

12

GENERAL DISCUSSION



INTRODUCTION

The aim of this thesis was to investigate the underlying determinants of socioeconomic inequalities in cardiovascular disease risk factors in early childhood. In general there is evidence that socioeconomic inequalities in cardiovascular disease originate in early childhood as we described that risk factors of cardiovascular disease in early childhood are associated with socioeconomic status. More specifically, in our studies low socioeconomic status was associated with lower birth weight, increased growth in infancy and early childhood, higher BMI, higher insulin resistance and higher blood pressure. The most important modifiable explanatory factors in these associations were maternal cigarette smoking and (shorter) breastfeeding duration in lower socioeconomic status families. This chapter answers the research questions, discusses the results, addresses some methodological limitations, and makes a number of recommendations for further research and public health practice.

REFLECTION ON THE RESULTS

Socioeconomic status in relation to birth outcomes

Maternal education is associated with small for gestational age (SGA) birth, preterm birth and low birth weight (chapter 2 and 3). It was expected that many lifestyle habits, such as smoking, environmental tobacco exposure and alcohol use, and psychological factors are responsible for the educational gradient in these birth outcomes. However this gradient can be explained by maternal cigarette smoking only (chapter 2 and 3) for about two-third in this population-based study. Yet, at the individual level more factors might contribute to the educational gradient in adverse birth outcomes. For example, maternal vitamin D status has a very small effect on the educational gradient in SGA, but vitamin D status might play a role in overweight women and women who conceived in the winter period in particular (chapter 4).

Adverse birth outcomes are not only related to perinatal mortality and morbidity,^{49,50} but also to higher blood pressure in childhood³²⁶ and cardiovascular disease in later life.^{75,332} Since fetal growth restriction (resulting in birth small for gestational age (SGA)), low birth weight, and preterm birth are also strongly related to socioeconomic status, this may lead to socioeconomic inequalities in cardiovascular disease in later life. This is supported by our study in which birth weight partly explains the educational inequalities in blood pressure and prehypertension at age five-six (chapter 11). Although in absolute numbers at an individual level the absolute differences in blood pressure may seem low, anticipated tracking and probable increase of these differences in later life signify the potential high impact of these findings in adulthood at public health level. Although causality cannot be proven, it seems of paramount importance to reduce the socioeconomic gradient in adverse birth outcomes.

Socioeconomic status in relation to early growth and childhood body composition

Socioeconomic status is associated with increased weight gain in the first year of life, increased weight-for-length gain between 1 and 5 years of age and body mass index (BMI) at age five-six (chapters 5, 7). Before the age of five-six years, socioeconomic status appears not to be associated with BMI (chapter 6). The higher BMI in children of low-educated mothers can be partly explained by maternal prepregnancy BMI, maternal smoking during pregnancy and increased weight gain in the first year of life (chapter 7). Increased weight gain in turn is also related to smoking during pregnancy and to shorter breastfeeding duration of low-educated mothers (chapter 5).

As an increased infant weight gain and early childhood weight-for-length gain is observed in children with low-educated mother, and accelerated growth in infancy and early childhood has been associated with increased risk of cardiovascular disease and its risk factors such as obesity,^{148,149,153} accelerated growth can partly explain the socioeconomic gradient in cardiovascular disease. This is supported by our study as we found that increased weight gain in the first year of life contributes to the socioeconomic gradient in childhood body mass index. Optimisation of infant and child growth can therefore reduce socioeconomic inequalities regarding cardiovascular disease in later life. Standardized birth weight appears not to play a role in the socioeconomic gradient in subsequent increased postnatal growth, but intrauterine growth restriction might play a role at the individual level as maternal education was not associated with standardized birth weight (chapter 5), but rather with small for gestational age birth (chapter 2). We also hypothesized that an earlier age at introduction of solids plays a role in the association between increased growth and socioeconomic status. Yet this factor seems to be overruled by breastfeeding duration which was strongly correlated with the infant's age at introduction of solids. As mentioned above, at preschool age there is no socioeconomic gradient in BMI and overweight (chapter 6), but at age five-six there is a socioeconomic gradient in BMI (chapter 7). This suggests that the socioeconomic gradient in BMI and overweight emerges after preschool age. Although the socioeconomic gradient in childhood overweight has been attributed to disbalance between consumption^{258,260} and expenditure of calories^{238,239} in the low socioeconomic group, we could not prove that these factors are responsible for the BMI differences in our study. Possibly because these factors were measured at a single time point, while overweight is a result of multiple factors over a period of time. Moreover, only small differences in consumption and expenditure of calories are needed to gain weight over a prolonged period of time. However, children with low-educated mothers have a higher intake of mono-/disaccharides, a lower intake of fibre (chapter 9) and a lower lean mass (chapter 8), suggesting a higher intake of calories and a lower expenditure of calories in the low socioeconomic group. As both fat mass and lean mass are associated with socioeconomic status, BMI as a measure of body composition may underestimate the socioeconomic gradient in true obesity (chapter 8).

Socioeconomic status in relation to cardiometabolic risk

At five-six years of age, the adverse consequences of a higher BMI in low socioeconomic status children are higher glucose levels, C-peptide levels, insulin resistance levels, and blood pressure. However, educational inequalities in glucose, C-peptide and insulin resistance are only partially explained by childhood BMI (chapter 10). As other pre- and postnatal factors seem not to play a role, we hypothesized that carbohydrate intake and stress in early childhood lead to a disturbance of glucose metabolism in children with low-educated mothers. In contrast to our hypothesis, there was no educational gradient in lipids. Dyslipidemia seems to originate from insulin resistance²⁹¹ and might therefore become clear later in life. Furthermore, childhood BMI explains about a quarter of the relation between maternal education and blood pressure/prehypertension (chapter 11). Additionally this association can be explained by a lower birth weight and shorter breastfeeding duration in the low-educated group. As described in the introduction, cardiometabolic risk factors in childhood might not only track to adulthood, but might also have a direct effect on later disease. Therefore, the socioeconomic gradient in the development of cardiovascular disease appears to originate in early childhood.

Explanatory factors: maternal smoking and breastfeeding

As maternal smoking and breastfeeding duration often influence the socioeconomic gradient in health in our study, these factors will be discussed in more detail. Maternal smoking during pregnancy is not only responsible for socioeconomic inequalities in small for gestational age birth, low birth weight, and preterm birth, but also for socioeconomic inequalities in first year weight gain, and childhood BMI. Within our study 33% of the low-educated women smoked during pregnancy, compared to 2% of high-educated women. This large difference explains about half the association of socioeconomic status with birth outcomes, comprising SGA, low birth weight and preterm birth (chapter 2,3).^{31,32} As there is a dose-dependent relationship between smoking and small for gestational age,²⁷ the contribution of maternal smoking may be larger as we only included a dichotomized variable for smoking. Several mechanisms for the adverse effects of smoking have been described. Firstly, smoking leads to impaired fetal oxygen delivery due to a reduction in the fraction of capillary volume in the placenta and an increased thickness of the villous membrane,¹⁰³ and smoking also decreases acute intervillous perfusion.¹⁰⁴ Secondly, fetal tissue oxygenation diminishes by carboxyhemoglobin formation. Thirdly, smoking damages fetal genetic material which can lead to chromosomal abnormalities.¹⁰⁵ Less established factors such as toxicity of other chemicals³³³ and direct impairment of lung development due to interaction of nicotine with nicotinic acetylcholine receptors³³⁴ might also play a role. In addition to the adverse effects of smoking on birth outcomes, smoking during pregnancy is associated with increased growth in infancy. In smokers' offspring growth is suggested to 'catch-up' after intra-uterine undernutrition,¹⁷² but growth might also increase because smokers have lower amounts of breastmilk and shorter duration

of breastfeeding, suggesting a higher intake of formula-feeding in smokers' offspring.¹⁶⁸ In our study, standardized birth weight and duration of breastfeeding appear not to explain the contribution of smoking in the association between socioeconomic status and increased weight gain. Data from rat studies suggested appetitive learning and attention deficits due to nicotine.^{335,336} These behavioural effects are associated with alterations of both the cholinergic and catecholaminergic neurotransmitter systems of the brain, which may result in persistent behavioural effects, including deficits in impulse control.³³⁵ Subsequently, food consumption and other appetitive behaviours may be less under control.¹⁷⁴ Since maternal smoking has been associated with a poor diet,³³⁷ smoking might reflect dietary factors. Therefore, behavioural and dietary factors might explain the role of smoking in the association of socioeconomic status to BMI at age five-six. Smoking is more common among lower socioeconomic groups in most Western populations.³³⁸ Low socioeconomic status groups are at risk for continuing smoking during pregnancy,³³⁹ they have lack of willpower and support to stop smoking in pregnancy,⁷⁰ while pregnancy provides a unique opportunity for interventions. Concerns regarding the risk of smoking for the fetus serve as motivator in a period of frequent contact with their physician. This allows multiple opportunities to assess and reinforce cessation of smoking. Fortunately, interventions of healthcare providers can lead to significant reductions in smoking during pregnancy.³⁴⁰ Interventions consisted of cognitive behaviour therapy, interventions based on stages of change, maternal feedback on fetal health status, provision of rewards, and pharmacotherapy. The most effective intervention appeared to be providing financial incentives.³⁴⁰ This intervention helped about 24% percent of women to quit smoking during pregnancy and increased birth weight by 124 g, though it is not known whether this intervention is more or less effective in low socioeconomic status groups. In general, lower educated smokers seem more likely served with a telephone helpline rather than clinic-based treatment centre, work-site, and website programs, but the effectiveness during pregnancy of these programs has not been established.⁷⁰

Shorter breastfeeding duration in low-educated mothers contributes to increased first year weight gain, higher body mass index and higher blood pressure in children with low-educated mothers. Although breastfeeding is recommended feeding infants for the first six months of life,³⁴¹ 46% of the low-educated Dutch women breastfeed their child for less than a month, compared to 19% of the high-educated women. In addition to preventive effects on infections, growth pattern in breastfed children represents the optimal³³⁰ with a decreased risk of cardiovascular diseases later in life. Breastfeeding might have a preventing effect due to its bioactive factors²³³ and the lower protein and energy content compared with formula. Furthermore, early programming of appetite regulation and satiety may affect growth and later body composition.³⁶ In addition, breastfeeding is associated with more fruit and vegetables consumption later in life.^{342,343} The effects on later cardiovascular health, such as blood pressure might also be due to the low sodium content as well as the high long-chain polyunsaturated acids content in breast milk.³³⁰ Although there are indications for effects on

later blood pressure³⁴⁴ and blood lipid levels,³⁴⁵ currently there is no convincing evidence that breastfeeding has an effect on cardiovascular disease mortality.³³⁰ Various studies have found that mothers with low socioeconomic status start breastfeeding less often and also breastfeed for a shorter period.^{168,169} Within the Generation R study these associations were partly explained by maternal obesity and maternal smoking.¹⁶⁸ Obese mothers may have delayed lactogenesis,³⁴⁶ and belong more often to environments with inadvertent health beliefs.¹⁶⁸ As smokers have a lower intention to breastfeed³⁴⁷ it is suggested that smoking may be a proxy for motivational factors rather than for chemical factors.¹⁶⁸ The association between maternal education and breastfeeding behaviour is probably largely explained by attitude, social support, and peer influence.³⁴⁸ Women may have family members or friends who have experienced nipple pain, or are concerned about diet, breast size, nipple shape, inadequate milk supply, and their ability to express milk after returning to employed work. Individual counselling should focus on all issues that negatively impact on breastfeeding. In a meta-analysis antenatal education and postnatal support programs improves exclusive breastfeeding rates.³⁴⁹ These programs include structured educational sessions for mothers and other members of the family, professional and lay support for breastfeeding mothers, motivational interviews, delayed or discouraged pacifier use, skin-to-skin contact, and a combination of these interventions. Education and additional support should be directed towards low-educated mothers in particular.

Socioeconomic status

Different indicators of socioeconomic status are used in this thesis. For example, we use maternal years of education after primary school, maternal level of education, family income adequacy, occupation, and neighbourhood income. Maternal education is associated with birth outcomes, growth, childhood BMI, glucose, and blood pressure. Childhood BMI and prehypertension are less strongly associated with income adequacy, which is not associated with glucose and blood pressure as continuous variable. Parental occupation and neighbourhood income are not associated with the outcomes. Maternal education reflects knowledge and beliefs, whereas income adequacy is likely to reflect the availability of economic and material resources. Socioeconomic differences in cardiovascular risk factors seem therefore not due to economic factors, but rather to knowledge and beliefs.

METHODOLOGICAL CONSIDERATIONS

Despite our recognition that different SES indicators may operate in a qualitatively different way in determining health, we were not able to investigate more socioeconomic indicators. To unravel the effect of one SES indicator in particular, it is important to include multiple socioeconomic indicators simultaneously in multivariable models.¹⁰⁰ Unfortunately, missing

data within SES indicators and missing SES indicators did not allow us to (i) examine different SES indicators as independent variables and (ii) to adjust for SES indicators as confounders. Given the results of pilot- subanalysis regarding occupation and neighbourhood income, we infer that a more comprehensive approach would not influence the results of this thesis. In addition, there are limitations of some SES indicators. For example, maternal education was based on years of education after primary school in birth-outcome studies whereas maternal education was based on the level of education in childhood-outcome studies. However, the results did not differ whether we use years of education or educational level. Furthermore, income adequacy is a subjective indicator of SES; an adequate income could be interpreted differently by participants.

Ethnicity

Ethnic differences are likely to reflect socioeconomic differences. To diminish the influence of ethnicity, only ethnic Dutch participants were selected for most studies. In chapter 11, all ethnic groups were included as ethnicity does not affect the association of blood pressure with socioeconomic status. Since ethnicity is based on country of birth of mother and grandmother, we have to bear in mind that the composition of the Dutch group may not be as homogenous as presented and residual confounding by ethnicity might be present. It is therefore possible that ethnicity can explain a small part of the examined socioeconomic gradients.

Selective loss to follow-up

As in most longitudinal cohort studies, the ABCD study did encounter selective loss to follow-up. The response rate in phase I of the study was 67% with an overrepresentation of younger, non-Western, and multiparae women among non-respondents.⁹⁹ As the associations found between risk factors and adverse pregnancy outcomes were similar for respondents and non-respondents, it was concluded that selection bias was acceptably low in this phase. In phase III, the response rate was 73%. In most chapters of this thesis we present and discuss a loss to follow-up analyses. This consistently shows a pattern with higher educated and healthier women in the analysed groups. It is likely that the low-educated mothers are not only under-represented, but even are more educated than the low-educated mothers in the population. Therefore, the presented associations are more likely to be underestimated rather than overestimated. We can think of no reason why this selective loss to follow-up should affect the explanatory pathways of socioeconomic status to health.

Confounding

Although we have adjusted for a wide range of confounders, residual confounding might be present. For example, maternal smoking and maternal BMI are strongly related to potential unmeasured confounders such as diet and activity patterns. This is supported by Leary et

al.²³⁴ who found that partner's smoking was only a little weaker associated with offspring body composition than maternal smoking. These associations may have a biological basis, through passive smoking, but it is likely that residual confounding will, at the least, contribute to the investigated associations. However we have not been able to include more potential confounders. Residual confounding might bias the investigated associations, but also the calculated proportions of mediation.

FUTURE DIRECTIONS

For research

Continuing the ABCD study and following the children into adulthood may allow us to see whether the investigated inequalities contribute to socioeconomic inequalities in cardiovascular disease in adulthood. In addition, more determinants of early life cardiovascular risk factors may be investigated as the associations of these factors with socioeconomic status could not entirely be explained. Especially physical activity and sedentary lifestyle should be addressed more extensively. Ideally, as recommended by Braveman et al. a large array of different socioeconomic status indicators should be measured. These should be selected systematically and should include economic resources, income, education, occupation, socioeconomic factors earlier in life, and neighbourhood socioeconomic conditions at any life stage.¹⁰⁰ This approach has to be ethnic group-specific as a given SES measure may have different meanings in different ethnic groups. SES measures may also have different meanings in different social groups. Therefore, it is important to replicate the analyses in other social groups, for example, in rural location. Finally, in this thesis we suggest that interventions might be helpful to reduce cardiovascular disease risk factors among low socioeconomic status children. However, more research is needed to confirm the effectiveness of interventions in lower socioeconomic status groups.

For practice

The socioeconomic gradient in cardiovascular risk factors seems to originate very early in life. Interventions to bring down this gradient should therefore start with antenatal and even preconceptional care. First, lower socioeconomic status pregnant women should be taught in disadvantages of smoking and should be motivated to quit smoking. The clinical practice guidelines released by the United States Department of Health and Human Services³⁵⁰ made three recommendations: offer psychosocial intervention, offer intervention throughout pregnancy, and offer pharmacotherapy. A telephone helpline and providing incentives might be helpful in particular in reducing smoking rates among lower socioeconomic status pregnant women. Second, lower socioeconomic status pregnant women should be motivated to start breastfeeding. Intervention programs should include education for mothers and their

family. All issues that negatively impact on breastfeeding should be counselled by antenatal and postnatal care providers.

FINAL CONCLUSION

Socioeconomic inequalities in cardiovascular disease seem to start very early in life, with higher rates of adverse birth outcomes, accelerated infant growth, overweight, and insulin resistance among children with low-educated mothers. In addition, children with low-educated mothers have a higher blood pressure and more prehypertension compared to children with high-educated mothers. As previous studies concluded that these factors are associated with cardiovascular disease, we infer that intervention programmes preventing cardiometabolic risk factors in the offspring should start with antenatal care among low socioeconomic status groups. Key determinants are smoking during pregnancy and breastfeeding duration. Obstetric care providers should focus on these determinants in low socioeconomic status women in particular. However, more research is needed to entirely unravel pathways between socioeconomic status and cardiovascular disease risk factors and to develop and evaluate effectiveness of interventions in low socioeconomic status women and their children.