative weight (z scores)									
	Birth weight		**0-1 m**		**1-3 m**		**3-6 m**		**6-12 m**	
	B	P	B	P	B	P	B	P	B	P
Mother										
Age (y)	0.02	<.001	-0.02	.001	-0.02	<.001	-0.02	.001	0.00	.769
BMI (kg/mt^2)	0.03	<.001	0.01	.179	0.02	<.001	0.01	.033	0.00	.950
Height (mt)	0.03	<.001	0.00	.284	-0.01	.070	0.00	.557	0.01	.063
Education (y)	0.03	<.001	-0.01	.084	-0.03	<.001	-0.01	.015	0.01	.044
Smoking										
No (ref)	-	-	-	-	-	-	-	-	-	-
1-5 cigarettes/day	-0.33	.006	0.22	.061	0.20	.092	0.20	.089	-0.09	.470
≥6 cigarettes/day	-0.56	<.001	0.04	.775	0.28	.039	0.33	.014	0.06	.686
Alcohol, yes	0.12	.011	-0.10	.041	-0.11	.019	0.01	.853	0.06	.173
Ethnicity										
Dutch (ref)	-	-	-	-	-	-	-	-	-	-
Surinamese	-0.46	.001	0.08	.551	0.29	.032	0.07	.621	-0.41	.003
Turkish	-0.38	.011	0.50	.001	0.40	.008	0.09	.532	0.11	.467
Moroccan	-0.20	.055	0.23	.026	0.54	<.001	0.47	<.001	0.09	.365
Other	-0.22	<.001	0.10	.110	0.19	.002	-0.05	.387	-0.12	.063
Hypertension										
No (ref)	-	-	-	-	-	-	-	-	-	-
Pre-existing	-0.11	.429	0.04	.781	0.37	.008	0.03	.859	-0.14	.322
Gestational	-0.30	<.001	-0.08	.267	0.09	.234	0.06	.405	0.03	.666
Child – At birth										
Pregnancy duration (w)	0.34	<.001	-0.01	.613	-0.11	<.001	0.00	.861	-0.02	.163

Table 5.2 continued. Association of confounding variables with conditional relative weight and conditional height (in standard deviation scores) and duration of full breastfeeding and timing of introduction of complementary feeding (continuous variables)

	Conditional height (z scores)							
	0-1 m		1-3 m		3-6 m		6-12 m	
	B	P	B	P	B	P	B	P
Mother								
Age (y)	0.00	.364	0.00	.881	-0.02	<.001	-0.01	.210
BMI (kg/mt^2)	-0.02	.003	0.00	.492	0.01	.107	0.01	.215
Height (mt)	2.67	<.001	1.90	<.001	1.02	.001	1.30	<.001
Education (y)	0.02	.005	-0.01	.108	-0.03	<.001	-0.02	.001
Smoking								
No (ref)	-	-	-	-	-	-	-	-
1-5 cigarettes/day	-0.13	.279	0.11	.336	0.25	.036	0.35	.003
≥6 cigarettes/day	-0.54	<.001	-0.05	.732	0.20	.141	0.22	.110
Alcohol, yes	-0.03	.558	0.00	.941	-0.12	.010	-0.07	.147
Ethnicity								
Dutch (ref)	-	-	-	-	-	-	-	-
Surinamese	-0.17	.207	-0.14	.305	0.44	.001	0.06	.648
Turkish	-0.06	.694	0.06	.675	0.34	.022	0.02	.883
Moroccan	-0.28	.006	-0.24	.023	0.26	.014	0.17	.102
Other	-0.07	.238	0.07	.243	0.06	.356	-0.02	.705
Hypertension								
No (ref)	-	-	-	-	-	-	-	-
Pre-existing	0.06	.658	-0.03	.837	-0.13	.361	0.15	.290
Gestational	0.05	.501	0.01	.920	-0.03	.703	0.09	.224
Child – At birth								
Pregnancy duration (w)	0.16	<.001	-0.01	.482	-0.07	<.001	-0.06	.001

Table 5.2 continued. Association of confounding variables with conditional relative weight and conditional height (in standard deviation scores) and duration of full breastfeeding and timing of introduction of complementary feeding (continuous variables)

	Duration of full breastfeeding (in 4 categories)		Timing of introduction of complementary feeding (in 3 categories)	
	B	P	B	P
Maternal				
Age (y)	0.02	.003	0.01	.069
BMI (kg/mt^2)	-0.01	.151	-0.01	.017
Height (mt)	0.75	.020	0.20	.277
Education (y)	0.05	<.001	0.01	<.001
Smoking				
No (ref)	-	-	-	-
1-5 cigarettes/day	-0.41	.001	-0.20	.004
≥6 cigarettes/day	-0.59	<.001	-0.25	.002
Alcohol, yes	-0.03	.556	-0.02	.499
Ethnicity				
Dutch (ref)	-	-	-	-
Surinamese	-0.45	.002	-0.21	.013
Turkish	0.05	.773	-0.03	.728
Moroccan	-0.14	.193	-0.10	.100
Other	0.16	.017	0.07	.078
Hypertension				
No (ref)	-	-	-	-
Pre-existing	-0.25	.091	-0.14	.106
Gestational	-0.09	.280	0.02	.622
Pregnancy duration (w)	0.07	<.001	0.02	.131
Child – At birth				
Birth weight (z-score)	0.10	<.001	0.01	.578

B values are linear regression coefficients indicating the change in conditional relative weight and conditional height (in standard deviation scores) and feeding variables (duration of full breastfeeding in 4 categories as follows: <1 month, 1-3 months, 3-6 months, >6 months; timing of introduction of complementary feeding in 3 categories as follows: <4 months, 4-6 months, >6 months) per unit change in the confounding variable (if a continuous variable) or between each category of the confounding variable and the reference category (if a categorical variable). Duration of full breastfeeding and timing of introduction of complementary feeding were treated as continuous variables.

Because some potential confounding variables were unequally distributed between ethnic groups and ethnicity was associated with all outcome variables, we adjusted for ethnicity when analysing the associations between confounding variables and childhood body composition (Table 5.3). We found that higher maternal BMI, taller stature, lower educational level and longer pregnancy duration were associated with greater childhood height (Table 5.3). Younger maternal age, higher pre-pregnancy BMI, lower educational level, smoking during pregnancy and maternal hypertension were associated with higher childhood BMI and higher FM (Table 5.3). In addition, maternal use of alcohol during pregnancy and shorter pregnancy duration were associated with lower childhood FM (Table 5.3). Higher pre-pregnancy BMI, taller stature, and longer pregnancy duration were associated with higher childhood FFM (Table 5.3).

Table 5.3. Association of potential confounding variables with outcome variables

	Height (z) (1)		BMI (z) (1)		FFM (z) (2)[a]		FM (z) (2)[b]	
	B	P	B	P	B	P	B	P
Mother								
Age (y)	-0.01	.247	-0.02	.001	-0.01	.116	-0.02	<.001
BMI (kg/mt^2)	0.02	<.001	0.06	<.001	0.02	.001	0.05	<.001
Height (mt)	5.70	<.001	-0.46	.166	1.99	<.001	0.50	.100
Education (y)	-0.02	.024	-0.03	<.001	0.00	.548	-0.04	<.001
Smoking								
No (ref)	-	-	-	-	-	-	-	-
1-5 cigarettes/day	-0.02	.881	0.24	.041	0.16	.079	0.30	.005
≥6 cigarettes/day	-0.07	.607	0.47	.001	0.14	.172	0.17	.160
Alcohol, yes	-0.06	.204	-0.05	.271	0.06	.087	-0.14	.002
Hypertension								
No (ref)	-	-	-	-	-	-	-	-
Pre-existing	0.24	.080	0.24	.090	-0.03	.596	0.26	.039
Gestational	0.00	.999	0.16	.041	-0.06	.576	0.16	.022
Child – At birth								
Pregnancy duration (w)	0.01	.005	0.03	.123	0.07	<.001	0.05	.002

[a]FFM-fat-free mass. [b]FM-fat mass.

B values are linear regression coefficients indicating the change in height, BMI, FFM and FM (all in standard deviation scores) per unit change in the confounding variable (if a continuous variable) or between each category of the confounding variable and its reference category (if a categorical variable). 1) adjusting for age at age 5 measurement, sex and maternal ethnicity 2) as in 1 but with the addition of childhood conditional height.

Relation of birth weight, conditional height and conditional relative weight in infancy with childhood height, BMI, FFM and FM

Higher birth weight and higher conditional height in all time periods were consistently associated with greater childhood height (e.g. a change of 1 SD in birth weight was associated with 0.23 SD higher childhood height) (Table 5.4). Higher conditional relative weight after 1 month was also associated with childhood height, but coefficients were smaller (Table 5.4). Birth weight and conditional relative weight in all time periods were positively associated with childhood BMI (Table 5.4). Furthermore, higher conditional height 6-12 months was associated with higher childhood BMI (Table 5.4). Birth weight and conditional relative weight and conditional height variables in all time periods were associated with higher childhood FFM and FM (Table 5.4). Birth weight and conditional height after 6 months were more strongly associated with FFM than with FM (Table 5.4). The association of FM was stronger with relative weight gain after 1 month than with linear growth after 1 month (Table 5.4).

Table 5.4. Association of birth weight, conditional height and conditional relative weight (all expressed in z scores) with childhood height, BMI, FFM and FM

	Height (z)			BMI (z)			FFM (z)[a]			FM (z)[b]		
	B	95% CI		B	95% CI		B	95% CI		B	95% CI	
Conditional height (z scores)												
0-1 m	0.35	0.32	0.38	-0.03	-0.07	0.00	0.17	0.15	0.20	0.15	0.11	0.18
1-3 m	0.30	0.27	0.33	0.00	-0.03	0.04	0.18	0.16	0.20	0.14	0.11	0.17
3-6 m	0.22	0.19	0.25	0.01	-0.02	0.05	0.13	0.11	0.16	0.11	0.08	0.14
6-12 m	0.30	0.27	0.33	0.04	0.01	0.08	0.20	0.18	0.22	0.15	0.12	0.18
Conditional relative weight (z scores)												
Birth weight	0.23	0.19	0.26	0.18	0.14	0.22	0.25	0.22	0.28	0.17	0.13	0.20
0-1 m	0.02	-0.01	0.05	0.20	0.17	0.24	0.11	0.09	0.13	0.11	0.08	0.14
1-3 m	0.11	0.08	0.13	0.30	0.27	0.34	0.18	0.15	0.20	0.23	0.19	0.26
3-6 m	0.11	0.08	0.14	0.23	0.20	0.27	0.16	0.14	0.19	0.17	0.14	0.20
6-12 m	0.14	0.11	0.16	0.28	0.24	0.31	0.21	0.19	0.23	0.20	0.17	0.23

[a]FFM-fat-free mass. [b]FM-fat mass

B values are linear regression coefficients indicating the change in the outcome (in standard deviation scores) per standard deviation change in the exposure. The analyses were adjusted for age, sex, maternal age, pre-pregnancy BMI, height, educational level, ethnicity, smoking, use of alcohol, hypertension and pregnancy duration. With FFM and FM we further adjusted for childhood conditional height (12 months-5 years).

Relation of feeding type with conditional height and conditional relative weight in infancy

In the first month, conditional relative weight of bottle fed infants was lower than that of infants who were fully breastfed (Figure 5.1, Table 5.5). Thereafter, until 6 months, longer duration of full breastfeeding was associated with lower conditional relative weight and lower conditional height (Figures 5.1 and 5.2, Tables 5.5 and 5.6). In addition, full breastfeeding longer than 6 months was associated with lower conditional relative weight between 6 to 12 months (Figure 5.1, Table 5.5). Introduction of complementary feeding after 6 months was associated with lower conditional relative weight and lower conditional height between 6-12 months (Tables 5.5 and 5.6).

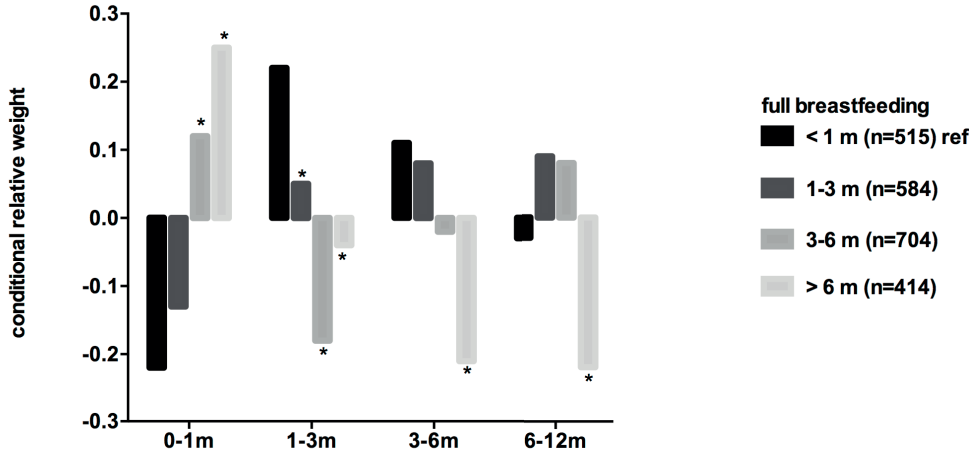

Figure 5.1. Conditional relative weight 0–1, 1–3, 3–6 and 6–12 months (all expressed in z scores) according to duration of full breastfeeding (* significantly different from reference category)

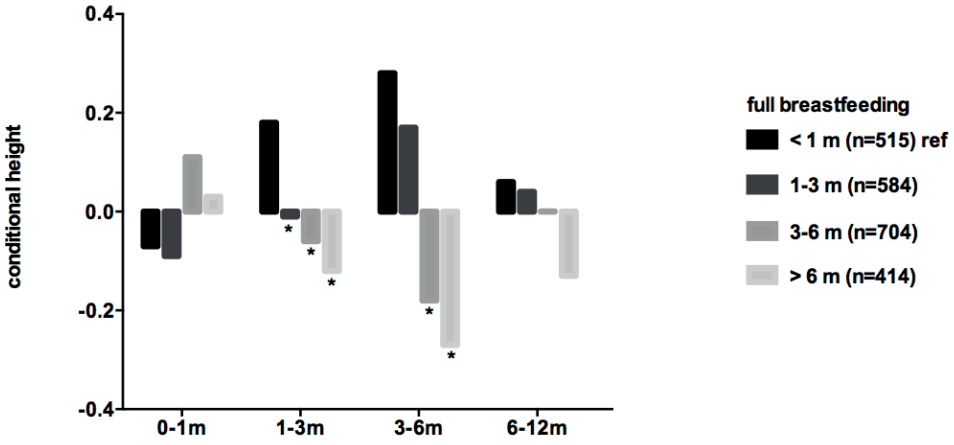

Figure 5.2. Conditional height 0–1, 1–3, 3–6 and 6–12 months (all expressed in z scores) according to duration of full breastfeeding (* significantly different from reference category)

Table 5.5. Association of duration of full breastfeeding and timing of introduction of complementary feeding with conditional relative weight (expressed in z scores)

	Conditional relative weight (z scores)											
	0-1 m			1-3 m			3-6 m			6-12 m		
	B	95% CI		B	95% CI		B	95% CI		B	95% CI	
Duration of full breast feeding												
<1 m (n=515) ref	-	-	-	-	-	-	-	-	-	-	-	-
1-3 m (n=584)	0.10	-0.01	0.22	-0.14	-0.26	-0.03	0.00	-0.12	0.12	0.13	0.01	0.25
3-6 m (n=704)	0.38	0.27	0.50	-0.31	-0.43	-0.20	-0.07	-0.19	0.04	0.11	-0.01	0.23
>6 m (n=414)	0.50	0.37	0.63	-0.20	-0.33	-0.07	-0.26	-0.40	-0.13	-0.17	-0.30	-0.04
Timing of introduction of complementary feeding												
<4 m (n=117) ref	-	-	-	-	-	-	-	-	-	-	-	-
4-6 m (n=826)	0.07	-0.11	0.25	-0.01	-0.18	0.17	-0.02	-0.19	0.16	-0.15	-0.33	0.03
>6 m (n=1260)	0.07	-0.11	0.24	-0.03	-0.21	0.14	-0.07	-0.25	0.10	-0.21	-0.38	-0.03

B values are linear regression coefficients indicating the change in conditional relative weight (in standard deviation scores) for each category of the feeding variables compared with the reference category. Adjusting for maternal age, pre-pregnancy BMI, height, educational level, ethnicity, smoking, use of alcohol, hypertension and pregnancy duration and mutually adjusting for feeding types.

Table 5.6. Association of duration of full breastfeeding and timing of introduction of complementary feeding with conditional height (expressed in z scores)

	Conditional height (z scores)											
	0-1 m			1-3 m			3-6 m			6-12 m		
	B	95% CI		B	95% CI		B	95% CI		B	95% CI	
Duration of full breast feeding												
<1 m (n=515) ref	-	-	-	-	-	-	-	-	-	-	-	-
1-3 m (n=584)	-0.05	-0.17	0.07	-0.19	-0.31	-0.08	-0.08	-0.20	0.03	0.02	-0.10	0.14
3-6 m (n=704)	0.10	-0.01	0.22	-0.25	-0.36	-0.13	-0.40	-0.51	-0.28	0.02	-0.09	0.14
>6 m (n=414)	0.05	-0.08	0.18	-0.31	-0.44	-0.17	-0.49	-0.62	-0.36	-0.12	-0.25	0.01
Timing of introduction of complementary feeding												
<4 m (n=117) ref	-	-	-	-	-	-	-	-	-	-	-	-
4-6 m (n=826)	-0.16	-0.33	0.02	-0.05	-0.23	0.13	0.07	-0.10	0.24	-0.14	-0.31	0.04
>6 m (n=1260)	-0.16	-0.33	0.01	-0.08	-0.26	0.10	-0.02	-0.19	0.15	-0.20	-0.37	-0.02

B values are linear regression coefficients indicating the change in conditional height (in standard deviation scores) for each category of the feeding variables compared with the reference category. Adjusting for maternal age, pre-pregnancy BMI, height, educational level, ethnicity, smoking, use of alcohol, hypertension and pregnancy duration and mutually adjusting for feeding types.

Relation of feeding type with childhood height, BMI, FFM and FM

Compared to full breastfeeding shorter than 1 month, full breastfeeding longer than 6 months was associated with shorter childhood height (Table 5.7). After adjusting for conditional height and conditional relative weight in all periods of infancy (i.e. accounting for the negative association between full breastfeeding and growth in infancy (Tables 5.5 and 5.6)), full breastfeeding longer than 3 months was positively associated with childhood height (Table 5.7). This indicates a positive association between full breastfeeding and growth in the period which we did not account for (i.e. between 1 and 5-6 years). Compared to full breastfeeding shorter than 1 month, full breastfeeding longer than 6 months was associated with lower childhood FFM and FM (Table 5.8). Adjusting for conditional height and conditional relative weight rendered the associations non-significant (Table 5.8). Compared to earlier introduction, introduction of complementary feeding after 4 months was associated with shorter childhood height while introduction of complementary feeding after 6 months was associated with lower childhood height, BMI, FFM and FM (Tables 5.7 and 5.8). After adjusting for conditional height and conditional relative weight, the associations were no longer statistically significant, with an exception for the association between introduction of complementary feeding after 4 months and shorter childhood height (Tables 5.7 and 5.8).

Table 5.7. Association of duration of full breastfeeding and timing of introduction of complementary feeding with height and BMI at age 5-6 years

	Height (z)							BMI (z)						
		Model 1			Model 2				Model 1			Model 2		
	mean (SD)	B	95% CI		B	95% CI		mean (SD)	B	95% CI		B	95% CI	
Duration of full breast feeding														
<1 m (n=515) ref	0.12 (1.00)	-	-	-	-	-	-	0.03 (1.13)	-	-	-	-	-	-
1-3 m (n=584)	0.04 (1.02)	-0.08	-0.18	0.03	0.01	-0.07	0.09	-0.06 (0.95)	0.00	-0.11	0.12	-0.01	-0.11	0.09
3-6 m (n=704)	0.05 (1.02)	-0.04	-0.15	0.06	0.11	0.03	0.19	-0.03 (0.95)	0.02	-0.09	0.13	0.04	-0.06	0.14
>6 m (n=414)	-0.01 (0.94)	-0.14	-0.26	-0.02	0.16	0.06	0.25	-0.10 (1.02)	-0.06	-0.19	0.07	0.03	-0.09	0.15
Timing of introduction of complementary feeding														
<4 m (n=117) ref	0.32 (1.04)	-	-	-	-	-	-	0.18 (1.18)	-	-	-	-	-	-
4-6 m (n=826)	0.09 (0.98)	-0.24	-0.40	-0.08	-0.13	-0.25	-0.01	0.02 (1.10)	-0.13	-0.30	0.05	-0.09	-0.24	0.06
>6 m (n=1260)	0.00 (1.00)	-0.31	-0.47	-0.15	-0.13	-0.25	-0.01	-0.10 (0.94)	-0.20	-0.37	-0.03	-0.12	-0.27	0.03

B values are linear regression coefficients indicating the difference in the outcome (in standard deviation scores) between each exposure category and the reference category. (1) Adjusting for the child's birth weight, sex, age at the age 5 health check and maternal age, pre-pregnancy BMI, height, educational level, ethnicity, smoking, use of alcohol, hypertension, pregnancy duration and mutual adjustments for feeding types; (2) as in 1 but with the addition of conditional relative weight and conditional height for all time periods of infancy.

Table 5.8. Association of duration of full breastfeeding and timing of introduction of complementary feeding with FFM and FM at age 5-6 years

	FFM (z)[a]							FM (z)[b]						
		Model 1			Model 2				Model 1			Model 2		
	mean (SD)	B	95% CI		B	95% CI		mean (SD)	B	95% CI		B	95% CI	
Duration of full breast feeding														
<1 m (n=514) ref	-0.01 (1.02)	-	-	-	-	-	-	0.12 (1.11)	-	-	-	-	-	-
1-3 m (n=575)	0.02 (1.00)	-0.04	-0.12	0.05	0.00	-0.07	0.07	0.03 (1.01)	-0.06	-0.16	0.05	-0.02	-0.11	0.07
3-6 m (n=698)	0.01 (0.98)	-0.05	-0.14	0.04	0.03	-0.04	0.10	-0.06 (0.93)	-0.09	-0.19	0.01	-0.02	-0.11	0.07
>6 m (n=410)	-0.04 (0.99)	-0.17	-0.27	-0.07	0.03	-0.05	0.11	-0.09 (0.94)	-0.20	-0.31	-0.08	-0.03	-0.13	0.08
Timing of introduction of complementary feeding														
<4 m (n=117) ref	0,21 (1.10)	-	-	-	-	-	-	0.32 (1.24)	-	-	-	-	-	-
4-6 m (n=816)	0,02 (1.00)	-0.13	-0.26	0.01	-0.04	-0.15	0.06	0.07 (1.09)	-0.13	-0.28	0.03	-0.06	-0.19	0.07
>6 m (n=1250)	-0.04 (0.99)	-0.16	-0.29	-0.03	-0.02	-0.12	0.09	-0.08 (0.91)	-0.23	-0.39	-0.08	-0.11	-0.25	0.02

[a]FFM-fat-free mass. [b]FM-fat mass.
B values are linear regression coefficients indicating the difference in the outcome (in standard deviation scores) between each exposure category and the reference category. (1) Adjusting for the child's birth weight, sex and age at the age 5 health check and maternal age, pre-pregnancy BMI, height, educational level, ethnicity, smoking, use of alcohol, hypertension, pregnancy duration, conditional height in childhood (12 months to 5 years) and mutual adjustments for feeding types; (2) as in 1 but with the addition of conditional relative weight and conditional height for all time periods of infancy.

DISCUSSION

This study demonstrated that higher birth weight and faster linear growth were associated with higher childhood FFM and to a lesser extent with higher FM. Faster relative weight gain was associated with higher childhood FM and to a lesser extent with FFM. Full breastfeeding longer than 6 months and introduction of complementary feeding after 6 months were associated with lower FFM and lower FM. These associations could be explained by slower linear growth and slower relative weight gain associated with longer duration of breastfeeding and introduction of complementary feeding after 6 months.

Many studies looking at the associations between infant feeding and early growth with overweight in later life were based on BMI or weight-for-height criteria, lacking the potential to disentangle the associations of early growth and feeding with the separate components of body composition (FFM and FM). Our data confirm findings from recent studies which have consistently shown positive associations between birth weight and later FFM and weaker associations with later FM.(41,135,136) Hence, higher birth weight appears to be associated with a more favourable body composition in later life, which is unclear when looking at BMI alone. Published results regarding associations of infant growth and later body composition have been inconsistent; studies from high-income countries showed a predominant positive correlation between early postnatal weight gain and later FM(34,137,138), whereas data from low- and middle-income countries suggest a predominant association with later life FFM.(41) In this study, we were able to separate linear growth from relative weight gain. Weight gain is a result of linear growth and soft tissue gain (FFM and FM); our conditional relative weight variables represent weight change that is separated from change in height. Conditional relative weight and conditional height variables are uncorrelated, and we expressed them in SD units to allow direct comparison of coefficients within regression models. Our variables therefore have advantages when compared with other representations of growth, and give more nuanced results than do those that are based on weight gain alone. While linear growth appeared to be predominantly associated with childhood height and FFM, relative weight gain appeared to be more strongly associated with childhood FM. Consistent with findings from earlier studies that compared growth of breastfed infants with widely used growth charts, we found that fully breastfed infants experienced faster relative weight gain in the first month of life, with subsequent slower linear growth until 6 months and slower relative weight gain until 12 months.(46,139) In accordance with findings from the ALSPAC study, we found an association between longer duration of breastfeeding and lower childhood FM.(64) Furthermore, the association of longer duration of full breastfeeding with lower childhood FFM supports evidence from a meta-analysis including 11 studies looking at FFM in breastfed vs. formula fed infants.(140) A recent systematic review including 21 studies showed that the timing of the introduction of complementary feeding had no clear association with childhood obesity.(67) Our findings indicate that introduction of complementary feeding after 6 months is associated with smaller childhood height, lower BMI, lower FFM and lower FM. In line with this it has been reported that breastfed infants who had complementary feeding introduced before 4 months of age had greater height at the age of 3 years.(141)

Strengths and limitations

This study had a number of strengths. Firstly, this is one of the first studies to look at associations of infant feeding, linear growth and relative weight gain with separate components of childhood body composition in term born children. Secondly, it was a large community based cohort. In contrast to some other large studies, birth weight was measured by professional health workers and childhood body composition was measured by trained research assistants. Therefore, we did not have some of the methodological limitations that may adversely affect some other large studies (for example, reliance on recalled birth data, lack of standardization and inaccuracy of body composition measurements). Thirdly, we had frequent serial measures of growth, between birth and 12 months, and our data were highly complete, enabling conditional regression analysis.

However, several factors have to be acknowledged as potential limitations of the current report. Firstly, despite a lot of effort to reduce attrition, there was substantial loss to follow up (we were able to analyse 2227 children of 5551 children with collected growth data). The group included in the analysis differed from the original cohort for some of the background variables. Further, as in some other longitudinal studies, participation was higher among people with higher educational level and lower among ethnic minority groups.(142) However, a non-response analysis of the ABCD cohort that was conducted earlier suggested that this selective response did not affect relations between risk factors during pregnancy and birth outcomes; therefore we think it is unlikely that nonparticipation would account for different effects of growth and infant feeding on childhood body composition.(143)

Secondly, the methods we used for the measurement of body composition are less precise than dual-energy x-ray absorptiometry (DXA), but DXA turned out not to be applicable on such a large population. Thirdly, we have no information as to why solids were introduced when they were. Perceived satiety may well have been a factor, with early introduction of solids being a marker for ‘hungry’ infants whose appetites continue to be bigger as children. Faster growth then precedes earlier introduction of complementary feeding rather than being a result of earlier introduction of complementary feeding. This phenomenon is referred to as reverse causality and an example of this concerning associations of breastfeeding and infant growth is described in a recent article of Kramer et al.(144) However, in our study sample infants that received earlier complementary feeding did not show faster growth in the preceding period. Finally, because height at birth is not routinely measured in the Netherlands we were not able to address the association between birth height and childhood body composition, and had to use birth weight as the anchor for our conditional measures. Adair et al.(41) similarly encountered the problem of partly missing birth height data and compared results with and without the inclusion of birth height. Associations of resulting conditional height and conditional relative weight with later life body composition were similar.(41)

Our findings suggest that faster infant weight gain is associated with a healthier childhood body composition, when it is caused by faster linear growth. Youth health-care physicians need to identify infants who have faster infancy weight gain without accompanying faster linear growth and give parents advice/education regarding their child's weight. Although full breastfeeding >6 months and introduction of complementary feeding >6 months were associated with lower childhood FM, full breastfeeding was also associated with lower FFM and to a lesser extent with shorter height. Nevertheless, breastfeeding has more potential benefits for mother and child; therefore, a longer duration of breastfeeding should be encouraged. Because introduction of complementary feeding >4 months was associated with shorter childhood height, more research is needed to confirm this finding and to place it in perspective of other potential long term health consequences of timing of introduction of complementary feeding like atopic diseases, type 1 and 2 diabetes and neuromuscular development.

Associations of infant feeding and timing of growth in early life with childhood glucose and lipid biomarkers

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Submitted

6

ABSTRACT

Context Small birth size and rapid childhood weight gain have been associated with a higher risk of type 2 diabetes and an adverse lipid profile. The timing of these effects, the relative importance of linear growth and weight gain and the role of infant growth and feeding need to be clarified.

Objective We assessed how markers of insulin resistance and lipid profile at age 5 y relate to birth weight, relative weight gain and linear growth during infancy (0-1 y) and childhood (1-5 y), and infant feeding (duration of exclusive breastfeeding and timing of introduction of complementary feeding).

Design Prospective cohort study (ABCD study), 5 y follow up.

Setting General population.

Participants 1604 children aged 5 y from 5551 children with collected growth data.

Main outcome measures Fasting glucose, C-peptide (<0.34 nmol/l vs. ≥0.34 nmol/l), total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides at 5 y.

Results Higher childhood glucose and C-peptide concentrations were associated with faster childhood linear growth (glucose 0.04 mmol/l . SD^{-1}, P=0.005; C-peptide ≥ 0.34 nmol/l: OR 1.25, P=0.001) and relative weight gain (glucose 0.04 mmol/l . SD^{-1}, P=0.003; C-peptide ≥ 0.34 nmol/l: OR 1.39, P<0.001). Lower birth weight was associated with higher 5 y cholesterol concentrations. Infant growth and feeding were largely unrelated to outcomes.

Conclusion After the age of one year faster growth in either weight or height is associated with higher childhood markers of insulin resistance. We found no consistent associations of growth in infancy and infant feeding with childhood glucose and lipid biomarkers.

INTRODUCTION

The World Health Organization has attributed 6% and 4.5% of deaths worldwide to high blood glucose and high cholesterol respectively.(114) Therefore, these factors are two of the most important modifiable cardiovascular risk factors globally. Data from diverse populations have shown that that there is persistence (tracking) of levels of glucose homeostasis variables(3,145-149) and serum lipid levels(4-6,150) from childhood to adulthood with reported correlation coefficients of 0.2-0.4(3) and 0.4-0.7(4-6) respectively. Fetal growth restriction has been identified as a risk factor for type 2 diabetes mellitus (T2DM)(21,22) and an adverse lipid profile(151-153) in later life. Studies addressing the relationship of growth in infancy with glucose and lipid biomarkers in later life have shown mixed results (Table 6.1). For instance, the Helsinki and Hertfordshire birth cohort studies showed that slower growth in infancy was associated with insulin resistance (IR), impaired glucose tolerance (GT)/type 2 diabetes mellitus (T2DM) and an adverse lipid profile (table 6.1). Some studies, including the Pelotas and Copenhagen birth cohort studies and Early Bird Diabetes Study showed no associations (Table 6.1). The ALSPAC birth cohort study and several small-for-gestational-age (SGA) cohorts showed that faster growth in infancy was associated with IR, T2DM and an adverse lipid profile (table 6.1). There is therefore confusion about what constitutes optimal infant growth for future cardiovascular health.

In contrast, greater weight gain in childhood (*after* infancy) has been consistently associated with IR, T2DM, and an adverse lipid profile in later life in numerous studies.(42-45) It is not clear however, whether the relationship of weight gain to later life T2DM (or conditions in its clinical spectrum) and lipid profile comes from the component of weight gain that is due to linear (skeletal) growth or to soft tissue (lean and fat) growth. Knowing this may provide insight into the mechanisms linking postnatal growth and later life T2DM and lipid profile. The Amsterdam Born Children and their Development (ABCD) study has measurements of both weight and height, and was unusual in collecting these at frequent intervals in infancy.

In the ABCD study we found that longer duration of breastfeeding and later introduction of complementary feeding were associated with slower growth in infancy(117) which was in accordance with other studies.(46,47) Early feeding may therefore be related to later life T2DM and lipid profile. Furthermore, infant feeding may have direct programming effects on later life T2DM and lipid profile, for example due to a different distribution of body fat(53), differences in endocrine responses(54), anti-inflammatory effects(51), differences in long-chain polyunsaturated fatty acids(51), and nutritional programming of cholesterol synthesis.(55) Breastfeeding has been associated with a reduced risk of T2DM(55) and with lower cholesterol concentrations(55) in later life when compared to formula feeding. The role of complementary feeding has received little attention until now. In a recent study no associations were found between timing of introduction of complementary feeding and childhood glucose and lipid biomarkers after adjusting for confounding variables.(68)

The aims of our study were to answer the following questions in a population based cohort: 1) Does growth in either weight or height during infancy have significant positive or negative associations with markers of IR and lipid profile at age 5 years?; 2) If so, are there periods in infancy when the associations are stronger?; 3) Is the association of childhood weight gain with IR and lipid profile related to linear growth or soft tissue growth?; 4) Are duration of breastfeeding and timing of introduction of complementary feeding associated with markers of IR and lipid profile at 5 years?

Table 6.1. Studies addressing the relation of infant growth with later life glucose and lipid biomarkers

Source	Setting	Infant growth measurement	Age/Period	Health outcome	Mean age at outcome	Results
Hales et al,(154) **1991**	Hertfordshire birth cohort (UK)	W	1y	GT T2DM	Adult	Lower W at 1y was associated with impaired adult GT and T2DM
Fall et al,(155) **1992**	Hertfordshire birth cohort (UK)	W	1y	TC LDL	Adult	Lower W at 1y was associated with higher adult TC and LDL in subjects that were breastfed at 1y
Miura et al,(156) **2001**	Ishikawa prefecture birth cohort (Japan)	WG LG	0m-3m 3m–1y 1y–3y	TC	Adult	No associations found
Soto et al,(157) **2003**	SGA vs. AGA cohort (Chile)	WG LG	0y-1y	IR GT TC TG	1y	Slower 0y-1y LG tended to be associated with lower 1y GT
Eriksson et al,(158) **2003**	Helsinki birth cohort (Finland)	W BMIG LG	±8 measurements between 0y-1y	T2DM	Adult	Lower W at 1y was associated with a higher incidence of adult T2DM. In children with birth weight > 3.5 kg slower LG 0m-3m was associated with a higher incidence of adult T2DM.
Bhargava et al,(159) **2004**	New Delhi birth cohort (India)	BMI BMIG LG	throughout infancy: 3-6m intervals	GT T2DM	Adult	Lower BMI at 2y was associated with lower adult GT and T2DM
Ong et al,(82) **2004**	ALSPAC birth cohort (UK)	WG	0y-3y	HOMA-IR Insulin secretion	8y	Faster WG 0y-3y was associated with higher 8y IR
Barker et al,(160) **2005**	Helsinki birth cohort (Finland)	BMI	2y	Glucose Insulin TC TG	Adult	Low BMI at 2y was associated with higher adult glucose, insulin and TG
Wadsworth et al,(161) **2005**	1946 British birth cohort	W	2y	T2DM	Adult	Lower W at 2y was associated with a higher prevalence of T2DM
Finken et al,(162) **2006**	POPS cohort (preterms) (The Netherlands)	WG	0m-3m 0y-1y	Insulin HOMA-IR	19y	Faster WG 0m-3m was associated with higher 19y insulin.
Finken et al,(163) **2006**	POPS cohort (preterms) The Netherlands)	WG	0m-3m 0y-1y	TC HDL LDL TG	19y	No associations found

Source	Setting	Infant growth measurement	Age/Period	Health outcome	Mean age at outcome	Results
Eriksson et al,(23) **2006**	Helsinki birth cohort (Finland)	WG BMIG LG	0m-6m 6m-1y 1y-2y	HOMA-IR GT T2DM	Adult	Slower WG and BMIG 0m-6m was associated with higher adult IR, impaired GT and T2DM Slower WG, BMIG and slower LG 6m-1y were associated with impaired adult GT and T2DM
Jeffery et al,(164) **2006**	Early Bird Diabetes Study cohort	W WG	3w 6w 0w-3w 0w-6 w	HOMA-IR	5y 6y 7y 8y	No associations found
Ekelund et al,(165) **2007**	The Stockholm Weight Development study (Sweden)	WG	0m-6m	Glucose Insulin HDL TG	17y	Faster 0m-6m WG was associated with lower 17y HDL and higher TG
Joglekar et al,(166) **2007**	Pune Maternal Nutrition Study (India)	WG LG	0m-6m 6m–1y	Glucose tolerance HOMA-IR TC HDL TG	6y	Faster WG and LG 6m–1y were associated with higher 6y IR
Fall et al,(167) **2008**	New Delhi birth cohort (India)	WG BMIG	0y-2y	GT HOMA-IR TC HDL TG	Adult	Faster 0y-2y WG was associated with higher adult IR and higher TG Slower 0y-2y BMIG was associated with lower adult GT
Kajantie et al,(168) **2008**	Helsinki birth cohort (Finland)	BMIG LG	0m-6m 6m-2y	TC HDL Non-HDL TG	Adult	Slower 0m-6m BMIG was associated with lower adult HDL and higher non-HDL Slower 6m-2y BMIG was associated with higher adult TG Slower 6m-2y LG was associated with higher adult TC, non-HDL and TG
Bouhours-Nouet et al,(169) **2008**	Obese children cohort (France)	WG	0y-2y	IS indexes (based on glucose tolerance test): whole body IS, hepatic IR, skeletal muscle IS	6y-15y	Slower WG 0y-2y was associated with lower 6y-15y whole body IS
Leunissen et al, (34) **2009**	PROGRAM study (relatively many SGA) (The Netherlands)	WG	0m-3m 3m-6m 6m-9m 9m-12m	IS index (Bergman minimal model) TC HDL LDL TG	Adult	Greater 0m-3m WG was associated with lower adult IS, lower HDL and higher TG

Source	Setting	Infant growth measurement	Age/Period	Health outcome	Mean age at outcome	Results
Horta et al,(170) **2009**	Pelotas birth cohort (Brazil)	WG	0m-20m	TC HDL LDL VLDL LDL/TC ratio	18y	No associations found
Larnkjaer et al,(171) **2010**	Copenhagen birth cohort study (Denmark)	WG	0m-9m 0m-3m 3m-6m 6m-9m	HOMA-IR	17y	No associations found
Deng et al,(172) **2010**	SGA vs. AGA cohort (China)	WG LG	0y–(1.5y-11.2y)	Insulin HOMA-IR HOMA%B	1.5y-11.2y	Faster WG was associated with higher insulin in > 6y old SGA children SGA children with faster LG had higher 1.5y-11.2y HOMA-IR than SGA children with slower LG or AGA children Faster LG was associated with higher insulin in ≤ 6y old SGA children.
Slining et al,(173) **2011**	Cebu cohort (Philippines)	WG	0m-4m 0y-2y	HOMA-IR	Adult	In males, faster WG 0y-2y was associated with higher adult IR
Perälä et al,(174) **2011**	Helsinki birth cohort (Finland)	BMIG	0y-1y	Postprandial responses: Glucose, Insulin, TG FFA	Adult	Slower BMIG 0y–1y was associated with higher adult postprandial insulin and TG
Bekkers et al,(175) **2011**	PIAMA birth cohort (The Netherlands)	WG	0y-1y	TC HDL TC/HDL	8y	Faster WG 0y-1y was associated with higher 8y TC/HDL
Fabricius-Bjerre et al,(176) **2011**	Danish cohort (SGA vs. AGA)	WG	0m-3m 0y-1y	Insulin HOMA-IR FPIR Glucose disappearance rate IS Disposition index TC HDL LDL TG	17y	Faster WG 0m-3m was associated with higher 17y insulin, IR, TC, LDL and TG Faster WG 0y-1y was associated with higher 17y IR

Source	Setting	Infant growth measurement	Age/Period	Health outcome	Mean age at outcome	Results
Kerkhof et al,(177) **2012**	PROGRAM study (relatively many SGA) (The Netherlands)	WFLG	0m-3m 3m-6m 6m-9m 9m-12m	IS index (Bergman minimal model) TC HDL LDL TG	Adult	Faster 0m-3m WFLG was associated with lower adult HDL and lower IS
Norris et al,(35) **2012**	COHORTS (Brazil, Guatemala, India, the Philippines, and South Africa)	WG	0y-2y	GT T2DM HOMA-IR	Adult	Faster 0y–2y WG was associated with higher adult IR
Adair et al,(41) **2013**	COHORTS (Brazil, Guatemala, India, the Philippines, and South Africa)	WG LG	0y-2y	Glucose	Adult	No associations found
Whitrow et al,(178) **2013**	Generation 1 birth cohort (Australia)	BMI	0m 6m 12m 2y	HOMA-IR	9y	No associations found
Krishnaveni et al,(179) **2015**	Mysore Parthenon cohort (India)	LG FMG FFMG	0y-1y 1y-2y	HOMA-IR TC HDL TG	13.5y	No associations found

AGA-appropriate-for-gestational-age, BMI-body mass index, BMIG-BMI gain, CU-catch up, FFA-free fatty acids, FFMG-fat-free mass gain, FMG-fat mass gain, FPIR-first-phase insulin response, GT-glucose tolerance, HDL-high-density-lipoprotein, HOMA-homeostatic model assessment, IR-insulin resistance, IS-insulin sensitivity, LDL-low-density-lipoprotein, LG-linear growth, SGA-small-for-gestational-age, T2DM-type 2 diabetes mellitus, TC-total cholesterol, TG-triglycerides, VLDL-very-low-density-lipoprotein, W-weight, WG-weight gain, WFLG-weight-for-length-gain, %B-β-cell capacity.

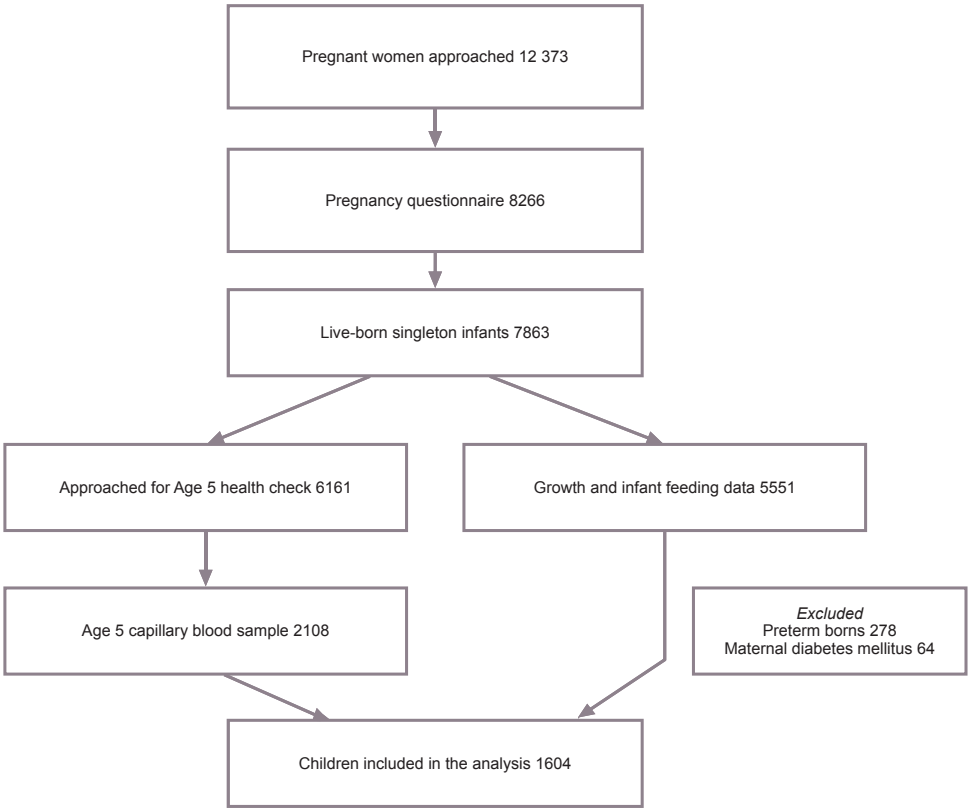
METHODS

The present study is part of the Amsterdam Born Children and their Development (ABCD) study, a population based prospective, longitudinal pregnancy cohort.(69) Approval was obtained from the research ethics committees of all participating hospitals and the Registration Committee of Amsterdam. All participants gave written informed consent for themselves and their children.

Study population

Between January 2003 and March 2004, all pregnant women living in Amsterdam were invited to participate in this study at their first visit (12–14th week of pregnancy) to an obstetric caregiver (Fig. 6.1). A questionnaire, including sociodemographic data, obstetric history and lifestyle, was sent to the pregnant woman's home address. Questionnaires were returned by 8266 women (response rate 67%). From this group 7863 gave birth to a viable singleton infant. Pregnancy duration, gender and birth weight were obtained from Youth Health Care (YHC) centres, which perform neonatal screening for congenital inborn errors of metabolism in all Dutch newborns. The YHC centres routinely invite them from birth onwards for regular health evaluations at set ages: 8 times between birth and 12 months of age: around 1, 2, 3, 4, 6, 7.5, 9 and 11 months. During these check-ups weight and supine height were measured and feeding patterns (duration of breastfeeding and timing of introduction of complementary feeding) were registered. When measuring height, the parent was asked to hold the infant's head in contact with a fixed board, and the YHC health worker stretched the infant out to its maximum length and then brought a moving board into contact with the heels. Growth- and infant feeding data were collected for a total of 5551 children. Prematurely born babies (with a pregnancy duration less than 37 weeks, n=278) and babies of mothers with pre-existing or gestational diabetes mellitus (n=64) were excluded. When the children reached the age of 5 years, the addresses of 6161 mothers were retrieved from the YHC registry. The mothers received an informed consent sheet for a health check of their child, for which 4158 (67%) women gave permission; 3955 (64%) women gave permission for a capillary blood sample. The health check included measurements by trained research assistants, including anthropometry, and was carried out in 3321 children aged 5 years; the capillary blood sample was taken from 2108 children (2008-2010).(87). The current study population included children whose birth weight and growth and infant feeding data were available, as well as anthropometry and fasting levels of lipid- and glucose biomarkers at age 5 years (n=1604). A subsample of 1252 children had available C-peptide concentrations.

Fig 6.1. Sampling procedure



Exposure variables: birth weight, postnatal growth and infant feeding

We used birth weight (birth height is not routinely measured in the Netherlands) and subsequent weight and height at 1, 3, 6, 12 months and 5 years of age. Using the maximum number of measurements available at all time points, sex-specific internal z scores were generated. If a measurement was not recorded at the exact age, we derived this value by interpolating between the nearest measurements. Because children without birth weight or 5 year measurements were excluded we did not need to extrapolate these measures. The age ranges accepted for interpolation at 1, 3, 6 and 12 months were 0-2 months, 2-4 months, 4-8 months and 9-15 months respectively. 95% of measurements were made within 0.3, 0.3, 0.4 and 0.9 months respectively from the exact age.

Using these measures of size, we derived measures of growth (i.e. change in size). Disentangling the consequences of relative weight gain and linear growth at different ages requires statistical methods to address the high correlation of weight with height, and of repeated measurements in the same individual over time. Our "conditional" size measures were standardised residuals derived from regressing current size on all prior size measures.(32,33,41,70-73) Conditional relative weight was current weight accounting for current height and all prior weight and height measures. Conditional height was current height accounting for prior height and weight measures (but not current weight). Current weight was not accounted for in

constructing conditional height because it does not contribute to current height. In contrast, we accounted for current height in constructing conditional weight because it does contribute to current weight. For example, childhood conditional relative weight was derived from regressing 5-year weight on 5-year height, weights and heights at 1, 3, 6 and 12 months, and birth weight. Conditional variables represent children's deviation from expected size, based on their own previous size and the growth of the other children in the study population, and can be interpreted as representing faster or slower relative weight gain or linear growth. Conditional regression analysis is designed to assess growth over distinct age periods and to eliminate collinearity problems caused by repeated measures.(73) Although the age intervals chosen increased in length, the correlations between measurements at the beginning and end of each interval were similar, as the child's growth stabilised. This justified the selection of shorter intervals at younger ages.
Duration of exclusive breastfeeding (excluding any other form of nutrition including formula feeding and complementary feeding) was categorised into 4 subgroups: no exclusive breastfeeding or <1 month, 1-3 months, 3-6 months and >6 months. Timing of introduction of complementary feeding (defined as any food other than breastfeeding or formula feeding) was divided into 3 subgroups: <4 months, between 4-6 months and >6 months.

Outcome measures

Capillary blood was collected with an ambulatory collection kit (Demecal: LabAnywhere, Haarlem, The Netherlands).(74) Outcome measures were fasting glucose concentration and C-peptide concentration (<0.34 nmol/l vs. ≥0.34 nmol/l) as markers of IR(180), total cholesterol concentration (TC), high-density-lipoprotein cholesterol concentration (HDL), low-density-lipoprotein cholesterol concentration (LDL) and triglyceride concentration (TG). All continuous variables were standardised using internal sex-specific z scores to allow comparisons across outcome measures. 63% (n=787) of the C-peptide concentrations fell below the laboratory detection limit of 0.34 nmol/l. Therefore, we chose to use C-peptide concentration as a dichotomous variable.

Confounding variables

Potential confounding variables that we considered were: the child's sex (male, female) and exact age (continuous, years) at the 5-year health check, and the following maternal characteristics: age (continuous, years), pre-pregnancy body mass index (BMI, continuous, kg/mt^2), height (continuous, cm), educational level (years of education after primary school, continuous), primiparity (yes, no), use of alcohol during pregnancy (yes, no), smoking during pregnancy (none, 1-5 cigarettes / day, ≥6 cigarettes / day), hypertension (none, pre-existing hypertension, pregnancy-induced hypertension), ethnicity (based on mother's country of birth: Dutch, Surinamese, Turkish, Moroccan, other) and pregnancy duration (continuous, weeks).(87)

Statistical analyses

We used multivariable linear regression to estimate associations of birth weight, conditional relative weight and conditional height 0-1, 1-3, 3-6, 6-12 months (infancy) and 12 months-5 years (childhood) with glucose, TC, HDL, LDL and TG concentrations at age 5 years, adjusting for all the above-mentioned potential confounding variables. We used multivariable logistic regression to estimate associations between birth weight, conditional relative weight and conditional height in 5 time periods with C-Peptide concentration ≥0.34 nmol/l, adjusting for all the above-mentioned potential confounding variables. We examined the association of infant feeding with the outcome measures using the same approach, further adjusting for birth weight. When looking at timing of introduction of complementary feeding as the exposure variable we adjusted for duration of full breastfeeding (defined as no formula feeding). Both exclusive breastfeeding and timing of introduction of complementary feeding were treated as categorical variables. Statistical analysis was carried out using IBM SPSS for Mac (version 21.0.0).

RESULTS

Descriptives

Compared to the cohort members who were not studied (n=3947), the study group (n=1604) mothers were older (mean 32.4 vs. 30.5 years, P<0.001), had a lower pre-pregnancy BMI (22.8 vs. 23.2 kg/mt^2, P=0.002) and taller stature (mean 1.70 vs. 1.68 mt, P<0.001). They were more likely to drink alcohol during pregnancy (30.1 vs. 19.5%, P<0.001), more likely to be of Dutch origin (40.8 vs. 19.9%, P<0.001), less likely to have pre-existing hypertension (2.6 vs. 4.1%, P=0.02), had a longer pregnancy duration (40.1 vs. 39.7 weeks, P<0.001), were more likely to initiate exclusive breastfeeding (77 vs. 68 %, P<0.001) and tended to breastfeed for longer (e.g. 14.3 vs. 11.8%, P=0.013 continued for > 6 months). The offspring had a higher birth weight (mean z score 0.10 vs. -0.05, P<0.001) and slower relative weight gain between 1-3 months (-0.08 vs. 0.04, P=0.001) and 3-6 months (-0.04 vs. 0.02, P=0.03). They had slower linear growth between 1-3 months (-0.05 vs. 0.02, P=0.02) and 3-6 months (-0.05 vs. 0.03, P=0.02). These differences between responders and non-responders were similar for people of Dutch origin and non-Dutch origin. The characteristics of the study sample are shown in Table 6.2. The mean values of the outcome measures were in good accordance with reference values derived from previous studies.(181,182) Mean glucose concentration was higher in boys than in girls (p<0.001). Girls had higher TC, LDL and TG concentrations compared to boys (all p<0.001).

Table 6.2. Maternal and child characteristics by sex (N=1604)

Measurement	Boys (n=838)		Girls (n=766)	
	Mean	SD	Mean	SD
Mother				
Age (y)	32.5	4.4	32.4	4.2
Pre-pregnancy BMI (kg/mt^2)	22.8	3.6	22.9	3.6
Height (mt)	1.70	0.07	1.70	0.07
Education after primary school (y)	10.0	3.6	10.2	3.4
Primiparous (% yes)	54.1		54.7	
Alcohol (% yes)	30.5		29.6	
Smoking				
Non-smoking (%)	93.8		95.0	
1-5 cigarettes/day (%)	3.8		2.2	
≥6 cigarettes/day (%)	2.4		2.7	
Ethnicity				
Dutch (%)	79.8		80.4	
Surinamese (%)	3.1		1.4	
Turkish (%)	1.6		1.4	
Moroccan (%)	4.7		2.7	
Other (%)	10.9		14.0	
Hypertension				
Pre-existing hypertension (%)	2.3		2.9	
Gestational hypertension (%)	8.0		9.5	
Child – At birth				
Pregnancy duration (weeks)	40.2	1.2	40.1	1.2
Birth weight (kg)	3.62	0.50	3.49	0.45
SGA (%)(119)	9.4		7.6	
LGA (%)(119)	12.3		10.3	
Child – 1-12 months measurements				
Weight (kg)				
1 month	4.57	0.55	4.29	0.49
3 months	6.38	0.69	5.83	0.63
6 months	8.07	0.84	7.45	0.77
12 months	10.19	1.03	9.54	0.99
Height (cm)				
1 month	55.2	2.1	54.2	1.9
3 months	62.0	2.1	60.4	1.9
6 months	68.4	2.1	66.7	2.0
12 months	76.5	2.5	74.9	2.3
Duration of exclusive breastfeeding (months)				
<1 month (%)	23.6		22.7	
1-3 months (%)	26.8		26.2	
3-6 months (%)	35.2		36.8	
>6 months (%)	14.3		14.2	
Age at introduction of complementary feeding (months)				
<4 months (%)	4.7		5.0	
4-6 months (%)	37.0		36.2	
>6 months (%)	58.3		58.8	

Measurement	Boys (n=838)		Girls (n=766)	
	Mean	SD	Mean	SD
Child – At age 5 health check				
Age (y)	5.7	0.5	5.7	0.5
Weight (kg)	21.1	3.0	20.8	3.2
Height (cm)	116.7	5.5	115.9	5.4
BMI (kg/mt^2)	15.4	1.3	15.4	1.5
Glucose (mmol/l)	4.65	0.57	4.50	0.48
C-peptide ≥0.34 nmol/l (%) (n=1252)	35.2		39.2	
TC (mmol/l)	3.95	0.65	4.16	0.70
HDL (mmol/l)	1.32	0.31	1.29	0.31
LDL (mmol/l)	2.21	0.61	2.45	0.67
TG (mmol/l)	0.61	0.27	0.70	0.33

BMI-body mass index, HDL-high-density-lipoprotein, LDL-low-density-lipoprotein, LGA-large-for-gestational-age, SGA-small-for-gestational-age, TC-total cholesterol, TG-triglycerides.

Confounding variables

The associations of confounding variables with size and growth, glucose, C-peptide ≥0.34 nmol/l, TC, HDL, LDL and TG concentrations and infant feeding are presented in Tables 6.3, 6.4, 6.5 and 6.6 respectively. To summarize these data briefly, lower birth weight was associated with the following maternal characteristics: younger age, lower pre-pregnancy BMI, shorter stature, lower educational level, smoking during pregnancy, primiparity, non-Dutch ethnicity, gestational hypertension and shorter pregnancy duration. Faster linear growth and relative weight gain tended to be associated with younger maternal age, higher pre-pregnancy BMI, lower educational level, smoking during pregnancy, primiparity and pre-existing and gestational hypertension. Faster linear growth was additionally associated with taller maternal stature and shorter pregnancy duration. Exceptions to the above were that faster linear growth during 0-1 months was associated with lower maternal BMI, higher educational level, not smoking during pregnancy and longer pregnancy duration. There were significant differences in growth between ethnic groups (Table 6.3).

Younger maternal age was associated with lower HDL and higher TG concentrations in the offspring. Higher pre-pregnancy BMI was associated with lower HDL and higher LDL concentrations in the offspring. Smoking during pregnancy was associated with lower offspring glucose concentration. Use of alcohol was associated with higher HDL concentration in the offspring. Offspring of primiparous women had lower C-Peptide, lower HDL, higher LDL and higher TG concentrations. Offspring of Surinamese mothers had higher C-Peptide and HDL concentrations. Offspring of Turkish mothers had higher HDL concentration (Table 6.4).

Women who exclusively breastfed for 3-6 months were thinner (P=0.011), better-educated (P<0.001), and had longer pregnancies (P<0.001), than women who breastfed for <1 month. They were less likely to smoke (P=0.05 and P<0.001), have gestational hypertension (P=0.003) and be of Surinamese (P=0.007) or Moroccan (P=0.02) origin, than women who breastfed for <1 month. Furthermore, their offspring's birth weight was higher (P<0.001) (Table 6.5).

Women who introduced complementary feeding >6 months were thinner (P=0.01) and better-educated (P<0.001). They were less likely to smoke (P=0.03) and be of Surinamese origin (P=0.001) than women who introduced complementary feeding <6 months (Table 6.6).

Table 6.3. Relation of confounding variables with birth weight, relative weight gain and linear growth (in standard deviation scores)

	Birth weight		Relative weight gain (z scores)									
			0-1 m		1-3 m		3-6 m		6-12 m		12 m-5 y	
	B	P	B	P	B	P	B	P	B	P	B	P
Mother												
Age (y)	0.01	.02	-0.02	.01	-0.02	.002	-0.01	.04	-0.01	.37	-0.02	.001
BMI (kg/mt^2)	0.04	<.001	0.01	.12	0.03	<.001	0.01	.05	0.00	.90	0.05	<.001
Height (mt)	2.91	<.001	-0.40	.28	-0.26	.48	-0.43	.24	-0.41	.26	-2.01	<.001
Education (y)	0.02	.01	-0.01	.19	-0.03	<.001	-0.01	.09	0.01	.24	-0.03	<.001
Smoking												
No (ref)	-	-	-	-	-	-	-	-	-	-	-	-
1-5 cigarettes/day	-0.31	.03	0.21	.15	-0.04	.79	0.12	.40	-0.02	.91	0.24	.09
≥6 cigarettes/day	-0.56	<.001	-0.01	.95	0.30	.06	0.42	.01	0.21	.18	0.14	.36
Alcohol, yes	0.09	.12	-0.10	.08	-0.11	.05	0.04	.46	-0.03	.57	-0.09	.09
Primiparity, yes	-0.26	<.001	-0.16	.002	0.12	.02	0.01	.80	0.04	.42	0.00	.93
Ethnicity												
Dutch (ref)	-	-	-	-	-	-	-	-	-	-	-	-
Surinamese	-0.35	.03	-0.01	.97	0.21	.19	-0.01	.95	-0.41	.01	0.27	.11
Turkish	-0.42	.04	0.56	.01	0.46	.02	0.13	.53	0.22	.27	0.59	.004
Moroccan	-0.19	.14	0.21	.11	0.46	<.001	0.54	<.001	0.17	.20	0.30	.02
Other	-0.12	.11	-0.01	.94	0.18	.02	-0.11	.14	-0.14	.06	0.05	.54
Hypertension												
No (ref)	-	-	-	-	-	-	-	-	-	-	-	-
Pre-existing	0.01	.95	0.01	.95	0.53	.001	0.11	.50	-0.18	.25	0.03	.84
Gestational	-0.28	.001	-0.04	.67	0.23	.009	0.08	.35	0.07	.44	0.14	.11
Child - At birth												
Pregnancy duration (w)	0.34	<.001	-0.02	.30	-0.10	<.001	-0.02	.46	0.02	.47	0.04	.08

Table 6.3 continued. Relation of confounding variables with birth weight, relative weight gain and linear growth (in standard deviation scores)

	Linear growth (z scores)									
	0-1 m		1-3 m		3-6 m		6-12 m		12 m-5 y	
	B	P	B	P	B	P	B	P	B	P
Mother										
Age (y)	0.00	.71	0.00	.94	-0.02	.009	0.00	.98	0.01	.20
BMI (kg/mt^2)	-0.02	.008	-0.01	.44	0.01	.26	0.01	.26	0.01	.22
Height (mt)	2.82	<.001	2.07	<.001	1.07	.003	1.30	<.001	3.48	<.001
Education (y)	0.02	.02	-0.01	.45	-0.03	<.001	-0.02	.002	0.01	.22
Smoking										
No (ref)	-	-	-	-	-	-	-	-	-	-
1-5 cigarettes/day	-0.14	.34	0.12	.40	0.27	.06	0.29	.04	-0.22	.13
≥6 cigarettes/day	-0.57	<.001	-0.11	.48	0.31	.05	0.40	.01	0.11	.48
Alcohol, yes	-0.04	.48	0.01	.91	-0.11	.04	-0.09	.08	0.01	.87
Primiparity, yes	0.18	<.001	0.15	.003	0.01	.88	-0.02	.65	0.08	.12
Ethnicity										
Dutch (ref)	-	-	-	-	-	-	-	-	-	-
Surinamese	-0.10	.56	-0.19	.26	0.43	.009	0.01	.93	0.02	.88
Turkish	0.00	1.00	0.17	.40	0.34	.10	0.17	.40	-0.58	.004
Moroccan	-0.47	<.001	-0.13	.31	0.23	.08	0.01	.94	-0.32	.02
Other	-0.11	.14	0.08	.27	0.11	.15	0.05	.52	-0.13	.08
Hypertension										
No (ref)	-	-	-	-	-	-	-	-	-	-
Pre-existing	0.08	.63	-0.05	.73	-0.13	.40	0.19	.22	0.25	.11
Gestational	0.01	.92	0.03	.73	-0.01	.91	0.05	.60	0.10	.24
Child - At birth										
Pregnancy duration (w)	0.15	<.001	-0.01	.74	-0.07	<.001	-0.04	.04	-0.06	0.07

B values are linear regression coefficients indicating the change in birth weight, relative weight gain and linear growth (in standard deviation scores) per unit change in the confounding variable (if a continuous variable) or between each category of the confounding variable and the reference category (if a categorical variable).

Table 6.4. Relation of confounding variables with childhood glucose, C-Peptide ≥ 0.34 nmol/l, TC, HDL, LDL and TG

	Glucose (z)		C-Peptide ≥ 0.34 nmol/l		TC (z)		HDL (z)		LDL (z)		TG (z)	
	B	P	OR	P	B	P	B	P	B	P	B	P
Mother												
Age (y)	-0.01	.40	1.00	.81	0.01	.10	0.01	.003	0.00	.65	-0.01	.02
BMI (kg/mt^2)	0.00	.95	1.03	.13	0.00	.73	-0.02	.01	0.01	.05	0.01	.10
Height (mt)	0.00	.24	1.00	.73	-0.01	.07	-0.01	.18	-0.01	.12	0.00	.56
Education (y)	-0.01	.39	0.99	.48	0.00	.83	0.01	.50	0.01	.38	-0.01	.08
Smoking												
No (ref)	-	-	-	-	-	-	-	-	-	-	-	-
1-5 cigarettes/day	-0.30	.04	0.72	.36	0.07	.64	0.08	.59	-0.01	.94	0.13	.37
≥6 cigarettes/day	-0.21	.17	0.67	.30	-0.11	.49	0.27	.09	-0.20	.19	-0.28	.08
Alcohol, yes	-0.04	.43	1.04	.77	0.03	.56	0.12	.02	-0.01	.90	-0.05	.33
Primiparity, yes	-0.09	.07	0.74	.01	0.03	.59	-0.16	.002	0.10	.04	0.11	.03
Ethnicity												
Dutch (ref)	-	-	-	-	-	-	-	-	-	-	-	-
Surinamese	0.09	.57	2.25	.03	0.06	.70	0.32	.05	-0.19	.26	-0.32	.06
Turkish	0.12	.54	1.65	.25	0.23	.26	0.50	.01	-0.02	.93	0.09	.65
Moroccan	-0.14	.28	1.22	.53	-0.18	.17	-0.02	.88	-0.18	.17	0.03	.82
Other	0.07	.39	1.17	.38	0.03	.72	0.11	.14	-0.01	.95	-0.09	.23
Hypertension												
No (ref)	-	-	-	-	-	-	-	-	-	-	-	-
Pre-existing	-0.05	.77	0.64	.27	-0.02	.88	-0.06	.51	-0.01	.95	-0.13	.43
Gestational	-0.01	.91	0.93	.73	0.16	.07	-0.05	.74	0.12	.16	0.13	.16
Child - At birth												
Pregnancy duration (w)	0.00	.68	0.99	.42	0.00	.77	0.00	.93	0.00	.89	0.00	.56

B values are linear regression coefficients indicating the change in the outcome (in standard deviation scores) per unit change in the confounding variable (if a continuous variable) or between each category of the confounding variable and its reference category (if a categorical variable) adjusting for the child's age and sex. OR indicates the likelihood of the outcome per unit change in the confounding variable (if a continuous variable) or of each category of the confounding variable compared to the reference category (if a categorical variable) adjusting for the child's age and sex. TC-total cholesterol, HDL-high-density-lipoprotein, LDL-low-density-lipoprotein, TG-triglycerides.

Table 6.5. Confounding variables by duration of exclusive breastfeeding

	Duration of exclusive breastfeeding (N=1600)							
	<1 m (reference) (n=368, 23.0%)		1-3 m (n=426, 26.6%)		3-6 m (n=577, 36.1%)		>6 m (n=229, 14.3%)	
Mother	**(Mean, SD)**		**(Mean, SD)**	**B**	**(Mean, SD)**	**B**	**(Mean, SD)**	**B**
Age (y)	(32.3, 4.7)	-	(32.0, 4.4)	-0.24	(32.6, 3.9)	0.38	(33.1, 4.5)	0.82 *
BMI (kg/mt^2)	(23.3, 4.0)	-	(22.7, 3.4)	-0.58 *	(22.7, 3.4)	-0.61 *	(22.9, 3.7)	-0.42
Height (mt)	(1.70, 0.07)	-	(1.70, 0.06)	0.01	(1.70, 0.07)	0.01	(1.70, 0.07)	0.01
Education (y)	(9.4, 3.8)	-	(9.6, 3.5)	0.13	(10.9, 3.1)	1.44 ***	(10.4, 3.6)	0.93 **
Mother	**Col %**		**Col %**	**OR**	**Col %**	**OR**	**Col %**	**OR**
Primiparous, yes	61.1	-	52.3	0.70 *	54.8	0.77	45.9	0.54 **
Alcohol, yes	26.6	-	36.2	1.56 **	30.3	1.20	23.6	0.85
Smoking								
No (reference)	89.7	-	93.7	-	96.9	-	94.4	-
1-5 cigarettes/day	4.6	-	3.3	0.68	2.4	0.49 *	3.1	0.35
≥6 cigarettes/day	5.7	-	3.1	0.51	0.7	0.11 **	2.6	0.21 *
Hypertension								
None (reference)	84.2	-	90.5	-	91.3	-	86.0	-
Pre-existing	3.3	-	3.3	0.94	1.7	0.49	2.2	0.66
Gestational	12.6	-	6.1	0.46 **	6.9	0.51 **	11.8	0.92
Mother	**Row %**		**Row %**	**OR**	**Row %**	**OR**	**Row %**	**OR**
Ethnicity								
Dutch (reference)	23.0	-	26.2	-	37.2	-	13.6	-
Surinamese	37.8	-	35.1	0.82	16.2	0.27 *	10.8	0.48
Turkish	12.5	-	37.5	2.63	45.8	2.27	4.2	0.57
Moroccan	28.3	-	31.7	0.98	18.3	0.40 *	21.7	1.30
Other	19.7	-	24.7	1.10	36.9	1.16	18.7	1.61
Child - At birth	**(Mean, SD)**		**(Mean, SD)**	**B**	**(Mean, SD)**	**B**	**(Mean, SD)**	**B**
Pregnancy duration (w)	(40.0, 1.3)	-	(40.1, 1.2)	0.08	(40.3, 1.2)	0.28 ***	(40.2, 1.3)	0.20
Birth weight (kg)	(3.48, 0.53)	-	(3.57, 0.47)	0.08 *	(3.60, 0.46)	0.11 ***	(3.58, 0.49)	0.09 *

B values are linear regression coefficients indicating the change in the confounding variable (if a continuous variable) for each category of the breastfeeding variable compared with the reference category. OR is the corresponding odds ratio (if a categorical variable). *P<0.05, **P<0.01, ***P<0.001.

Table 6.6. Confounding variables by timing of introduction of complementary feeding

	Timing of introduction of complementary feeding (N=2203)					
	<4 m (n=77, 4.9%)		4-6 m (n=581, 36.6%)		>6 m (reference) (n=928, 58.5%)	
Mother	**(Mean, SD)**	**B**	**(Mean, SD)**	**B**	**(Mean, SD)**	
Age (y)	(32.1, 5.2)	-0.50	(32.2, 4.4)	-0.40	(32.6, 4.1)	-
BMI (kg/mt^2)	(23.8, 4.2)	1.06 *	(22.9, 3.6)	0.10	(22.8, 3.6)	-
Height (mt)	(1.69, 0.07)	-0.01	(1.70, 0.07)	0.00	(1.70, 0.07)	-
Education (y)	(8.6, 3.8)	-1.69 ***	(10.0, 3.6)	-0.24	(10.3, 3.4)	-
Mother	**Col %**	**OR**	**Col %**	**OR**	**Col %**	
Primiparous, yes	48.1	0.76	53.9	0.96	55.0	-
Alcohol, yes	24.7	0.80	32.2	1.16	29.0	-
Smoking						
No (reference)	88.3	-	93.1	-	95.7	-
1-5 cigarettes/day	6.5	2.97 *	3.6	1.57	2.4	-
≥6 cigarettes/day	5.2	2.90	3.3	1.73	1.9	-
Hypertension						
None (reference)	87.0	-	90.0	-	88.0	-
Pre-existing	6.5	2.53	2.1	0.78	2.6	-
Gestational	6.5	0.70	7.9	0.83	9.4	-
Mother	**Row %**	**OR**	**Row %**	**OR**	**Row %**	
Ethnicity						
Dutch (reference)	4.7	-	37.1	-	58.2	-
Surinamese	18.9	4.86 **	32.4	1.05	48.6	-
Turkish	0.0	0.00	54.2	1.86	45.8	-
Moroccan	8.3	1.95	38.3	1.13	53.3	-
Other	3.0	0.58	31.8	0.77	65.2	-
Child - At birth	**(Mean, SD)**	**B**	**(Mean, SD)**	**B**	**(Mean, SD)**	
Pregnancy duration (w)	(40.2, 1.2)	-0.22	(40.1, 1.2)	-0.02	(40.1, 1.2)	-
Birth weight (kg)	(3.53, 0.52)	-0.06	(3.58, 0.48)	0.03	(3.55, 0.49)	-

B values are linear regression coefficients indicating the change in the confounding variable (if a continuous variable) for each category of the complementary feeding variable compared with the reference category. OR is the corresponding odds ratio (if a categorical variable). *P<0.05, **P<0.01, ***P<0.001.

Relationships of birth weight and growth with glucose, C-peptide and lipids

Higher childhood glucose and C-peptide concentrations were associated with faster childhood relative weight gain (glucose 0.04 mmol/l . SD^{-1}, P=0.003; C-peptide ≥0.34 nmol/l: OR 1.39, P<0.001) and faster childhood linear growth (glucose 0.04 mmol/l . SD^{-1}, P=0.005; C-peptide ≥0.34 nmol/l: OR 1.25, P=0.001) (Table 6.7). Lower birth weight was associated with higher childhood TC and HDL concentrations (-0.04 mmol/l . SD^{-1}, P=0.04 and -0.03 mmol/l . SD^{-1}, P<0.001 respectively) (Table 6.7). Faster relative weight gain in the first month was associated with higher glucose concentration (0.03 mmol/l . SD^{-1}, P=0.04) (Table 6.7). Faster relative weight gain 3-6 months and slower childhood relative weight gain were associated with lower HDL concentration (-0.02 mmol/l . SD^{-1}, P=0.009 and 0.02 mmol/l . SD^{-1}, P=0.007 respectively) (Table 6.7). Slower linear growth 0-1 month was associated with higher TC concentration (-0.04 mmol/l . SD^{-1}, P=0.02) (Table 6.7).

Relationships of infant feeding with glucose, C-peptide and lipids

An exploration of infant feeding and childhood glucose, C-peptide and lipid profile was largely negative. Compared with breastfeeding for <1 month, exclusive breastfeeding for 1-3 months was associated with lower childhood TG concentrations (-0.05 mmol/l, P=0.02) (Table 6.8).

Table 6.7. Relationships of birth weight, relative weight gain and linear growth (all expressed in z scores) with childhood glucose, C-Peptide ≥0.34 nmol/l, TC, HDL, LDL and TG

	Glucose (z)			C-Peptide ≥0.34 nmol/l			TC (z)			HDL (z)			LDL (z)			TG (z)		
	B	95% CI		OR	95% CI		B	95% CI		B	95% CI		B	95% CI		B	95% CI	
	Relative weight gain																	
Birth weight	-0.01	-0.07	0.05	0.94	0.81	1.08	-0.06	-0.12	0.00	-0.11	-0.17	-0.05	-0.02	-0.08	0.04	-0.04	-0.10	0.02
0-1 m	0.05	0.00	0.10	1.02	0.90	1.15	0.00	-0.05	0.05	0.00	-0.04	0.05	0.00	-0.05	0.05	0.01	-0.04	0.06
1-3 m	0.05	0.00	0.10	1.09	0.96	1.24	-0.01	-0.06	0.04	-0.02	-0.07	0.03	0.00	-0.06	0.05	0.02	-0.03	0.07
3-6 m	-0.01	-0.06	0.04	1.07	0.95	1.20	-0.02	-0.07	0.03	-0.06	-0.11	-0.02	0.00	-0.05	0.05	0.00	-0.05	0.06
6-12 m	-0.03	-0.08	0.02	1.11	0.98	1.26	0.02	-0.03	0.07	-0.01	-0.06	0.04	0.03	-0.02	0.08	-0.02	-0.07	0.02
12 m-5 y	0.08	0.03	0.13	1.39	1.23	1.58	0.05	-0.01	0.10	0.07	0.02	0.12	0.02	-0.04	0.07	0.05	0.00	0.10
	Linear growth																	
0-1 m	0.01	-0.04	0.06	1.02	0.90	1.15	-0.06	-0.11	-0.01	-0.05	-0.10	0.00	-0.02	-0.07	0.03	-0.02	-0.07	0.04
1-3 m	0.03	-0.02	0.07	0.97	0.86	1.10	0.01	-0.04	0.06	0.02	-0.03	0.07	0.01	-0.04	0.06	-0.02	-0.07	0.03
3-6 m	0.00	-0.05	0.05	1.03	0.92	1.17	0.02	-0.03	0.07	0.03	-0.02	0.08	0.02	-0.03	0.07	0.01	-0.04	0.06
6-12 m	-0.01	-0.06	0.04	1.02	0.91	1.16	-0.01	-0.06	0.04	0.01	-0.04	0.06	-0.01	-0.06	0.04	-0.03	-0.08	0.02
12 m-5 y	0.07	0.02	0.13	1.25	1.10	1.42	-0.03	-0.08	0.02	0.01	-0.04	0.06	-0.01	-0.06	0.04	0.00	-0.06	0.05

B values are linear regression coefficients indicating the change in the outcome (in standard deviation scores) per standard deviation change in the exposure. OR indicates the likelihood of the outcome per standard deviation change in the exposure. The analyses were adjusted for the child's age and sex and maternal age, pre-pregnancy BMI, height, educational level, primiparity, ethnicity, smoking, use of alcohol, hypertension and pregnancy duration. TC-total cholesterol, HDL-high-density-lipoprotein, LDL-low-density-lipoprotein, TG-triglycerides.

Table 6.8. Relationships of duration of exclusive breastfeeding and timing of introduction of complementary feeding with childhood glucose, C-Peptide ≥0.34 nmol/l, TC, HDL, LDL and TG

	Glucose (z)				C-Peptide ≥0.34 nmol/l			TC (z)				HDL (z)				LDL (z)				TG (z)			
	mean (SD)	B	95% CI		OR	95% CI		mean (SD)	B	95% CI		mean (SD)	B	95% CI		mean (SD)	B	95% CI		mean (SD)	B	95% CI	
uration of exclusive breast feeding																							
<1 m (n=368) ref	0.00 (1.09)	-	-	-	-	-	-	0.00 (1.02)	-	-	-	0.00 (1.01)	-	-	-	-0.03 (1.03)	-	-	-	0.10 (1.13)	-	-	-
1-3 m (n=426)	-0.02 (0.97)	-0.07	-0.21	0.07	0.97	0.69	1.36	0.05 (1.01)	0.06	-0.08	0.20	0.01 (0.98)	-0.04	-0.18	0.10	0.07 (1.08)	0.11	-0.03	0.24	-0.06 (0.91)	-0.16	-0.31	0.02
3-6 m (n=577)	0.03 (0.96)	0.00	-0.13	0.14	1.09	0.79	1.50	-0.01 (0.99)	-0.02	-0.15	0.12	-0.01 (1.00)	-0.03	-0.17	0.10	-0.01 (0.96)	0.00	-0.13	0.13	-0.02 (1.00)	-0.11	-0.25	0.02
>6 m (n=229)	-0.06 (1.02)	-0.09	-0.25	0.08	0.81	0.54	1.22	-0.05 (0.98)	-0.04	-0.21	0.12	0.01 (1.05)	-0.02	-0.18	0.15	-0.07 (0.88)	-0.04	-0.20	0.13	-0.03 (0.91)	-0.10	-0.27	0.07
iming of introduction of complementary feeding																							
<4 m (n=77)	-0.18 (0.79)	-0.16	-0.40	0.07	1.36	0.78	2.36	-0.06 (1.13)	-0.06	-0.30	0.17	0.08 (1.00)	0.09	-0.15	0.33	-0.10 (1.04)	-0.09	-0.33	0.14	-0.11 (0.90)	-0.16	-0.40	0.09
4-6 m (n=581)	0.05 (1.04)	0.06	-0.04	0.17	1.17	0.91	1.52	-0.01 (1.00)	-0.02	-0.12	0.09	-0.01 (1.03)	0.00	-0.11	0.10	0.01 (1.01)	0.00	-0.10	0.11	0.01 (1.08)	-0.01	-0.12	0.10
>6 m (n=928) ref	-0.01 (0.99)	-	-	-	-	-	-	0.01 (1.00)	-	-	-	0.00 (0.97)	-	-	-	0.01 (0.99)	-	-	-	0.00 (0.96)	-	-	-

B values are linear regression coefficients indicating the difference in the outcome (in standard deviation scores) between each exposure category and the reference category. OR indicates the likelihood of the outcome of each exposure category compared to the reference category. (1) Adjusting for the child's birth weight, age and sex and maternal age, pre-pregnancy BMI, height, educational level, primiparity, ethnicity, smoking, use of alcohol, hypertension and pregnancy duration; (2) as in 1 but with the addition of conditional relative weight and conditional height for all time periods of infancy. TC-total cholesterol, HDL-high-density-lipoprotein, LDL-low-density-lipoprotein, TG-triglycerides.

DISCUSSION

This study showed that faster relative weight gain and linear growth after the age of 1 year were associated with higher childhood glucose and C-peptide concentrations (as markers of IR). Lower birth weight was associated with higher total and HDL-cholesterol in childhood. Growth in infancy, and infant feeding, were largely unrelated to childhood glucose and lipid biomarkers.
Conditional relative weight gain and linear growth are, by construction, uncorrelated, enabling us to separate the associations of glucose and C-peptide concentrations with relative weight gain from those with linear growth. By expressing them in SD units, we were able to compare the size of their effects, and compare effects of different periods. Weight gain is a result of both soft tissue gain and linear growth; our relative weight gain variables represent soft tissue growth distinct from skeletal growth and therefore give more information than weight gain alone, which is correlated with height gain.
A 1 SD increase in relative weight or linear growth in childhood was associated with a 0.04 mmol/l higher childhood glucose concentration and with a 1.3-1.4 higher odds of having a childhood C-peptide concentration ≥0.34 nmol/l. Associations of childhood relative weight gain and linear growth with childhood glucose and C-peptide concentrations were equal in strength, a finding that is consistent with other studies in children and adults.(42,166,179,183) The positive association between childhood relative weight gain and childhood markers of IR may be mediated by the effects of adiposity on IR, through an increased release of adipocytokines, such as tumor necrosis factor (TNF)-alpha, or decreased production of protective adipocytokines, such as adiponectin.(184) Relative weight gain comprises both fat and lean tissue gain. Gain in lean mass is regulated by growth hormone after infancy(121), which in turn has an antagonistic effect on insulin action.(185) We were not able, in our study, to distinguish between fat and lean tissue gain in our children.
We are not sure what the positive association between childhood linear growth and childhood markers of IR means. A possible explanation is that both faster childhood linear growth and childhood IR are caused by a common underlying cause (e.g. of genetic origin), possibly mediated by growth hormone. Children who are more insulin resistant have a compensatory rise in insulin secretion, and this might stimulate the skeletal IGF-1 receptors in turn leading to faster linear growth.(172)
A 1 SD lower birth weight was associated with 0.04 mmol/l higher childhood TC (corresponding to 0.09 mmol/l . kg^{-1}) and 0.03 mmol/l higher HDL concentration. These results are consistent, although somewhat higher than those from a systematic review (a 1 kg lower birth weight was associated with a 0.05 mmol/l higher TC in later life).(186) These associations are small and may have little clinical significance.

Growth in infancy, was largely unrelated to childhood glucose and lipid biomarkers, which is in accordance with the Pelotas(170) and Copenhagen(171) birth cohort studies and Early Bird Diabetes Study(164) (table 6.1).

Three systematic reviews have shown that breastfeeding is associated with a reduced risk of type 2 diabetes and with a lower TC concentration in later life when compared to formula feeding.(55,187,188) However, there is little evidence to suggest effects of early feeding on adult blood glucose or insulin concentrations.(55) In accordance with this, we did not find any associations between exclusive breastfeeding and markers of IR. Exclusive breastfeeding for 1-3 months was

associated with 0.05 mmol/l lower childhood TG when compared with exclusive breastfeeding for less than 1 month. Because no other subgroup of exclusive breastfeeding for more than 3 months was associated with childhood TG, this may be a chance finding. However, as was suggested previously, childhood might be too early to detect potential benefits of breastfeeding on cholesterol homoeostasis, possibly because of amplification of early dietary effects on later lipoprotein concentrations with increasing age.(189) In accordance with the Dutch Generation R Study(68), timing of introduction of complementary feeding was not associated with childhood markers of IR and lipid profile.
Strengths of our study were that it was a large community based cohort study with extensive prospective data on confounding factors. In contrast to some other large studies, anthropometry was carried out by professional health workers, as was the collection of information about infant feeding. Therefore, we had detailed information about duration of exclusive breastfeeding and timing of introduction of complementary feeding. Measurements were made in the Youth Health Care centres at slightly varying ages, but always within days or weeks of the selected ages, and so interpolation is likely to have had only modest effects on the results. Few other studies that we are aware if have frequent serial measures of growth between birth and 12 months, and our data were highly complete, enabling conditional regression analysis. As we reported earlier, compared with the WHO growth standards, children in our study had faster mean linear growth and faster mean weight gain between 1 and 5 years.(190) However, we cannot say whether the associations that we found were due to the higher prevalence of faster growth in our population.

A limitation was that, despite considerable effort, there was substantial loss to follow up (we were able to analyse 1604 children with complete growth data out of 5551 children in the original cohort). The analysis sample differed from the original cohort in several characteristics, which could bias our results if associations differed between those who did and did not take part in the study. Because length at birth is not always measured in the Netherlands we were not able to explore associations between birth height and childhood glucose and lipid biomarkers, and had to use birth weight as the anchor for our conditional measures. However, Adair et al.(41) compared results with and without the inclusion of birth length and found that associations of subsequent relative weight gain and linear growth with later life plasma glucose concentrations were similar.(41) Because 63% of C-peptide concentrations fell below the laboratory detection limit we were not able to use homeostasis model assessment (HOMA2-B; HOMA2-IR) to quantify beta cell function and IR.(191) Instead, we chose to use C-peptide as dichotomous variable as marker of IR.(180) Due to the observational nature of our study it is not possible to attribute causality or to exclude the possibility that the demonstrated associations might be due to residual confounding. Finally, we studied a large number of associations, and some significant findings may have arisen by chance.

In conclusion, our findings suggest that faster growth after the age of 1 year and up to 5 years, in either height or weight is associated with higher childhood markers of IR. While it would not seem advisable (nor probably feasible) to limit childhood linear growth, it seems reasonable to recommend avoiding consistent upward crossing of centiles for body weight in childhood. Exclusive breastfeeding is associated with many health benefits(128) but is largely unrelated to childhood glucose and lipid biomarkers.

General discussion

7

INTRODUCTION

The aims of this thesis were: 1) to determine the putative independent role of maternal hypertension on the offspring's growth and 2) to examine the associations of early growth and infant feeding with childhood cardiovascular risk factors.

In general, there is evidence that maternal hypertension is associated with faster offspring growth in infancy. Early growth and infant feeding are associated with childhood blood pressure (BP), body composition and glucose and lipid biomarkers.

More specifically, in the studies presented in this thesis **maternal pre-existent hypertension and pregnancy-induced hypertension** were associated with faster growth in weight and height in infancy.

Lower ***birth weight*** was associated with higher childhood diastolic BP, lower fat-free mass (FFM), lower fat mass (FM), higher total cholesterol (TC) concentration and higher high-density-lipoprotein cholesterol (HDL) concentration.

Faster ***relative weight gain*** (weight gain independent of height) in infancy (0-1y) was associated with higher childhood FM, higher FFM and after the age of one month with greater childhood height and higher childhood BP. Relative weight gain in infancy was not associated with childhood glucose and lipid biomarkers. After the age of 1 year and up to 5 years (childhood), faster relative weight gain was associated with higher childhood BP and with higher markers of insulin resistance (IR). Of note, the associations of relative weight gain in childhood with FFM and FM were not tested.

Faster ***linear growth*** in infancy (0-1y) was associated with greater childhood height, higher childhood FFM and higher FM and after the age of one month with higher childhood BP. Linear growth in infancy was not associated with childhood glucose and lipid biomarkers. After the age of 1 year and up to 5 years, faster linear growth was associated with higher childhood BP and with higher markers of IR. Of note, the associations of linear growth in childhood with FFM and FM were not tested.

When compared to ***breastfeeding*** less than 1 month, breastfeeding for longer than 3 months was associated with lower childhood BP while breastfeeding for longer than 6 months was associated with smaller childhood height, lower FFM and lower FM. Duration of breastfeeding was not associated with childhood glucose and lipid biomarkers.

When compared to ***introduction of complementary feeding*** before 4-6 months, introduction of complementary feeding after 6 months was associated with lower childhood BP and smaller childhood height, lower BMI, lower FFM and lower FM. Timing of introduction of complementary feeding was not associated with childhood glucose and lipid biomarkers.

The current chapter answers the research questions, discusses the results, addresses some methodological limitations, and makes a number of recommendations for future research and public health practice.

REFLECTION ON THE RESULTS

Maternal pregnancy health and the offspring's early growth

The 'Developmental Origins of Health and Disease' hypothesis postulates that several chronic diseases in adulthood originate from adaptation to the (compromised) nutritional environment during early (antenatal or postnatal) life.(10) One adverse antenatal factor that is potentially associated with fetal adaptation (reprogramming) is maternal hypertension. As maternal hypertension is one of the factors associated with placental dysfunction(12), resulting in restricted maternoplacental delivery of nutrients and oxygen to the fetus, the offspring of mothers with hypertension are expected to have a higher risk of retarded fetal growth and preterm birth.(13-18) It is unknown whether maternal hypertension is related to faster postnatal growth in the offspring, independent from birth weight and pregnancy duration. As presented in chapter 2, the offspring of women with pre-existing hypertension and pregnancy-induced hypertension were respectively 1.9 and 1.4 times more likely to have faster growth in weight during infancy. Offspring of women with pre-existing hypertension with a below average birth weight had an even 2.6 times higher odds for faster growth in weight during infancy. Part of the demonstrated associations seemed to work through a reduction in birth weight and shorter pregnancy duration. There appeared to be additional weight gain in the offspring of mothers with pre-existing hypertension. The offspring of women with pre-existing hypertension and pregnancy-induced hypertension were 1.8 and 1.4 times more likely to have faster growth in height during infancy. These associations appeared to work entirely through a reduction in birth weight and pregnancy duration.

As proposed in the recent literature, a reduction of fetal growth constitutes a surrogate marker of a coordinated fetal response to a compromised intrauterine environment.(9) Growth acceleration is than mainly related to this fetal response.(9) When translating this to our findings, a reduction in birth weight in offspring of hypertensive women may be a sign for permanent alterations in the constitution of an infant, with further induction of growth acceleration in weight as a result. Growth of these infants should be monitored more attentively. We found some indication for a possible attenuating effect of the use of antihypertensive drugs on offspring accelerated growth in weight. This suggests a better condition of women who are prescribed anti-hypertensive drugs with a resultant better offspring.

Validation of assessment of body composition, one of the outcome measures

Field methods that accurately assess body composition in children are scarce. Currently, body mass index (BMI=weight/height^2) is the most commonly used routine measure that gives an indication of relative weight. International BMI-for-age cut offs have been proposed to classify overweight as well as undernutrition.(100) However, BMI levels among children should be interpreted with caution. Although high BMI-for-age is a good indicator of excess fat mass (FM), BMI differences among thinner children can be largely due to fat-free mass (FFM).(101) Following this, to identify the need for intervention in case of suspected overweight or undernutrition, more information is needed about whole body FM and whole body FFM which is reflected in body composition. Bio-impedance analysis (BIA) appears a feasible, reasonably accurate and affordable tool for epidemiologic studies of body composition of school-aged children. BIA estimates FFM (and indirectly FM) by measuring the resistance

(*R*) of body tissue to a weak imperceptible current. The measured *R* is first of all used to estimate total body water (TBW).(103) For the estimation of TBW in children, a large number of BIA equations are available. An important practical concern is that the prediction equations are population specific. Therefore, it is recommended to validate equations in the population or sample in which they are used by comparing BIA to a reference method, such as hydrometry.(104) When compared to the Deuterium dilution method, the Kushner BIA equation for school age children which is incorporated in the Bodystat system, underestimated total body water (TBW) and therefore fat-free mass (FFM) (chapter 3). This underestimation was non-systematic which means values cannot simply be converted to get an accurate value of TBW. Application of a recalibrated equation showed a small non-significant bias. Importantly, this bias was systematic, thereby allowing more robust assessment of body composition in (pre)school aged children for use in epidemiological field studies (chapter 3).

Associations of early growth and infant feeding with childhood cardiovascular risk factors (findings are summarised in table 7.1)

Birth weight

Recent findings have pointed out that CVDs may originate from prenatal environmental factors resulting in fetal growth restriction.(8,9) We found that lower birth weight was associated with higher childhood diastolic BP (chapter 4) and a more favourable lipid profile (chapter 6). These associations were small and may have little clinical significance. In addition, lower birth weight was associated with a less favourable childhood body composition, namely smaller childhood height and primarily with a lower childhood FFM (chapter 5). Indeed, in humans, the number of muscle fibers is set before birth with little hyperplasia during postnatal life.(192) Our data confirm findings from recent studies which have consistently shown negative associations between birth weight and later BP(19,20) and childhood TC(186) and positive associations between birth weight and later height and FFM, and weaker positive associations with later FM.(41,135,136)

Postnatal growth

There is convincing evidence for an independent role of faster postnatal growth on CVDs.(25-35) There is confusion about what constitutes optimal infant growth for future cardiovascular health. In contrast, there is consistent evidence for an association between faster childhood growth and future cardiovascular risk factors.(32,33,39-45) It is not clear, whether the relationship of weight gain to later life cardiovascular risk factors comes from the component of weight gain that is due to linear (skeletal) growth or to soft tissue (lean and fat) growth.
Conditional relative weight gain and linear growth are, by construction, uncorrelated, enabling us to separate the associations of cardiovascular risk factors with relative weight gain from those with linear growth. By expressing them in SD units, we were able to compare the size of their effects, and compare effects of different periods. Weight gain is a result of both soft tissue gain and linear growth; our relative weight gain variables represent soft tissue growth distinct from skeletal growth and therefore give more information than weight gain alone, which is correlated with height gain. Similar to findings from 3 other large cohort studies, faster growth after the first 1-3 months and up to 5 years, in either weight or height, was associated with higher

childhood systolic and diastolic BP (chapter 4).(33,39,41) In contrast, in the Pelotas birth cohort study, childhood weight gain, but not linear growth was associated with adolescent BP.(32) Another large birth cohort study in Hong Kong showed that higher BMI gain between 3–7 years and faster linear growth between 7–11 years predicted higher adolescent BP.(40) Associations were strongest for growth in young childhood (1-5y) (chapter 4). The positive association between relative weight gain and childhood BP may be related to the same mechanisms which are thought to cause adiposity-related higher BP, namely activation of the sympathetic nervous system, primary sodium retention, increased renin activity, increased levels of angiotensinogen and aldosterone, insulin resistance and inflammation.(120) However, relative weight gain comprises both fat and lean tissue gain. Gain in lean mass is regulated by insulin-like growth factor-1 during infancy, and by growth hormone after infancy(121), these hormones have been associated with changes in blood vessel structure and later higher BP.(61) We were not able, in our study, to distinguish between fat and lean tissue gain in our infants and children. It has been suggested that the positive relationship between height and systolic BP may represent a physiological adaptation by which the cardiovascular system accommodates to the relative length of the arterial tree by a commensurate variation in perfusion pressure.(122,123) It is not clear whether this has pathological consequences, but the evidence suggests not; taller people actually have a lower risk of cardiovascular disease, despite higher BP.(124,125)

Published results regarding associations of infant weight gain and later body composition have been inconsistent; studies from high-income countries showed a predominant positive correlation between early postnatal weight gain and later FM(34,137,138), whereas data from low- and middle-income countries suggest a predominant association with later life FFM.(41) As discussed in chapter 5, this study showed that faster infant weight gain was associated with a healthier childhood body composition (including greater childhood height), when it was caused by faster linear growth.

Growth in infancy was not associated with childhood glucose and lipid biomarkers (chapter 6), which is in accordance with the Pelotas(170) and Copenhagen(171) birth cohort studies and Early Bird Diabetes Study(164). Faster growth in childhood, in either weight or height, was associated with higher markers of IR (chapter 6), confirming other studies in children and adults.(42,166,179,183) The positive association between childhood relative weight gain and childhood markers of IR may be mediated by the effects of adiposity on IR, through an increased release of adipocytokines, such as tumor necrosis factor (TNF)-alpha, or decreased production of protective adipocytokines, such as adiponectin.(184) Relative weight gain comprises both fat and lean tissue gain. Gain in lean mass is regulated by growth hormone after infancy(121), which in turn has an antagonistic effect on insulin action.(185) We were not able, in our study, to distinguish between fat and lean tissue gain in our children. We are not sure what the positive association between childhood linear growth and childhood markers of IR means. A possible explanation is that both faster childhood linear growth and childhood IR are caused by a common underlying cause (e.g. of genetic origin), possibly mediated by growth hormone. Children who are more insulin resistant have a compensatory rise in insulin secretion, and this might stimulate the skeletal IGF-1 receptors in turn leading to faster linear growth.(172)

Breastfeeding

Early feeding is an example of potential modifiable factors for the prevention of future CVDs, either directly (e.g. due to differences in sodium intake(48,49)), or through an effect of growth. Consistent with findings from earlier studies that compared growth of breastfed infants with widely used growth charts, we found that fully breastfed infants experienced faster relative weight gain in the first month of life, with subsequent slower linear growth until 6 months and slower relative weight gain until 12 months (chapter 5).(46,139) Compared with exclusive breastfeeding for less than 1 month, exclusive breastfeeding for longer than 3 months was associated with a 0.81 to 1.70 mm Hg lower childhood systolic BP (chapter 4). The associations appeared to be partly mediated through growth in infancy, however no formal tests were performed to prove mediation (chapter 4). This is consistent with findings from a meta-analysis in 2005, which showed that initiation of breastfeeding was associated with a 0.6 mm Hg lower later life systolic BP.(57) A follow-up study at age 13–16 years of preterm infants, randomised to breast milk or preterm formula showed that the proportion of human milk in the neonatal period was inversely related to later mean arterial BP.(56) However, the findings differ from those of the PROBIT study, a large randomised controlled trial (RCT) of breastfeeding promotion.(58) There were no differences in systolic or diastolic blood pressure between children in the intervention and control groups at 6.5 years.(58) RCTs in general yield a higher level of evidence than observational studies, but the difference in duration of breastfeeding between the intervention and control groups in PROBIT (72.7% vs. 60% of mothers were still breastfeeding at 3 months) may have been too small to produce a detectable difference in BP.(58) In accordance with findings from the ALSPAC study, we found an association between longer duration of breastfeeding and lower childhood FM (chapter 5).(64) Furthermore, the association of longer duration of full breastfeeding with lower childhood FFM supports evidence from a meta-analysis including 11 studies looking at FFM in breastfed vs. formula-fed infants.(140) To a lesser extent, longer duration of full breastfeeding was associated with shorter childhood height. The associations appeared to be mediated through growth in infancy, however no formal tests were performed to prove mediation (chapter 5). Three systematic reviews have shown that breastfeeding is associated with a reduced risk of type 2 diabetes and with a lower TC concentration in later life when compared to formula feeding.(55,187,188) However, there is little evidence to suggest effects of early feeding on adult blood glucose or insulin concentrations.(55) In accordance with this, we did not find any associations between exclusive breastfeeding and markers of IR. Nor did we find any associations between exclusive breastfeeding and lipid profile (chapter 6). However, as was suggested previously, childhood might be too early to detect potential benefits of breastfeeding on cholesterol homoeostasis, possibly because of amplification of early dietary effects on later lipoprotein concentrations with increasing age.(189)

Timing of introduction of complementary feeding

The introduction of complementary feeding before 4 months and between 4–6 months was associated with a 1.21 mm Hg higher diastolic and a 0.91 mm Hg higher

systolic BP respectively when compared with the introduction of complementary feeding after 6 months (chapter 4). This is consistent with recent findings from the Generation R study group showing that introduction of complementary feeding before compared with after 5 months was associated with a 0.86 mm Hg higher diastolic and a 0.94 mm Hg higher systolic BP.(66) In our study, the association appeared to be partly mediated through growth in infancy, however no formal tests were performed to prove mediation (chapter 4). Higher sodium intake due to earlier introduction of complementary feeding may be another factor.(48,49) Although an association with childhood overweight may partially explain our findings, controlling for 5-year BMI and height hardly altered the effect estimates (chapter 4). A recent systematic review including 21 studies showed that the timing of the introduction of complementary feeding had no clear association with childhood obesity.(67) Our findings indicate that the introduction of complementary feeding after 6 months is associated with smaller childhood height, lower BMI, lower FFM and lower FM. In line with this, it has been reported that breastfed infants who had complementary feeding introduced before 4 months of age had greater height at the age of 3 years.(141) The associations appeared to be mediated through growth in infancy, however no formal tests were performed to prove mediation (chapter 5). In accordance with the Dutch Generation R Study(68), timing of introduction of complementary feeding was not associated with childhood markers of IR and lipid profile (chapter 6).

Table 7.1. Summary table: associations of early growth and infant feeding with childhood cardiovascular risk factors

	Blood Pressure		Body composition				Glucose biomarkers		Lipid biomarkers			
	SBP	DBP	Height	BMI	FFM	FM	Glucose	C-peptide	TC	HDL	LDL	TG
Birth weight	0	-	+	+	+	+	0	0	-	-	0	0
Infancy												
Relative weight gain												
0-1 m	0	0	0	+	+	+	+	0	0	0	0	0
1-3 m	+	+	+	+	+	+	0	0	0	0	0	0
3-6 m	+	+	+	+	+	+	0	0	0	-	0	0
6-12 m	+	+	+	+	+	+	0	0	0	0	0	0
Linear growth												
0-1 m	0	0	+	0	+	+	0	0	-	0	0	0
1-3 m	+	0	+	0	+	+	0	0	0	0	0	0
3-6 m	+	+	+	0	+	+	0	0	0	0	0	0
6-12 m	+	+	+	+	+	+	0	0	0	0	0	0
Childhood												
Relative weight gain												
12 m-5 y	+	+	NT	NT	NT	NT	+	+	0	+	0	0
Linear growth												
12 m-5 y	+	+	NT	NT	NT	NT	+	+	0	0	0	0
Longer duration of breastfeeding	-	-	-	0	-	-	0	0	0	0	0	-
Later introduction of complementary feeding	-	-	-	-	-	-	0	0	0	0	0	0

0 no association was found between exposure variable and outcome measure, + a positive association was found, - a negative association was found, DBP-diastolic blood pressure, NT-not tested, SBP-systolic blood pressure.

METHODOLOGICAL CONSIDERATIONS

Regarding exposure variables

When looking at the association between maternal hypertension during pregnancy and the offspring's early growth, hypertensive disorders in women were self-reported and not quantified. Quantified BP data would have enabled us to assess a possible effect of severity of hypertension on the infants' growth more accurately. Moreover, it would have shed light on whether well-managed hypertension would have (the same) effect on offspring growth patterns.
Birth weight was used as a proxy for intrauterine growth. This is a rather crude measure for fetal growth restriction as there may be appropriate for gestational age children who suffered from intrauterine growth restriction (e.g. this may be the case for children with a greater growth potential or in children in whom growth restriction in one trimester is compensated by faster growth in another trimester). In contrast, there are small for gestational age children who are constitutionally small but not growth retarded.
Because length at birth is not always measured in the Netherlands we were not able to explore associations between birth length and childhood cardiovascular risk factors, and had to use birth weight as the anchor for our conditional measures. However, Adair et al.(41) compared results with and without the inclusion of birth length, and found that associations of subsequent relative weight gain and linear growth with later life cardiovascular risk factors were similar.
Relative weight gain (weight gain independent of height) comprises both fat and lean tissue gain. We were not able, in our study, to distinguish between fat and lean tissue gain in our infants and children. This may have provided a better insight into the mechanisms linking postnatal growth and later life CVDs.
We have no information as to why solids were introduced when they were. Perceived satiety may well have been a factor, with early introduction of solids being a marker for 'hungry' infants whose appetites continue to be bigger as children. Faster growth then precedes earlier introduction of complementary feeding rather than being a result of earlier introduction of complementary feeding. In that case, an association of faster infant growth with childhood cardiovascular risk factors is than falsely attributed to earlier introduction of complementary feeding. This phenomenon is referred to as reverse causality and an example of this concerning associations of breastfeeding and infant growth is described in a recent article of Kramer et al.(144) However, in our study sample, infants that received earlier complementary feeding did not show faster growth in the preceding period. Similarly, we have no information as to why women discontinued breastfeeding. This may be because faster growing infants were not satisfied with their mother's own milk production.(144) In that case, an association of faster infant growth with childhood cardiovascular risk factors is than falsely attributed to shorter duration of breastfeeding.

Regarding outcome measures

The methods we used for the measurement of body composition are less precise than dual-energy x-ray absorptiometry, but dual-energy x-ray absorptiometry turned out not to be applicable on such a large population.
Because 63% of C-peptide concentrations fell below the laboratory detection limit we were not able to use homeostasis model assessment (HOMA2-B; HOMA2-IR) to

quantify beta cell function and IR.(191) Instead, we chose to use C-peptide as dichotomous variable as marker of IR.(180)

Other methodological considerations

Despite considerable effort, there was substantial loss to follow up (in the studies addressing associations of early growth and infant feeding with childhood cardiovascular risk factors we were able to analyse respectively 2227 and 1604 children with complete growth data out of 5551 children in the original cohort). The analysis samples differed from the original cohort in several characteristics, which could bias our results if associations differed between those who did and did not take part in the study.
Due to the observational nature of our study it is not possible to attribute causality or to exclude the possibility that the demonstrated associations might be due to residual confounding.
Finally, we studied a large number of associations, and some significant findings may have arisen by chance. This may be more of a concern with the infant feeding associations than with the growth associations, which were highly consistent. Lastly, Conditional regression analysis requires to have observations at (or near to) each time-point in order for the full set of conditionals to be calculated.(73) This has reduced the sample size available.

FUTURE DIRECTIONS

For research

Continuing the ABCD study and following the children into adulthood allows us to see whether the demonstrated associations may persist into adulthood and whether new associations do emerge. In addition, future studies should further explore the role of maternal hypertension, preferably by quantifying maternal BP, on the offspring's growth. The potential modifying effect of antihypertensive drugs should be examined. Further studies are needed, particularly in populations with different infant feeding practices and other patterns of confounding factors, to assess the long-term effect of exclusive breastfeeding and timing and nature of the weaning diet on later life cardiovascular disease risk, including later life height and body composition.

For practice

Measurement of maternal BP early in pregnancy or preferably even before conception can potentially identify mothers with unknown pre-existing hypertension so that these women can be monitored more closely and, if necessary, be treated. Furthermore, as a reduction in birth weight in offspring of hypertensive women may be a sign for permanent alterations in the constitution of an infant, with growth acceleration in weight as a result, growth of these infants should be monitored more attentively. While it would not seem advisable (nor probably feasible) to limit linear growth, it seems reasonable to recommend avoiding consistent upward crossing of centiles for body weight in infancy and especially in childhood in all children, at least in high-income settings. There is still uncertainty about whether the associations between breastfeeding and lower BP and lower FM in later life are causal in nature. However, in light of other known health benefits(128), we think that promotion of a longer duration of breastfeeding is an important public health recommendation. The

best timing of introduction of complementary feeding should be placed in perspective of its other potential long-term health consequences like atopic diseases, type 1 and 2 diabetes and neuromuscular development.(49)

FINAL CONCLUSION

Lower birth weight is associated with higher childhood diastolic BP, a less favourable body composition and in contrast a more favourable lipid profile. Faster infant weight gain is associated with a higher childhood BP and, only when it is caused by faster linear growth, with a healthier childhood body composition. Faster childhood weight gain is associated with a higher childhood BP and higher markers of IR. Breastfeeding for more than 3-6 months and introduction of complementary feeding after 6 months seem to have a potential beneficial effect on later life BP and FM, while they may also be associated with later life smaller height and lower FFM.

However, the associations of faster childhood growth in either weight or height with higher childhood BP and higher markers of IR seem to be most relevant clinically.

SUMMARY

Cardiovascular diseases are the number one cause of death globally. Intermediate risk factors for developing cardiovascular diseases are raised blood pressure, raised blood glucose, raised blood lipids and overweight and obesity. Although it is clear that genetic factors and adult lifestyle contribute to the propensity towards obesity and associated conditions, recent findings have pointed out that cardiovascular diseases may originate from prenatal environmental factors resulting in fetal growth restriction and prematurity. In addition, there is convincing evidence for an independent role of faster postnatal growth. Studies addressing the relationship of growth in infancy with future cardiovascular risk factors have shown mixed results. There is therefore confusion about what constitutes optimal infant growth for future cardiovascular health. In contrast, there is consistent evidence for an association between faster childhood growth and future cardiovascular risk factors. It is not clear however, whether the relationship of weight gain to later life cardiovascular risk factors comes from the component of weight gain that is due to linear (skeletal) growth or to soft tissue (lean and fat) growth. Early feeding is an example of potential modifiable factors for the prevention of future cardiovascular diseases, either directly, or through an effect of growth. This thesis focusses on the association of maternal pregnancy health with the offspring's early growth and on associations of early growth and infant feeding with childhood cardiovascular risk factors. The background of this thesis is further addressed in **chapter 1**. This chapter also describes the ABCD study in which the studies of this thesis were performed. The ABCD study is a prospective cohort study in which information about pregnancy, birth outcomes, postnatal growth and infant feeding patterns has been included. At age 5, children underwent a health check, including measures of anthropometry, body composition, blood pressure and glucose and lipid biomarkers. In the first part of this thesis, we focus on the association of maternal pregnancy health with the offspring's early growth. In **chapter 2,** the relation of maternal hypertension with infant growth is examined. The offspring of women with pre-existing hypertension and pregnancy-induced hypertension are more likely to have faster growth in weight and height during infancy. Part of the demonstrated associations seem to work through a reduction in birth weight and shorter pregnancy duration. Moreover, there appears to be additional weight gain in the offspring of mothers with pre-existing hypertension. We found some indication for a possible attenuating effect of the use of antihypertensive drugs on offspring accelerated growth in weight. In the second part of this thesis, one of the outcome measures was validated. **Chapter 3** provides evidence that the Kushner BIA equation for school age children, which is incorporated in the Bodystat system, underestimates fat-free mass. This underestimation is non-systematic which means values cannot simply be converted. Application of a recalibrated equation shows a small non-significant bias. Importantly this bias is systematic, thereby allowing more robust assessment of body composition in (pre)school aged children for use in epidemiological field studies. In the third part of this thesis, we address associations of early growth and infant feeding with childhood cardiovascular risk factors. In **chapter 4** we demonstrate that lower birth weight and faster growth after the first month and up to 5 years, in either weight or height, are associated with higher childhood BP. Childhood growth appears to be the most influential period. Breastfeeding for more than 3 months and introduction of complementary feeding after 6 months are associated with lower childhood blood pressure. **Chapter 5** describes that lower birth weight is associated

with a less favourable body composition and when faster infant weight gain is caused by faster linear growth, it is associated with a healthier childhood body composition. Breastfeeding for more than 6 months and introduction of complementary feeding after 6 months are associated with a lower childhood fat mass, while they are also associated with smaller height and lower fat-free mass. **Chapter 6** provides evidence for an association between faster growth in childhood, in either weight or height, and higher markers of insulin resistance. Lower birth weight has a small association with a more favourable childhood lipid profile and growth in infancy and infant feeding are unrelated to childhood glucose and lipid biomarkers. **Chapter 7** is a general discussion with a reflection on the results and methodological considerations including loss to follow up, the observational nature of our study and therefore the inability to attribute causality and the possibility of residual confounding. Furthermore, this chapter makes recommendations for future research and public health practice. In short, it seems reasonable to promote a longer duration of breastfeeding and to recommend avoiding consistent upward crossing of centiles for body weight in infancy and especially in childhood.

SAMENVATTING

Vroege groei, zuigelingenvoeding en risicofactoren voor hart- en vaatziekten op de kinderleeftijd

Hart- en vaatziekten zijn de nummer één doodsoorzaak wereldwijd. Risicofactoren voor het ontwikkelen van hart- en vaatziekten zijn het hebben van een verhoogde bloeddruk, een hoge bloedsuikerwaarde, een hoge cholesterolwaarde en overgewicht en obesitas. Het is duidelijk dat genetische factoren en levensstijl op volwassen leeftijd bijdragen aan de kans op het krijgen van obesitas en aanverwante ziekten. Recent onderzoek toont echter aan dat factoren tijdens de zwangerschap die resulteren in groeivertraging van het ongeboren kind en vroeggeboorte, mogelijk ten grondslag liggen aan het ontstaan van hart- en vaatziekten. Daarnaast lijkt versnelde groei na de geboorte een rol te spelen in de ontstaansmechanismen van hart- en vaatziekten. Onderzoeken die hebben gekeken naar de relatie tussen groei tijdens de zuigelingentijd en toekomstige risicofactoren voor hart- en vaatziekten lieten inconsistente uitkomsten zien. Daarom bestaat er onduidelijkheid over wat optimale groei tijdens de zuigelingentijd is als het gaat om het risico op het ontstaan van hart- en vaatzieken. Er bestaat echter eenduidig bewijs voor een verband tussen snellere groei tijdens de kindertijd en risicofactoren voor hart- en vaatziekten. Gewicht kan toenemen door groei in de lengte (en groei van het skelet) of door toename van zacht weefsel (o.a. spieren en vet). Het is onduidelijk of het verband tussen gewichtstoename en risicofactoren voor hart- en vaatziekten op latere leeftijd voortkomt vanuit de component van gewichtstoename door lengtetoename of door toename van zacht weefsel. Vroege voeding is een voorbeeld van een potentieel beïnvloedbare factor die een rol zou kunnen spelen in het voorkomen van toekomstige hart- en vaatziekten, ofwel door een rechtstreeks effect, of indirect via een veranderde groei. Dit proefschrift richt zich op het verband tussen de gezondheid van de moeder tijdens de zwangerschap en de vroege groei van het kind en verder op de verbanden tussen vroege groei en zuigelingenvoeding met risicofactoren voor hart- en vaatziekten op de kinderleeftijd. De achtergrond van dit proefschrift wordt verder uitgewerkt in **hoofdstuk 1**. Dit hoofdstuk beschrijft de ABCD studie waarop dit proefschrift gebaseerd is. De ABCD studie is een prospectieve cohort studie met gegevens over de zwangerschap, geboorte-uitkomsten, groei en zuigelingenvoeding. Op 5-jarige leeftijd is een gezondheidsonderzoek uitgevoerd met onder andere de meting van lichaamsomvang, lichaamssamenstelling, bloeddruk en bloedwaarden van glucose en cholesterol. Het eerste deel van dit proefschrift richt zich op het verband tussen de gezondheid van de moeder tijdens de zwangerschap en de vroege groei van hun kind. In **hoofdstuk 2** wordt er gekeken naar het verband tussen hypertensie bij de moeder en groei van het kind tijdens de zuigelingentijd. De kinderen van vrouwen met pre-existente hypertensie (al voor de zwangerschap bestaande hypertensie) en zwangerschapshypertensie hebben meer kans om een versnelde gewichtstoename en versnelde lengtegroei te hebben tijdens de zuigelingentijd. Een deel van de verbanden kunnen worden verklaard doordat deze kinderen een lager geboortegewicht en een kortere zwangerschapsduur hebben gehad. Daarnaast lijkt er sprake te zijn van extra gewichtstoename bij de kinderen van moeders met pre-existente hypertensie. Er zijn aanwijzingen voor een mogelijk beschermend effect van het gebruik van bloeddrukverlagende medicatie op deze versnelde gewichtstoename. In het tweede deel van dit proefschrift wordt de methode voor het verkrijgen van één van de uitkomstmaten gecontroleerd op

juistheid. **Hoofdstuk 3** levert er bewijs voor dat de 'Kushner BIA formule' voor kinderen op de schoolleeftijd, welke is geïncorporeerd in het Bodystat systeem, vet-vrije massa onderschat. Deze onderschatting is niet-systematisch van aard. Dat betekent dat de verkregen waarden niet simpelweg kunnen worden omgerekend naar de juiste waarde. Het toepassen van een door ons opnieuw gekalibreerde formule laat een kleine, niet significante, afwijking zien. Van belang is dat deze afwijking systematisch van aard is waardoor een robuustere bepaling van lichaamssamenstelling van kleuters mogelijk is voor gebruik in epidemiologische studies. In het derde deel van dit proefschrift richten we ons op de verbanden tussen vroege groei en zuigelingenvoeding met risicofactoren voor hart- en vaatziekten op de kinderleeftijd. In **hoofdstuk 4** demonstreren we dat een lager geboortegewicht en snellere groei na de eerste maand en tot aan 5 jaar, in zowel gewicht als lengte, geassocieerd zijn met een hogere bloeddruk op de kinderleeftijd. Groei tijdens de kindertijd lijkt de meest invloedrijke periode te zijn. Het langer dan 3 maanden geven van borstvoeding en het starten met bijvoeding na 6 maanden zijn geassocieerd met een lagere bloeddruk op de kinderleeftijd. **Hoofdstuk 5** beschrijft dat een lager geboortegewicht geassocieerd is met een minder gezonde lichaamssamenstelling en verder dat wanneer snellere gewichtstoename tijdens de zuigelingentijd wordt veroorzaakt door snellere lengtetoename dat het geassocieerd is met een gezondere lichaamssamenstelling. Het langer dan 6 maanden geven van borstvoeding en het starten van bijvoeding na 6 maanden zijn geassocieerd met een lagere vetmassa op de kinderleeftijd, terwijl ze ook geassocieerd zijn met een kortere lengte en een lagere vet-vrije massa. **Hoofdstuk 6** levert bewijs voor een associatie tussen snellere groei tijdens de kindertijd, in zowel gewicht als lengte, en hogere markers voor insuline resistentie. Lager geboortegewicht heeft een zwak verband met een gezonder cholesterolprofiel op de kinderleeftijd. Groei tijdens de zuigelingentijd en zuigelingenvoeding zijn niet geassocieerd met glucose en cholesterol biomarkers op de kinderleeftijd. **Hoofdstuk 7** is een algemene discussie met een reflectie op de resultaten en methodologische overwegingen, onder andere uitval van deelnemers, het observationele karakter van onze studie en daarmee het onvermogen om causaliteit toe te kennen en de mogelijkheid van residuele confounding. Verder staan in dit hoofdstuk aanbevelingen voor toekomstig onderzoek en de volksgezondheid. Samengevat lijkt het redelijk om een langere borstvoedingsduur te stimuleren en om aan te bevelen dat het consequent opwaarts doorkruisen van gewichtsgroeilijnen tijdens de zuigelingentijd, maar met name de kindertijd vermeden moet worden.

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List of abbreviations

LIST OF ABBREVIATIONS

ABCD	Amsterdam Born Children and their Development
AGA	Appropriate-for-gestational-age
AMC	Academic Medical Center
ANOVA	Analysis of variance
BIA	Bioelectrical Impedance Analysis
BMI	Body Mass Index
BMIG	BMI gain
BP	Blood pressure
BV	Body volume
CU	Catch up
CVD	Cardiovascular diseases
DOHaD	Developmental Origins of Health and Disease
DXA	Dual-energy x-ray absorptiometry
FFA	Free fatty acids
FFM	Fat-free mass
FFMG	Fat-free mass gain
FM	Fat mass
FMG	Fat mass gain
FPIR	First-phase insulin response
GT	Glucose tolerance
HDL	High-density-lipoprotein
HOMA	Homeostatic model assessment
ht	Height
IR	Insulin resistance
IUGR	Intrauterine growth retardation
IS	Insulin sensitivity
LCPUFAs	Long-chain polyunsaturated fatty acids
LDL	Low-density-lipoprotein
LG	Linear growth
LGA	Large-for-gestational-age
m	Month(s)
mt	Meters
NT	Not tested
OR	Odds Ratio
P10	10^{th} percentile of the Dutch reference
P90	90^{th} percentile of the Dutch reference
R	Resistance
SD	Standard deviation
SDS	Standard deviation scores
SEE	Standard error of the estimate
SGA	Small-for-gestational-age
TBW	Total body water
TC	Total cholesterol
TG	Triglycerides
T2DM	Type 2 diabetes mellitus
VLDL	Very-low-density-lipoprotein
VUmc	VU university medical center
w	Week(s)
WG	Weight gain

WFLG	Weight-for-length-gain
wt	Weight
y	year(s)
YHC	Youth Health Care
%B	β-Cell capacity
3C	Three-component
$^{2}H_2O$	Deuterium water
ΔSDS	Change in standard deviation score

Dankwoord

DANKWOORD

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List of publications

LIST OF PUBLICATIONS

de Beer M, Vrijkotte TGM, Fall CHD, van Eijsden M, Osmond C, Gemke RJBJ. Associations of infant feeding and timing of weight gain and linear growth during early life with childhood blood pressure: findings from a prospective population based cohort study. *PLoS One* 2016;11:e0168920.

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About the author

ABOUT THE AUTHOR

The author of this thesis was born on September 3th, 1979 in Hoorn, the Netherlands. In 1997 she finished secondary school at the Martinus college in Grootebroek. The following three-and-a-half years she studied developmental psychology at the Vrije Universiteit in Amsterdam after which she started her medical training at the same university. Her research internship concerned health related quality of life in obese adolescents, under supervision of prof.dr. Reinoud Gemke (Department of Pediatrics, VU University medical center, Amsterdam) and prof.dr. Hans Koot (Department of Developmental Psychology, Vrije Universiteit, Amsterdam). In 2005 and 2007 she finished developmental psychology and medical school respectively. Subsequently she started her PhD project at the Amsterdam Born Children and their Development study supervised by prof.dr. Reinoud Gemke and dr. Tanja Vrijkotte (Department of Social Medicine, Academic Medical Center, Amsterdam) which resulted in the thesis you are holding. In this period, she was able to complete a master in epidemiology at the EMGO institute. She received the young investigator award at the DOHaD 2009 world congress in Santiago, Chili, for the work described in chapter 5. At this congress, she got into contact with prof.dr. Clive Osmond and prof.dr. Caroline Fall (MRC Lifecourse Epidemiology Unit, Southampton General Hospital, Southampton, United Kingdom), two of the leading researchers in the field of DOHaD research. One year later she visited the MRC Lifecourse Epidemiology Unit in Southampton to work with them for a period of two months. In 2010 she started her training in pediatrics at the VU University medical center, which she completed in 2016. She is currently working as pediatrician at the Fundashon Mariadal hospital in Kralendijk, Bonaire. Marieke is married to Baris Soyogul and they live on Bonaire with their son Olivier and daughter Milou.