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General introduction

CARDIOVASCULAR DISEASE

Cardiovascular diseases, such as coronary heart disease and cerebrovascular disease, are the number one cause of death globally: more people die annually from cardiovascular diseases than from any other cause.[1] Although over 80% of cardiovascular disease deaths take place in low- and middle-income countries,[1] in high-income countries yet one in three people dies from cardiovascular disease.[2] In the last decades the incidence of cardiovascular diseases decreased, but morbidity and mortality rates are still very high. Therefore, it is important to identify risk groups and risk factors to prevent cardiovascular diseases, preferably at an early age.

EARLY LIFE RISK FACTORS FOR CARDIOVASCULAR DISEASE

Adult risk factors for cardiovascular disease are cigarette smoking, unhealthy diet and obesity, physical inactivity, raised blood pressure, diabetes and raised lipids.[1] In addition, an increasing body of evidence indicates that early life influences are important in the development of cardiovascular disease (Developmental Origins of Health and Disease (DOHaD) hypothesis). For example, cardiovascular disease is convincingly associated with small for gestational age birth. David Barker and his colleagues have published many studies, starting in 1989 with the observation that adult men with the lowest weights at birth had the highest death rates from ischemic heart disease.[3] The epidemiologic observations that smaller size or relative thinness at birth is associated with increased rates of coronary heart disease, stroke and their preceding risk factors (hypertension, impaired glucose tolerance, dyslipidemia, and obesity) have been extensively replicated.[4] The association between low birth weight and later cardiovascular disease could be due to undernutrition in pregnancy or overnutrition in infancy as newborns with low birth weight on average have compensatory accelerated growth during (early) infancy.[5] Although of potential short-term benefit, such accelerated growth may have important adverse consequences. Accelerated growth in childhood has been associated with cardiovascular disease[6] and its risk factors, such as insulin resistance,[6,7] adiposity,[8,9] higher blood pressure,[10] and an adverse lipid profile.[8] Many studies have shown that several cardiometabolic risk factors may already be present in early childhood and track into adulthood. For example, children with elevated blood pressure are more likely to have hypertension in adulthood[11,12] and childhood glucose and lipid profile seem to track from childhood into adulthood as well.[13] Cardiometabolic risk factors in childhood might not only track to adulthood, but might also have a direct effect on later disease. In a very large cohort (n >200,000) it was demonstrated that a higher BMI during childhood was associated with an increased risk of cardiovascular disease in adulthood.[14] In addition, the Bogalusa Heart Study and the Cardiovascular Risk in Young Finns Study recently reported that a poorer risk-factor profile during childhood was associated with thicker adult carotid intima media thickness independently of adult risk factors and behaviors.[15,16] Hence, development of risk factors occurs in early life and increases the risk for adult disease, at least in part through an atherosclerotic process expected to precede the development of clinically recognizable cardiovascular disease.

SOCIOECONOMIC INEQUALITIES

Low socioeconomic status (i.e. low income, low education, unemployment, neighborhood disadvantage) is a powerful determinant of cardiovascular disease in adulthood. For example, the adjusted risk of developing heart failure was increased by about 30-50%[17] and there is also strong evidence for higher rates of mortality and incidence of stroke in low socioeconomic groups.[18] These higher rates of cardiovascular disease are observed among less educated,[19] lower grade occupated,[20] and those who live in a disadvantaged neighborhood.[21] Independent of adult socioeconomic status, there is an association between cardiovascular disease in adulthood and socioeconomic status during childhood.[22] The association between childhood socioeconomic status and cardiovascular disease in adulthood might be explained by the socioeconomic patterning of early life risk factors for cardiovascular disease. Therefore, it is necessary to investigate the socioeconomic gradient in fetal, infant, and childhood risk factors of cardiovascular disease and to get more insight into the pathways through which these associations arise.

The pathways through which socioeconomic disadvantage can lead to health and disease can be grouped into a number of complementary perspectives: the 'specific determinants' perspective, the 'selection' perspective, and the 'life course' perspective.[23] The specific determinants perspective implies that the causal effect of socioeconomic disadvantage on health arises from health determinants, as these are unequally distributed across different socioeconomic groups. In the selection perspective, health determines socioeconomic position, instead of socioeconomic position determining health. The 'life course' perspective integrates these perspectives into one framework.[23] The results in this thesis are based on the 'specific determinants' perspective, which notion was derived from the widely adopted Lalonde report from 1974.[24] The aim of this thesis is to investigate the underlying determinants of socioeconomic inequalities in cardiovascular risk factors in early childhood. A conceptual framework is presented in Figure 1.1. The remainder of this chapter first describes the relation of socioeconomic status to several early life risk factors, then describes the data and methods used, and finally presents the research questions.

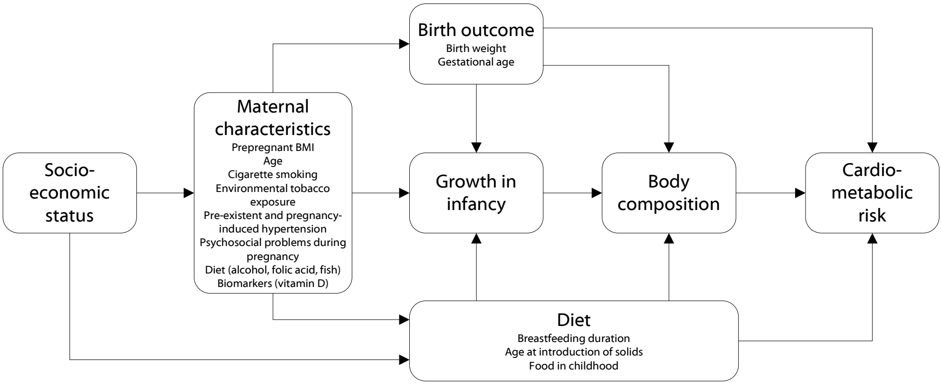

Figure 1.1. Conceptual framework of this thesis

Birth outcomes

Indicators of socioeconomic status have frequently been associated with higher rates of preterm birth,[25,26] small for gestational age,[27] and low birth weigth.[25,26] It has been hypothesized that these associations can for instance be explained by behavior (e.g. maternal smoking[28]), psychosocial circumstances,[29] or biological factors (e.g. low maternal vitamin D level) as these factors are both unfavourably present among socioeconomic disadvantaged groups and determinants of adverse birth outcomes.[30] Although much research has focussed on socioeconomic differences in adverse birth outcomes, little research has evaluated the underlying pathways. Some studies highlighted a single factor, such as maternal smoking and a shorter height[31-34] as explanatory factors in the relation of socioeconomic status to adverse birth outcomes. However, few studies examined more than one factor and even fewer examined the interrelationships of a series of relevant determinants.

Early growth and childhood body composition

Generally, children with low socioeconomic status have not only a lower birth weight, but are also more likely to be overweight from the age of 5 year onwards.[35] This would suggest that children with low socioeconomic status have on average an increased growth velocity in the first years of life. However, it is unknown whether there is indeed a relation of socioeconomic status to growth velocity in the first years of life and which factors contribute to this relation. Potential contributors are maternal smoking, intrauterine growth restriction, and breastfeeding duration as these factors are associated with growth velocity in the offspring.[36-38] The few studies that examined the socioeconomic gradient in overweight before the age of 5 have produced inconsistent results,[39,40] but children from 5 year onwards in the low socioeconomic status group are at higher risk for overweight.[35] The association between overweight and socioeconomic status might be explained by more energy intake and less energy expenditure, but also by the determinants of overweight from fetal life onwards, including birth weight and infant feeding practice. Most studies addressing the socioeconomic gradient in childhood overweight use BMI as indicator of overweight. It was suggested that BMI, including both fat mass and lean mass, may underestimate the socioeconomic gradient in overweight, because low socioeconomic status children may have less lean mass, including muscles and bone.[41] Therefore it seems important to separate lean mass from fat mass. However, there are no studies that have examined the pathways underlying the socioeconomic gradient in growth and body composition.

Cardiometabolic risk factors

There is growing evidence that overweight children are at increased risk of developing an unfavourable cardiometabolic risk profile, including high blood pressure, high cholesterol, and high fasting insulin. For example, researchers of the Bogalusa Heart Study reported that 58% of overweight children had at least one cardiometabolic risk factor.[42] As children from lower socioeconomic background are more likely to be overweight, they might also be at risk for an adverse glucose and lipid profile and higher blood pressure. However, these relationships have not been established and it is not known whether overweight and other factors play a role in these relationships. From the DOHaD perspective, the socioeconomic gradient in BMI, lipids, glucose and blood pressure might be – partially – explained by pregnancy characteristics, birth outcomes, and infant feeding practices.

DATA AND METHODS

The aims of study were achieved using data from a large population-based cohort, the Amsterdam Born Children and their Development (ABCD) study. The main objectives of the ABCD study are to investigate pregnancy characteristics, birth outcomes, and children's health in Amsterdam and the role of early determinants of health in later life, with special attention to ethnic disparities. Although initially socioeconomic inequalities were not a primary goal of study, we anticipated that socioeconomic status was a confounder in the associations with ethnicity and therefore information was collected about socioeconomic status.[43] The sampling procedure of the ABCD study is depicted in Figure 1.2.

Phase I

Between January 2003 and March 2004, all pregnant women in Amsterdam were asked to participate in the ABCD study during their first antenatal visit to their obstetric caregiver. Of the 12 373 women who were approached, 8266 women completed the pregnancy questionnaire (median 16 weeks, IQR 14-18 weeks) covering sociodemograhic characteristics, obstetric history, lifestyle and psychosocial conditions and an informed consent sheet for follow-up. In addition, 4389 pregnant women (53%) participated in the biomarker study. At a median

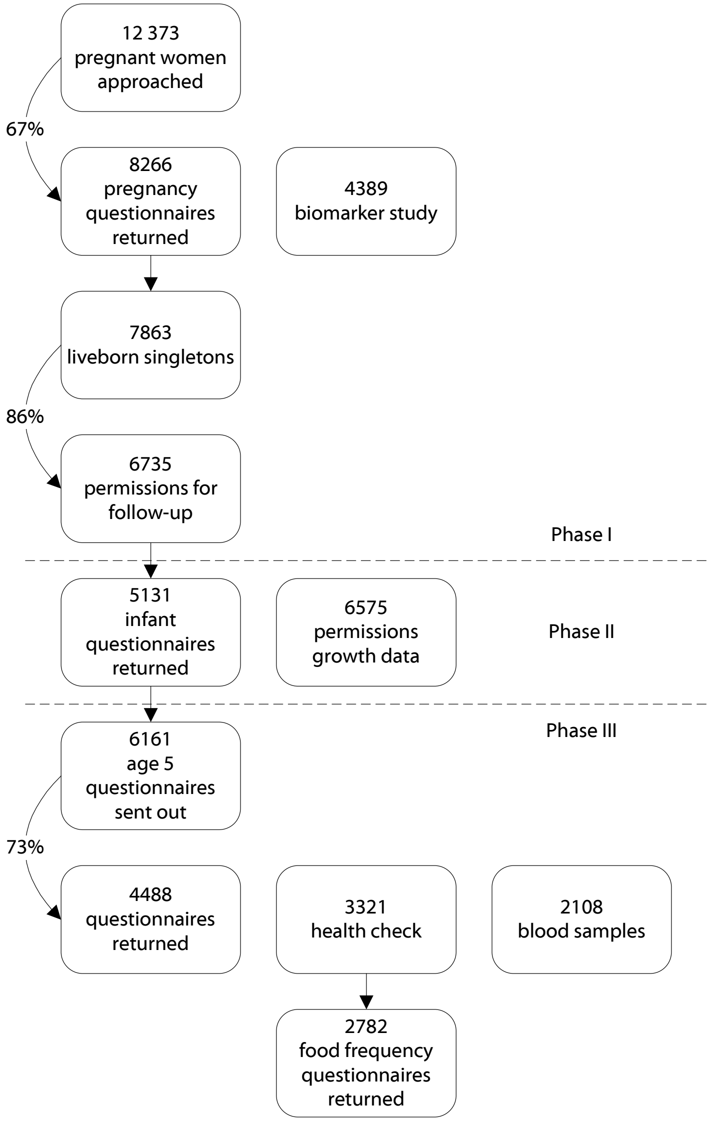

Figure 1.2. Sampling procedure of the ABCD study

of 13 weeks gestation (IQR 14-18 weeks) blood samples were collected to measure maternal micronutrient status and metabolic function. 7863 women gave birth to viable singleton infants. Date of delivery, infant sex, birth weight and gestational age (based on ultrasound or, if unavailable (<10%), on the timing of the last menstrual period) as provided by the obstetric care provider was collected by the Public Health Service's Youth Health Center. Supplementary information concerning complications during pregnancy and neonatal outcomes was obtained by probabilistic medical record linkage with The Netherlands Perinatal Registry (www.perinatreg.nl). 6735 women gave permission for follow-up at age 3 months, and every 5 years thereafter. Regarding socioeconomic status information was available about maternal years of education after primary school, maternal occupation and neighbourhood income. Years of education were asked in the pregnancy questionnaire and neighbourhood income data were registered by Statistics Netherlands, based on mean income in a neighbourhood. Retrospectively information about paternal occupation was collected from the Public Health Service Records. Maternal and paternal occupation during pregnancy were encoded with the CBS (Statistics Netherlands) 2001 job classification.[44]

Phase II

Postpartum, at a median 13 weeks (IQR 12-14), the mothers received a questionnaire concerning the course of their pregnancy and delivery, infant's health, development, growth, feeding practice, and maternal lifestyle during and after pregnancy. Also questions about whether or not the mother and the father had paid work and if so how many hours a week. 5131 mothers of singletons filled out this questionnaire.

Until the children are 4 years old, Youth Health Center nurses and medical doctors conducted standardized routine measurements to monitor children's growth and feeding patterns. 6575 women gave permission to collect data for the ABCD study. Follow-up data included infant nutrition (i.e. duration of breastfeeding, age at introduction of solid foods) and infant and child weight and length at an average of eight time points in the first 14 months and six time points between the ages of 14 months and 4 years.

Phase III

Two weeks after their child's fifth birthday, 6161 mothers received a questionnaire. 4488 mothers returned the questionnaire containing family socio-demographics, maternal lifestyle and psychosocial conditions, family history of medical conditions and an informed consent sheet for granting permission to participate in a health check at school. In addition, highest maternal education level and family income adequacy were obtained from this questionnaire. The health check consisted of a fasting capillary blood sample to assess glucose, total cholesterol, HDL, LDL, triglycerides, and C-peptide,[45] as well as anthropometric measurements (height, weight, waist and hip circumference), body composition (fat mass and fat-free mass)[46], blood pressure, cardiac function (heart rate, heart rate variability, and pre-ejection period), and cognitive function. Cardiac function was measured by VU Ambulatory Monitoring System and the cognitive function was examined using four tasks from the Amsterdam Neuropsychological Tasks (ANT) program.[47] A total of 3321 children completed the health check and 2108 blood samples were collected. Two weeks before the health check, mothers received a self-administered food frequency questionnaire (FFQ), which was developed and validated by TNO Food (Zeist, The Netherlands).[48] It consists of 77 food items for which the frequency of consumption and portion size are to be reported.

RESEARCH QUESTIONS

The following research questions will be addressed in this thesis:

Socioeconomic status in relation to birth outcomes

1. What is the relation of socioeconomic status to small for gestational age birth and which factors can explain this relation? (chapter 2)
2. What is the relation of socioeconomic status to small for gestational age, low birth weight and preterm birth and can environmental tobacco exposure explain this relation on top of maternal smoking? (chapter 3)
3. What is the role of maternal vitamin D status in explaining the relation of socioeconomic status to small for gestational age? (chapter 4)

Socioeconomic status in relation to early growth and childhood body composition

4. What is the relation of socioeconomic status to growth in infancy/early childhood and which early life factors can explain this relation? (chapter 5)
5. What is the relation of socioeconomic status to overweight/obesity and other cardio-metabolic risk factors at preschool age? (chapter 6)
6. What is the relation of socioeconomic status to body composition at age five-six and which early life factors can explain this association? (chapter 7)
7. Is BMI an adequate proxy of the socioeconomic gradient in overweight/obesity? (chapter 8)
8. What is the role of carbohydrate/fibre intake in explaining the relation of socioeconomic status to overweight/obesity? (chapter 9)

Socioeconomic status in relation to cardiometabolic risk

9. What is the relation of socioeconomic status to lipid- and glucose metabolism at age five-six and which early life factors can explain this relation? (chapter 10)
10. What is the relation of socioeconomic status to blood pressure and hypertension at age five-six and which early life factors can explain this relation? (chapter 11)

In the general discussion (chapter 12), the answers to the abovementioned research questions are summarized and discussed within the broader perspective of the current literature. Furthermore, methodological considerations, and recommendations for practice and future research are discussed.