Fetal Origins of Socioeconomic Inequalities in Early Childhood Health

The Generation R Study

Lindsay Marisia Silva

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The Generation R Study

Prenataal ontstaan van sociaal-economische gezondheidsverschillen bij jonge kinderen

Het Generation R Onderzoek

Proefschrift

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Lindsay Marisia Silva
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Overige leden:	Prof.dr. A.J. van der Heijden
	Prof.dr. S.A. Reijneveld
	Dr. J.C. van der Wouden
Copromotor:	Dr. H. Raat

Contents

Chapter 1

Introduction

1.1 SOCIOECONOMIC STATUS AND HEALTH

In the last few decades, socioeconomic inequalities in health have become a major topic of public health research. In all European countries with available data, including the Netherlands, inequalities in morbidity and mortality by socioeconomic status, as indicated by education, occupation or income, have been shown to be substantial[1]. Despite increases in prosperity, there is no evidence that the socioeconomic inequalities in health are declining[2]. In fact, in several European countries the relative gap in mortality between upper and lower socioeconomic groups has even widened[3]. In the Netherlands, as shown by a recent report, having a low educational level is associated with a life expectancy reduction of 6.9 years for men and 5.7 years for women, and a reduction of healthy life expectancy, i.e. life expectancy without disabilities, of respectively 12.7 and 13.8 years[4] (see figure 1.1). These findings clearly underscore the impact of socioeconomic health inequalities on public health, and the need for interventions to reduce these inequalities. Therefore, the Dutch government has set the goal to reduce the existing socioeconomic health inequalities with 25% by the year 2020[5].

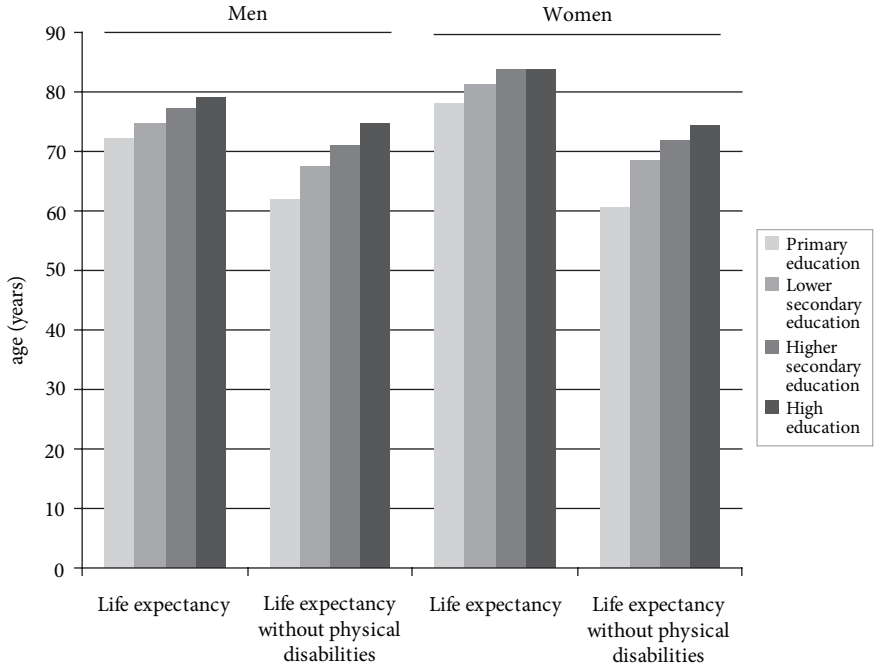

Figure 1.1 **Healthy life expectancy at birth, 1997/2005.** *Source:* Statistics Netherlands[6]

Greatest success in reducing inequalities in health is likely to be achieved by targeting diseases that have the greatest impact on inequalities in health. Some prior studies have examined the contribution of specific diseases to socioeconomic health differences and found that among those that contribute most are ischemic heart diseases and other cardiovascular diseases[7 8].

While men suffer more from cardiovascular diseases than women, women also show substantial socioeconomic inequalities in cardiovascular disease[9 10]. In relative terms, the inequalities in cardiovascular disease and its risk factors appear even larger among women than among men[7 9-12]. Furthermore, evidence shows that, among women, the contribution of cardiovascular diseases to socioeconomic inequalities in total mortality is larger than among men[7 13]. Given the above, and given that previous studies have been able to explain a relatively low proportion of the inequalities in women[9], studying the origins of socioeconomic inequalities in cardiovascular disease among women is particularly interesting.

1.2 HOW DOES SOCIOECONOMIC STATUS AFFECT HEALTH?

Tackling socioeconomic health disparities requires knowledge of the pathways through which low socioeconomic status leads to poor health. Our understanding of these pathways has progressed during the past two decades[14]. The causal effect of low socioeconomic status on health is likely to act through more specific health determinants that are unequally distributed across socioeconomic groups, mainly material factors (e.g. maternal deprivation, bad working and housing conditions, financial resources), psychosocial factors (psychosocial stress, lack of social support), and health-related behaviors (smoking, excessive alcohol consumption, diet)[15-19]. In turn, these factors may have biological impacts and eventually lead to disease. Selection mechanisms, which postulate that health (or a determinant of health) determines socioeconomic status in stead of the other way around, may also have a role in explaining socioeconomic health inequalities[18] (see figure 1.2).

Despite increases in knowledge, the exact mechanisms how low socioeconomic status 'gets under the skin' to cause ill-health are still far from clear.

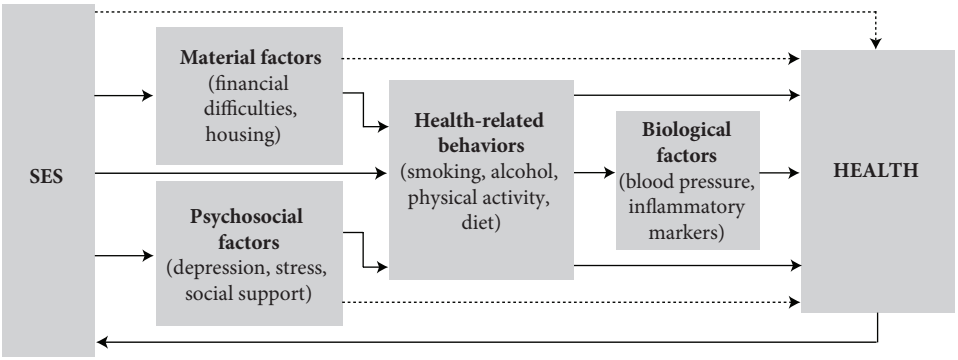

Figure 1.2 **Theoretical model of pathways by which socioeconomic status (SES) might influence health.**

In the continuing search for understanding the causal pathways, recent articles have made it clear that researchers should adopt a so-called '*life-course perspective*'[20]. This postulates that socioeconomic disadvantage in one stage of the life-course may translate into a health disadvantage in the next. This perspective suggests that at least part of the socioeconomic inequalities in adult health is a result of socioeconomic conditions in an earlier stage in life. Several studies have provided evidence supporting this hypothesis[21-25]. For example, Power et al[24] and Beebe-Dimmer et al[21] showed that, independent of adult socioeconomic position, childhood socioeconomic position was associated with adult mortality, in particular cardiovascular mortality. Investigators have postulated different ways in which this link between circumstances in childhood and adult health occurs[26 27]. This may be through latent effects, pathway effects, or through longitudinal accumulation[26]. In the latency model, it is assumed that specific biological factors or developmental opportunities at critical periods in life have a lifelong impact on health, independent of subsequent life circumstances. The second model assumes that early life environment sets individuals onto life trajectories that in turn affect health status over time. The last model assumes that accumulation over time of exposures to unfavourable environments affect later health status.

1.3 IMPACT OF SOCIOECONOMIC STATUS ON CHILDHOOD HEALTH

Early socioeconomic circumstances do not only affect long-term health; their effect on health is also evident during childhood. It is well-recognized that children living in socioeconomic disadvantage generally have a worse health than socioeconomically advantaged children. This gradient has been investigated for different dimensions of childhood health, including mortality[28], general health status[4 29 30], growth[31-33], injuries and accidents[34], mental health[35] and specific diseases such as infectious diseases[36 37]. For example, prevalence and also severity of respiratory tract infections are higher in children of low socioeconomic status when compared with those of high socioeconomic status[36 37]. Regarding growth, children of low socioeconomic status have been shown to be shorter than their counterparts of high socioeconomic status[32 38-40], which may suggest a relatively slow linear growth in children of low socioeconomic status.

There is evidence suggesting that socioeconomic differences in health become larger as children get older, and, as mentioned above, that they might contribute to the origins of health differences in adult life[29 41]. This underlines the importance of research on the nature of socioeconomic differences in health early in life. However, while over the last few decades there has been an increase in research regarding the impact of socioeconomic status on child health, some issues are still not completely clear.

First, compared to numerous studies on health of school-aged children, until now, relatively few studies focused solely on socioeconomic health differences among infants and toddlers[29 42-44]. As a result, relatively little is known about the nature and magnitude of the socioeconomic gradient in early childhood health outcomes. For example, as previously mentioned, socioeconomic inequalities in height suggest inequalities in growth. However, while the first two years of life form a critical period for height development[45], relatively little is known about the effect of socioeconomic status on growth during this period, and how this effect relates to the development of socioeconomic inequalities in attained height.

A second issue has to do with the explanation of the socioeconomic gradient in child health. Proposed pathways through which socioeconomic status likely affects child health include nutrition, childcare practices, the physical/environmental home or neighborhood conditions, material conditions, parental mental health and parental health-related behaviours[29 30 44]. However, despite previous efforts to elucidate the mechanisms underlying the socioeconomic gradient in child health[29 30 44], these mechanisms are not fully understood.

1.4 POTENTIAL ROLE OF INTRAUTERINE CIRCUMSTANCES IN EXPLAINING SOCIOECONOMIC INEQUALITIES IN CHILDHOOD HEALTH

On the basis of the 'fetal-origins hypothesis' (also known as the 'Barker hypothesis')[46], which highlights the importance of experiences in the womb for health later in life, researchers' attention has shifted to the possible role of intrauterine and perinatal circumstances in the explanation of the socioeconomic gradient in child health[30]. The existing literature suggests that socioeconomic status has its impact on health even in the womb: a low maternal socioeconomic status has been shown to increase the risk for low birth weight[47 48], prematurity[49-51] and perinatal mortality[52-54] in the offspring. These findings indicate that socioeconomic status at the time of pregnancy is associated with circumstances that negatively influence the course of pregnancy, intrauterine growth, and delivery. In turn, these adverse pregnancy outcomes are associated not only with a variety of medical problems during infancy and childhood, such as respiratory problems, and an impaired growth, neurodevelopment and cognitive development, but also with adult health outcomes, including cardiovascular diseases[55-58].

Given the above, one might hypothesize that the impact of adverse socioeconomic circumstances at time of pregnancy creates vulnerabilities in the offspring that, independently of postnatal socioeconomic circumstances, might result in an increased risk for adverse health outcomes in childhood and, later, in adulthood (see figure 1.3).

We hypothesized that socioeconomic circumstances might affect health of the offspring from fetal life onwards through intrauterine effects of material factors, psychosocial factors, maternal health-related behaviors (e.g. nutrition, smoking and alcohol consumption), and maternal physical health[59-66]. These indirect intrauterine effects of socioeconomic status on the offspring's health should be distinguished from its effect acting through postnatal factors, such as postnatal maternal and psychosocial factors, feeding practices, and child care practices (figure 1.4).

A further understanding of the origins of socioeconomic inequalities in child health, and, more in particular, of the possible role of (indirect) intrauterine effects of socioeconomic circumstances in the genesis of these inequalities, requires more insight in the different hypothesized pathways as illustrated in figure 1.4. The aim of this thesis was to contribute to a further understanding by studying the nature, magnitude and explanation of socioeconomic inequalities in aspects of maternal, fetal and early childhood health. The following specific research questions were formulated:

1a Are there socioeconomic inequalities in maternal health during pregnancy that may affect fetal, perinatal and long-term health of the offspring?

1b How can these inequalities be explained?

2a Are there socioeconomic inequalities in fetal and/or perinatal health?

2b How can these inequalities be explained?

3a Are there socioeconomic inequalities in early childhood health?

3b To what extent can these inequalities be explained by intrauterine exposures of the child?

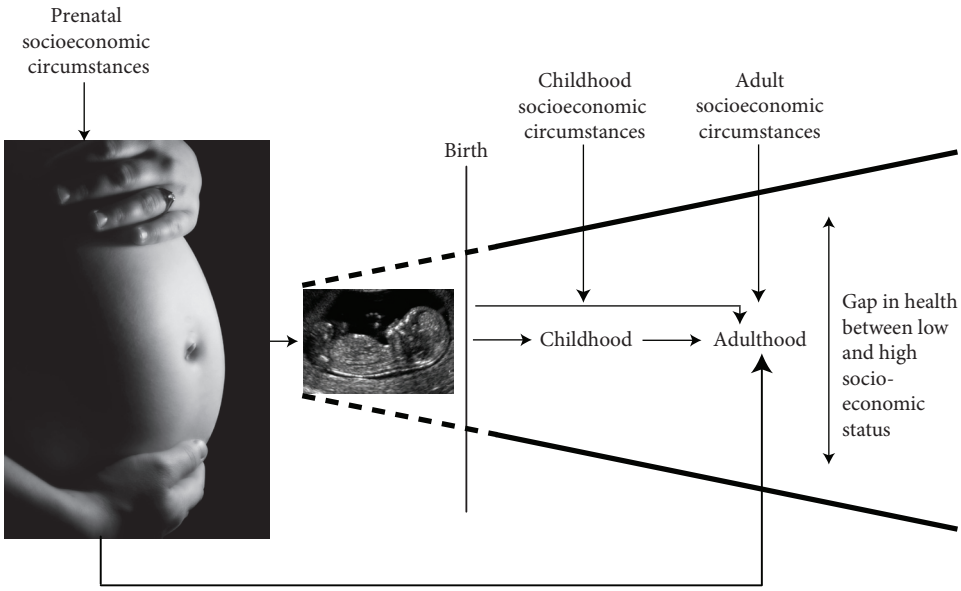

Figure 1.3 **Hypothesized model of emergence of socioeconomic inequalities in child and adult health.**
(Pictures reproduced with permission from The Generation R Study Group)

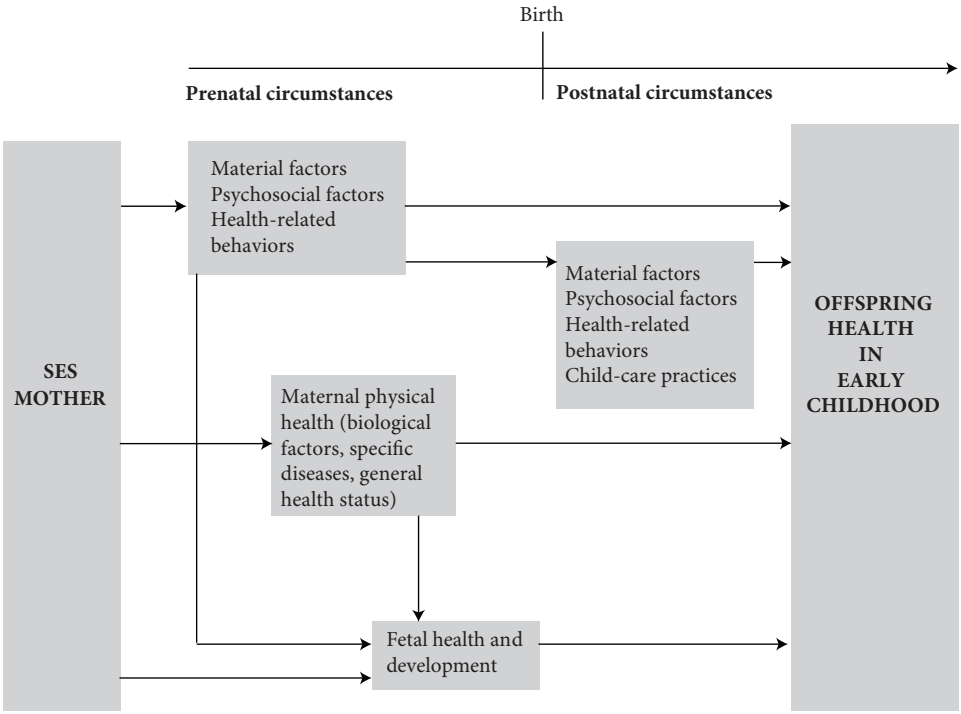

Figure 1.4 **Theoretical model of pathways by which maternal socioeconomic status (SES) might influence health of the offspring.**

1.5 METHODS AND DATA SOURCE

The specific studies described in this thesis were all embedded in The Generation R Study[67-69]. This is a prospective population-based cohort study conducted in Rotterdam, the Netherlands, which was designed to identify early environmental and genetic causes of normal and abnormal growth, development and health from fetal life until young adulthood. Pregnant women with a delivery date between April 2002 and January 2006 were eligible. While enrollment ideally took place in early pregnancy, it was possible until after the birth of the child. Extensive assessments have been carried out in mothers and fathers during the pregnancy and are currently being performed in their children, who form a prenatally recruited birth-cohort. Assessments during pregnancy took place in early pregnancy (gestational age <18 weeks), midpregnancy (gestational age 18-25 weeks) and late pregnancy (gestational age ≥25 weeks). Postnatal assessments are

performed through a home-visit at the age of 3 months, through questionnaires at the ages of 2, 6, 12, 18, 24, 30, 36 and 48 months, and through the routine visits to the child health centers at the ages 2, 3, 4, 6, 11, 14, 18, 24, 30, 36 and 45 months.

In total, 9778 mothers of various ethnicities were included, of whom 8880 were enrolled during pregnancy. These 9778 mothers gave birth to 9745 live born children. Of the 9745 children, 1163 were not approached for participation in the postnatal follow-up studies, because they were born outside the study area. Of the remaining 8582 children, 689 (8%) did not have consent from their parents for the postnatal phase, leaving 7893 children for the postnatal follow-up studies[69].

The studies described in chapters 2 to 6 of this thesis were primarily focussed on data collected from the pregnant women, the studies described in chapters 7 and 8 were focussed on the children.

1.6 OUTLINE

Chapters 2, 3, 4, and 5 are devoted to the associations of maternal socioeconomic status with maternal health during pregnancy. More specifically, they describe the associations of maternal socioeconomic status with the risk for complications during pregnancy that may be a threat to the unborn child's health, and the possible explanations for these associations. Among the most important complications are the so-called hypertensive complications, including preeclampsia (chapter 2) and gestational hypertension (chapter 4). These are leading causes of maternal and perinatal mortality and of morbidity, including maternal liver and kidney dysfunction, abruptio placentae, cesarean delivery, preterm birth and fetal growth restriction[70-74].

Another important pregnancy complication is gestational diabetes mellitus (chapter 5). Gestational diabetes is associated with various adverse maternal and infant outcomes such as preeclampsia and fetal macrosomia, and has been implicated in the development of childhood diabetes[75-77].

Chapter 6 describes the association between maternal socioeconomic status and a key indicator of fetal health: fetal growth. In addition, the contribution of more proximal determinants of fetal growth to the explanation of this association is examined.

Chapters 7 and 8 focus on the socioeconomic inequalities in two early-childhood health outcomes, and the contribution of prenatal and postnatal factors to these inequalities. The first outcome is linear growth in early childhood (chapter 7), since childhood growth is internationally recognized as an important health indicator[78]. The second outcome is upper

respiratory tract infections in early childhood (chapter 8). Upper respiratory tract infections form the most frequent disease in early childhood and can affect the quality of life of both the children and their families[79].

Finally, chapter 9 provides a more general discussion of the main findings from the previous chapters, as well as a discussion of methodological aspects of the study. This chapter ends with an outline of the implications for public health policy and clinical practice, and suggestions for future research.

Table 1.1 **Overview of the different studies presented in this thesis**.

Chapter	Sample	N	Main Socioeconomic indicator	Focus	Outcome
2	Generation R Cohort, Dutch only	3475	Maternal educational level	Mother	Preeclampsia
3	Generation R Cohort, Dutch only	3142	Maternal educational level	Mother	Blood pressure
4	Generation R Cohort, Dutch only	3262	Maternal educational level	Mother	Gestational hypertension
5	Generation R Cohort	7025	Maternal educational level	Mother	Gestational diabetes
6	Generation R Cohort, Dutch only	3545	Maternal educational level	Unborn child	Fetal growth
7	Generation R Cohort, Dutch only	2972	Maternal educational level	Child	Height and linear growth
8	Generation R Cohort	5554	Maternal educational level	Child	Upper respiratory tract infections

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Part I:

Socioeconomic status and maternal health during pregnancy

Chapter 2

Low socioeconomic status is a risk factor for preeclampsia;

The Generation R Study

Based on: Silva LM, Coolman M, Steegers EAP, Jaddoe VWV, Moll HA, Hofman A, Mackenbach JP, Raat H. Low socioeconomic status is a risk factor for preeclampsia; The Generation R Study.

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ABSTRACT

Objectives: To examine whether maternal socioeconomic status, as indicated by maternal educational level, is associated with preeclampsia, and if so, to what extent known risk factors for preeclampsia mediate the effect of educational level.

Methods: In The Generation R Study, a population-based cohort study, we examined data of 3547 pregnant women. Odds ratios (OR) of preeclampsia for low, mid-low and mid-high educational level compared to high educational level were calculated after adjustment for confounders and additional adjustment for a selection of potential mediators (family history, material factors, psychosocial factors, substance use, working conditions, pre-existing medical conditions, maternal anthropometrics and blood pressure at enrollment) that individually caused more than 10% change in the OR for low education.

Results: Adjusted for the confounding effects of age, gravidity and multiple pregnancy, women with a low educational level were more likely to develop preeclampsia (OR 5.12; 95% CI: 2.20,11.93) than women with high educational level. After additional adjustment for financial difficulties, smoking in pregnancy, working conditions, body mass index and blood pressure at enrollment, the OR was 4.91 (95% CI: 1.93,12.52).

Conclusions: Low maternal socioeconomic status is a strong risk factor for preeclampsia. Only a small part of this association can be explained by the mediating effects of established risk factors for preeclampsia. Further research is needed to disentangle the pathway from low socioeconomic status to preeclampsia.

INTRODUCTION

Preeclampsia, marked by hypertension and proteinuria, is a leading cause of perinatal and maternal morbidity and mortality and complicates 5-7% of first pregnancies and 1-3% of all pregnancies[1-4]. The exact pathogenesis is unknown, but it has been suggested that preeclampsia may be an early adult manifestation of the metabolic syndrome[5]. This is based on observations that the metabolic abnormalities in preeclampsia resemble those in the metabolic syndrome[6] and that women with a history of preeclampsia have an increased risk for development of cardiovascular disease later in life[7 8].

Known risk factors for preeclampsia are age above 35 years, nulliparity, history of preeclampsia in previous pregnancies, family history of preeclampsia, multiple pregnancy, pre-existing medical conditions like diabetes, gestational diabetes, time between pregnancies, high body mass index and high blood pressure in early pregnancy[9 10]. Psychosocial stressors and strenuous working conditions have also been associated with increased risk for preeclampsia[11 12]. Surprisingly, smoking has been shown to reduce the risk for preeclampsia[13]; the underlying mechanism is unknown. Low socioeconomic status is a marked risk factor for obesity, high blood pressure, the metabolic syndrome and cardiovascular disease[14-17], and may also be associated with an increased risk for preeclampsia. However, only few studies of preeclampsia have evaluated its association with maternal socioeconomic status and showed inconsistent results[10 18-23]: some have found socioeconomic circumstances to be negatively associated with preeclampsia[18-20], others have found no association[21-24].

Within the framework of The Generation R Study, a large prenatally recruited birth cohort study with extensive assessments during pregnancy[25], we examined the association between socioeconomic status and preeclampsia. We used maternal education as indicator of socioeconomic status as it has been described as the most consistent socioeconomic predictor of cardiovascular disease risk factors[26]. The present study was restricted to an ethnic homogeneous population, since literature indicates that prevalence of preeclampsia and its risk factors[27], as well as socioeconomic disparities in preeclampsia may differ by ethnic groups[20].

We also evaluated whether a possible association can be explained by the mediating effects of known risk factors for preeclampsia, including family history of hypertensive complications in pregnancy, material factors, psychosocial factors, substance use, working conditions, pre-existing medical conditions, maternal anthropometrics and blood pressure at enrollment.

METHODS

Design

This study was embedded in The Generation R Study, a population-based prospective cohort study from fetal life until young adulthood. The Generation R Study was designed to identify early environmental and genetic determinants of growth, development and health, and has been described previously in detail[25 28]. Briefly, the cohort includes 9778 mothers and their children (response rate 61%) of different ethnicities living in Rotterdam, the Netherlands[28]. Enrollment was aimed in early pregnancy, but was possible until birth of the child. Assessments in pregnancy, including physical examinations, ultrasound assessments and questionnaires, were planned in early pregnancy (gestational age <18 weeks), midpregnancy (gestational age 18-25 weeks) and late pregnancy (gestational age ≥25 weeks). The study was conducted in accordance with the guidelines proposed in the World Medical Association Declaration of Helsinki and has been approved by the Medical Ethical Committee of the Erasmus MC, University Medical Center Rotterdam. Written consent was obtained from all participants.

Study population

All pregnant women who were resident in the study area at their delivery date from April 2002 until January 2006 were invited to participate. Of the total of 9778 enrolled women, 91% (n=8880) were enrolled in pregnancy[28]. Women with a Dutch ethnicity (n=4057, 45.7%) comprised the largest ethnic subgroup and were selected for present analyses. A woman was of Dutch ethnicity, when she reported that both her parents were born in the Netherlands[29]. Of the women who participated with more than one pregnancy in this study (8.3%), data on the second (n=332) or third pregnancy (n=5) were excluded from analyses to avoid clustering. We excluded women with missing information on their educational level (n=21), cases of induced abortions (n=14), fetal death before 20 weeks of gestation (n=7), women lost to follow-up (n=3), and women without information on diagnosis of preeclampsia (n=72), gravidity (n=5), anthropometrics (n=17), or blood pressure at enrollment (n=34), leaving 3547 subjects for analyses.

Socioeconomic status

The highest educational level achieved by mother was used as indicator of maternal socioeconomic status. Maternal education was assessed by questionnaire at enrollment, according to the Dutch standard classification[30], and was categorized into four educational levels: high (university or PhD

degree), mid-high (higher vocational training), mid-low (more than 3 years general secondary school, intermediate vocational training, or first year of higher vocational training), and low education (no education, primary school, lower vocational training, intermediate general school, or 3 years or less general secondary school).

Preeclampsia

After each delivery, the present community midwife or obstetrician completed a delivery report. According to Dutch standards of antenatal care, all women whose pregnancies are complicated by preeclampsia should deliver in a hospital under medical supervision of an obstetrician. The delivery reports of study participants who delivered under medical supervision were retrieved and screened by a trained medical record abstractor. Based on the documentation of any kind of hypertensive complications or fetal growth retardation on the delivery report, 398 women were suspected to have preeclampsia. To confirm presence of preeclampsia, the same abstractor conducted detailed reviews of hospital charts of these women. Preeclampsia was defined according to criteria described by the International Society for the Study of Hypertension in Pregnancy (ISSHP): development of systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg after 20 weeks of gestation in a previously normotensive woman plus proteinuria (defined as two or more dipstick readings of 2+ or greater, one catheter sample reading of 1+ or greater, or a 24-hour urine collection containing at least 300 mg of protein)[31]. Neither women with eclampsia nor with hemolysis, elevated liver enzyme and low platelet syndrome (HELLP) were defined as cases.

Potential confounders and mediators

Information on all factors was collected during pregnancy. Categories are indicated in parentheses.

Potential confounders

The following risk factors were considered to potentially confound the effect of maternal education on preeclampsia.

General characteristics. Maternal age was assessed at enrollment in one of the research centers and categorized into three groups (<30 years, 30-35 years, ≥35 years). Gravidity (primigravida, multigravida) was obtained by questionnaire. Presence of multiple pregnancy (singleton pregnancy, twin pregnancy) was determined by fetal ultrasound in early pregnancy.

Potential mediators

Known risk factors for preeclampsia that may be in the pathway from socioeconomic status to preeclampsia were considered potential mediators.

Family history

Information about history of gestational hypertension (no, yes, do not know) and preeclampsia (no, yes, do not know) in a first-degree relative was retrieved from questionnaire.

Material factors

Employment status (not employed, part-time employed, fulltime employed), and presence of financial difficulties in the preceding year (no, yes) were assessed by questionnaire.

Psychosocial factors

Presence of long-lasting difficulties (score in tertiles) was measured by questionnaire with a 12 item-checklist covering financial problems, social deprivation, neighborhood problems and problems in relationships[32]. Maternal psychopathology was assessed by questionnaire using the Global Severity Index (score in tertiles) of the Brief Symptom Inventory[33].

Substance use

Smoking and alcohol consumption (never, before pregnancy, until pregnancy known, continued in pregnancy) were assessed by questionnaire.

Working conditions during pregnancy

Through the questionnaire in midpregnancy, participants were asked whether (yes, no) they had been exposed to the following working conditions in the preceding three months: prolonged sitting, prolonged working behind a monitor screen – these two were defined as sedentary working conditions –, prolonged standing, prolonged walking, prolonged working in a warm environment, lifting or carrying loads of 5 kilograms or more, lifting or carrying loads of 25 kilograms or more – these were defined as physically demanding working conditions – and prolonged vehicle driving and nightshifts[34].

Medical conditions at enrollment

Presence of pre-existing diabetes and raised cholesterol (no, yes, do not know) were assessed by questionnaire at enrollment.

Anthropometrics and blood pressure at enrollment

Maternal anthropometrics and blood pressure were assessed in one of the research centers at enrollment. Height and weight were measured without shoes and heavy clothing. Body mass index (BMI) was calculated from height and weight (weight/height^2) and categorized into normal weight (<25 kg/m^2), overweight (25-30 kg/m^2), and obese (≥30 kg/m^2) according to WHO standards. Systolic and diastolic blood pressure were measured using an Omron 907® Automated Blood Pressure Monitor[35]. BMI and blood pressure values were adjusted for gestational age at time of measurement.

Statistical analyses

We assessed the frequency distributions of preeclampsia and risk factors for preeclampsia according to educational level. To test the trend across educational levels, chi-squared tests for trend were used for categorical factors and one-way analysis of variance for continuous factors.

Multivariate logistic regression was used to calculate the odds ratios (OR) of preeclampsia and their 95% confidence intervals (CI) for levels of education, adjusted for the potential confounding effects of age, gravidity and multiple pregnancy, and additionally adjusted for potential mediators. The highest educational level was set as reference. Missing data on categorical factors were included in the analyses as a separate category.

The conceptual hierarchical framework

To take into account the interrelations between potential mediators, a conceptual hierarchical framework (box 2.1) was developed[36]. We hypothesized maternal education (hierarchical level 1 in box 2.1) to be the most distal factor that may directly or indirectly determine all proposed mediators. The next hierarchical level (hierarchical level 2) comprised family history, which is partly determined by socioeconomic status. Hierarchical level 3 included material and psychosocial factors, which are partly determined by maternal education. Hierarchical level 4 included substance use, working conditions during pregnancy, medical conditions, anthropometrics and blood pressure at enrollment, which are partly determined by maternal education, psychosocial and material factors. Since substance use and working conditions may affect blood pressure[37 38], hierarchical level 4 was divided into two sublevels: hierarchical level 4a (substance use and working conditions during pregnancy) and hierarchical level 4b (medical conditions, anthropometrics and blood pressure at enrollment).

Box 2.1 **Conceptual hierarchical framework of maternal education and potential mediators**

Hierarchical levels of maternal education and potential mediators:

- Hierarchical level 1: Maternal education
- Hierarchical level 2: Family history of hypertensive disorders in pregnancy
- Hierarchical level 3: Material and psychosocial factors
- Hierarchical level 4a: Substance use and working conditions during pregnancy
- Hierarchical level 4b: Medical conditions, anthropometrics and blood pressure at enrollment

Outcome: preeclampsia

Hierarchical logistic models

We started with model 1, which represented the overall effect of maternal education. To evaluate the individual mediating effects of all potential mediators, these factors were added separately to model 1. For each adjustment, the percentage change in OR for the educational levels with an increased risk for preeclampsia was calculated ($100x[OR_{model\ 1} - OR_{+mediator}]/[OR_{model\ 1} - 1]$). We defined factors that caused an attenuation of the OR as mediator, and factors that caused an increase of the OR as suppressor in the association between maternal education and preeclampsia[39].

Next, hierarchical logistic models were built. Starting with model 1, factors from the next hierarchical levels were stepwise added. Only those factors that individually produced at least 10 percent change[40] in the odds ratio for the educational level with the highest risk were included. Because BMI may affect preeclampsia risk through increases in blood pressure[41], blood pressure was added to the logistic models in a separate step.

All analyses were performed using Statistical Package of Social Sciences version 11.0 for Windows (SPSS Inc, Chicago, IL, USA).

RESULTS

Of the 3547 women in this study, mean age was 31.2 years (sd: 4.6); 34.7% were younger than 30 years and 18.0% were 35 years or older. Of these women, 54.4% were primigravida. The median gestational age at enrollment was 13.8 weeks (90% range: 10.9,21.9). The median gestational age at delivery was 40.1 weeks (90% range: 36.7,42.1); the newborns had a mean birth weight of 3471 grams (sd: 563.4).

Of all women, 17.6% were low educated and 31.5% were high educated (Table 2.1). Fifty-one women (1.5%) developed preeclampsia; this percentage was 0.8%, 0.8%, 2.1% and

2.9% for women with high, mid-high, mid-low and low education respectively (p for trend <0.001, table 2.1).

Age, employment status, family history of hypertension in pregnancy, alcohol consumption during pregnancy, sedentary working conditions, prolonged vehicle driving (p for trend <0.001) and night shifts (p for trend <0.05) were positively associated with level of education (see also table 2.1). Gravidity, family history of preeclampsia, financial difficulties, long lasting difficulties, psychopathology, smoking during pregnancy, physically demanding working conditions, BMI, blood pressure (p for trend <0.001) and pre-existing diabetes (p for trend <0.05), were negatively associated with level of education (see also table 2.1).

Table 2.1 **Distribution of preeclampsia and a selection of risk factors by level of maternal education (n=3547).**

		Level of maternal education				
	Total n=3547	**High n=1118 (31.5%)**	**Mid-high n=885 (25.0%)**	**Mid-low n=918 (25.9%)**	**Low n=626 (17.6%)**	**P for trend***
Preeclampsia (%)	1.5	0.8	0.8	2.1	2.9	<0.001
General characteristics						
Age						
<30 years (%)	34.7	16.3	30.2	46.8	56.2	
30-35 years (%)	47.3	61.6	49.8	38.9	30.7	<0.001
≥35 years (%)	18.0	22.1	20.0	14.3	13.1	
Gravidity						
Primigravida (%)	54.4	56.7	56.5	56.6	43.9	<0.001
Multiple pregnancy						
Twin pregnancy (%)	1.4	1.3	1.7	1.6	1.0	0.69
Material factors						
Financial difficulties						
Yes (%)	10.6	4.2	8.0	12.7	22.7	<0.001
Missing (%)	12.2	6.8	6.4	13.8	27.8	
Substance use						
Smoking						
Never (%)	49.0	59.7	52.9	45.1	30.0	
Before pregnancy (%)	19.4	20.2	21.1	19.1	15.8	
Until pregnancy known (%)	8.1	7.5	9.2	9.0	6.4	<0.001
Continued in pregnancy (%)	17.1	5.2	10.3	20.7	42.5	
Missing (%)	6.5	7.4	6.6	6.1	5.3	

Table 2.1 Continued

	Level of maternal education					
	Total n=3547	**High n=1118 (31.5%)**	**Mid-high n=885 (25.0%)**	**Mid-low n=918 (25.9%)**	**Low n=626 (17.6%)**	**P for trend***
Working conditions						
Prolonged sitting						
Yes (%)	69.3	86.2	76.5	62.9	38.7	<0.001
Missing (%)	11.0	6.4	6.3	12.6	23.2	
Prolonged working behind a monitor screen						
Yes (%)	60.6	82.0	62.9	53.5	29.4	<0.001
Missing (%)	11.1	6.6	6.6	12.6	23.0	
Prolonged walking						
Yes (%)	41.1	30.1	44.3	47.1	47.4	<0.001
Missing (%)	11.0	6.7	6.1	12.5	23.2	
Prolonged vehicle driving						
Yes (%)	13.5	19.3	15.0	9.4	6.9	<0.001
Missing (%)	10.9	6.4	6.0	12.7	23.0	
Anthropometrics and BP at enrollment						
BMI†						
Normal weight (%)	67.4	76.9	73.1	60.2	52.6	
Overweight (%)	23.5	19.6	21.7	26.1	29.2	<0.001
Obese (%)	9.1	3.5	5.2	13.6	18.2	
Systolic BP† in mmHg (mean, sd)	117.8 (12.3)	116.1 (11.3)	117.1 (11.9)	119.6 (12.9)	119.4 (12.9)	<0.001
Diastolic BP† in mmHg (mean, sd)	68.8 (9.5)	68.0 (8.7)	68.4 (9.3)	69.9 (10.0)	69.1 (10.3)	<0.001

Abbreviations: BMI, body mass index; BP, blood pressure; sd, standard deviation.

* P-values are derived from chi-squared tests for trend across educational levels (categorical factors) and for (linear) trend component of one-way analysis of variance (continuous factors).

† Values of body mass index, systolic and diastolic blood pressure at enrollment are adjusted for gestational age at enrollment.

Compared to women with high education, women with low and mid-low education had an increased risk for preeclampsia after adjustment for age, gravidity and multiple pregnancy (model 1, tables 2.2 and 2.3), with the highest risk in the lowest educational level (OR 5.12; 95% CI: 2.20,11.93).

Table 2.2 **Change in odds ratios of preeclampsia for levels of education after individual adjustment for potential mediators (n=3547).**

Level of maternal education	High (ref) (n=1118) OR	Mid-high (n=885) OR (95% CI)	Mid-low (n=918) OR (95% CI)	Change* 1	Low (n=626) OR (95% CI)	Change* 2
Model 1. (includes maternal education, age, gravidity and multiple pregnancy)	1.00	1.05 (0.39,2.84)	3.01 (1.34,6.81)		5.12 (2.20,11.93)	
Family history						
Model 1 + family history of hypertension in pregnancy	1.00	1.06 (0.39,2.86)	3.02 (1.33,6.83	+0.5%	5.23 (1.33,6.83)	+2.7%
Model 1 + family history of preeclampsia	1.00	1.05 (0.39,2.84)	2.99 (1.32,6.76)	-1%	5.14 (2.20,12.01)	+0.5%
Material factors						
Model 1+ employment status	1.00	1.00 (0.37,2.71)	2.88 (1.26,6.56)	-6.5%	4.96 (2.07,11.89)	-3.9%
Model 1+ financial difficulties	1.00	1.04 (0.38,2.81)	2.91 (1.28,6.60)	-5.0%	4.55 (1.90,10.89)	-13.8%
Psychosocial factors						
Model 1 + long lasting difficulties	1.00	1.04 (0.38,2.82)	2.96 (1.31,6.69)	-2.5%	4.95 (2.11,11.59)	-4.1%
Model 1 + maternal psychopathology	1.00	1.08 (0.40,2.93)	3.12 (1.38,7.08)	+5.5%	5.19 (2.21,12.19)	+1.7%
Substance use						
Model 1 + smoking	1.00	1.06 (0.39,2.88)	3.27 (1.45,7.41)	**+12.9%**	6.56 (2.77,15.54)	+35.0%
Model 1 + alcohol consumption	1.00	1.02 (0.38,2.78)	2.88 (1.26,6.61)	-6.5%	4.84 (2.01,11.65)	-6.8%
Working conditions						
Model 1+ prolonged sitting	1.00	1.08 (0.40,2.94)	3.21 (1.42,7.29)	+10.0%	5.73 (2.39,13.76)	+14.8%
Model 1+ prolonged working behind a monitor screen	1.00	1.15 (0.42,3.11)	3.33 (1.46,7.57)	**+15.9%**	6.00 (1.46,7.57)	+21.4%
Model 1 + prolonged standing	1.00	1.12 (0.41,3.04)	3.14 (1.38,7.15)	+6.5%	5.28 (2.22,12.55)	+3.9%
Model 1 + prolonged walking	1.00	1.00 (0.37,2.71)	2.77 (1.22,6.32)	**-11.9%**	4.42 (1.86,10.50)	-17.0%
Model 1 + prolonged working in a warm environment	1.00	1.11 (0.41,3.01)	3.20 (1.41,7.27)	9.5%	5.21 (2.20,12.31)	+2.2%

Table 2.2 Continued

Level of maternal education	High (ref) (n=1118) OR	Mid-high (n=885) OR (95% CI)	Mid-low (n=918) OR (95% CI)	Change* 1	Low (n=626) OR (95% CI)	Change* 2
Working conditions						
Model 1 + lifting or carrying weights > 5 kilograms	1.00	1.04 (0.38,2.81)	2.92 (1.29,6.62)	-4.5%	4.77 (2.02,11.23)	-8.5%
Model 1 + lifting or carrying weights >25 kilograms	1.00	1.05 (0.39,2.84)	2.95 (1.30,6.70)	-3.0%	4.79 (2.03,11.30)	-8.0%
Model 1 + prolonged vehicle driving	1.00	1.02 (0.38,2.75)	2.80 (1.23,6.34)	-10.4%	4.51 (1.92,10.64)	-14.8%
Model 1 + night shifts	1.00	1.04 (0.39,2.83)	2.94 (1.30,6.65)	-3.5%	4.72 (2.01,11.12)	-9.7%
Pre-existing medical conditions						
Model 1 + pre-existing diabetes	1.00	1.06 (0.39,2.86)	3.03 (1.34,6.84)	+1.0%	4.96 (2.13,11.59)	-3.9%
Model 1 + pre-existing raised cholesterol	1.00	1.05 (0.39,2.83)	3.06 (1.35,6.91)	+2.5%	5.24 (2.25,12.19)	+2.9%
Anthropometrics and BP at enrollment						
Model 1 + BMI	1.00	1.01 (0.37,2.73)	2.54 (1.11,5.82)	-23.4%	4.06 (1.71,9.65)	-25.7%
Model 1 + systolic BP	1.00	1.01 (0.37,2.74)	2.73 (1.20,6.21)	-13.9%	4.68 (2.00,10.96)	-10.7%
Model 1 + diastolic BP	1.00	1.01 (0.37,2.74)	2.71 (1.19,6.15)	-14.9%	4.68 (1.99,11.00)	-10.7%

Abbreviations: ref, reference category; OR, odds ratio; CI, confidence interval; BMI, body mass index; BP, blood pressure.

* Change 1 and change 2 represent the change in odds ratio relative to model 1 for mid-low and low education respectively after individual adjustment for potential mediators ($100x[OR_{model\ 1} - R_{+mediator}]/[OR_{model\ 1} - 1]$). Changes in odds ratio for mid-high education are not presented since there was no increased risk for preeclampsia in the subgroup with mid-high education compared to the subgroup with high education.

Table 2.3 **Hierarchical logistic regression models fitted on preeclampsia (n=3547).**

	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4a OR (95% CI)	Model 4b OR (95% CI)
Maternal education					
High (ref)	1.00	1.00	1.00	1.00	1.00
Mid-high	1.05 (0.39,2.84)	1.04 (0.38,2.81)	1.06 (0.39,2.89)	1.02 (0.37,2.80)	1.02 (0.37,2.80)
Mid-low	3.01 (1.34,6.81)	2.91 (1.28,6.60)	3.19 (1.39,2.89)	2.69 (1.15,6.27)	2.61 (1.12,6.08)
Low	5.12 (2.20,11.93)	4.55 (1.90,10.89)	6.32 (2.53,15.74)	5.00 (1.97,12.68)	4.91 (1.93,12.52)
Material factors					
Financial difficulties					
No (ref)		1.00	1.00	1.00	1.00
Yes		1.26 (0.54,2.98)	1.58 (0.66,3.81)	1.46 (0.61,3.54)	1.52 (0.62,3.71)
Missing		1.60 (0.78,3.29)	1.60 (0.32,7.98)	1.40 (0.29,6.82)	1.37 (0.29,6.56)
Substance use					
Smoking					
Never (ref)			1.00	1.00	1.00
Before pregnancy			0.80 (0.37,1.72)	0.81 (0.38,1.76)	0.83 (0.38,1.81)
Until pregnancy known			1.37 (0.58,3.24)	1.44 (0.61,3.42)	1.60 (0.67,3.82)
Continued in pregnancy			0.37 (0.15,0.95)	0.40 (0.16,1.03)	0.45 (0.18,1.16)
Missing			1.21 (0.45,3.27)	1.26 (0.47,3.39)	1.26 (0.46,3.42)
Working conditions					
Prolonged sitting					
No (ref)			1.00	1.00	1.00
Yes			1.32 (0.46,3.78)	1.31 (0.45,3.82)	1.21 (0.41,3.58)
Missing*			-	-	-
Prolonged working behind a monitor screen					
No (ref)			1.00	1.00	1.00
Yes			2.13 (0.83,5.51)	2.12 (0.81,5.53)	2.15 (0.81,5.70)
Missing*			-	-	-
Prolonged walking					
No (ref)			1.00	1.00	1.00
Yes			1.65 (0.87,3.13)	1.65 (0.87,3.12)	1.70 (0.90,3.23)
Missing*			-	-	-
Prolonged vehicle driving					
No (ref)			1.00	1.00	1.00
Yes			0.43 (0.13,1.43)	0.43 (0.13,1.42)	0.44 (0.13,1.44)
Missing*			-	-	-

Table 2.3 Continued

	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4a OR (95% CI)	Model 4b OR (95% CI)
Anthropometrics and BP at enrollment					
BMI†					
Normal weight (ref)				1.00	1.00
Overweight				1.64 (0.86,3.12)	1.32 (0.68,2.58)
Obese				2.71 (1.29,5.68)	1.64 (0.72,3.74)
Systolic BP†					1.00 (0.97,1.02)
Diastolic BP†					1.05 (1.01,1.09)

Abbreviations: OR, odds ratio; CI, confidence interval; ref, reference category; BMI, body mass index; BP, blood pressure
* Due to small or zero cells, results for these categories were invalid. Since these effects were not of primary interest they are not presented.
† Values of body mass index, systolic and diastolic blood pressure at enrollment are adjusted for gestational age at enrollment.
Model 1: Maternal education, age, gravidity, and multiple pregnancy
Model 2: Model 1 + financial difficulties
Model 3: Model 2 + smoking, prolonged sitting, prolonged working behind a monitor screen, prolonged walking, prolonged vehicle driving
Model 4a: Model 3 + body mass index at enrollment
Model 4b: Model 3 + body mass index, systolic and diastolic blood pressure at enrollment

Individual adjustment for financial difficulties, prolonged walking, prolonged vehicle driving, BMI, systolic and diastolic blood pressure at enrollment attenuated the OR for low education with >10%, while adjustment for smoking, prolonged sitting and prolonged working behind a monitor screen increased the OR for low education with >10% (table 2.2). These factors were included in the hierarchical logistic models.

Financial difficulties, when added to model 1 (model 2, table 2.3), mediated 14% of the effect of low education (adjusted OR: 4.55; 95% CI: 1.90,10.89). Adding smoking and the selected working conditions in model 3 resulted in an increase of the OR for low education (adjusted OR 6.32; 95% CI: 2.53,15.74), which was mostly due to the effect of smoking; women who continued smoking in pregnancy had a reduced risk for preeclampsia (OR 0.37, 95% CI: 0.15, 0.95) compared to never smokers.

In model 4a, BMI at enrollment was added, which mediated 25% of the effect of low education (adjusted OR: 5.00; 95% CI: 1.97,12.68). Adjusted for the other factors in this model, obesity was associated with an increased risk for preeclampsia (OR: 2.71; 95% CI: 1.29,5.68). Additional adjustment for systolic and diastolic blood pressure at enrollment in the final model (model 4b) resulted in further mediation, but not elimination, of the effect of low education

(OR: 4.91; 95% CI: 1.93,12.52), and partial mediation of the effect of obesity. Diastolic blood pressure at enrollment was significantly associated with preeclampsia risk in this model (OR per mmHg increase: 1.05; 95% CI: 1.01,1.09). The effect of smoking was no longer significant due to additional adjustment for BMI and blood pressure at enrollment .

DISCUSSION

This study showed that low educated pregnant women had a five-fold increased risk for preeclampsia compared to high educated women. Although the effect of low education was in part mediated by financial difficulties, occupational exposure to prolonged walking and prolonged vehicle driving, BMI and blood pressure at enrollment, this association remained largely unexplained.

Methodological considerations

Present results were based on a population-based prospective cohort study in which a large number of women were enrolled early in pregnancy, and information on numerous potential confounders and mediators was available. We used medical chart review and applied standard international criteria for a consistent preeclampsia definition.

The response rate among Dutch pregnant women in The Generation R Study was relatively high (68%)[42], but there was some selection towards a relatively high educated, and somewhat healthier study population[28]. It is possible that non-responders are lower educated with higher risk for preeclampsia compared to responders, leading to some underestimation and loss of power of the estimated effect of low maternal education.

Socioeconomic status refers to the "social and economic factors that influence what positions individuals or groups hold within the structure of society"[43]. It is a complex and multifactorial construct. The most frequently used indicators of socioeconomic status are educational level, income level and occupational class[43 44]. In this study, we used educational level as single indicator of maternal socioeconomic status. Education is an important determinant of employment and economic circumstances, and thus reflects material resources but also non-economic social characteristics, such as general and health-related knowledge which influences health behaviour, literacy, problem-solving skills and prestige[44 45]. It has been shown to be the strongest and most consistent socioeconomic predictor of cardiovascular disease risk factors[26]. Additionally, level of education as socioeconomic indicator can be applied to teenage and unemployed mothers, unlike for example occupational class. However, educational level does not entirely capture the material and financial aspects of socioeconomic status[44 45].

Information on maternal education and many of the evaluated risk factors was derived from questionnaires, which may have induced some misclassification. Misclassification of potential mediating risk factors may have contributed to the lack of explanation of the observed association between maternal education and preeclampsia.

Comparison with other studies

The incidence of preeclampsia in this cohort was 1.5%, which is lower than that reported in some other studies. A Danish birth cohort study, for example, reported an incidence of 3%[1]. This may be due to regional differences in preeclampsia incidence, but may also be due to differences in case definition and data collection[9]. For our study, we conducted detailed analyses of hospital charts of all participants with suspected preeclampsia, with regard to the strict criteria of hypertension and proteinuria. In contrast, many other studies were based on self-reported diagnoses of preeclampsia or hospital registries[1].

Our study supports others that found a comparable association between measures of socioeconomic status and preeclampsia[18-20]. Healterman et al.[18] found an OR of preeclampsia of 2.3 (95% CI: 1.2, 4.4) for women with primary education compared to women with education higher than primary school. The lower magnitude of effect compared to our results is probably due to the difference in the educational composition of the reference category. When we repeated our analyses, after categorizing maternal education into two levels similar to Healterman et al, we found a comparable effect (OR: 2.47, 95% CI: 0.86,7.08).

Our findings challenge studies that did not find an association between socioeconomic status and development of preeclampsia[10 21-23]. This discrepancy may be attributable to differences in exposure definition or case definition. Lawlor et al.[21] used occupation of the women's partners as indicator of maternal socioeconomic status, which may influence risk for preeclampsia differently than maternal education. Parazzini et al.[23] and Savitz et al.[22] not only included preeclampsia, but also pregnancy-induced hypertension without proteinuria in the outcome definition, leading to a more heterogeneous group.

Mediating and suppressing mechanisms

Part of the observed effect of low education on preeclampsia was mediated by higher rates of financial difficulties, occupational exposure to prolonged walking, and obesity, higher blood pressure levels at enrollment, and lower rates of occupational exposure to prolonged vehicle driving among low educated women. The effect of vehicle driving on preeclampsia has been poorly studied, but emotional stress, of which financial difficulties may be a source[46], and occupational exposure to prolonged walking have been associated with increased risk for

preeclampsia[12]. Overactivation of the sympathetic nervous system may be involved in this association[46 47]. However, the effects of these factors on preeclampsia were not statistically significant in our study, and further research is necessary to elucidate the underlying mechanisms from low socioeconomic status through emotional and physical stress to preeclampsia.

BMI at enrollment had the highest mediating effect. Obesity was a significant risk factor for preeclampsia, and in turn, more than half the effect of obesity was mediated through blood pressure early in pregnancy. These findings are in line with current hypotheses on the underlying mechanism of how obesity leads to preeclampsia; it may act through raised triglyceride levels, increased systemic inflammation and increases in blood pressure from early pregnancy[9 48]. Even within the normal range, the risk for preeclampsia is known to increase with increased blood pressure in early pregnancy[10].

In contrast, part of the effect of low education on preeclampsia was suppressed by lower rates of sedentary working conditions and higher rates of continued smoking in pregnancy among low educated women. These factors partly masked the vulnerability of low educated women to develop preeclampsia. Although the increased risk for preeclampsia associated with sedentary working conditions was not significant in our study, our results were comparable with those of a recent study by Saftlas et al[49]. They suggest that women who spend a lot of their work time sitting have a higher risk for preeclampsia compared to women who spend less time sitting. Regular physical activity may reduce the risk for preeclampsia.

Smoking in pregnancy had the largest suppressing effect on the risk for preeclampsia in low educated women. As described before[13], we found continued smoking in pregnancy to be protective of preeclampsia. The underlying mechanism is unclear, but our findings suggest that the effect of smoking acts partly through changes in blood pressure.

Conclusions and perspectives for future research

We conclude that low socioeconomic status, as indicated by a low level of education, is a strong risk factor for preeclampsia. Remarkably, this association remains largely unexplained, although we included a wide range of known risk factors for preeclampsia in our study. This implies that the established risk factors for preeclampsia included in this study do not fully capture the underlying pathway by which socioeconomic circumstances affect preeclampsia risk. Other potential determinants of preeclampsia that were not available for the current study, such as leisure time physical activity, dietary factors, periodontal health, metabolic factors (e.g. cholesterol and fatty acid levels), parameters of endothelial function, and factors related to vascular inflammation (e.g. c-reactive protein), or currently unknown risk factors may also contribute to the explanation[6 50-53].

As preeclampsia is considered an early adult predictor of cardiovascular disease, our findings extend the literature on socioeconomic inequalities in cardiovascular disease[14] by demonstrating that low socioeconomic status is also associated with preeclampsia. The observed socioeconomic gap in preeclampsia may represent the emergence of socioeconomic inequalities in cardiovascular disease morbidity and mortality in women. Given the short and long term adverse health consequences associated with preeclampsia, further research is needed to disentangle the pathway from low socioeconomic status to preeclampsia. Understanding this association may contribute to earlier diagnosis and development of effective interventions and may reduce morbidity and mortality from this disease.

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Chapter 3

No midpregnancy fall in diastolic blood pressure in women with a low educational level;

The Generation R Study

Based on: Silva LM, Steegers EAP, Burdorf A, Jaddoe VWV, Arends LR, Hofman A, Mackenbach JP, Raat H. No midpregnancy fall in diastolic blood pressure in women with a low educational level: the Generation R Study.

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ABSTRACT

Low socioeconomic status has been associated with preeclampsia. The underlying mechanism, however, is unknown. Preeclampsia is associated with relatively high blood-pressure levels in early pregnancy, and with an absent midpregnancy fall in blood pressure. At present, little is known about the associations between socioeconomic status, blood-pressure level in early pregnancy, blood-pressure change during pregnancy and preeclampsia.

We studied these associations in 3142 pregnant women participating in a population-based cohort study. Maternal educational level (high, mid-high, mid-low and low) was used as indicator of socioeconomic status. Systolic and diastolic blood pressure were measured in early, mid and late pregnancy. Relative to women with high education, those with low and mid-low education had higher mean systolic and diastolic blood-pressure levels in early pregnancy; this was explained largely by a higher pre-pregnancy body mass index. While women with high, mid-high and mid-low education had a significant midpregnancy fall in diastolic blood pressure, those with low education did not (change from early to midpregnancy: -0.38 mm Hg; 95% CI: -1.33, 0.58). The latter could not be explained by pre-pregnancy body mass index, smoking, or alcohol consumption during pregnancy. The absence of a midpregnancy fall also tended to be related to the development of preeclampsia, especially among women with a low education (OR: 3.8; 95% CI: 0.80, 18.19).

The absence of a midpregnancy fall in diastolic blood pressure in women with a low education may be a sign of endothelial dysfunction that is manifested during pregnancy. This might partly explain these women's susceptibility to preeclampsia.

INTRODUCTION

Cardiovascular disease is the leading cause of death in Western countries[1]. One important determinant of cardiovascular disease is socioeconomic status (SES), as indicated by educational level, occupational class or income level. Cardiovascular disease and its risk factors, including hypertension, are more common in people of low SES than in those of high SES[2-4]. These socioeconomic differences appear to be stronger in women than in men[2]. The mechanisms underlying the socioeconomic differences in cardiovascular health have not been completely elucidated[5].

Research indicates that hypertensive diseases of pregnancy, including preeclamspia, may be early manifestations of essential hypertension and cardiovascular disease in later life. It has therefore been postulated that pregnancy may be a 'stress-test' that reveals women with hypertensive tendencies[6 7]. Previous studies have shown that the risk for preeclampsia is also higher in women of low SES[8 9]. However, the pathways underlying this association remain unclear[9].

Although the exact etiology of preeclampsia is unknown, it is known that an important role in its pathophysiology is played by endothelial cell dysfunction[10 11]. It has been suggested that this endothelial dysfunction is initiated by factors from the placenta that are released in response to reduced trophoblastic perfusion. In women who develop preeclamspia, endothelial cell injury is believed to lead to intravascular coagulation, loss of fluid from the intravascular space and increased sensitivity to vasopressors[11]. The latter results in an abnormal cardiovascular adaptation to pregnancy, which is reflected in an abnormal pattern of blood-pressure change during pregnancy[10 12]. In pregnant women who are clinically healthy, blood pressure – most notably diastolic blood pressure – falls steadily until the middle of gestation, and then rises again until delivery[12]. In women who develop preeclampsia, this midpregnancy fall in blood pressure does not occur; instead, blood pressure tends to remain stable during the first half of pregnancy, and then to rise continuously until delivery[12]. It is also the case that, even before preeclampsia manifests itself, these women have higher blood pressure levels in early pregnancy than pregnant women who remain normotensive[12].

At present, little is known about the association of SES with blood-pressure level or with the pattern of blood-pressure change during pregnancy. There are two reasons we would benefit from studying these associations. First, it would improve our knowledge of the magnitude of socioeconomic differences in blood-pressure level during pregnancy. Second, it would indicate whether endothelial function in young pregnant women may be affected by SES, and

whether any such effects may be involved in the association of SES with preeclampsia and later cardiovascular disease.

In a large birth cohort study recruited prenatally, we therefore studied the associations of maternal educational level as an indicator of SES with blood-pressure level in early pregnancy, and with the pattern of blood-pressure change during pregnancy. Maternal educational level was used as indicator of SES because it has been described as the most consistent socioeconomic predictor of cardiovascular disease risk[13]. We also examined the extent to which educational differences in blood pressure during pregnancy are explained by pre-pregnancy body mass index (BMI), and by smoking and alcohol consumption during pregnancy. Finally, we explored the relationship between educational level, blood-pressure change during pregnancy, and the incidence of preeclampsia.

METHODS

The Generation R Study

This study was embedded within The Generation R Study, a population-based prospective cohort study from fetal life until young adulthood that has previously been described in detail[14]. Briefly, the cohort comprises 9778 (response 61%) mothers of various ethnicities and their children living in Rotterdam, the Netherlands[14]. All children were born between April 2002 and January 2006.

Assessments in pregnancy took place in early pregnancy (gestational age <18 weeks), midpregnancy (gestational age 18-25 weeks) and late pregnancy (gestational age ≥25 weeks). The study was conducted in accordance with the guidelines proposed in the World Medical Association Declaration of Helsinki[15] and has been approved by the Medical Ethical Committee of the Erasmus MC, University Medical Center Rotterdam. Written consent was obtained from all participating parents.

Study population

Ninety-one percent (n=8880) out of a total of 9778 women were enrolled during pregnancy. Since socioeconomic inequalities in blood pressure may differ between ethnic groups[2], the present study was restricted to women with a Dutch ethnicity (n=4057). A woman was classified as Dutch if both her parents were born in the Netherlands[16].

For several reasons, 915 women were excluded from analysis (see figure 3.1), which made 3142 women eligible for the primary analyses.

Additional analyses were performed in a subgroup of 2441 women on whom blood-pressure measurements in both early and midpregnancy were available, as well as information about diagnosis of preeclampsia (see figure 3.1).

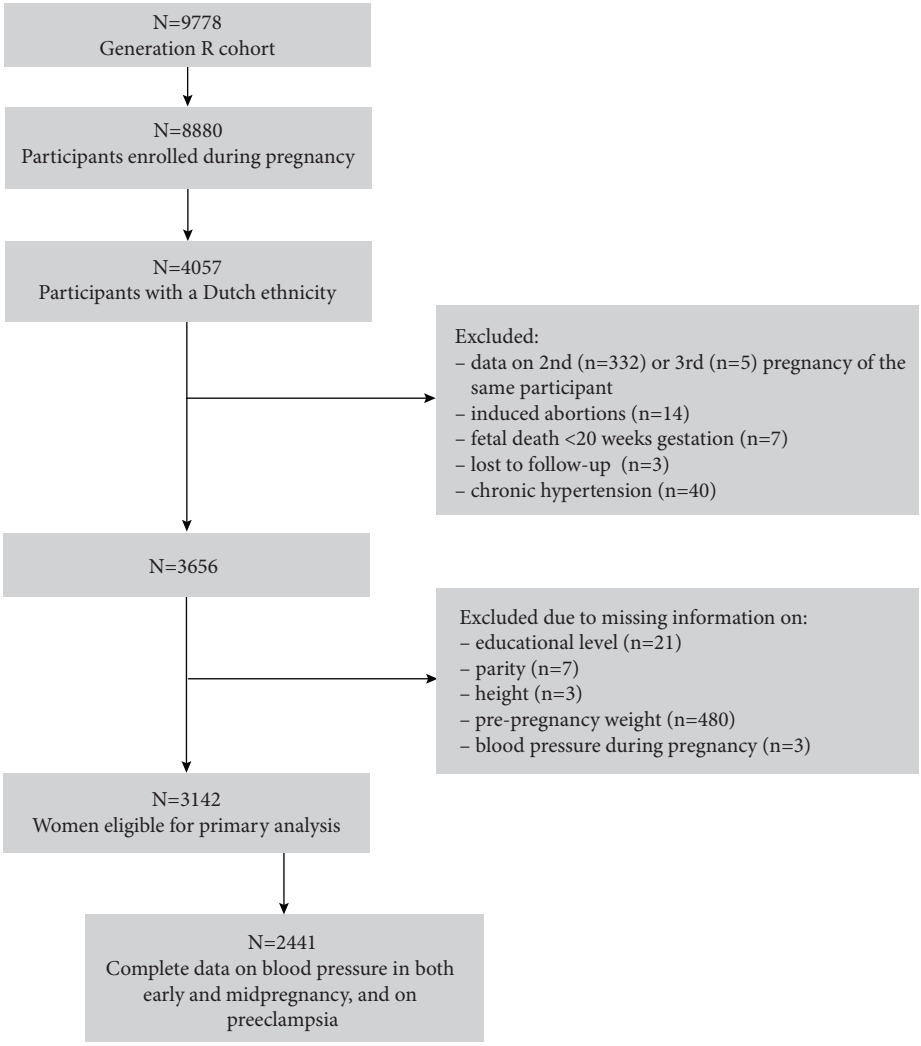

Figure 3.1 **Flow chart participants.**

Educational level

On the basis of a questionnaire used at enrollment, we established the highest education each mother had achieved. This was categorized into four levels: high (university or higher), mid-high (higher vocational training), mid-low (>3 years of general secondary school, or intermediate vocational training completed, or first year of higher vocational training), and low education (no education, primary school, lower vocational training, intermediate general school, or £3 years of general secondary school)[17].

Blood pressure

At the research centers, the validated Omron 907® automated digital oscillometric sphygmanometer (OMRON Healthcare Europe B.V. Hoofddorp, the Netherlands) was used to measure systolic (SBP) and diastolic blood pressure (DBP) in early, mid and late pregnancy[18]; participants were seated in an examination room in a chair with back support, and were asked to relax. Blood-pressure measurement started after 5-10 minutes rest. A cuff was placed around the non-dominant upper arm, which was supported at the level of the heart, with the bladder midline over the brachial artery pulsation. If the circumference of the upper arm exceeded 33 centimeters, a larger cuff was used. Per participant, the mean value of two blood-pressure readings over a 60 seconds interval was documented.

Preeclampsia

The data collection regarding the development of preeclampsia in our study population has been described elsewhere[9]. Briefly, the presence of doctor-diagnosed preeclampsia was retrieved from hospital charts and was determined on the basis of the criteria described by the International Society for the Study of Hypertension in Pregnancy (ISSHP)[19] (see table 3.1).

Table 3.1 **Applied criteria for the diagnosis of preeclampsia.**

Criteria preeclampsia
1) New onset hypertension (i.e. SBP ≥140 mmHg and/or a DBP ≥90 mmHg after 20 weeks of gestation in a previously normotensive woman)
and
2) Proteinuria (i.e. two or more dipstick readings of 2+ or greater, one catheter sample reading of 1+ or greater, or a 24-hour urine collection containing at least 300 mg of protein)

Potential mediators and confounders

Maternal educational level cannot affect blood pressure directly, but is likely to act through other more proximal determinants of blood pressure[20]. We considered pre-pregnancy BMI, smoking and alcohol consumption during pregnancy to be potential mediators in the pathway between maternal education and blood pressure (see figure 3.2); these factors are known to contribute substantially to socioeconomic inequalities in blood pressure in the general population[2]. Pre-pregnancy BMI was calculated on the basis of height and pre-pregnancy weight (weight/height^2); height was measured at enrollment in one of the research centers, and pre-pregnancy weight was established at enrollment through questionnaire. Maternal smoking and alcohol consumption (yes, no) were established using questionnaires in early, mid-and late pregnancy.

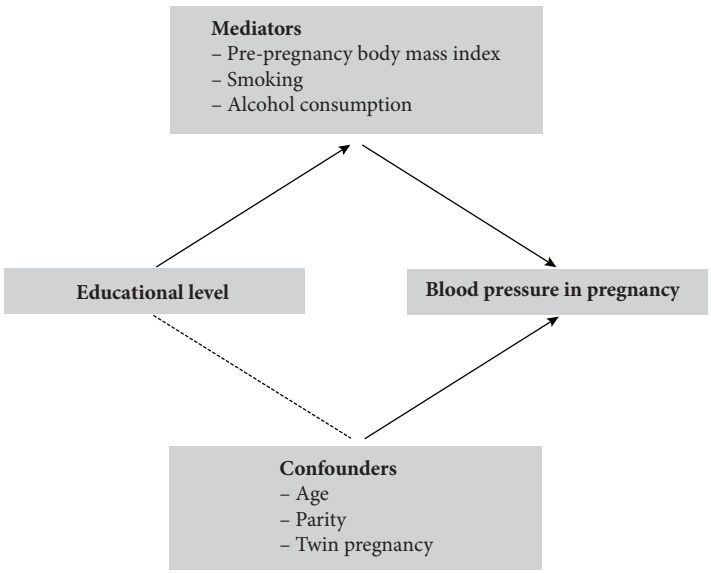

Figure 3.2 **Simplified conceptual framework for the association between maternal educational level and blood pressure in pregnancy.**

Maternal age, parity and twin pregnancy were treated as potential confounders in this study (see figure 3.2), since they could not be considered indisputable mediators[21]. Maternal age was established at enrollment. Parity (para 0, para ≥1) was obtained by questionnaire at enrollment. The presence of twin pregnancy was determined by fetal ultrasound.

Statistical analyses

Regression analyses adjusting for gestational age was used to calculate the mean blood-pressure levels in early, mid and late pregnancy for each educational level. In further analyses, linear mixed models were used with blood pressure as a repeated outcome measure. These models take account of the correlation between repeated measures on the same subject, and allow for incomplete outcome data[22]. To establish educational differences in blood-pressure change from early to midpregnancy and from mid to late pregnancy, we considered each pregnancy period (early, mid and late pregnancy) as a fixed effect in the linear mixed models, with early pregnancy as the reference period. Educational level and an interaction term of educational level with pregnancy period were then added to the mixed models. The highest educational level was set as reference. All linear mixed models were adjusted for the gestational age at the times of blood-pressure measurement.

To calculate the overall effect of education on blood pressure, we started with a linear mixed model that included the potential confounders (basic model). Next, the potential mediators were added to the basic model, first separately and then simultaneously (full model).

For each confounder and mediator, an interaction term with pregnancy period was tested for significance. If the test was significant, these interactions were retained in the model. Missing data on smoking and alcohol consumption were included as separate categories.

Additionally, to evaluate whether educational differences in blood-pressure change were associated with the risk for preeclampsia, we used logistic regression in a subset of the study population (n=2441).

A p-value of 0.05 was taken to indicate statistical significance. Statistical analyses were performed using Statistical Package of Social Sciences version 15.0 for Windows (SPSS Inc, Chicago, IL, USA) and the Statistical Analysis System (SAS) for Windows, version 8.2.

RESULTS

Maternal and birth characteristics of the study population are described in table 3.2. Compared with women with a high educational level, those with a low level were younger, shorter, and heavier. During pregnancy, they were more likely to smoke, but less likely to consume alcohol (p for all <0.05, table 3.2). Preeclampsia was more common in women with a low educational level than in those with a high level (p for trend: 0.004). Gestational age at delivery and birth weight of the newborn were inversely associated with educational level (p<0.001).

Table 3.2 **Maternal and birth characteristics of the study population (n=3142)***.

Maternal and birth characteristics	Level of maternal education					
	Total N=3142	High N=1004 (32.0%)	Mid-high N=774 (24.6%)	Mid-low N=826 (26.3%)	Low N=538 (17.1%)	P for trend†
Age (years)	31.1 (4.6)	32.9 (3.2)	31.9 (3.8)	29.9 (4.8)	28.4 (5.7)	<0.001
Parity						
Para 0 (%)	65.2	64.2	68.0	67.8	59.1	0.234
Twin pregnancy (%)	1.5	1.5	1.9	1.3	1.1	0.463
Height (cm)	170.8 (6.4)	171.5 (6.0)	171.4 (6.5)	170.6 (6.5)	168.9 (6.6)	<0.001
Pre-pregnancy BMI (kg/m^2)	23.2 (3.9)	22.5 (2.9)	22.7 (3.4)	23.8 (4.4)	24.2 (5.0)	<0.001
Smoking‡						
Early pregnancy (% yes)	26.4	13.3	20.7	31.4	51.7	<0.001
Midpregnancy (% yes)	15.8	5.4	10.1	19.2	37.9	<0.001
Late pregnancy (% yes)	13.3	4.5	9.0	16.5	31.2	<0.001
Alcohol consumption§						
Early pregnancy (% yes)	64.6	79.9	71.8	55.6	39.8	<0.001
Midpregnancy (% yes)	47.1	64.5	53.1	35.4	23.8	<0.001
Late pregnancy (% yes)	41.3	59.7	47.7	28.8	17.3	<0.001
Preeclampsia (%)||	1.6	0.9	1.2	2.0	2.7	0.004
Gestational age at delivery¶ (weeks)	40.1 (35.6,42.3)	40.3 (35.3,42.4)	40.3 (36.3,42.2)	40.1 (35.8,42.3)	39.9 (34.4,42.2)	<0.001
Birth weight newborn# (grams)	3475.9 (554.2)	3534.9 (546.1)	3523.2 (534.8)	3455.6 (553.3)	3329.7 (570.7)	<0.001

* Values are means (with standard deviations) or median (with 95% range) for continuous factors, or percentages for categorical factors. † p-values are for chi-squared test for trend (categorical factors), and for (linear) trend component of one-way analysis of variance or kruskall-wallis test (continuous factors).

‡ Data on smoking in early, mid and late pregnancy was missing in 3.2%, 2.5% and 3.8% respectively. § Data on alcohol consumption in early, mid and late pregnancy was missing in 1.7%, 1.1% and 3.3% respectively. || Data on preeclampsia was missing in 1.8%. ¶Data on gestational age at delivery was missing in 0.4%. # Data on birth weight newborn was missing in 2.3%.

Blood-pressure measurements in early pregnancy were made at a median gestational age of 13.1 weeks (95% range: 9.8, 17.3), those in midpregnancy at 20.4 weeks (95% range: 18.6, 23.4) and those in late pregnancy at 30.2 weeks (95% range: 28.6, 32.6).

Figures 3.3 and 3.4 show that throughout pregnancy women with a low and mid-low education had higher mean SBP and DBP levels than women with a high education. These differences were statistically significant, except for the difference in mean DBP in early pregnancy between women with a low education and those with a high education.

Educational level and blood pressure in early pregnancy

Table 3.3 shows the educational differences in blood-pressure level in early pregnancy as calculated on the basis of the linear mixed models. After adjustment for confounders, mean SBP in early pregnancy in women with low and mid-low education were respectively 2.67 mm Hg higher (95% CI: 1.27,4.07) and 3.02 mm Hg higher (95% CI: 1.83,4.21) than in women with high education (basic model, table 3.3). Additional adjustment for maternal pre-pregnancy BMI, smoking and alcohol consumption (full model) attenuated these differences to 0.63 mm Hg (95% CI: -0.78,2.04) and 1.51 mm Hg (95% CI: 0.35,2.67) respectively. This attenuation was due mainly to the adjustment for pre-pregnancy BMI.

In the basic model, mean DBP in early pregnancy was 1.49 mm Hg higher (95% CI: 0.55,2.44) in women with a mid-low education than in women with a high education (table 3.3). Additional adjustment for pre-pregnancy BMI, smoking and alcohol consumption during pregnancy (full model) attenuated this difference to 0.41 mm Hg (95% CI: -0.49,1.31). Again, this attenuation was due mainly to the adjustment for pre-pregnancy BMI.

Educational level and blood-pressure change during pregnancy

Mean SBP increased as pregnancy progressed in all educational subgroups (figure 3.3). The magnitude of increase did not differ between educational levels ($p \geq 0.05$).

In all educational subgroups except one, mean DBP decreased from early to mid-pregnancy, followed by an increase from mid to late pregnancy (figure 3.4). In the basic model, the change in mean DBP from early to midpregnancy was -1.82 mm Hg (95% CI: -2.58,-1.05) in women with a high education, -2.07 mm Hg (95% CI: -2.91, -1.24) in women with a mid-high education, and -1.60 mm Hg (95% CI: -2.43,-0.77) in women with a mid-low education (table 3.4). The exception was the subgroup of women with low education, in whom there was no significant fall in DBP (change: -0.38 mm Hg; 95% CI: -1.33,0.58). In this subgroup, the change in DBP from early to midpregnancy was also significantly different from that in women

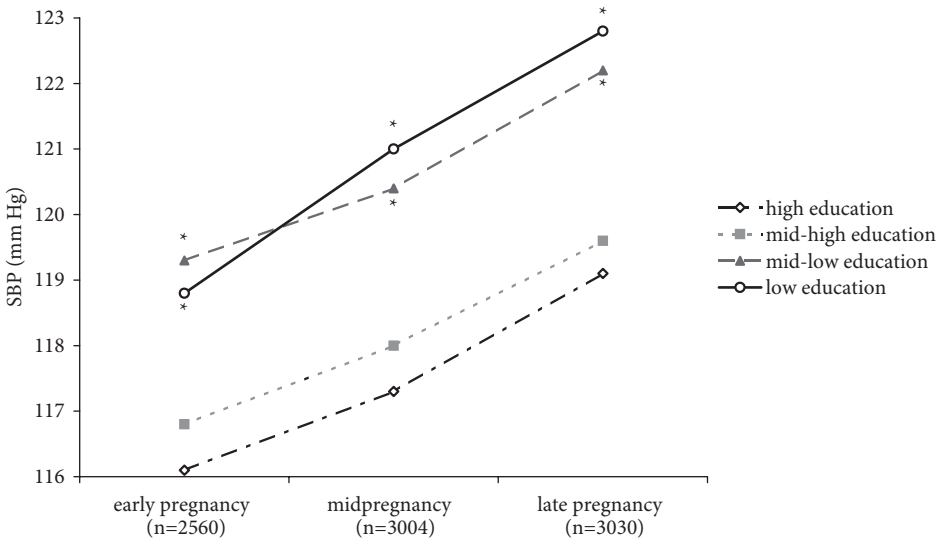

Figure 3.3 **Mean SBP in early, mid and late pregnancy, stratified by educational level. All values are adjusted for gestational age at time of blood-pressure measurement.** * Mean blood pressure significantly different from that in subgroup of women with high education at level p<0.001.

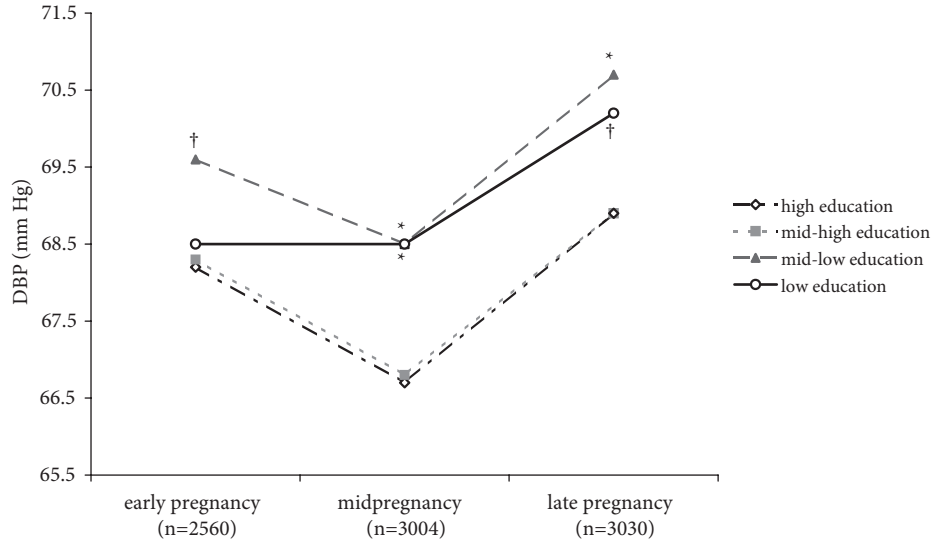

Figure 3.4 **Mean DBP in early, mid and late pregnancy, stratified by educational level. All values are adjusted for gestational age at time of blood-pressure measurement**. * Mean blood pressure significantly different from that in subgroup of women with a high education at level p<0.001. † Mean blood pressure significantly different from that in subgroup of women with a high education at level p<0.01.

Table 3.3 **Educational differences in blood pressure in early pregnancy** (n=3142)*.

Blood pressure	Mean difference (95% CI) in blood pressure in early pregnancy				
	Basic model†	Basic model† + BMI	Basic model† + smoking	Basic model† + alcohol	Full model‡
SBP (mm Hg)					
High education	Reference	Reference	Reference	Reference	Reference
Mid-high education	0.78 (-0.39,1.95)	0.47 (-0.65,1.59)	0.90 (-0.27,2.08)	0.70 (-0.47,1.87)	0.51 (-0.61,1.64))
Mid-low education	3.02 (1.83,4.21)	1.42 (0.28,2.56)	3.29 (2.09,4.50)	2.82 (1.62,4.01)	1.51 (0.35,2.67)
Low education	2.67 (1.27,4.07)	0.39 (-0.96,1.74)	3.27 (1.83,4.72)	2.34 (0.92,3.75)	0.63 (-0.78,2.04)
DBP (mm Hg)					
High education	Reference	Reference	Reference	Reference	Reference
Mid-high education	0.30 (-0.62,1.23)	0.05 (-0.82,0.92)	0.45 (-0.48,1.37)	0.23 (-0.70,1.16)	0.13 (-0.74,1.00)
Mid-low education	1.49 (0.55,2.44)	0.22 (-0.67,1.11)	1.83 (0.88,2.78)	1.29 (0.35,2.24)	0.41 (-0.49,1.31)
Low education	0.53 (-0.58,1.64)	-1.27 (-2.31,-0.22)	1.28 (0.14,2.41)	0.21 (-0.90,1.33)	-0.80 (-1.89,0.29)

* Data are derived from linear mixed models fitted on SBP and DBP.

† Basic model: adjusted for gestational age, maternal age, parity and twin pregnancy.

‡ Full model: Basic model + pre-pregnancy BMI, smoking and alcohol consumption at time of blood-pressure measurement.

Table 3.4 **Change in mean DBP from early to midpregnancy (and 95% confidence intervals), stratified by educational level** (n=3142)*

Educational level	Change in mean DBP in mm Hg (95% CI) from early to midpregnancy				
	Basic model†	Basic model† + BMI	Basic model† + smoking	Basic model† + alcohol	Full model‡
High education	-1.82 (-2.58,-1.05)	-1.82 (-2.59,-1.05)	-1.95 (-2.72,-1.17)	-1.93 (-2.70,-1.16)	-1.98 (-2.76,-1.21)
Mid-high education	-2.07 (-2.91,-1.24)	-2.04 (-2.88,-1.21)	-2.26 (-3.11,-1.40)	-2.21 (-3.05,-1.37)	-2.26 (-3.11,-1.41)
Mid-low education	-1.60 (-2.43,-0.77)	-1.59 (-2.42,-0.76)	-1.80 (-2.66,-0.93)	-1.76 (-2.59,-0.92)	-1.83 (-2.70,-0.96)
Low education	-0.38 (-1.33,0.58)‖	-0.34 (-1.30,0.61)‖	-0.61 (-1.66,0.44)§	-0.51 (-1.47,0.45)‖	-0.61 (-1.66,0.43)§

* Data are derived from linear mixed models fitted on DBP.

† Basic model: adjusted for gestational age, maternal age, parity and twin pregnancy.

‡ Full model: Basic model + pre-pregnancy BMI, smoking and alcohol consumption at time of blood-pressure measurement.

§ Significantly different from change in DBP in subgroup with high education at level $p<0.05$

‖ Significantly different from change in DBP in subgroup with high education at level $p<0.01$

with a high education ($p<0.01$). After additional adjustment for pre-pregnancy BMI, smoking and alcohol consumption (full model), the change in women with a low education was –0.61 mmHg (95% CI: -1.66, 0.43) and was still significantly different from that in women with a high education ($p<0.05$).

There were no educational differences in the change in mean DBP from mid to late pregnancy ($p\geq0.05$).

Additional logistic regression analyses (n=2441) showed that, relative to women who had a midpregnancy fall (n=1280; 52.4%), those in whom there was no fall (n=1161; 47.6%) tended to have a higher risk for subsequent development of preeclampsia (OR: 1.39; 95% CI: 0.71,2.79). Within the subgroup of women with low education (n=383), this OR was 3.8 (95% CI: 0.80,18.19).

DISCUSSION

This population-based prospective cohort study produces two major findings. First, relative to women with a high education, those with a low and a mid-low education had higher mean SBP and DBP levels from early pregnancy onwards. These differences were due largely to a higher pre-pregnancy BMI in women with a lower educational level. Second, even after adjusting for pre-pregnancy BMI, smoking and alcohol consumption during pregnancy, the fall in DBP one would normally expect in midpregnancy was not found in women with a low education. This absence of midpregnancy fall tended to be related to the development of preeclampsia, particularly in the subgroup of women with a low educational level.

Methodological considerations

The main strength of this study lies in its population-based prospective design, which was characterized by the enrollment of a large number of women early in pregnancy[14]. Repeated blood-pressure measurements during pregnancy with the use of a validated automated instrument enabled us to add to the literature by demonstrating that an indicator of SES is associated both with blood-pressure level and with the pattern of blood-pressure change during pregnancy.

To various extents, our results may have been influenced by the following limitations.

First, although the OMRON 907 device has been validated according to the Association for the Advancement of Medical Instrumentation (AAMI) Standard[23] as well as the preliminary criteria of the International Protocol (IP)[18], further validation studies using the final IP criteria

are needed to make definite statements about the accuracy of the device. Furthermore, during the day blood pressure varies according to a circadian rhythm[24]. We were unable to account for this, because our study did not include ambulatory blood-pressure measurements. These limitations probably introduced some random measurement error, which may have weakened the association between educational level and blood pressure. The presence of systematical bias, however, is unlikely, since we do not assume that inaccurate measurements or the influence of the circadian rhythm on blood pressure change differed systematically by educational level.

A second possible limitation is that, although the response rate among Dutch pregnant women in The Generation R Study was relatively high (68%)[25], there was also some selection towards a study population that was relatively highly educated and more healthy[14]. Because the sample size of the women with a low educational level was relatively small, the effect estimates regarding this subgroup had relatively wide confidence intervals. Therefore, the absence of a significant midpregnancy fall in this subgroup might be due to low precision. Future studies with larger sample sizes will have to confirm our findings.

The last possible limitation is that our information on relevant covariates – including pre-pregnancy weight, and smoking and alcohol consumption during pregnancy – was derived from questionnaires, which may have led to some misclassification. In The Generation R Study, however, weight was also measured at the research centers in early, mid and late pregnancy, and these measurements explained 94% of the variance of pre-pregnancy weight. This supports the validity of self-reported information on pre-pregnancy weight.

Educational level and blood pressure in early pregnancy

Previous studies in the general, non-pregnant population have described socioeconomic inequalities in blood pressure and essential hypertension[2 3]. A review by Colhoun et al.[2] showed that most studies conducted in developed countries found age-adjusted differences of about 2-3 mm Hg in mean SBP between the highest and lowest socioeconomic groups. This is in line with our results. In our study, educational differences in blood-pressure levels in early pregnancy were explained largely by educational differences in pre-pregnancy BMI. This indicates that the well-known socioeconomic gradient in overweight in women[26] is an important pathway through which educational inequalities in blood pressure during pregnancy arise.

Nonetheless, the known determinants of blood pressure that were included in our models were not able to fully explain the relatively high SBP in early pregnancy in women with a mid-low education. Part of the explanation must thus be provided by other determinants of blood pressure, such as physical activity, diet, or psychosocial stress[2].

Remarkably, blood pressure in early pregnancy was higher in women with a mid-low education than in those with a low education. However, this does not imply that the latter are better off than the former: in early pregnancy, women with a low education had the highest pulse pressure (i.e., the difference between SBP and DBP) (data not shown). An elevated pulse pressure is an indicator of poor arterial compliance, and is an additional risk indicator both for preeclampsia and for cardiovascular disease[27 28].

Educational level and diastolic blood-pressure change during pregnancy

In our study, women with a low educational level did not show a midpregnancy fall in DBP, even after adjustment for important determinants of blood pressure. In additional analyses, we also tested whether weight change between the pre-pregnancy period and early pregnancy, or that between early pregnancy and midpregnancy could explain the absence of a midpregnancy fall in these women; it did not (data not shown). Even when we restricted the analyses to normotensive pregnancies, the results did not change (data not shown). In healthy pregnancies, this fall is a physiological phenomenon that is triggered by a decrease in total peripheral vascular resistance, which is due in turn to vasodilatation starting in early gestation[29]. The lack of such a fall, which has been noted in preeclamptic patients, suggests failure of this normal cardiovascular adaptation to pregnancy due to endothelial dysfunction[10 12]. Recent studies have provided evidence that endothelial dysfunction, as indicated by a lower flow-mediated vasodilatation, precedes the development of preeclampsia, suggesting that endothelial dysfunction is a possible cause of preeclampsia[10 30].

The absence of a midpregnancy fall in DBP in women with a low educational level, which seemed to predispose them toward the development of preeclampsia, may therefore reflect an adverse effect of a low educational level on endothelial function, which in turn interferes with normal vascular adjustments to pregnancy. A key factor of endothelial function is vascular inflammation, and there is evidence that indicators of low SES are associated with higher levels of vascular inflammation markers[31]. This supports our hypothesis.

In conclusion, a low educational level as an indicator of a low SES is associated not only with higher blood-pressure levels from early pregnancy onwards, but also with the lack of a midpregnancy fall in DBP. In turn, the lack of such a fall seemed to predispose women toward the development of preeclampsia.

PERSPECTIVES

In subgroups of the population with a low SES, the findings presented here may have consequences for fetal, childhood and maternal health. Higher blood-pressure levels during pregnancy are related to impaired fetal growth, lower birth weight, and higher blood-pressure levels in the offspring[32 33]. Preeclampsia is also a leading cause of perinatal and maternal mortality. This underscores the need for programs and policies aimed at improving vascular health, particularly among women of low SES.

We speculate that, in women of low SES, the failure of DBP to fall is a sign of latent endothelial dysfunction which is manifested during pregnancy, and which may partly explain these women's susceptibility to preeclampsia[8 9]. This hypothesis may be confirmed by future studies on the role of measures of vascular function, e.g., flow-mediated vasodilatation[30], in the relationship between SES, blood pressure and hypertensive complications during pregnancy. If so, it will help us further understand the mechanisms underlying the socioeconomic gap in women's cardiovascular disease.

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Chapter 4

Maternal educational level and risk of gestational hypertension;

The Generation R Study

Based on: Silva LM, Coolman M, Steegers EAP, Jaddoe VWV, Moll HA, Hofman A, Mackenbach JP, Raat H. Maternal educational level and risk of gestational hypertension: the Generation R Study.

J Hum Hypertens. 2008 Jul;22(7):483-92.

ABSTRACT

We examined whether maternal educational level as an indicator of socioeconomic status is associated with gestational hypertension. We also examined the extent to which the effect of education is mediated by maternal substance use (i.e., smoking, alcohol consumption and illegal drug use), pre-existing diabetes, anthropometrics (i.e., height and body mass index (BMI)), and blood pressure at enrollment.

This was studied in 3262 Dutch pregnant women participating in The Generation R Study, a population-based cohort study. Level of maternal education was established by questionnaire at enrollment, and categorized into high, mid-high, mid-low and low. Diagnosis of gestational hypertension was retrieved from medical records using standard criteria. Odds ratios (OR) of gestational hypertension for educational levels were calculated, adjusted for potential confounders, and additionally adjusted for potential mediators.

Adjusted for age and gravidity, women with mid-low (OR: 1.52; 95% CI: 1.02,2.27) and low education (OR: 1.30; 95% CI: 0.80,2.12) had a higher risk of gestational hypertension than women with high education. Additional adjustment for substance use, pre-existing diabetes, anthropometrics and blood pressure at enrollment attenuated these ORs to 1.09 (95% CI: 0.70,1.69) and 0.89 (95% CI: 0.50,1.58) respectively. These attenuations were largely due to the effects of BMI and blood pressure at enrollment.

Women with relatively low educational levels have a higher risk of gestational hypertension, which is largely due to higher BMI and blood pressure levels from early pregnancy. The higher risk of gestational hypertension in these women is probably caused by pre-existing hypertensive tendencies that manifested themselves during pregnancy.

INTRODUCTION

Gestational hypertension is associated with perinatal morbidity, including preterm birth and fetal growth retardation[1 2]. It is characterized by *de novo* hypertension after the twentieth week of pregnancy without proteinuria, and complicates about 7-18% of first pregnancies and 4-9% of all pregnanies[1 3-5].

While little is known about the pathophysiology of gestational hypertension, studies have shown that it is associated with features of the metabolic syndrome[6] and with later development of essential hypertension and cardiovascular disease[7 8]. This suggests that these conditions may have similar pathologic mechanisms.

Known risk factors for gestational hypertension are high maternal age, twin pregnancy, pre-existing diabetes, obesity and high-normal blood pressure in early pregnancy[2 9]. In some studies, smoking during pregnancy has been associated with a lower risk of gestational hypertension[10 11].

Because low socioeconomic status is a marked risk factor for obesity, metabolic syndrome, hypertension and cardiovascular disease, [12-14] socioeconomic status is also likely to be associated with gestational hypertension. As early as the 1950s, researchers described associations between measures of socioeconomic status and hypertension during pregnancy[15-19]. However, most earlier studies focused primarily on preeclampsia, which is characterized by hypertension and proteinuria, and which is thought to have a different aetiology than gestational hypertension[20]. The results of these studies also conflict. For example, in 1955 Nelson studied maternal social class as measured by the husband's occupation in relation to the incidence of preeclampsia, and found no association[17]. In contrast, Davies et al., [15] and, more recently, Haelterman et al[16] found that, relative to women with a higher educational level, those with a low educational level had a higher risk of peeclampsia. We found only two studies that evaluated socioeconomic status in relation to isolated gestational hypertension[18 19]. Surprisingly, these found no associations, but this may have been due to the study design or to the chosen measures of socioeconomic status. For example, while these two studies used occupation of the woman's partner[18] and the woman's area of residence[19] as measures of socioeconomic status, such measures may not reflect all aspects of a pregnant woman's individual socioeconomic circumstances.

Given the adverse health consequences for the offspring of mothers with gestational hypertension, it is important for clinical practice and for public health policy to know whether socioeconomically disadvantaged women run a higher risk of gestational hypertension. Studying the association between socioeconomic status and gestational hypertension might also improve our insight into the causes of socioeconomic inequalities in women's cardiovascular health.

Working within the framework of The Generation R Study, a large birth-cohort study recruited prenatally [21], we studied the association between maternal educational level as an indicator of maternal socioeconomic status and gestational hypertension. We also examined whether such an association can be explained by the mediating effects of substance use (i.e., smoking, alcohol consumption and illegal drug use), pre-existing diabetes, and maternal anthropometrics and blood pressure at enrollment. We used level of maternal education as it has been found to be the strongest and most consistent socioeconomic predictor of cardiovascular health[22]. Since the literature indicates that socioeconomic disparities in hypertensive complications of pregnancy may differ between ethnic groups, the present study was restricted to an ethnically homogeneous population [23].

MATERIALS AND METHODS

The Generation R Study

The present study was embedded within The Generation R Study, a population-based prospective cohort study from fetal life until young adulthood. The Generation R Study has previously been described in detail[21 24]. Briefly, the cohort includes 9778 (response rate 61%) mothers and children of various ethnicities living in Rotterdam, the Netherlands[24]. While enrollment ideally took place in early pregnancy, it was possible until the birth of the child. All children were born between April 2002 and January 2006.

Assessments during pregnancy included physical examinations, ultrasound assessments and questionnaires, and took place in early pregnancy (gestational age <18 weeks), mid-pregnancy (gestational age 18-25 weeks) and late pregnancy (gestational age ≥25 weeks). The study was conducted in accordance with the guidelines proposed in the World Medical Association Declaration of Helsinki, and has been approved by the Medical Ethical Committee at the Erasmus MC, University Medical Center Rotterdam (Erasmus MC). Written consent was obtained from all participating parents.

Study population

Of the 9778 women, 91% (n=8880) were enrolled during pregnancy[24]. Women of Dutch ethnicity (n=4057) comprised the largest ethnic subgroup, and were selected for the analyses described below. A woman was classified as Dutch if she reported that both her parents had been born in the Netherlands[25]. Of the women who participated in this study with more than one pregnancy (8.3%), data on the second (n=332) or third pregnancy (n=5) were excluded from

analyses to avoid clustering. Women who had been included after 25 weeks of gestation (n=77) were also excluded, since we were mainly interested in the effects of maternal anthropometrics and blood pressure early in pregnancy. To restrict the study to adult pregnant women, women younger than 20 years of age (n=63) were excluded. We also excluded twin pregnancies (n=51), cases of induced abortion, fetal deaths before 20 weeks of gestation, women lost to follow-up (n=23), and women lacking information on their educational level (n=20), diagnosis of gestational hypertension (n=65), gravidity (n=5), anthropometrics (n=17), or blood pressure at enrollment (n=29). Finally, since this study focused on *de novo* and isolated hypertension in pregnancy, we excluded women with pre-existing hypertension and those who developed pre-eclampsia, eclampsia, or hemolysis, elevated liver enzyme and low platelet (HELLP) syndrome (n=108). This left 3262 women for analysis.

Educational level

On the basis of a questionnaire used at enrollment, we established the highest education achieved by each mother. This was categorized into four levels: 1.) high (university or PhD degree), 2.) mid-high (higher vocational training), 3.) mid-low (more than three years general secondary school, intermediate vocational training or first year of higher vocational training), and 4.) low (no education, primary school, lower vocational training, intermediate general school, or three years or less at general secondary school)[26].

Gestational hypertension

After each participant had given birth, the attending community midwife or obstetrician completed a delivery report. The reports on those participants who had given birth under the medical supervision of an obstetrician were selected and screened by a trained medical-record abstractor.

On the basis of documentation on the delivery report of any kind of hypertensive complication or fetal growth retardation, 398 women were suspected of having gestational hypertension. To confirm the presence of gestational hypertension, the same abstractor conducted detailed reviews of these women's hospital charts. Gestational hypertension was defined according to the criteria described by the International Society for the Study of Hypertension in Pregnancy (ISSHP)[27]: development of systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg without proteinuria after 20 weeks of gestation in previous normotensive women.

Potential mediators and confounders

Level of maternal education cannot directly affect the risk of gestational hypertension, but is likely to act through more proximal risk factors, so-called mediators[28]. We considered the following factors to be potential mediators in the pathway between maternal education and gestational hypertension: factors involving substance use, i.e., smoking, alcohol consumption and illegal drug use; pre-existing diabetes; maternal anthropometrics; and blood pressure at enrollment (figure 4.1). Categories are indicated below in parentheses.

Substance use

Smoking, alcohol consumption and illegal drug use, including marijuana, hashish, cocaine, heroin and ecstasy (never, before conception, until pregnancy was known, continued in pregnancy) were established using questionnaires in early, mid and late pregnancy.

Pre-existing diabetes

Presence of pre-existing diabetes (no, yes, unknown) was established by questionnaire at enrollment. Because we could not assume that women who answered "no" to this question had actually been tested for diabetes, we recoded "no" into "unknown".

Anthropometrics and blood pressure at enrollment

Maternal anthropometrics and blood pressure were measured at enrollment in one of the research centers. Height and weight were measured without shoes and heavy clothing, and body mass index (BMI) was calculated from height and weight (weight/height^2). BMI was categorized according to WHO standards into normal weight (<25 kg/m^2), overweight (25-30 kg/m^2), and obese (≥30 kg/m^2). Systolic and diastolic blood pressure were measured using an Omron 907® Automated Blood Pressure Monitor (OMRON Healthcare Europe B.V. Hoofddorp, the Netherlands)[29].

Gestational age at enrollment varied from 5.1 to 24.9 weeks, and was correlated with level of education. We therefore adjusted BMI and blood-pressure values for gestational age at time of measurement. First, we performed a separate linear regression analysis with gestational age at time of enrollment as predictor and BMI/blood pressure as outcome. Next, per woman, we added the difference between the fitted BMI/blood pressure value at the individual's gestational age at enrollment and the actual BMI/blood pressure observation to the fitted value at the population median gestational age at enrollment (14 weeks).

All models were adjusted for age and gravidity, treating them as potential confounders, since the effects of these factors in the association between maternal education and gestational

hypertension were not of primary interest in this study, and since they cannot be considered indisputable mediators (figure 4.1). Maternal age was assessed at enrollment in one of the research centers and categorized into four groups (20-25 years, 25-30 years, 30-35 years, ≥35 years). Gravidity (1st pregnancy, ³2nd pregnancy) was obtained through questionnaires at enrollment in the study.

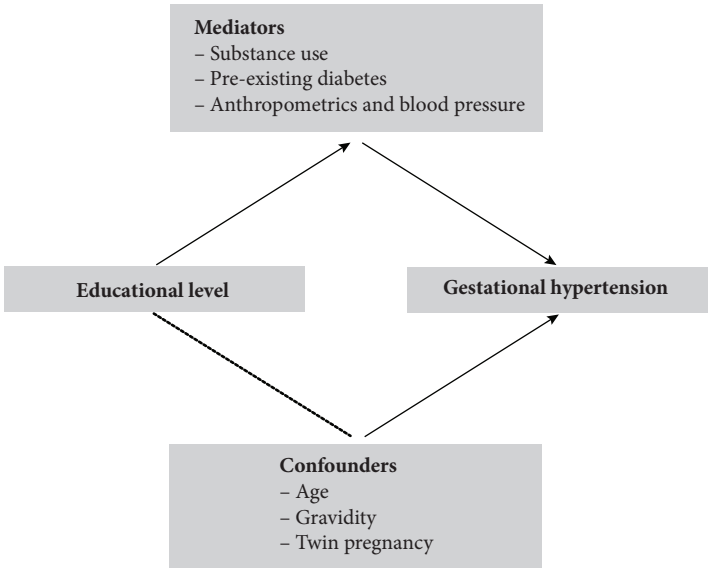

Figure 4.1 **Simplified conceptual framework for the association between maternal educational level and gestational hypertension.**

Statistical analyses

We assessed the frequency distribution of potential confounders and mediators according to educational level. Chi-squared tests for trend were used for categorical factors, and Spearman correlation coefficients for continuous factors.

Multivariate logistic regression was used to calculate the odds ratios (OR) of gestational hypertension and their 95% confidence intervals (CI) for levels of education after adjustment for the potential confounders (model 1), and after additional adjustment for potential mediators. The highest educational level was set as reference. Missing data on categorical factors were included as separate categories.

First, to evaluate the individual mediating effects of all potential mediators, these factors were added separately to model 1. For each adjustment, we calculated the percentage change in OR for the educational levels with a higher risk of gestational hypertension compared to the reference ($100x\{OR_{model\ 1} - OR_{+mediator}\}/\{OR_{model\ 1} - 1\}$). When the OR attenuated to lower than 1, the change was set at 100%. Factors that caused an attenuation of the OR were defined as mediators in the association between maternal education and gestational hypertension[30].

In the subsequent analyses, hierarchical logistic models[31] were built for two reasons: 1.) to evaluate the mediating effects of substance use, pre-existing diabetes, anthropometrics and blood pressure at enrollment in the association between maternal education and gestational hypertension; and 2.) their own effects on gestational hypertension, taking due account of the conceptual hierarchical relationships between these factors. We hypothesized that, as an indicator of socioeconomic status, maternal education was the factor most distal to gestational hypertension that might influence risk of gestational hypertension through substance use, pre-existing diabetes, anthropometrics and blood pressure at enrollment. In turn, substance use might influence gestational hypertension risk directly, or indirectly through diabetes[32] or changes in anthropometrics[33]. Finally, we hypothesized that pre-existing diabetes, height and BMI at enrollment might influence gestational hypertension risk directly, or indirectly through blood pressure changes[9].

For the logistic hierarchical models, we started with model 1, then added smoking, alcohol consumption and illegal drug use (model 2). To this model, we then added pre-existent diabetes, height and BMI at enrollment (model 3). In the final model (model 4), additional adjustment was made for systolic and diastolic blood pressure at enrollment.

All analyses were performed using the Statistical Package of Social Sciences version 11.0 for Windows (SPSS Inc, Chicago, IL, USA).

RESULTS

Of the 3262 women in the study, mean age was 31.3 years (SD: 4.3), 8.9% were between 20 and 25 years old, 17.6% were 35 years or older, and 53.6% were primigravida. The median gestational age at enrollment was 13.6 weeks (90% range: 10.9, 21.2). Participants gave birth at a median gestational age of 40.3 weeks (90% range: 37.1, 42.1); their children had a mean birth weight of 3492 grams (SD: 547.9).

Of all women, 16.3% had a low educational level and 32.6% had a high educational level (Table 4.1). Gestational hypertension developed in 180 women (5.5%); the respective

percentages for women with high, mid-high, mid-low and low education were 5.1%, 4.4%, 7.2% and 5.6% (chi-squared: 6.77; degrees of freedom: 3; p-value: 0.08).

Age, alcohol consumption in pregnancy and height were positively associated with level of education (p for trend <0.001). Gravidity, smoking and illegal drug use during pregnancy, BMI, systolic and diastolic blood pressure at enrollment were negatively associated with level of education (p for trend <0.05). Women with a mid-low educational level had the highest systolic and diastolic blood pressure values at enrollment (table 4.1).

Compared with women with high education, those with a mid-low and low education had a higher risk of gestational hypertension after adjustment for age and gravidity; those with a mid-low education had the highest risk (OR: 1.52; 95% CI: 1.02, 2.27; model 1, tables 4.2 and 4.3). The OR for women with a low educational level did not reach statistical significance (OR: 1.30; 95% CI: 0.80, 2.12).

Individual adjustment for each potential mediator resulted in +2% to –71% changes in the OR for mid-low education and +10% to -100% change in the OR for low education (table 4.2). The largest attenuations were caused by BMI, systolic and diastolic blood pressure at enrollment.

Table 4.3 presents the hierarchical logistic models fitted on gestational hypertension. Part of the effect of a mid-low and low educational level on gestational hypertension was mediated by substance use. When added to model 1, substance use, in particular alcohol consumption, attenuated the ORs by 21% and 63% to 1.39 (95% CI: 0.92, 2.11) and 1.11 (95% CI: 0.64, 1.92) respectively (model 2). While alcohol consumption tended to reduce the risk of gestational hypertension in this model, this effect was not significant. In contrast, smoking before conception was associated with a higher risk of gestational hypertension than never smoking was (OR: 1.68; 95% CI: 1.14, 2.46).

Pre-existing diabetes, height and BMI at enrollment further mediated more than half the effect of mid-low education (OR: 1.12; 95% CI: 0.73, 1.71; model 3) and all of the remaining effect of low education (OR: 0.83; 95%: 0.48, 1.44). This mediation was due mainly to BMI at enrollment. After adjustment for the other factors in model 3, overweight (OR: 2.43; 95% CI: 1.70, 3.46) and obesity (OR: 5.15; 95% CI: 3.34, 7.95) were significant risk factors for gestational hypertension. Systolic and diastolic blood pressure at enrollment, when added in model 4, further mediated the effect of mid-low education with 25% (in relation to model 3) to an OR of 1.09 (95% CI: 0.70, 1.69). This final OR for mid-low education corresponded with a total attenuation of 83% relative to model 1.

Table 4.1 **Distribution of general characteristics, substance use, pre-existing diabetes, anthropometrics and blood pressure at enrollment in the total study population and by educational level.**

	Level of maternal education					
	Total n=3262	**High n=1063 (32.6%)**	**Mid-high n=843 (25.8%)**	**Mid-low n=823 (25.2%)**	**Low N=533 (16.3%)**	**P for trend***
General characteristics						
Age, in years (mean, sd)	31.3 (4.3)	32.9 (3.2)	31.9 (3.8)	30.0 (4.5)	29.2 (5.0)	<0.001
Age, categorical						
20-25 years (%)	8.9	0.1	3.3	15.9	24.2	
25-30 years (%)	25.1	16.2	27.5	31.2	29.6	<0.001
30-35 years (%)	48.4	62.1	49.3	39.9	33.2	
≥35 years (%)	17.6	21.6	19.9	13.0	13.0	
Gravidity						
1st pregnancy (%)	53.6	56.4	56.1	55.3	41.3	<0.001
Parity						
Nulliparous (%)	64.6	64.9	67.9	67.1	55.0	0.004
Substance use						
Smoking						
Never (%)	49.4	59.7	52.9	45.8	29.1	
Before conception (%)	19.4	20.1	21.1	19.1	15.8	
Until pregnancy was known (%)	8.3	7.7	8.9	9.5	6.5	<0.001
Continued in pregnancy (%)	16.4	5.1	10.3	19.9	43.3	
Missing (%)	6.5	7.4	6.8	5.7	5.3	
Alcohol consumption						
Never (%)	13.1	3.4	9.9	17.8	30.0	
Before conception (%)	19.0	13.9	15.9	23.6	27.0	
Until pregnancy was known (%)	15.2	13.0	16.1	17.9	14.1	<0.001
Continued in pregnancy (%)	49.4	67.3	54.8	36.2	25.7	
Missing (%)	3.3	2.4	3.3	4.5	3.2	
Illegal drug use						
Never (%)	86.7	90.5	86.7	85.0	81.8	
Before conception (%)	4.4	1.8	5.0	5.8	6.7	
Until pregnancy was known (%)	2.1	0.6	1.8	1.7	6.2	<0.001
Continued in pregnancy (%)	0.8	0.1	0.3	1.3	1.9	
Missing (%)	6.0	7.0	6.2	6.2	3.4	

Table 4.1 Continued

	Level of maternal education					
	Total n=3262	**High n=1063 (32.6%)**	**Mid-high n=843 (25.8%)**	**Mid-low n=823 (25.2%)**	**Low N=533 (16.3%)**	**P for trend***
Pre-existing diabetes						
Unknown (%)	92.4	91.6	92.1	92.4	94.7	
Yes (%)	0.2	0.1	0	0.4	0.4	0.097
Missing (%)	7.4	8.3	7.9	7.2	4.9	
Anthropometrics and BP at enrollment						
Height, in cm (mean, sd)	170.7 (6.4)	171.4 (6.0)	171.3 (6.3)	170.6 (6.5)	168.9 (6.7)	<0.001
BMI†, in kg/m2 (mean, sd)	24.2 (4.0)	23.3 (3.1)	23.5 (3.3)	24.9 (4.5)	25.7 (5.0)	<0.001
BMI†, categorical						
Normal weight (%)	68.2	77.6	73.8	60.8	52.4	
Overweight (%)	23.3	18.8	21.9	26.1	29.8	<0.001
Obese (%)	8.5	3.6	4.3	13.1	17.8	
SBP†, in mm Hg (mean, sd)	117.4 (11.9)	116.0 (11.2)	116.3 (9.1)	119.1 (12.5)	118.6 (12.3)	<0.001
DBP†, in mm Hg (mean, sd)	68.5 (9.2)	68.0 (8.6)	68.3 (9.1)	69.4 (9.8)	68.5 (9.5)	0.017

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure.

* p-values are for chi-squared test for trend (categorical factors) or Spearman correlation coefficient (continuous factors).

† Values of body mass index and systolic and diastolic blood pressure at enrollment are adjusted for gestational age at enrollment.

Additionally, blood pressure mediated half the effect of overweight (OR: 1.70; 95% CI: 1.17, 2.45) and 72% of the effect of obesity (OR: 2.13; 95% CI: 1.31, 3.47) on gestational hypertension risk. Adjusted for all other factors in model 4, the risk of gestational hypertension increased significantly with increasing systolic (OR per mm Hg increase: 1.02; 95% CI: 1.00, 1.04) and diastolic blood pressure (OR per mm Hg increase: 1.07; 95% CI: 1.04, 1.09). The effect of smoking hardly changed after adjustment for BMI and blood pressure at enrollment.

Table 4.2 **Odds ratios, and change in odds ratios of gestational hypertension for the different levels of maternal education after individual adjustment for each potential mediating factor.**

Maternal education	High (n=1063) OR	Mid-high (n=843) OR (95% CI)	Mid-low (n=823) OR (95% CI)	Change a*	Low (n=533) OR (95% CI)	Change b*
Model 1. (includes maternal education, age, and gravidity)	1.00	0.87 (0.56,1.34)	1.52 (1.02,2.27)		1.30 (0.80,2.12)	
Substance use						
Model 1 + smoking	1.00	0.86 (0.55,1.32)	1.51 (1.01,2.25)	-2%	1.26 (0.76,2.11)	-13%
Model 1+ alcohol consumption	1.00	0.85 (0.55,1.31)	1.44 (0.95,2.16)	-15%	1.19 (0.71,1.98)	-37%
Model 1 + illegal drug use	1.00	0.87 (0.56,1.34)	1.52 (1.02,2.27)	-0%	1.33 (0.81,2.18)	+10%
Pre-existing diabetes						
Model 1 + pre-existing diabetes	1.00	0.87 (0.56,1.34)	1.52 (1.02,2.27)	-0%	1.30 (0.79,2.11)	-0%
Anthropometrics and BP at enrollment						
Model 1+ height	1.00	0.87 (0.56,1.34)	1.53 (1.02,2.27)	+2%	1.31 (0.80,2.14)	+3%
Model 1+ BMI (categorical)	1.00	0.83 (0.54,1.28)	1.15 (0.76,1.74)	-71%	0.87 (0.53,1.45)	-100%
Model 1 + SBP	1.00	0.81 (0.52,1.26)	1.26 (0.84,1.90)	-50%	1.10 (0.66,1.81)	-67%
Model 1 + DBP	1.00	0.83 (0.53,1.29)	1.31 (0.87,1.98)	-40%	1.18 (0.70,1.96)	-40%

OR: odds ratio; CI: confidence interval; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure.

* Change a and change b represent the respective changes in odds ratio for mid-low and low education relative to model 1 after individual adjustment for potential mediators ($100x[OR_{\text{model 1}} - OR_{+mediator}]/[OR_{model\ 1} - 1]$). Since the subgroup with mid-high education did not have a higher risk of gestational hypertension than the subgroup with high education, changes in odds ratio for mid-high education are not presented.

Table 4.3 **Hierarchical logistic regression models fitted on gestational hypertension.**

	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)
Maternal education				
High (ref)	1.00	1.00	1.00	1.00
Mid-high	0.87 (0.56,1.34)	0.83 (0.54,1.29)	0.81 (0.52,1.25)	0.79 (0.50,1.24)
Mid-low	1.52 (1.02,2.27)	1.39 (0.92,2.11)	1.12 (0.73,1.71)	1.09 (0.70,1.69)
Low	1.30 (0.80,2.12)	1.11 (0.64,1.92)	0.83 (0.48,1.44)	0.89 (0.50,1.58)
Substance use				
Smoking				
Never (ref)		1.00	1.00	1.00
Before conception		1.68 (1.14,2.46)	1.63 (1.10,2.40)	1.70 (1.14,2.53)
Until pregnancy was known		1.20 (0.67,2.16)	1.20 (0.66,2.16)	1.41 (0.77,2.58)
Continued in pregnancy		1.28 (0.79,2.09)	1.21 (0.74,1.97)	1.35 (0.81,2.24)
Missing		1.41 (0.48,4.11)	1.53 (0.48,4.85)	1.58 (0.46,5.48)
Alcohol consumption				
Never (ref)		1.00	1.00	1.00
Before conception		0.89 (0.53,1.49)	1.01 (0.59,1.70)	1.02 (0.60,1.76)
Until pregnancy was known		0.85(0.49,1.48)	1.00 (0.56,1.76)	1.07 (0.59,1.91)
Continued in pregnancy		0.68 (0.41,1.13)	0.86 (0.52,1.45)	0.97 (0.57,1.64)
Missing		0.50 (0.15,1.70)	0.59 (0.17,2.08)	0.71 (0.20,2.54)
Illegal drug use				
Never (ref)		1.00	1.00	1.00
Before conception		1.11 (0.56,2.20)	1.36 (0.68,2.72)	1.39 (0.68,2.81)
Until pregnancy was known		0.48 (0.11,2.01)	0.59 (0.14,2.52)	0.67 (0.16,2.91)
Continued in pregnancy		0.66 (0.09,5.06)	0.59 (0.07,4.68)	0.68 (0.08,5.47)
Missing		1.13 (0.37 (3.47)	1.45 (0.39,5.43)	1.54 (0.37,6.35)
Pre-existing diabetes				
Unknown (ref)			1.00	1.00
Yes			1.49 (0.16,14.13)	1.27 (0.13,12.67)
Missing			0.69 (0.20,2.34)	0.60 (0.17,2.19)

Table 4.3 Continued

	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)
Anthropometrics and BP at enrollment				
Height			1.01 (0.99,1.04)	1.00 (0.98,1.03)
BMI				
Normal weight (ref)			1.00	1.00
Overweight			2.43 (1.70,3.46)	1.70 (1.17,2.45)
Obese			5.15 (3.34,7.95)	2.13 (1.31,3.47)
SBP				1.02 (1.00,1.04)
DBP				1.07 (1.04,1.09)

CI: confidence interval; ref: reference category; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure

Model 1: Adjusted for age and gravidity

Model 2: Model 1 + smoking, alcohol consumption and illegal drug use

Model 3: Model 2 + pre-existing diabetes, height and body mass index at enrollment

Model 4: Model 3 + systolic and diastolic blood pressure at enrollment (full model)

DISCUSSION

This study showed that women with relatively low levels of education had a higher risk of gestational hypertension than women with a high level. This higher risk was explained by unequal distributions of known risk factors for gestational hypertension across educational levels, particularly by the higher rates of overweight and obesity and the relatively high blood pressure levels at enrollment found in lower educated women.

Methodological considerations

The main strength of this study lies in its population-based prospective design, in which a large number of women were enrolled early in pregnancy. The detailed information available on known risk factors for gestational hypertension enabled us to explain much of the association we observed between maternal education and gestational hypertension. Furthermore, the use of a conceptual hierarchical framework afforded insight into the interrelationships between maternal education and mediators, and their combined effects on gestational hypertension.

An additional strength was the use of medical chart review and applied standard international criteria for a consistent definition of gestational hypertension.

Although other measures of socioeconomic status exist, such as income level and occupational class[34], for our study we selected maternal educational level as a main indicator of socioeconomic status. We did this for two reasons:

1) not only does educational level partly reflect material resources because it structures occupation and income, it also reflects non-economic social characteristics, such as general and health-related knowledge, literacy, problem-solving skills and prestige[35 36];
2) educational level has also been shown to be the strongest and most consistent socioeconomic predictor of cardiovascular health[22].

To various extents, our results may have been influenced by the following limitations.

First, the response rate among pregnant Dutch women in The Generation R Study was relatively high (68%)[37], but there was some selection towards a relatively high educated, and healthier study population[24].

Second, review of delivery reports and hospital charts was restricted to women who had been referred for delivery under medical care. However, in Dutch practice, community midwives often remain responsible for the care of women with a diastolic blood pressure between 90 and 100 mm Hg, provided that proteinuria does not develop. In the event of a diastolic blood pressure between 95 and 100 mmHg, they are required to consult an obstetrician. All women with gestational hypertension with a diastolic blood pressure over 100 mm Hg should receive antenatal care and give birth in the hospital under the supervision of an obstetrician. Our study may therefore have missed mild cases of gestational hypertension with a diastolic blood pressure up to 100 mm Hg.

Third, in all logistic models, we adjusted for gravidity, to take account of the protective effect of a previous pregnancy, including those which ended in spontaneous abortions. Although a woman's risk of gestational hypertension is highest during her first pregnancy, the literature indicates that a change of partner between pregnancies may cause the risk to revert towards the same level as a primigravida[38]. Unfortunately, in this study we had no information on change of partners between pregnancies.

Finally, our study may have been vulnerable to misclassification, particularly with regard to substance-use factors, which were measured using questionnaires. Similarly, in accordance with the Dutch Standard Classification[25], we assigned a Dutch ethnicity to a participant if both her parents had been born in the Netherlands. However, when identifying immigrant descent in Dutch residents, this classification goes no further than the second generation. The number

of third-generation immigrants is nonetheless likely to have been very small and not to have affected our conclusions.

Comparison with other studies

Socioeconomic differences in blood pressure and prevalence of hypertension have been consistently reported among the general, adult population[14 39]. According to a review by Colhoun, Hemingway and Poulter[39], most studies performed in developed countries associate indicators of low socioeconomic status with higher blood pressures; these associations are stronger in women than in men, and are largely explained by socioeconomic differences in BMI.

Hypertension during pregnancy, particularly preeclampsia, has also been associated with level of education as a measure of socioeconomic status [15 16]. However, two studies that evaluated the association between indicators of socioeconomic status and isolated gestational hypertension[18 19] did not find an association. Although this contrasts with our own findings, the discrepancy in both cases is probably due to differences in study design or in exposure definition. One study[18] depended on retrospective data and had to deal with a large amount of missing data. The same study also primarily used occupation of the women's partners as an indicator of maternal socioeconomic status – which, because it reflects other aspects of socioeconomic status, may therefore influence risk of gestational hypertension differently than maternal education does. The second study[19] examined an area-based measure of socioeconomic status in relation to occurrence of gestational hypertension. However, an area-based measure of socioeconomic status is unlikely to fully capture health risks that are associated with socioeconomic status at an individual level.

Educational level and risk of gestational hypertension

Relative to women with a high educational level, those with a low educational level and those with a mid-low educational level had, respectively, a 30% and 52% higher risk of gestational hypertension. The finding that the highest risk was not found in women with the lowest educational level somewhat weakens the evidence for a firm conclusion that maternal education level is negatively associated with gestational hypertension risk. However, this finding was probably attributed to chance; women with low education comprised the smallest subgroup, and the difference in gestational hypertension incidence between mid-low and low educated women was not statistically significant (7.2% versus 5.6%; chi-squared: 1.25; degrees of freedom:1; p-value: 0.263).

Another hypothetical explanation for this finding is that women with a low education received better medical care, due for example to their coverage under social medicine schemes. However, this is unlikely: in the Netherlands, obligatory health insurance ensures equal primary prenatal care for everyone.

Referral bias is a third possible explanation. As previously discussed, mild cases of gestational hypertension were not necessarily referred to an obstetrician. If women with a low education with gestational hypertension were more likely to remain under a midwife's care, these cases may have been selectively missed in our study.

The last possible explanation is the selection bias that would have resulted if low educated women who did not participate in this study had a higher risk of gestational hypertension than low educated women who did participate. However, among the participants we found a clear linear trend across educational levels in a variety of other factors, such as smoking, alcohol consumption and BMI. This makes selection bias less likely.

Mediating mechanisms

Most of the higher risk of gestational hypertension in women with mid-low and low education was mediated by relatively high rates of overweight and obesity at enrollment in these subgroups. While obesity is an important risk factor for gestational hypertension, the underlying biological mechanism is not completely clear. A recent study suggested that obesity most increases the risk of gestational hypertension through higher blood-pressure levels[9]. Our results indeed suggest that at least half the effect of overweight and obesity acts through relative increases in blood pressure early in pregnancy. In women with a mid-low education, relatively high blood pressure levels at enrollment further contributed independently of BMI to the explanation of their increased risk of developing gestational hypertension.

Blood pressure in early pregnancy has been shown to be positively associated with the risk of gestational hypertension, even when it is within the normal range[9]. Normal pregnancy is characterized by hemodynamic changes, which cause a steady decrease in blood pressure in the first half of pregnancy, followed by a rise in blood pressure in the second half until delivery[40]. It is plausible that the higher the blood pressure is at the start of pregnancy, the higher the blood pressure will be when hemodynamic demands increase in the second half of pregnancy, and the sooner blood pressure will cross the threshold level of hypertension.

The higher risk of gestational hypertension in women with mid-low and low education was explained to a lesser extent by lower rates of alcohol consumption before and during pregnancy. This was due to a trend shown in our data towards a protective effect on gestational

hypertension of alcohol consumption, which seemed to act through changes in BMI and blood pressure. Moderate alcohol consumption is known to lower blood pressure and to reduce the risk of development of essential hypertension in the non-pregnant population[41]. It is unknown whether moderate alcohol consumption during pregnancy has a similar effect on gestational hypertension.

Maternal smoking and illegal drug use did not contribute an explanation of the effects of a mid-low and low educational level. Remarkably, we observed that smoking before conception and during pregnancy tended to increase the risk of gestational hypertension, significantly so for smoking before conception. This is in contrast with many other studies which reported that women who smoke during pregnancy have a lower risk of gestational hypertension than women who have never smoked[11]. However, with regard to the effect of smoking before conception, studies have shown conflicting results. Zhang et al.[42] found that past smoking was associated with a lower risk of gestational hypertension, whereas a more recent study by England et al.[10] showed that women who smoked before pregnancy did not have a lower risk.

In non-pregnant women, cessation of smoking has been associated with a higher risk of hypertension than continued smoking or never smoking[43], a finding that appears to support our results. Further study is needed to confirm a similar association between cessation of smoking and gestational hypertension.

Implications and conclusions

It has been postulated that gestational hypertension is a "sign of latent hypertension unmasked by pregnancy"[44]. The present study supports this hypothesis. The educational subgroups with the highest risk of gestational hypertension had the highest blood pressure values at enrollment, and their increased risk of gestational hypertension was almost entirely explained by factors that are also associated with essential hypertension[45]. These findings suggest that the relatively high risk of gestational hypertension in women with relatively low levels of education may reflect pre-existing hypertensive tendencies that are disclosed by the physiological stress of pregnancy.

We conclude that a relatively low educational level is associated with a higher risk of gestational hypertension. The educational inequalities observed in gestational hypertension may represent an early manifestation of the socioeconomic differences in morbidity and mortality from cardiovascular disease in women[13]. Strategies to reduce educational inequalities in gestational hypertension should be aimed primarily at reducing the burden of overweight and obesity in lower socioeconomic groups.

SUMMARY TABLE

What is known about this topic

- Gestational hypertension is associated with perinatal morbidity and with hypertension and cardiovascular disease later in the mother's life.
- Socioeconomic disadvantage is associated with a higher prevalence of hypertension and cardiovascular disease, especially among women.

What this study adds

- Women with a relatively low educational level have a higher risk of gestational hypertension, which is largely due to higher body mass index and blood pressure levels from early pregnancy.
- This higher risk of gestational hypertension in women with a relatively low educational level probably reflects pre-existing hypertensive tendencies that are disclosed during pregnancy.
- Our findings may represent an early manifestation of the marked socioeconomic gap in cardiovascular disease in women.

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Chapter 5

Low educational level is a risk factor for gestational diabetes;

Results from a prospective cohort study

Based on: Silva LM, Murray SE, Steegers EAP, Jaddoe VWV, Moll HA, Hofman A, Mackenbach JP, Raat H. Low educational level is a risk factor for gestational diabetes; results from a prospective cohort study.

Submitted

ABSTRACT

Objective: To investigate whether maternal educational level is associated with gestational diabetes, and to what extent risk factors for gestational diabetes mediate the effect of educational level.

Study Design and Setting: We examined data of 7025 pregnant women participating in a population-based cohort study in Rotterdam, the Netherlands. Highest achieved education was categorized into five levels. Diagnosis of gestational diabetes was retrieved from delivery records. Odds ratios (OR) of gestational diabetes were calculated for levels of education, adjusting for confounders and potential mediators.

Results: Adjusted for ethnicity, age and parity, women in the lowest educational level were three times more likely to develop gestational diabetes than women in the highest level (OR 3.15; 95% CI: 1.24, 7.90). Additional adjustment for family history of diabetes, smoking and alcohol use attenuated the OR to 2.46 (95% CI: 0.94, 6.45). The addition of body mass index (BMI) further attenuated the OR to 1.69 (95 % CI: 0.64, 4.47).

Conclusion: Low maternal educational level is a risk factor for gestational diabetes. This effect was largely mediated by known risk factors for gestational diabetes, most notably BMI These findings support the importance of diabetes screening and healthy-lifestyle support for pregnant women of low socioeconomic status.

INTRODUCTION

Gestational diabetes mellitus is associated with various adverse maternal and infant outcomes such as preeclampsia and fetal macrosomia, and negatively affects childhood growth and glucose regulation[1-3]. As the worldwide prevalence of diabetes, which includes gestational diabetes, is predicted to rise from 2.8% in 2000 to 4.4% in 2030[4], health complications associated with exposure to maternal hyperglycemias during pregnancy will also increase. One such study, conducted in North America[5], has investigated the growing rate of childhood diabetes and has attributed much of the increased prevalence of childhood type 2 diabetes in the last 30 years to increased exposure to gestational diabetes, thus perpetuating the cycle of this costly disease.

As numerous studies have shown, obesity is a major risk factor in the development of gestational diabetes[6 7], followed by age[8], family history of diabetes, personal history of abnormal glucose tolerance and ethnicity[9-11]. Identifying other risk factors that contribute to the development of gestational diabetes is critical to understanding some of the mechanisms responsible for the increasing rates of obesity and type 2 diabetes in youth. Low socioeconomic status, as indicated by educational level, occupational class or income level, has been identified by many studies as a major risk factor in the development of type 2 diabetes[11 12]. However, markedly fewer studies have examined the association between measures of socioeconomic status and gestational diabetes. One such study conducted in Turin, Italy determined low socioeconomic status, assessed by educational level and employment, to be a risk factor in the development of gestational diabetes[13]. However, the results were based on a relatively small case-control study and further studies are needed to confirm the results of such findings within a larger study population. Furthermore, it is unclear to what extent other risk factors for gestational diabetes contribute to the association between socioeconomic status and gestational diabetes.

Therefore, within The Generation R study, which is a large prenatally recruited birth-cohort study with extensive assessments during pregnancy[14], we examined whether educational level as indicator of maternal socioeconomic status is associated with risk for gestational diabetes. We also evaluated to what extent risk factors for gestational diabetes, i.e. family history of diabetes, smoking and alcohol use, and body mass index (BMI), contribute to the explanation of any association between educational level and gestational diabetes. We did this by applying a conceptual framework using a hierarchical approach[15], which enabled us to handle the hierarchical interrelationships between the risk factors.

In this study, maternal educational level was used as indicator of maternal socioeconomic status, since level of education has been linked to greater differentiation in health outcomes than other socioeconomic factors[16].

METHODS

The Generation R Study

This study was embedded in The Generation R Study, a population-based prospective cohort study from fetal life until young adulthood. The Generation R Study has been described previously in detail[14 17]. Briefly, the cohort includes 9778 (response rate 61%) mothers and their children of different ethnicities living in Rotterdam, the Netherlands[14]. Enrollment was aimed in early pregnancy but was possible until birth of the child. All children were born between April 2002 and January 2006. Assessments in pregnancy, including physical examinations, ultrasound assessments and questionnaires, were planned in early pregnancy (gestational age <18 weeks), midpregnancy (gestational age 18-25 weeks) and late pregnancy (gestational age ≥25 weeks). The study was conducted in accordance with the guidelines proposed in the World Medical Association Declaration of Helsinki and has been approved by the Medical Ethical Committee of the Erasmus MC, University Medical Center Rotterdam. Written consent was obtained from all participating parents.

Study Population

Of the 9778 women, 8880 (91%) were enrolled in pregnancy and eligible for the present analysis[14]. We excluded from the analyses women with missing information on educational level (n=817) and on diagnosis of gestational diabetes (n=365). We also excluded women with self-reported pre-existing diabetes (n=31), twin pregnancies (n=85), and induced abortions (n=18), leaving 7564 subjects. Of the women who participated with more than one pregnancy, data on the second or third pregnancy (n=483) were left out of the analyses to avoid clustering. Additionally, women with missing information on parity (n=8) or BMI (n=48) were excluded, leaving 7025 subjects for analysis.

Educational Level Assessment

Using a questionnaire at enrollment, the highest education achieved by mother was established, and was categorized into five educational levels: high (university or PhD degree), mid-high (higher vocational training), middle (more than 3 years general secondary school, intermediate

vocational training), mid-low (lower vocational training, intermediate general school, or 3 years, or less general secondary school), and low education (no education, primary school)[18].

Diagnosis of Gestational Diabetes

Gestational diabetes was diagnosed by a community midwife or an obstetrician according to Dutch midwifery and obstetric guidelines using the following criteria: random glucose level >11.0 mmol/L, fasting glucose ≥7.0 mmol/l or a fasting glucose between 6.1 and 6.9 mmol/L with a subsequent abnormal glucose tolerance test. The presence of gestational diabetes was retrieved from birth records after delivery. In the Netherlands it is advised that, in case of gestational diabetes, antenatal care and delivery takes place under the responsibility of an obstetrician.

Potential mediators and confounders

Level of maternal education cannot affect the risk for gestational diabetes directly but is likely to act through more proximal risk factors, so-called mediators[19]. We considered the following factors to be potential mediators in the pathway between maternal education and gestational diabetes (figure 5.1). Categories are indicated in parentheses.

Family History

History of diabetes (no, yes, do not know) in a first degree relative was retrieved from the first questionnaire.

Substance use during pregnancy

Smoking and alcohol consumption (no, yes until pregnancy was known, yes continued during pregnancy) was assessed by questionnaire in early, mid- and late pregnancy.

Body mass index

Height and weight were measured without shoes and heavy clothing at enrollment in one of the research centers. Body mass index (BMI) was calculated from height and weight (weight/height^2), adjusted for gestational age at time of enrollment, and categorized into normal weight (<25 kg/m^2), overweight (25-30 kg/m^2), and obese (≥30 kg/m^2) according to WHO standards.

All models were adjusted for maternal ethnicity, age and parity; since these factors cannot be considered indisputable mediators, we treated them as potential confounders in our study (figure 5.1)[19]. Ethnicity (Dutch and other European, Moroccan, Turkish, Dutch Antillean,

Surinamese, Capeverdian, and Other) was documented at enrollment by questionnaire and classified according to the Dutch Standard Classification[20]. Maternal age was assessed at enrollment in one of the research centers. Parity (in this study defined as number of previous live births (0, ≥1) was obtained from questionnaire at time of enrollment.

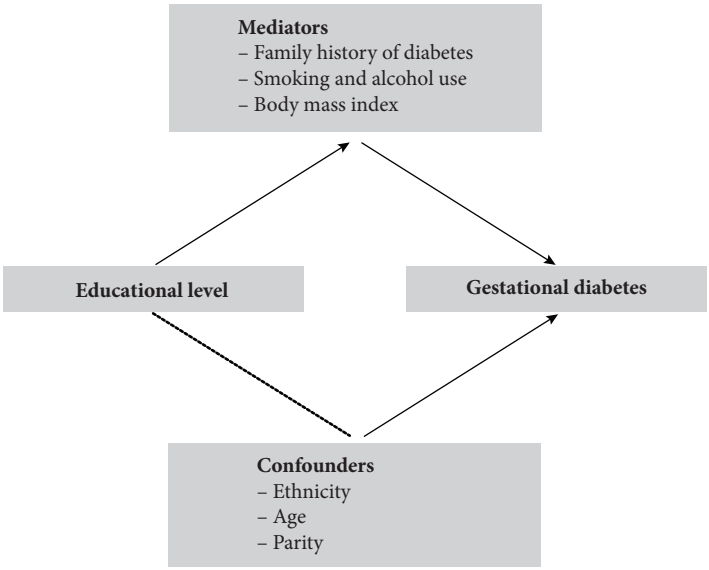

Figure 5.1 **Simplified conceptual framework for the association between maternal educational level and gestational diabetes.**

Statistical Analyses

We established the frequency distribution by educational level of potential confounders and mediators. Chi-squared tests were used to test trends across educational levels for categorical factors, and one-way analysis of variance (ANOVA) for continuous factors.

Missing data on categorical factors (affecting less than 3%) were recoded and included in the reference level.

Multiple logistic regression was used to calculate odds ratios (OR) for gestational diabetes and the corresponding 95% confidence intervals (CI) for levels of education, adjusted for the confounding effects ethnicity, age and parity (model 1), and additionally adjusted for potential mediators. The highest educational level was used as reference. Possible interaction

between ethnicity and educational level was tested in the form of an interaction term and added to the final model if the term was statistically significant.

First, the individual mediating effects of all potential mediators were evaluated by individual addition to model 1. For each adjustment, the percentage change in OR relative to model 1 for the educational level with the highest risk for gestational diabetes was calculated ($100x \{OR_{model\ 1} - OR_{+mediator}\}/\{OR_{model\ 1} - 1\}$). We defined factors that caused an attenuation of the OR as mediators in the association between socioeconomic status and gestational diabetes[15 21].

Second, hierarchical logistic models[15] were constructed to asses the effects of family history of diabetes, substance use and BMI on the association of maternal education with gestational diabetes, accounting for the hierarchical relationships between these factors. Maternal education as an indicator of socioeconomic status has been identified in this study as the most distal factor to gestational diabetes, which may influence risk for gestational diabetes through family history of diabetes, substance use and BMI. A positive family history of diabetes, which may indicate a genetic predisposition to develop diabetes, has been associated both with a low socioeconomic status[12], as well as an increased risk for development of gestational diabetes[22]. Substance use is partly determined by socioeconomic status and may also influence the risk for gestational diabetes directly or indirectly through changes in BMI. Finally, BMI is the most temporally proximal factor to gestational diabetes and may be influenced by all other potential mediators[6 22].

The logistic hierarchical models began with model 1, to which family history of diabetes was added (model 2). Smoking and alcohol consumption were added to model 2 (model 3). In the final model (model 4) additional adjustment was made for BMI.

A p-value of 0.05 was taken to indicate statistical significance. All analyses were completed through the use of Statistical Package of Social Sciences version 11.0 for Windows (SPSS Inc, Chicago, IL, USA).

RESULTS

Of the 7025 women in the study, the mean age was 29.7 years (SD: 5.3) and 60.8% were nulliparous. The median gestational age at enrollment was 15.5 weeks (90% range: 10.9, 22.9). Women delivered at a median gestational age of 40.1 weeks (90% range: 36.9, 42.1) with a mean birth weight of 3406.9 grams (SD: 560.8).

Table 5.1 **Distribution of age, parity, ethnicity, family history of diabetes, smoking and alcohol use, and body mass index in the total study population and by educational level (n=7025)*.**

		Level of maternal education					
	Total N=7025	**High N=1540 (21.9%)**	**Mid-high N=1331 (18.9%)**	**Middle N=2195 (31.2%)**	**Mid-low N=1127 (16.0%)**	**Low N=832 (11.8%)**	**P for trend†**
General characteristics							
Age (years)	29.7 (5.3)	32.8 (3.4)	31.3 (4.1)	28.6 (5.1)	27.0 (5.5)	27.7 (5.9)	<0.001
Parity							
0 (%)	60.8	65.8	67.7	63.5	56.1	39.8	<0.001
≥1 (%)	39.2	34.2	32.3	36.5	43.9	60.2	
Ethnicity							
Dutch + other European (%)	57.2	82.8	73.7	48.2	45.7	22.8	
Moroccan (%)	6.4	1.0	3.2	6.9	10.1	15.1	
Turkish (%)	9.2	1.8	4.1	10.4	10.7	26.1	
Surinamese (%)	9.2	1.6	5.5	13.4	15.6	9.4	<0.001
Dutch Antillean (%)	3.6	0.6	2.2	4.9	5.4	5.3	
Capeverdian (%)	4.2	0.3	1.7	5.6	6.7	8.3	
Other (%)	10.2	11.8	9.6	10.6	5.7	13.0	
Family history of diabetes							
No (%)	81.4	87.9	87.0	79.6	75.1	73.4	
Yes (%)	16.2	11.2	11.8	17.3	21.6	22.0	<0.001
Do not know (%)	2.5	0.9	1.2	3.1	3.4	4.6	
Substance use							
Smoking							
No (%)	75.6	85.5	80.7	74.1	60.7	69.6	
Until pregnancy was known (%)	7.2	7.7	8.4	7.4	6.4	4.6	<0.001
Continued during pregnancy (%)	17.2	4.8	10.9	18.5	32.9	25.8	
Alcohol use							
No (%)	52.1	25.8	39.4	60.2	67.2	79.3	
Until pregnancy was known (%)	11.3	11.9	14.1	12.3	10.5	3.6	<0.001
Continued during pregnancy (%)	36.6	62.2	46.4	27.5	22.4	17.1	
BMI (continuous) (kg/m^2)‡	24.6 (4.5)	23.4 (3.2)	23.9 (3.7)	24.9 (4.7)	25.7 (5.4)	25.6 (4.9)	<0.001
BMI (categorical)‡							
Normal weight (%)	63.5	75.5	69.9	60.8	53.4	52.2	
Overweight (%)	25.1	20.5	23.6	25.8	28.2	29.7	<0.001
Obese (%)	11.4	4.0	6.5	13.4	18.4	18.1	

* Values are means (with standard deviation) for continuous factors or percentages for categorical factors.
BMI: body mass index. † P-values are for chi-squared tests for trend (categorical factors) or for (linear) trend component of one-way analysis of variance (continuous factors). ‡ Values of BMI at enrollment are adjusted for gestational age at enrollment.

From the total study population, 11.8% were in the lowest educational level and 21.9% were in the highest educational level (Table 5.1). Gestational diabetes was diagnosed in 68 women (1.0%). Stratified by educational level, these percentages were 0.6%, 0.8%, 1.0%, 1.1% and 1.6% for women of high, mid-high, middle, mid-low and low education respectively.

Age and alcohol use during pregnancy were positively associated with level of education (p for trend <0.001) while parity, family history of diabetes, smoking during pregnancy, and BMI (p for trend <0.001) were negatively associated with level of education.

Table 5.2 **Odds ratios (with associated 95% confidence interval) and change in odds ratios of gestational diabetes for the different levels of maternal education after individual adjustment for each potential mediator (n=7025).**

	Level of maternal education				
	High N=1540 (21.9%)	**Mid-high N=1331 (18.9%)**	**Middle N=2195 (31.2%)**	**Mid-low N=1127 (16.0%)**	**Low N=832 (11.8%)**
Model 1	1.00	1.40 (0.50, 3.33)	2.02 (0.92, 4.43)	2.28 (0.92, 5.58)	3.15 (1.24, 7.90)
Model 2	1.00	1.42 (0.61, 3.38)	1.96 (0.89, 4.30)	2.20 (0.89, 5.40)	3.04 (1.20, 7.71)
Change 1*					+ 5.1%
Model 3	1.00	1.42 (0.59, 3.38)	2.06 (0.93, 4.54)	2.34 (0.94, 5.85)	3.22 (1.25, 8.30)
Change 2*					- 3.3%
Model 4	1.00	1.30 (0.54, 3.09)	1.67 (0.76, 3.80)	1.82 (0.73, 4.53)	2.49 (0.97, 6.4)
Change 3*					- 30.7%
Model 5	1.00	1.24 (0.52, 2.95)	1.44 (0.65, 3.19)	1.45 (0.58, 3.61)	1.99 (0.74, 5.11)
Change 4*					- 53.9%

Model 1: Baseline model adjusted for ethnicity, age and parity
Model 2: Model 1 + family history of diabetes
Model 3: Model 1 + smoking
Model 4: Model 1 + alcohol use
Model 5: Model 1 + body mass index
* Change in OR for low education in relation to Model 1 after individual adjustment for potential mediators:
Change 1 = ((OR Model 1 - OR Model 2) / (OR Model 1-1))*100%
Change 2 = ((OR Model 1 - OR Model 3) / (OR Model 1-1))*100%
Change 3 = ((OR Model 1 - OR Model 4) / (OR Model 1-1))*100%
Change 4 = ((OR Model 1 - OR Model 5) / (OR Model 1-1))*100%

Compared to women with high education, women with low education had a significantly increased risk for gestational diabetes after adjustment for ethnicity, age and parity (OR 3.15; 95% CI: 1.24, 7.90) (model 1, tables 5.2 and 5.3).

Additional individual adjustment for potential mediators resulted in a change of the OR for low education ranging from + 5.1% to –53.9% (table 5.2). The greatest attenuation was due to adjustment for BMI (-53.9%) (model 5, table 5.2).

Table 5.3 **Hierarchical logistic models fitted on gestational diabetes (n=7025)**

	Model l OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)
Maternal education				
High (ref)	1.00	1.00	1.00	1.00
Mid-High	1.40 (0.59,3.33)	1.42 (0.60,3.38)	1.33 (0.56,3.18)	1.18 (0.64,4.47)
Middle	2.02 (0.92,4.43)	1.96 (0.89,4.30)	1.68 (0.75,3.77)	1.25 (0.55,2.83)
Mid-Low	2.28 (0.93,5.58)	2.20 (0.89,5.40)	1.80 (0.71,4.62)	1.22 (0.47,3.14)
Low	3.15 (1.24,7.90)	3.04 (1.20,7.71)	2.46 (0.94,6.45)	1.69 (0.64,4.47)
	Change 1*	**Change 2***	**Change 3***	
	- 5.1 %	**- 28.4 %**	**- 52.7%**	
Family history of diabetes				
No (ref)	1.00	1.00	1.00	
Yes	1.92 (1.09,3.38)	1.93 (1.09,3.39)	1.66 (0.94,2.93)	
Do not know	2.43 (0.73,8.10)	2.48 (0.74,8.29)	2.98 (0.89,10.00)	
Smoking				
No (ref)		1.00	1.00	
Until pregnancy was known		0.50 (0.12,2.09)	0.48 (0.11,2.01)	
Continued during pregnancy		0.94 (0.48,1.83)	0.93 (0.48,1.82)	
Alcohol use				
No (ref)		1.00	1.00	
Until pregnancy was known		0.56 (0.21,1.46)	0.60 (0.23,1.57)	
Continued during pregnancy		0.51 (0.27,0.95)	0.59 (0.31,1.09)	
Body mass index				
Normal weight (ref)			1.00	
Overweight			3.65 (1.99,6.78)	
Obese			6.48 (3.34,12.57)	

OR: odds ratio; CI: confidence interval; ref: reference category

Model 1 : Baseline model adjusted for ethnicity, age and parity

Model 2 : Model 1 + family history of diabetes

Model 3 : Model 2 + smoking and alcohol use

Model 4: Model 3 + body mass index

* Represents the change in odds ratio for low education as the variables are added in a hierarchical fashion:

Change 1: $((OR_{Model\ 1} - OR_{Model\ 2})/ (OR_{Model\ 1} - 1))*100\%$

Change 2: $((OR_{Model\ 2} - OR_{Model\ 3})/ (OR_{Model\ 2} - 1))*100\%$

Change 3: $((OR_{Model\ 3} - OR_{Model\ 4})/ (OR_{Model\ 3} - 1))*100\%$

Table 5.3 contains hierarchical logistic models fitted on gestational diabetes. A small part of the effect of low education on occurrence of gestational diabetes was mediated by family history of diabetes, which attenuated the OR with 5.1% to 3.04 (95% CI: 1.20, 7.71) when added to model 1 (model 2). A positive family history of diabetes was associated with an increased risk for gestational diabetes within this model (OR: 1.92; 95% CI: 1.09, 3.38). The addition of smoking and alcohol in model 3 further mediated 28.4% of the effect of low education to an OR of 2.46 (95% CI: 0.94, 6.45). This attenuation was primarily due to the effect of alcohol use. Smoking and in particular alcohol use tended to reduce the risk for gestational diabetes in this model, but these effects were not significant. Model 4 included BMI, which led to the greatest attenuation of the OR by 52.7% to 1.69 (95% CI: 0.64, 4.47). Adjusted for the other factors in model 4, overweight (OR: 3.65; 95% CI: 1.99, 6.78) and obesity (OR: 6.48; 95% CI: 3.34, 12.57) were strong risk factors for gestational diabetes. The interaction term of educational level and ethnicity was added to model 4; however, no statically significant interaction was present and thus was left out of the model.

DISCUSSION

Results from this study indicate that a low educational level as indicator of a low socioeconomic status is associated with a three times higher risk for developing gestational diabetes compared with a high educational level. The mediating effects of family history of diabetes, substance use, and BMI explained a great part of the increased risk, most notably BMI.

Methodological considerations

The main strength of this study lies in the population-based prospective design, in which a large number of women were enrolled early in pregnancy, and information on relevant potential confounders and mediators was available. Therefore it was possible to include indicators of known risk factors for gestational diabetes in the explanatory models[6 8 22]. When studying the contribution of these known risk factors to the explanation of the effect of educational level on gestational diabetes risk, treating all risk factors as temporally and hierarchically equivalent might produce misleading results[15]. Therefore, we did not simply add all risk factors simultaneously to the model, but rather took account of the interrelationships between them by using a conceptual hierarchical framework. This approach generally helps to interpret results in the light of social and biological knowledge.

Socioeconomic status refers to the "social and economic factors that influence what positions individuals or groups hold within the structure of society"[23]. It is a multifactorial construct. The most frequently used indicators of socioeconomic status are educational level, income level and occupational class[23 24]. In this study, we used educational level as single indicator of maternal socioeconomic status. Education is an important determinant of employment and economic circumstances, and thus reflects material resources but also non-economic social characteristics, such as general and health-related knowledge which influences health behaviour, literacy, problem-solving skills and prestige[23 24]. Furthermore, level of education has been linked to greater differentiation in health outcomes than other socioeconomic indicators[16].

Some limitations should also be recognized. First, our findings can only be generalized to other populations with caution. The percentages of women with lower educational levels were somewhat lower than expected from the general population[14].

Second, while the diagnostic criteria used to identify cases of gestational diabetes in this study compare well to those used by the American Diabetes Association[25], some cases of gestational diabetes may have been missed, as suggested by the relatively low incidence of gestational diabetes[26]. This was because measurement of blood glucose levels was not a standard prenatal procedure. Although presence of glucosuria is routinely tested, measurements of blood glucose levels are usually performed when glucose intolerance is suspected based on for example polydipsia, polyuria or macrosomia. Cases of gestational diabetes without overt symptoms might have remained unrecognized by the prenatal caregiver and consequently not been included in our study, leading to a reduction of power to detect associations between risk factors and gestational diabetes.

Third, the use of regression adjustment to assess mediation has been criticized, since the required assumptions on causality cannot be verified. Furthermore, the percentage change can be similar for different absolute changes in effect estimates[27]. However, as there do not appear to be alternative methods that overcome these problems, this method is a helpful approach to investigate the contribution of risk factors to socioeconomic differences in health[28 29].

Finally, information on educational attainment and most of the included risk factors were collected using questionnaires, which might have induced some misclassification.

Comparisons with other studies

Our results are comparable with findings of a case-control study performed in Turin, Italy[13], which reported that women with primary school education had an increased risk for gestational

diabetes (OR 1.87; 95% CI: 1.1-3.2) compared to women of a higher educational level, after adjustment for age, BMI, parental diabetes, and previous pregnancies. The smaller OR in our final model is probably due to the fact that we also adjusted for alcohol use, which contributed to the attenuation of the association between educational level and gestational diabetes.

Mediating Mechanisms

The largest part of the increased risk for gestational diabetes in low-educated women was explained by relatively high rates of overweight and obesity in this subgroup. Excess adipose tissue has been demonstrated to lead to the release of free fatty acids, which are involved in the development of insulin resistance during pregnancy. When accompanied by dysfunction of pancreatic cells, blood glucose levels can become unstable, resulting in the development of diabetes[30]. Mechanisms linking obesity to the development of diabetes illustrate the need to reduce the burden of overweight and obesity through lifestyle changes in lower socioeconomic groups.

Relatively low rates of alcohol use in lower educated subgroups contributed substantially to the explanation of the increased risk for gestational diabetes among low-educated women. This was because, although not statistically significant, alcohol consumption was associated with a reduced risk for gestational diabetes in our data. While alcohol consumption is generally acknowledged to have a protective effect on the development of type 2 diabetes by enhancing insulin production[31], we found no published studies describing a similar effect of alcohol consumption on gestational diabetes. Residual confounding by other unmeasured lifestyle factors such as dietary habits might be driving the reduction in risk for gestational diabetes with alcohol consumption during pregnancy.

A positive family history of diabetes explained only 5% of the effect of low education and therefore hardly contributed to the explanation of the increased risk for gestational diabetes associated with low education.

Although smoking is an established risk factor for type 2 diabetes[32] and was more prevalent among lower educated women than higher educated women in our study, smoking did not contribute to mediation of the effect of low education. In contrast to what was expected, smoking, in particular in the first trimester, tended to reduce the risk for gestational diabetes, although the reduction was not significant. Thus, the specific role of smoking in the development of gestational diabetes has yet to be clarified.

In total, family history of diabetes, substance use, and body mass index explained most, but not all of the association between educational level and gestational diabetes. Additional

data that were not available at the present time in The Generation R Study, including dietary and physical-activity patterns, are also likely to be implicated in the association between socioeconomic status and gestational diabetes, and should be the focus of further study.

Conclusions

Several previous studies have demonstrated the link between higher degrees of social deprivation and adverse health outcomes, including the development of type 2 diabetes[11 12]. Our study extends these findings by demonstrating that among women of lower socioeconomic status the incidence of gestational diabetes is also higher, which is mainly due to higher rates of overweight and obesity. Since a hyperglycemic intrauterine environment has been implicated in the pathogenesis of type 2 diabetes later in life[33], socioeconomic inequalities in gestational diabetes may contribute to the maintenance of the increased burden of type 2 diabetes in lower socioeconomic subgroups. Our findings support the importance of diabetes screening and healthy-lifestyle support for pregnant women of low socioeconomic status. Early identification and prevention programs within high-risk subgroups may aid in reducing the alarming increase in gestational diabetes, and consequently, type 2 diabetes.

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Part II:

Socioeconomic status and health of the unborn child

Chapter 6

Mother's educational level and fetal growth; the genesis of health inequalities

Based on: Silva LM, Jansen PW, Steegers EAP, Jaddoe VWV, Arends LR, Tiemeier H, Verhulst FC, Moll HA, Hofman A, Mackenbach JP, Raat H. Mother's educational level and fetal growth; the genesis of health inequalities.

Submitted

ABSTRACT

Objectives: To study level of maternal education (high, mid-high, mid-low and low) and its association with fetal weight, head circumference, abdominal circumference, and femur length, measured in different periods of pregnancy. Main hypotheses: low maternal education is associated with a slower fetal growth and equally affects different parts of the fetal body.

Design: Population-based prospective cohort study (The Generation R Study).

Setting and participants: Pregnant women living in Rotterdam, the Netherlands, who gave birth between April 2002 and January 2006. Analyses were restricted to 3545 pregnant women with a Dutch ethnicity and available data.

Main outcome measures: Fetal weight, head circumference, abdominal circumference and femur length, measured with ultrasound in mid and late pregnancy.

Results: In fetuses of women with low education relative to those of women with high education, fetal growth was slower, leading to a lower fetal weight that was statistically significant from late pregnancy onwards. In these fetuses, growth of the head (-0.16 mm/week; 95% CI: -0.25 to 0.07), abdomen (-0.10 mm/week; 95% CI: -0.21 to 0.01) and femur (-0.03 mm/week; 95% CI: -0.05 to 0.005) were all slower; from midpregnancy onwards, head circumference was significantly smaller, and from late pregnancy onwards, femur length was also significantly smaller. The negative effect of low education was greatest for head circumference (difference in standard-deviation score in late pregnancy: -0.26; 95% CI: -0.36 to 0.16). This effect remained statistically significant even after adjustment for various potential mediators (adjusted difference: -0.14; 95% CI: -0.25 to 0.03).

Conclusion: Low maternal education impairs fetal growth and appears to affect growth of the fetal brain more than that of peripheral and abdominal tissues. This might have consequences for later cognitive ability, educational attainment and job performance for the offspring of low-educated mothers.

INTRODUCTION

Fetal growth is an important determinant of future health[1-5]. An impaired fetal growth increases the risk of perinatal and neonatal death[1], and of various medical and developmental problems in childhood[3 4 6]. Furthermore, there is accumulating evidence that poor fetal growth is associated with chronic diseases in adult life, particularly cardiovascular diseases[2 5].

Fetal growth is determined by a complex interplay of genetic and environmental factors[7]. One important environmental factor is socioeconomic status, as indicated by educational level, income level or occupation. Compared with women of high socioeconomic status, those of low socioeconomic status give birth to babies with a lower birth weight[8 9]. These socioeconomic inequalities in birth weight suggest that factors related to a low socioeconomic status of the mother impair fetal growth[9]. Until now, only one study actually related socioeconomic status to direct measures of fetal growth rather than size at birth[10]. However, the authors used an area-based index of socioeconomic status rather than an individual-based measure, and studied fetal-growth characteristics measured only in midpregnancy, which limited the possibility to assess fetal-growth patterns. Because prospective population-based studies on the effect of maternal socioeconomic status on fetal growth trajectories are lacking, it is not known whether 1) socioeconomic differences in fetal growth are constant over time, 2) from which moment onwards differences in fetal size become apparent, and 3) whether low socioeconomic status equally affects different parts of the fetal body.

Therefore, among pregnant women participating in a population-based cohort study, we studied level of maternal education as an indicator of socioeconomic status and its association with fetal weight, head circumference, abdominal circumference, and femur length, measured in different periods of pregnancy. Assuming that a low maternal education is associated with a slower fetal growth, we expected that educational differences in fetal size can be observed from late pregnancy onwards, since in that period inter-individual variability in fetal size is highest[11]. Because available data suggest that socioeconomic status does not affect proportionality at birth[12], we hypothesized head circumference, abdominal circumference, and femur length to be equally affected by low maternal education.

METHODS

The Generation R Study

The present study was embedded within The Generation R Study, a population-based prospective cohort study from fetal life until young adulthood. The Generation R Study has previously been described in detail[13]. Briefly, all mothers with an expected delivery date between April 2002 and January 2006 and living in Rotterdam, the Netherlands, were eligible for participation in the study. While enrollment ideally took place in early pregnancy, it was possible until after the birth of the child. In total, 9778 mothers of various ethnicities and their children were included and followed-up (participation rate 61%)[13].

Assessments during pregnancy took place in early pregnancy (gestational age <18 weeks), midpregnancy (gestational age 18-25 weeks) and late pregnancy (gestational age ≥25 weeks). The study was conducted in accordance with the guidelines proposed in the World Medical Association Declaration of Helsinki, and has been approved by the Medical Ethical Committee at the Erasmus University Medical Center Rotterdam. Written consent was obtained from all participating parents.

Study population

Of the 9778 women, 91% (n=8880) were enrolled during pregnancy[13]. Because educational inequalities in pregnancy outcome may differ between ethnic groups[14], we restricted the present analyses to women with a Dutch ethnicity (n=4057). A woman was classified as Dutch if she reported that both her parents had been born in the Netherlands[15]. For several reasons, 512 women were excluded from analysis (figure 6.1), leaving a study population of 3545 women.

Educational level

At enrollment, we used a questionnaire to establish the highest education achieved by each mother. This was categorized into four levels: 1.) high (university degree), 2.) mid-high (higher vocational training), 3.) mid-low (>3 years general secondary school, intermediate vocational training), and 4.) low (no education, primary school, lower vocational training, intermediate general school, or 3 years or less general secondary school)[16].

Fetal ultrasound measurements and birth weight

Trained sonographers carried out fetal ultrasound measurements in early, mid and late pregnancy, which were used to establish gestational age and to measure fetal-growth characteristics[17]. For

the analyses presented below, we used the measurements in mid and late pregnancy of head circumference, abdominal circumference and femur length, as measurements in early pregnancy were intended primarily for pregnancy dating. All growth characteristics were measured to the nearest millimetre using standardized procedures[18]. The estimated fetal weight was calculated on the basis of head circumference, abdominal circumference and femur length[19]. For the models for estimated fetal weight, we also used information on birth weight and gestational age at birth, which was obtained from midwife and hospital registries. Longitudinal growth curves and gestational-age adjusted standard-deviation (SD) scores were constructed for all growth measurements[17].

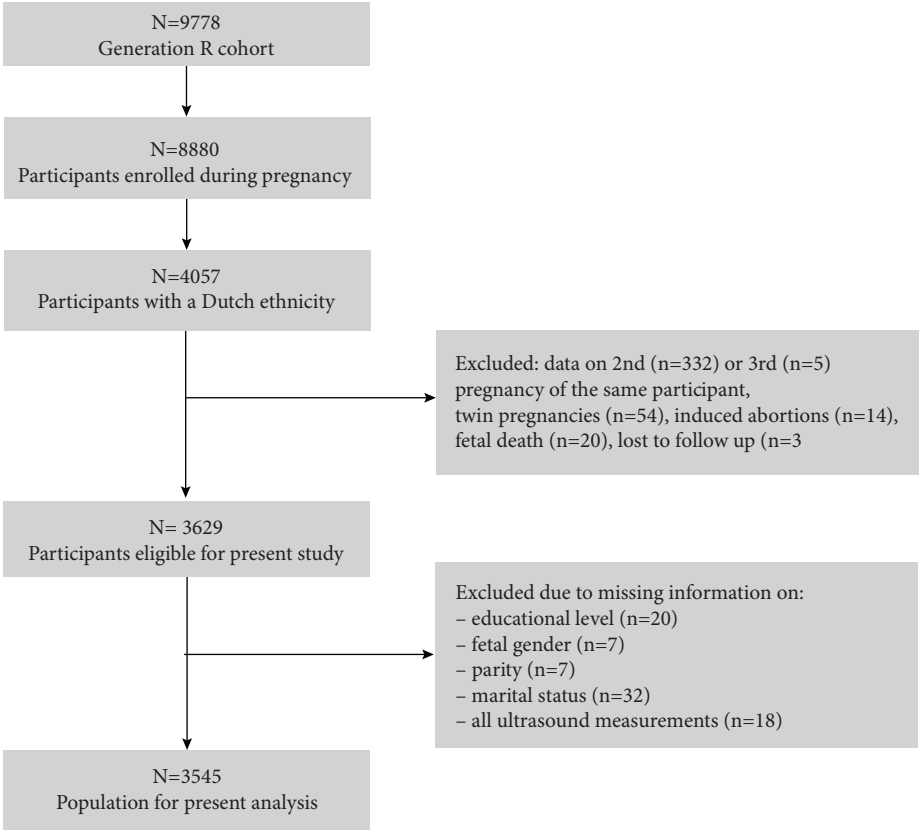

Figure 6.1 **Flow chart participants**

Covariates

Any effect of educational level on fetal growth is probably an indirect one, acting through other more proximal determinants of fetal growth, so-called mediators[20]. The factors listed below were included in this study as potential mediators, because these factors have been shown to contribute significantly to explaining socioeconomic inequalities in size at birth[8].

Maternal anthropometrics

Maternal height was measured in the research centers. Pre-pregnancy weight was established at enrollment through questionnaire. On the basis of height and pre-pregnancy weight (weight/height^2) we calculated pre-pregnancy body mass index (BMI).

Smoking

Through questionnaires in early, mid and late pregnancy, we obtained information on smoking during pregnancy (no, until pregnancy was known, continued in pregnancy).

Psychosocial and material factors

Using questionnaires during pregnancy we established marital status (married/cohabiting, single motherhood), whether the pregnancy was planned (yes, no), and the presence of financial difficulties (yes, no).

All models were adjusted for fetal gender, and maternal age and parity. As we did fetal gender, we treated maternal age and parity as potential confounders, since they cannot be considered indisputable mediators[20]. Information on fetal gender was obtained from midwife and hospital registries. Maternal age was established at enrollment in the study. Parity, which in this study was defined as the number of previous live births (0, ≥1), was obtained through a questionnaire at enrollment.

Statistical analyses

We started by evaluating the effect of educational level on overall fetal growth, after which we separately analysed the associations of educational level with head circumference, abdominal circumference and femur length. These associations were examined using longitudinal multilevel analysis, as this type of analysis takes account of the correlation between repeated measures on the same subject and allows for incomplete outcome data[21]. The best fitting model to predict each growth characteristic as a function of gestational age was built using fractional polynomials[22]. To these models we added educational level as a main determinant

Table 6.1 **General characteristics in the total study population and by maternal educational level (n=3545)*.**

	Maternal education					
	Total (n=3545)	**High (n=1109)**	**Mid-high (n=877)**	**Mid-low (n=925)**	**Low (n=634)**	**P for trend†**
Pregnancy characteristics						
Maternal age (years)	31.1 (4.6)	32.9 (3.2)	31.9 (3.8)	30.0 (4.8)	28.6 (5.6)	<0.001
Parity (% nullipara)	65.0	64.3	68.1	68.1	57.3	0.049
Infant gender (% girls)	49.6	49.6	49.6	50.7	47.8	0.706
Gestational age at birth (median in weeks, 95% range)	40.3 (35.7,42.4)	40.3 (35.9,42.4)	40.3 (36.3,42.4)	40.1 (35.9,42.3)	39.9 (34.3,42.3)	<0.001
Birth weight (grams)	3470.5 (561.6)	3538.6 (538.9)	3509.5 (547.8)	3448.5 (563.8)	3329.0 (589.3)	<0.001
Maternal anthropometrics						
Height (cm)	170.7 (6.4)	171.4 (6.0)	171.3 (6.3)	170.5 (6.4)	168.8 (6.7)	<0.001
Pre-pregnancy weight (kg)‡	67.8 (12.4)	66.4 (9.7)	66.9 (11.3)	69.2 (13.3)	69.8 (15.9)	<0.001
Pre-pregnancy BMI (kg/m^2)‡	23.3 (4.0)	22.5 (2.9)	22.7 (3.5)	23.8 (4.4)	24.4 (5.3)	<0.001
Smoking						
No (%)	68.7	80.4	74.3	65.3	45.6	
Until pregnancy known (%)	8.0	7.8	9.0	8.8	6.0	
Continued during pregnancy (%)	17.3	5.1	10.7	20.1	43.5	<0.001
Missing (%)	6.0	6.7	5.9	5.8	4.9	

Table 6.1 Continued

	Maternal education					
	Total (n=3545)	**High (n=1109)**	**Mid-high (n=877)**	**Mid-low (n=925)**	**Low (n=634)**	**P for trend†**
Psychosocial and material factors						
Pregnancy was planned						
No (%)	18.1	9.4	14.7	21.5	33.0	<0.001
Missing (%)	5.4	5.5	6.3	4.4	5.2	
Marital status (% single)	8.2	3.5	4.6	8.8	20.3	<0.001
Financial difficulties						
Yes (%)	10.7	4.1	8.3	12.5	22.7	<0.001
Missing (%)	11.8	5.9	5.8	13.4	27.9	

BMI: body mass index

* Values are means (with standard deviations) or medians (with 95% range) for continuous factors, or percentages for categorical factors.

† p-values are for chi-squared test for trend (categorical factors), and for (linear) trend component of one-way analysis of variance or kruskall-wallis test (continuous factors).

‡ Data on pre-pregnancy weight and pre-pregnancy BMI was missing in 13.2%.

(reference: high education), and an interaction term of educational level with gestational age. The best-fitting model structures are presented in annex 6.1. These models were based on 10387 observations for fetal weight and birth weight, 6845 for head circumference, 6876 for abdominal circumference, and 6882 for femur length.

Using the same strategy, additional models were constructed for the SD scores for each growth characteristic (annex 6.1*).* To evaluate educational differences in fetal size, SD scores were compared between educational subgroups at specific time-points in pregnancy, i.e. at 20, 30 and 40 weeks for estimated fetal weight, and at 20 and 30 weeks for head circumference, abdominal circumference, femur length.

For each growth characteristic, we started with a model that included the confounders (basic model). Next, this model was additionally adjusted for the potential mediators (fully adjusted model) to establish to what extent educational differences in fetal growth or size could be explained by these factors.

For each covariate, an interaction term with gestational age was tested for significance. If the test was significant, these interactions were retained in the model. A p-value of 0.05 was taken to indicate statistical significance; for interaction terms we used a p-value of 0.10. Because additional interaction terms between educational level and covariate*gestational age would lead to difficult to interpret results, these were not included in the models.

To handle missing values in the covariates (all ≤13%, see table 6.1) we applied multiple imputation based on five imputed data sets ('PROC MI' procedure in SAS 9.1.3)[23]. Imputations were based on the relationships between all covariates included in this study.

Statistical analyses were performed using Statistical Package of Social Sciences version 15.0 for Windows (SPSS Inc, Chicago, IL, USA) and the Statistical Analysis System (SAS) for Windows (SAS Institute Inc, USA), version 9.1.3.

RESULTS

Table 6.1 shows a description of the study population. Of the 3545 women in this study, 17.9% were in the lowest educational level and 31.3% in the highest. Compared with women with a high education, those with a low education were younger, shorter, heavier before pregnancy, less likely to be nulliparous, and gave birth to lighter babies; they were also more likely to smoke during pregnancy (p for trend for all <0.05).

The mean values for the fetal-growth characteristics at the median gestational ages in mid and late pregnancy are presented in annex 6.2.

Educational level and estimated fetal weight

Relative to fetuses of women in the highest educational subgroup, those of women with mid-high, mid-low and low education had a slower fetal growth (figure 6.2). Fetal growth rate was lowest in the fetuses of women with a low educational level, and the difference in fetal growth rate increased as pregnancy progressed. Women with a low educational level had significantly smaller fetuses from 30 weeks onwards (difference at 30 weeks: -0.16 SD; 95% CI: -0.25,-0.08; table 6.2). This difference became larger towards term (difference at 40 weeks: -0.35 SD; 95% CI: -0.46,-0.24). After adjustment for the potential mediators, the educational differences in estimated fetal weight attenuated, but at 40 weeks they remained statistically significant.

Educational level and head circumference, abdominal circumference and femur length

Educational level was associated with growth of the fetal head, abdomen and femur, with the slowest growth in the lowest educational subgroup (table 6.3). Relative to fetuses of women with a high educational level, in fetuses of women with a low educational level growth of the head was on average 0.16 mm/week slower (95% CI: -0.25,-0.07), growth of the abdomen 0.10 mm/week slower (95% CI: -0.21, 0.01) and that of the femur 0.03 mm/week slower (95% CI: -0.05,-0.005). Adjustment for the potential mediators attenuated the difference in head growth and that in femur growth, but not the difference in abdominal growth. The largest attenuations were due to the adjustment for smoking, followed by maternal height (data not shown). The difference in head growth remained statistically significant after full adjustment.

Table 6.4 presents the educational differences in size of the fetal head, abdomen and femur at 20 and 30 weeks gestation, expressed in SD-scores. Compared with fetuses of women with a high educational level, those of women with a low educational level had a significantly smaller head circumference from 20 weeks onwards; femur length was significantly smaller from 30 weeks onwards (basic models). Although abdominal circumference was also smaller in these fetuses, the difference did not reach statistical significance. The effect of low education was larger for head circumference than for femur length or abdominal circumference. After adjustment for the potential mediators, only the difference in SD score for head circumference at 30 weeks gestation remained significant.

Table 6.2 **Associations between maternal educational level and standard deviation scores for estimated fetal weight at 20, 30 and 40 weeks gestation (n=3545).**

	Difference in standard deviation score (and 95% CI) for estimated fetal weight at 20 weeks gestation	
Educational level	Basic model*	Fully adjusted†
High	Reference	Reference
Mid-high	0.02 (-0.07,0.11)	0.02 (-0.07,0.12)
Mid-low	0.08 (-0.01,0.17)	0.07 (-0.02,0.17)
Low	0.02 (-0.09,0.13)	0.05 (-0.07,0.17)
	Difference in standard deviation score (and 95% CI) for estimated fetal weight at 30 weeks gestation	
Educational level	**Basic model***	**Fully adjusted†**
High	Reference	Reference
Mid-high	-0.009 (-0.08,0.06)	0.002 (-0.07,0.07)
Mid-low	-0.03 (-0.10,0.05)	-0.01 (-0.09,0.06)
Low	-0.16 (-0.25,-0.08)	-0.07 (-0.16,0.02)
	Difference in standard deviation score (and 95% CI) for estimated birth weight at 40 weeks gestation	
Educational level	**Basic model***	**Fully adjusted†**
High	Reference	Reference
Mid-high	-0.04 (-0.13,0.05)	-0.02 (-0.11,0.06)
Mid-low	-0.13 (-0.22,-0.04)	-0.10 (-0.19,-0.008)
Low	-0.35 (-0.46,-0.24)	-0.18 (-0.29,-0.07)

Values are based on multilevel models. CI: confidence interval. * Basic model: adjusted for fetal gender, and maternal age and parity. † Fully adjusted: adjusted for fetal gender, maternal age and parity, maternal height, pre-pregnancy BMI, smoking during pregnancy, single motherhood, whether the pregnancy was planned and financial difficulties. The following covariate*gestational age interactions were also included: gender*gestational age, gender*ln(gestational age), age*gestational age, parity*gestational age, height*gestational age, BMI* gestational age, smoking*gestational age, financial difficulties*gestational age.

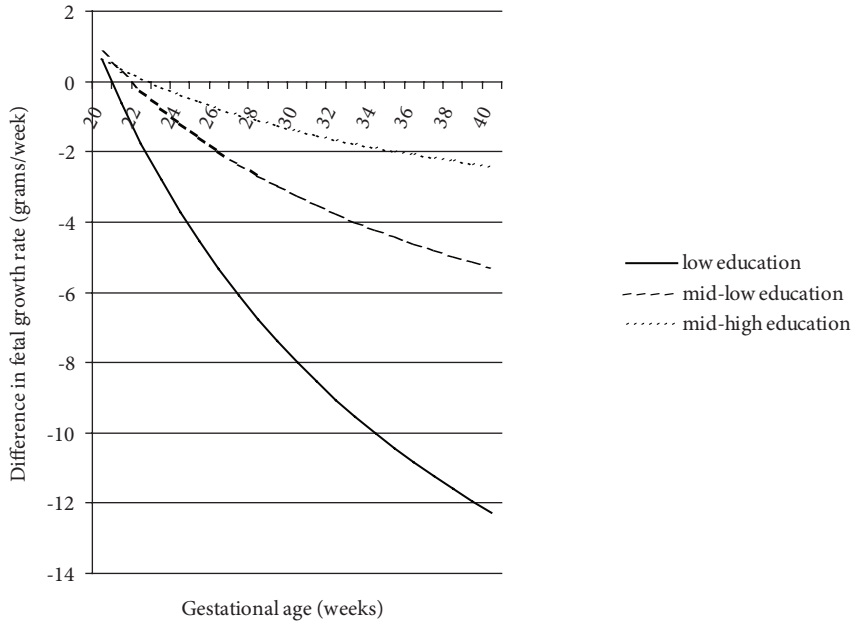

Figure 6.2 **Estimated differences in fetal growth rate for fetuses of women with low, mid-low and mid-high education relative to fetuses of women with high education (n=3545).** Values are based on multilevel models. All values are adjusted for fetal gender, and maternal age and parity. The following covariate*gestational age interactions were also included: gender*gestational age, gender*ln(gestational age), age*gestational age, parity*gestational age.

Table 6.3 **Associations between maternal educational level and growth of the fetal head, abdomen and femur (n=3545).**

	Differences (and 95% CI) in fetal head circumference growth (mm/week)	
Educational level	**Basic model***	**Fully adjusted†**
High	Reference	Reference
Mid-high	-0.03 (-0.11,0.05)	-0.02 (-0.09,0.05)
Mid-low	-0.09 (-0.17,-0.02)	-0.07 (-0.15,-0.001)
Low	-0.16 (-0.25,-0.07)	-0.10 (-0.19,-0.01)
	Differences (and 95% CI) in fetal abdominal circumference growth (mm/week)	
Educational level	**Basic model***	**Fully adjusted†**
High	Reference	Reference
Mid-high	0.02 (-0.09,0.12)	0.02 (-0.08,0.12)
Mid-low	-0.01 (-0.11,0.09)	-0.04 (-0.14,0.07)
Low	-0.10 (-0.21,0.01)	-0.10 (-0.22,0.02)
	Differences (and 95% CI) in fetal femur length growth (mm/w	
Educational level	**Basic model***	**Fully adjusted†**
High	Reference	Reference
Mid-high	-0.003 (-0.02,0.02)	0.001 (-0.02,0.02)
Mid-low	-0.01 (-0.03,0.004)	-0.003 (-0.02,0.01)
Low	-0.03 (-0.05,-0.005)	0.0005 (-0.02,0.02)

Values are based on multilevel models. CI: confidence interval. * Basic model: adjusted for fetal gender, and maternal age and parity. † Fully adjusted: adjusted for fetal gender, maternal age and parity, maternal height, pre-pregnancy BMI, smoking during pregnancy, single motherhood, whether the pregnancy was planned and financial difficulties. The following covariate*gestational age interactions were also included: for head-circumference model: gender*gestational age, parity*gestational age, height*gestational age, BMI* gestational age, smoking*gestational age; for abdominal-circumference model: parity*gestational age, BMI* gestational age, smoking*gestational age; for femur-length model: gender*gestational age, parity*gestational age, height*gestational age, smoking*gestational age.

Table 6.4 **Associations between maternal educational level and fetal head circumference, abdominal circumference and femur length (in standard deviation scores) at 20 and 30 weeks gestation (n=3545).**

	20 weeks gestation					
Educational level	**HC (SD score) Basic model***	**HC (SD score) Fully adjusted†**	**AC (SD score) Basic model***	**AC (SD score) Fully adjusted†**	**FL (SD score) Basic model***	**FL (SD score) Fully adjusted†**
High	Reference	Reference	Reference	Reference	Reference	Reference
Mid-high	-0.09 (-0.19,0.005)	-0.09 (-0.18,0.008)	0.005 (-0.09,0.10)	0.006 (-0.09,0.10)	0.01 (-0.08,0.11)	0.01 (-0.08,0.11)
Mid-low	-0.09 (-0.19,0.003)	-0.09 (-0.18,0.01)	-0.004 (-0.09,0.09)	0.002 (-0.09,0.10)	0.11 (0.02,0.21)	0.10 (0.004,0.19)
Low	-0.14 (-0.26,-0.03)	-0.10 (-0.22,0.03)	-0.03 (-0.14,0.08)	0.01 (-0.11,0.13)	0.03 (-0.08,0.13)	0.04 (-0.08,0.16)
	30 weeks gestation					
Educational level	**HC (SD score) Basic model***	**HC (SD score) Fully adjusted†**	**AC (SD score) Basic model***	**AC (SD score) Fully adjusted†**	**FL (SD score) Basic model***	**FL (SD score) Fully adjusted†**
High	Reference	Reference	Reference	Reference	Reference	Reference
Mid-high	-0.07 (-0.16,0.01)	-0.06 (-0.14,0.03)	0.02 (-0.07,0.11)	0.03 (-0.06,0.11)	-0.01 (-0.10,0.07)	-0.001 (-0.08,0.08)
Mid-low	-0.14 (-0.23,-0.06)	-0.11 (-0.20,-0.03)	0.001 (-0.09,0.09)	-0.006 (-0.10,0.08)	0.02 (-0.07,0.10)	0.04 (-0.04,0.13)
Low	-0.26 (-0.36,-0.16)	-0.14 (-0.25,-0.03)	-0.09 (-0.19,0.02)	-0.04 (-0.15,0.07)	-0.12 (-0.22,-0.02)	-0.006 (-0.11,0.10)

Values are based on multilevel models and represent differences in head circumference, abdominal circumference and femur length (expressed in standard-deviation scores) relative to fetuses of women with high educational level. HC: head circumference; AC: abdominal circumference; FL: femur length; SD-score: standard deviation score. * Basic model: adjusted for fetal gender, and maternal age and parity. † Fully adjusted: adjusted for fetal gender, maternal age and parity, maternal height, pre-pregnancy BMI, smoking during pregnancy, single motherhood, whether the pregnancy was planned and financial difficulties. The following covariate*gestational age interactions were also included: for head-circumference model: gender*gestational age, parity*gestational age, height*gestational age, BMI* gestational age, smoking*gestational age; for abdominal-circumference model: parity*gestational age, BMI* gestational age, smoking*gestational age; for femur-length model: gender*gestational age, parity*gestational age, height*gestational age, smoking*gestational age.

DISCUSSION

The present study is the first to present a longitudinal assessment of the effect of an individual-level indicator of socioeconomic status on fetal growth. We demonstrated that a low maternal educational level is associated with a progressively slower fetal growth, causing differences in fetal weight that are statistically significant from late pregnancy onwards. This study also suggests that low maternal educational level predominantly affects growth of the fetal head, followed by growth of the fetal femur and abdomen.

Methodological considerations

The main strength of this study lies in its population-based prospective design, with enrollment of a large number of women early in pregnancy, and extensive measurements during pregnancy[13].

Although there are other measures of socioeconomic status, including income level and occupational class[24], we selected maternal educational level as a main indicator of socioeconomic status for two reasons: first educational level not only partly reflects material resources because it structures occupation and income, it also reflects non-economic social characteristics, such as general and health-related knowledge, literacy, problem-solving skills and prestige[24 25]; second, educational level has been shown to be the best socioeconomic predictor of pregnancy outcomes[26]. Furthermore, when we repeated the analyses using household income level as determinant, we found comparable results. There was one exception: income-related differences in fetal head circumference were statistically significant only from 30 weeks gestation onwards.

When interpreting the results of this study, one should take account of a number of limitations.

First, our study was conducted in a Dutch, urban population, which limits generalizability of our results to non-Dutch or rural populations. Furthermore, although the participation rate was relatively high (61%, among Dutch women 68%)[13], there was some selection towards a study population that was relatively highly educated and more healthy[27].

Second, while fetal ultrasound examinations are a more reliable basis than the last menstrual period for establishing gestational age[28], it also has a disadvantage: the growth variation before the first measurement of the fetal characteristics that were used for pregnancy dating, i.e. crown-rump length and biparietal diameter, was set to zero[17]. Since these characteristics are correlated throughout pregnancy with head circumference, abdominal circumference and femur length, our study may have underestimated the variation in the latter three growth characteristics, resulting in an underestimation of our effect estimates.

Finally, our study may have been vulnerable to misclassification, because many covariates were measured using questionnaires. In particular, smoking behaviour and pre-pregnancy weight may have been underreported. The effect on our results of this misclassification is difficult to predict, since we cannot be certain whether this misclassification was random or not.

Maternal educational level and fetal growth

The educational differences in fetal growth were large enough to result in apparent differences in fetal size already during pregnancy. As we hypothesized, differences in fetal weight were significant from late pregnancy onwards. In contrast with our expectations, however, the effect of low maternal education was not equal for the various body segments of the foetus. Relative to growth of the fetal femur and abdomen, the adverse effect of a low educational level seemed greatest for growth of the fetal head.

Clear educational differences in fetal head circumference were detectable already at 20 weeks gestation. By 30 weeks, significant educational differences in femur length could also be detected, but not in abdominal circumference, although there was a clear trend towards a smaller abdominal circumference in fetuses of lower educated women. The timing of the emergence of significant educational differences in head, femur and abdomen might be explained by the different growth patterns of the various fetal-growth components. Peak growth velocity for head circumference is steeper and occurs earlier (around 18 weeks) than that for femur length (around 20 weeks) and abdomen (around 22 weeks)[11 29].

Regarding the magnitude of the educational differences in size of the different body segments, one should take account of the timing of the ultrasound measurements. In our study, only 2.5% of these measurements took place after the 32nd week of gestation. For physiological pregnancies, it has been shown that the difference in abdominal circumference between smaller and larger babies increases with increasing gestational age[29]. Therefore, the observed educational differences in abdominal circumference might have been larger if we had had availability to more growth measurements near term. It is thus important that our results are confirmed in future studies with more comprehensive fetal-growth data and with information on proportionality at birth.

One possible explanation for a low maternal education being relatively more strongly associated with fetal head circumference is that the factors that mediate the effect of maternal education affect fetal head growth more than growth of the fetal femur and abdomen. In support of this explanation, we found the most important mediators to be maternal smoking and maternal height. Maternal smoking during pregnancy, which was more prevalent among

women with a low educational level than those with a high level, is known to cause fetal growth restriction including a smaller head circumference[30]. Maternal height, which was positively associated with educational level, has been found to be a significant determinant of disproportionality at birth; shorter mothers tend to give birth to babies that are shorter and have smaller heads for their weight[12], which corresponds with the type of growth impairment associated with low maternal education.

The potential mediators included in this study, however, explained only about half the educational differences in fetal head circumference at 30 weeks gestation. The remaining effect may be due to other factors, such as nutritional factors or genetic factors[7 31]. Since head circumference is associated with academic achievements[3 32] and maternal head circumference is a strong predictor of neonatal head circumference[33], there may be a common genetic link between head circumference of the mother, her educational achievement and head growth of her offspring. We had no information on head circumference of the mother. This merits further investigation.

In conclusion, this unique study demonstrates that a low socioeconomic status of the mother impairs fetal growth, and suggests that it affects growth of the fetal brain more than it affects peripheral and abdominal tissues.

The socioeconomic inequalities in fetal growth as demonstrated here may represent the genesis of socioeconomic health inequalities in infancy, childhood and adulthood. In particular, since fetal head growth is associated with future cognitive functioning and academic achievement[3 32], the observed socioeconomic inequalities in fetal head growth might have consequences for later cognitive ability, educational attainment and job performance for the offspring of low-educated mothers. Taking measures to narrow inequalities in fetal growth should be an important public health issue. Smoking during pregnancy being the most important modifiable factor explaining these inequalities, such measures should primarily be aimed at reducing smoking rates among pregnant women of low socioeconomic status. The use of a video in order to raise awareness of the consequences of smoking during pregnancy, a self-help manual and health counselling by midwives have been shown to be successful in helping pregnant women to stop smoking[34], and should be applied more intensively to women with a low educational level. Further research is needed to provide other entry points for interventions and to study the short and long term consequences of socioeconomic inequalities in intra-uterine growth.

What is already known on this topic

- Women of low socioeconomic status give birth to lighter babies.
- This suggests that low socioeconomic status impairs fetal growth.
- Prospective population-based studies on the effect of maternal socioeconomic status on fetal growth trajectories are lacking

What this study adds

- A low maternal educational level (as measure of her socioeconomic status) is associated with a progressively slower fetal growth, causing differences in fetal weight that are observable from late pregnancy onwards.
- Relative to growth of the fetal femur and abdomen, the adverse effect of a low educational level seemed greatest for growth of the fetal head.
- This might have consequences for later cognitive ability, educational attainment and job performance for the offspring of low-educated mothers.

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ANNEX 6.1. Model structures for analyses with estimated fetal weight, head circumference, abdominal circumference, and femur length

Estimated fetal weight = $\beta_0 + \beta_1$*educational level + β_2*gestational age + β_3 * ln(gestational age) + β_4*gestational age*ln(gestational age) + β_5*educational level* gestational age + β_6* educational level *ln(gestational age).
Head circumference = $\beta_0 + \beta_1$*educational level + β_2*gestational age + β_3*gestational age^2 + β_4*gestational age^2*ln(gestational age) + β_5*educational level *gestational age.
Abdominal circumference = $\beta_0 + \beta_1$*educational level + β_2*gestational age + β_3*gestational age^2 + β_4*gestational age^2*ln(gestational age) + β_5*educational level *gestational age.
Femur length = $\beta_0 + \beta_1$*educational level + β_2*gestational age + β_3*gestational age^3 + β_4*educational level*gestational age.
Best-fitting model for analyses with standard-deviation (SD) scores for estimated fetal weight, head circumference, abdominal circumference, and femur length:
SD score = $\beta_0 + \beta_1$*educational level + β_2*gestational age + β_3*educational level*gestational age.

ANNEX 6.2. Estimated fetal weight, head circumference, abdominal circumference and femur length at median gestational age in mid and late pregnancy in the total study population.

	Midpregnancy (median 20.5 weeks)	Late pregnancy (median: 30.4 weeks)
Estimated fetal weight (grams)	371.9 (43.7)	1622.0 (188.7)
Head circumference (mm)	178.1 (6.3)	285.4 (9.3)
Abdominal circumference (mm)	155.9 (8.2)	264.6 (13.2)
Femur length (mm)	33.1 (1.8)	57.4 (2.2)

Values are means (with standard deviations)

Part III:

Socioeconomic inequalities in early childhood health

Chapter 7

Children of low socioeconomic status show accelerated linear growth in early childhood; results from The Generation R Study

Based on: Silva LM, Van Rossem L, Jansen PW, Hokken-Koelega ACS, Moll HA, Hofman A, Mackenbach JP, Jaddoe VWV, Raat H. Children of low socioeconomic status show accelerated linear growth in early childhood; results from The Generation R Study.

Submitted

ABSTRACT

Context: People of low socioeconomic status are shorter than those of high socioeconomic status. Socioeconomic inequalities in linear growth in the first two years of life might contribute to these inequalities in attained height.

Objective: To 1) study maternal educational level (high, mid-high, mid-low, and low) as a measure of socioeconomic status and its association with repeatedly measured height in children aged 0-2 years; and 2) to examine to what extent known determinants of postnatal growth contribute to this association.

Design, setting and participants: This study was based on data from 2972 mothers and their children participating in The Generation R Study, a population-based cohort study in Rotterdam, the Netherlands (participation rate 61%). All children were born between April 2002 and January 2006.

Main Outcome Measure(s): Height was measured at 2 months (mid-90% range 1.0-3.9), 6 months (mid-90% range 5.6-11.4), 14 months (mid-90% range 13.7-17.9) and 25 months of age (mid-90% range 23.6-29.6).

Results: At 2 months, children in the lowest educational subgroup were shorter than those in the highest (difference: -0.87 cm; 95% CI: -1.16, -0.58). Between 1 and 18 months, they grew faster than their counterparts. By 14 months, children in the lowest educational subgroup were taller than those in the highest (difference at 14 months: 0.40 cm; 95% CI: 0.08,0.72). Adjustment for other determinants of postnatal growth did not explain the taller height. On the contrary, the differences became even larger (difference at 14 months: 0.61 cm; 95% CI: 0.26,0.95; and at 25 months: 1.00 cm; 95% CI: 0.57,1.43)

Conclusions: Compared with children of high socioeconomic status, those of low socioeconomic status show an accelerated linear growth until the 18th month of life, leading to an overcompensation of their initial height deficit. The long-term consequences of these findings remain unclear and require further study.

INTRODUCTION

Height is a widely accepted marker of population health[1]. Adult height is negatively associated with morbidity and mortality from various diseases, including respiratory and cardiovascular diseases and different types of cancer[2-4]. This link between height and health is believed to be founded on circumstances in early life, as linear growth in childhood is considered a proxy of early life environmental conditions[2]. The first two years of life in particular are critical for height development, as they form the period of fastest growth in the entire postnatal life span[5 6]. Poor growth in the first two years of life has been shown to track into adulthood[7], indicating the importance of early growth for future height and health.

One environmental factor that is associated with height is socioeconomic status; the lower one's educational or income level, the shorter one's attained height[8]. The shorter height is likely to be due to a smaller size at birth, a slower linear growth during childhood, or both. While low socioeconomic status is known to be associated with a smaller birth size[9], much less is known on its association with linear growth during early postnatal life. A positive association between socioeconomic status and height has been demonstrated in children, but most studies focused on children older than 4 years[10-13]. Much fewer studies examined the effect of socioeconomic status on height in younger children, most of which were based on cross-sectional analyses[14-16]. Investigating the association between socioeconomic status and growth trajectories, however, requires longitudinal analyses of repeated height measurements. Studying this association in the first years of life would indicate whether the development of socioeconomic inequalities in adult height can be partly attributed to inequalities in linear growth during this critical period. Therefore, using data from a population-based cohort study, we studied maternal educational level as a measure of socioeconomic status in relation to repeatedly measured height in children aged 0-2 years, hypothesizing that a low maternal education is associated with a slower linear growth in early childhood. Furthermore, we included other determinants of early postnatal growth to examine to what extent they contribute to any socioeconomic differences in early growth.

METHODS

The Generation R Study

This study was embedded within The Generation R Study, a population-based prospective cohort study from fetal life until young adulthood that has previously been described in detail[17 18].

Ideally, enrollment took place in early pregnancy, but was possible until the birth of the child. All children were born between April 2002 and January 2006 and form a prenatally recruited birth-cohort. Of all eligible children in the study area, 61% participated in the study[18]. The study was conducted in accordance with the guidelines proposed in the World Medical Association Declaration of Helsinki and has been approved by the Medical Ethical Committee of the Erasmus MC, University Medical Center Rotterdam. Written consent was obtained from all participating parents.

Population for analyses

Out of the 7893 mothers and their children who participated in the postnatal cohort, 6969 had been included prenatally. We restricted our analyses to the subgroup with mothers of Dutch ethnicity[19], because socioeconomic status may interact with ethnicity regarding their effects on growth and health[15, 20], and because growth patterns may differ by ethnicity[21 22]. Of the 6969 mothers, 3478 had a Dutch ethnicity ánd gave consent for receiving questionnaires. We excluded twins (n=90), and the second or third child (n=327) of the same mother, since data were correlated. We also excluded participants without information on maternal educational level (n=16) and those without height measurements (n=73), leaving a study population of 2972 mothers and their children.

Maternal educational level

Using a questionnaire at enrollment, we established mother's highest achieved education, and categorized this according to the Dutch Standard Classification into: 1. high (university or higher), 2. mid-high (higher vocational training), 3. mid-low (more than three years of general secondary school, or intermediate vocational training completed), and 4. low education (no education, primary school, lower vocational training, intermediate general school, or three years or less of general secondary school)[23].

Height measurements

In the Netherlands, all pre-school children visit Child Health Centers according to a standard schedule. We collected height measurements that were taken from our participants around the ages 1, 2, 3, 4, 6, 11, 14, 18, and 24 months by well-trained staff. Up to and including the second birthday, height was measured to the nearest millimeter using a neonatometer with the child in supine position. After the second birthday, height was measured in standing position. Length at birth was not available, since this was not routinely measured in healthy-born neonates.

Covariates

Any effect of maternal education on the child's linear growth is probably an indirect one, acting through more proximal determinants of early growth, so-called mediators[24]. Therefore, we evaluated the contribution of known determinants of early growth[25-28] to any differences in growth between educational subgroups. These determinants are listed below:

Information on whether mother s*moked during pregnancy* (no, yes) was assessed through questionnaires during pregnancy. *Birth weight* and *gestational age at birth* were obtained from midwife and hospital registries. *Maternal and paternal height* were measured at our research centers. Information on *breastfeeding at 2 months* (yes, no) and *breastfeeding duration* (never breastfed, <4 months, 4-6 months, ≥6 months) was derived from questionnaires that were distributed at the child's age of 2, 6, and 12 months. The presence of older *siblings* was established when the child was 6 months old. Information on *day-care attendance* was collected at the ages 6, 12 and 24 months.

Because it has been suggested that body mass or fatness partly regulates linear growth[29 30], we additionally evaluated the contribution of the child's body mass index (BMI) at time of height measurement, as well as the change in BMI during the preceding periods. BMI was calculated from height and weight (weight/height^2); weight measurements took place at the same ages as the height measurements.

Maternal age at enrollment, and *gender* were treated as potential confounders.

Statistical analyses

Because the height measurements peaked around the ages 2, 6, 14 and 25 months, they were organized into four measurement points at 2 (mid-90% range 1.0-3.9), 6 (mid-90% range 5.6-11.4), 14 (mid-90% range 13.7-17.9) and 25 months of age (mid-90% range 23.6-29.6). For each subject, standard-deviation scores (SDS) at all four measurement points were calculated using internally derived gender-specific means and standard deviations: SDS=(measurement – population mean)/ population standard deviation.

The association between maternal education and the child's linear growth was evaluated in three stages. First, we used linear regression to estimate the average height at each age in each educational subgroup adjusted for the child's age at measurement.

In the second stage, we analyzed the association between maternal education and linear growth velocity using longitudinal multilevel analysis[31]. The best fitting model to predict height as a function of age was built using fractional polynomials[32]. To this model we added educational level as a main determinant (reference: high education), and an interaction term of educational level with age. The best-fitting model structure was:

Height = β_0 + β_1*educational level + β_2*age + β_3*√age+ β_4*educational level *age + β_5*educational level*√age.

Differences in linear growth velocity between levels of maternal education were then calculated using the derivative of the above model.

Finally, the contribution of covariates to differences in height between educational levels was evaluated by adding these covariates to the linear regression models, first separately, then simultaneously (full model). Then, the full model was additionally adjusted for BMI and the change in BMI between 2 and 6 months, between 6 and 14 months, and between 14 and 25 months. We adjusted for only those covariates that were independent predictors of height when all other covariates were accounted for. Day-care attendance was not included in the models for height at 2 months, since this determinant was assessed áfter the height measurement. For each covariate, an interaction term with educational level was tested for significance. To handle missing values in the covariates (see table 7.1) we applied multiple imputation based on five imputed data sets ('PROC MI' procedure in SAS 9.1.3)[33]. For simplicity, the results were not stratified by gender, because the effect of educational level on growth velocity did not differ by gender (p for interaction education*age*gender >0.4). Statistical analyses were performed using Statistical Package of Social Sciences version 15.0 for Windows (SPSS Inc, Chicago, IL, USA) and the Statistical Analysis System (SAS) for Windows (SAS Institute Inc, USA), version 9.1.3. A p-value of <0.05 was taken to indicate statistical significance; for interaction terms we used a p-value of 0.10.

RESULTS

Of the 2972 children, 34.6% of their mothers had a high educational level, and 14.0% had a low educational level (table 7.1). Compared with women with a high education, those with a low education were younger, shorter, and were more likely to smoke during pregnancy. Their children were on average lighter at birth, were less likely to be breastfed, and were less likely to go to day care (p for trend all <0.05; table 7.1).

Maternal educational level and linear growth

In total, 2613 children were measured around 2 months, 2840 around 6 months, 2679 around 14 months, and 2427 around 25 months. Multilevel analyses were based on 10559 observations.

Table 7.1 **General characteristics of the study population (n=2972)*.**

	Maternal educational level					
	Total N=2972	**High N=1029 (34.6%)**	**Mid-high N=793 (26.7%)**	**Mid-low N=735 (24.7%)**	**Low N=415 (14.0%)**	**P for trend¶**
Maternal characteristics						
Age at enrollment (yrs)	31.5 (4.3)	33.0 (3.2)	32.0 (3.7)	30.4 (4.6)	28.9 (5.5)	<0.001
Nulliparous (%)	65.5	65.1	68.3	67.5	57.8	0.098
Smoking during pregnancy (%)	25.0	14.2	20.8	29.5	51.0	<0.001
Height (cm)	170.9 (6.4)	171.4 (6.1)	171.4 (6.3)	171.8 (6.4)	169.0 (6.9)	<0.001
Height father (cm)	184.1 (7.2)	184.9 (6.9)	184.1 (6.9)	183.6 (7.4)	182.6 (7.5)	<0.001
Child characteristics						
Gender (% boys)	50.3	50.6	49.4	48.0	54.9	0.520
Birth weight (g)	3492.6 (545.8)	3552.9 (517.8)	3504.1 (541.2)	3457.2 (564.1)	3383.5 (569.1)	<0.001
Gestational age at birth (weeks)	40.3 (36.0,42.4)	40.3 (36.3,42.4)	40.3 (36.1,42.4)	40.1 (35.7,42.4)	40.0 (34.9,42.3)	<0.001
Breastfeeding at 2 months (%)	66.7	81.4	72.6	54.4	35.2	<0.001
Breastfeeding duration						<0.001
Never (%)	11.6	4.6	6.9	18.2	27.6	
<4 months (%)	45.3	38.3	42.9	52.3	55.8	
4-6 months (%)	12.1	16.3	14.2	8.7	2.6	
≥6 months (%)	31.0	40.8	36.0	20.8	14.0	
Siblings (% yes)	31.0	32.5	29.4	28.6	35.4	0.852
Day care at 12 months (% yes)	68.7	89.2	71.4	51.4	28.2	<0.001
Day care at 24 months (% yes)	76.9	91.6	78.4	65.0	47.1	<0.001

Table 7.1 Continued

	Maternal educational level					
	Total N=2972	**High N=1029 (34.6%)**	**Mid-high N=793 (26.7%)**	**Mid-low N=735 (24.7%)**	**Low N=415 (14.0%)**	**P for trend¶**
BMI (kg/m^2)						
2 months	15.8 (1.5)	15.8 (1.4)	15.8 (1.5)	15.8 (1.5)	15.7 (1.4)	0.227
6 months	17.2 (1.3)	17.1 (1.3)	17.1 (1.3)	17.2 (1.4)	17.2 (1.4)	0.596
14 months	17.1 (1.3)	17.2 (1.3)	17.1 (1.3)	17.1 (1.4)	17.0 (1.3)	0.014
25 months	16.5 (1.3)	16.6 (1.3)	16.5 (1.3)	16.4 (1.4)	16.5 (1.5)	0.019

Yrs: years; cm: centimeters; g: grams; BMI: body mass index; kg: kilograms; m: meters.

* Data were missing for parity (n=3), smoking during pregnancy (n=201), breastfeeding at 2 months (n=237) breastfeeding duration (n=564), siblings (n=974), day-care attendance at 12 months (n=617), day-care attendance at 24 months (n=591), maternal height (n=3), paternal height (n=434), BMI 2 months (n=359), BMI 6 months (n=132), BMI 14 months (n=295), and BMI 25 months (n=549).

¶ P values for trend are derived from chi-squared test for trend (categorical factors) or for the linear trend test of the 1-way analysis of variance.

Compared with children of high-educated mothers, those of low-educated mothers were shorter at 2 months (p<0.001; figure 7.1). After 2 months, children of mothers with a low educational level showed a relative catch-up growth, while those of mothers with a high level showed a relative catch-down growth. At 6 months there were no differences in height between educational subgroups, but by 14 months, children of mothers with a low educational level were taller than those of mother with a high level (p=0.046). This difference was no longer statistically significant at 25 months (p=0.089).

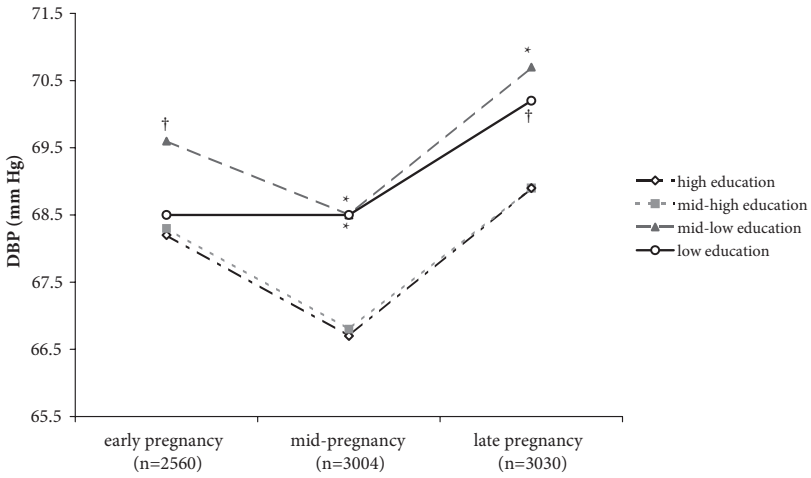

Figure 7.1 **Internally derived standard deviation scores (SDS) for height, stratified by maternal educational level.** All Values are SDS +/- standard errors, adjusted for the child's age at measurement. * Significantly different from height SDS in the high-education subgroup at level p<0.05. § Significantly different from height SDS in the high-education subgroup at level p<0.001.

Results from the multilevel analyses indicated that there were differences in growth velocity between educational subgroups (p for educational-level*age and educational-level*√age interactions <0.001). Between 1 and 18 months of age, children of mothers with a low or mid-low educational level grew faster than those of mothers with a high level (figure 7.2). This difference in growth velocity became smaller with increasing age, and by the 19th month there

was no difference in growth velocity. After the 20th month, the association between educational level and linear growth velocity reversed; children of mothers with a low educational level tended to have a slower growth than those of mothers with a high level.

Contribution of covariates

Table 7.2 presents the contribution of covariates to the differences in height (in centimeters) between educational subgroups at 2, 6, 14 and 25 months of age. Gender, maternal age and siblings were not included in these models, since there were no educational differences in gender or presence of siblings (see table 7.1) and since maternal age was not an independent predictor of height at any age (data not shown).

At 2 months, the variables smoking during pregnancy, birth weight and gestational duration contributed most to the shorter height of children in the lowest educational subgroup compared with the highest; adjustment for these factors together reduced the difference in height from -0.87 cm (95 % CI: -1.16,-0.58) to -0.17 cm (95% CI: -0.38,0.04). When we adjusted for all covariates the differences in height disappeared.

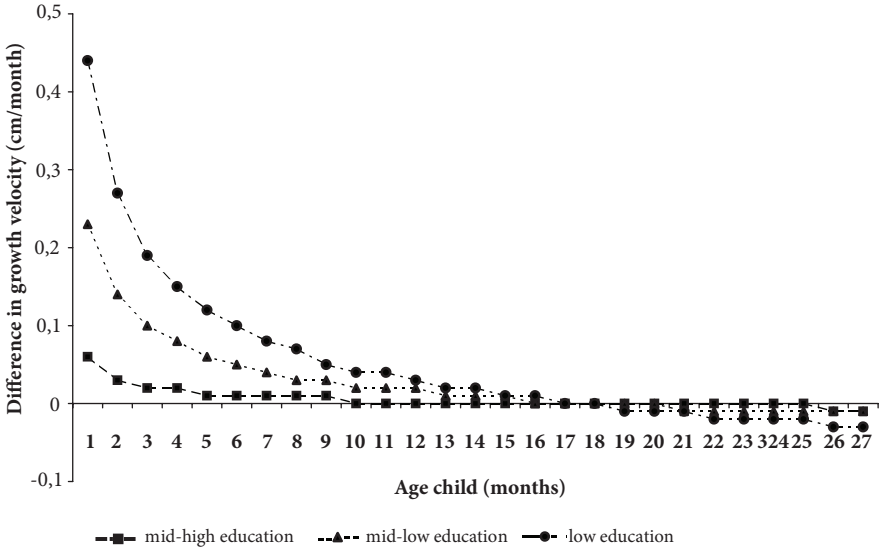

Figure 7.2 **Difference in linear growth velocity between children of mothers with low, mid-low and mid-high education compared with those of mothers with high education (n=2972).** Growth curves are derived from longitudinal multilevel analysis. Difference in growth velocity = β_1*educational level +β_2*0.5*1/√age*educational level.

Table 7.2 **Differences in child's height at 2, 6, 14 and 25 months of age between maternal educational levels*.**

Models	Maternal educational level			
	High education	Mid-high education	Mid-low education	Low education
2 months (n=2613)				
Model 1	Reference	-0.25 (-0.48,-0.01)	-0.35 (-0.59,-0.11)	-0.87 (-1.16,-0.58)
Model 1+ smoking in pregnancy, birth weight & gestational age	Reference	-0.09 (-0.25,0.07)	0.02 (-0.15,0.19)	-0.17 (-0.38,0.04)
Model 1+ maternal and paternal height	Reference	-0.19 (-0.41,0.03)	-0.20 (-0.43,0.03)	-0.43 (-0.71,-0.15)
Model 1+ breastfeeding at 2 months	Reference	-0.22 (-0.46,0.01)	-0.28 (-0.53,-0.03)	-0.74 (-1.05,-0.43)
Full model[1]	Reference	-0.06 (-0.22,0.10)	0.09 (-0.07,0.26)	0.06 (-0.15,0.28)
Full model[1] + BMI at 2 months	Reference	-0.05 (-0.21,0.11)	0.09 (-0.08,0.26)	0.04 (-0.17,0.25)
6 months (n=2840)				
Model 1	Reference	-0.22 (-0.45,0.01)	0.03 (-0.21,0.27)	0.06 (-0.23,0.34)
Model 1+ smoking in pregnancy, birth weight & gestational age	Reference	-0.10 (-0.31,0.10)	0.24 (0.03,0.446)	0.43 (0.16,0.69)
Model 1+ maternal and paternal height	Reference	-0.13 (-0.35,0.08)	0.21 (-0.01,0.43)	0.51 (0.24,0.78)
Model 1+ breastfeeding duration	Reference	-0.24 (-0.47,0.01)	-0.08 (-0.33,0.16)	-0.10 (-0.40,0.20)
Model 1+ day-care attendance 6 months	Reference	-0.24 (-0.47,-0.001)	-0.001 (-0.25,0.25)	0.001 (-0.32,0.32)
Full model[2]	Reference	-0.14 (-0.34,0.06)	0.09 (-0.13,0.31)	0.34 (0.06,0.63)
Full model[2] + BMI at 6 months	Reference	-0.14 (-0.34,0.06)	0.09 (-0.13,0.31)	0.33 (0.14,0.05)
Full model[2] + change in BMI 2-6 months	Reference	-0.15 (-0.34,0.05)	0.08 (-0.14,0.29)	0.33 (0.05,0.61)
14 months (n=2679)				
Model 1	Reference	-0.04 (-0.30,0.22)	0.28 (0.007,0.54)	0.40 (0.08,0.72)
Model 1+ smoking in pregnancy, birth weight & gestational age	Reference	0.04 (-0.20,0.28)	0.44 (0.19,0.70)	0.77 (0.45,1.08)
Model 1+ maternal and paternal height	Reference	0.03 (-0.21,0.26)	0.46 (0.21,0.71)	0.95 (0.65,1.25)
Model 1+ breastfeeding duration	Reference	-0.05 (-0.31,0.20)	0.21 (-0.06,0.49)	0.31 (-0.02,0.65)
Model 1+ day-care attendance 12 months	Reference	-0.14 (-0.40,0.13)	0.07 (-0.22,0.36)	0.07 (-0.30,0.44)

Table 7.2 Continued

Models	Maternal educational level			
	High education	Mid-high education	Mid-low education	Low education
		14 months (n=2679)		
Full model [3] + BMI at 14 months	Reference	-0.07 (-0.31,0.16)	0.20 (-0.05,0.46)	0.60 (0.26,0.95)
Full model [3] + change in BMI 2-6 months	Reference	-0.07 (-0.30,0.16)	0.21 (-0.05,0.46)	0.61 (0.26,0.95)
Full model [3] + change in BMI 6-14 months	Reference	-0.08 (-0.31,0.15)	0.18 (-0.07,0.44)	0.60 (0.26,0.94)
		25 months (n=2427)		
Model 1	Reference	-0.08 (-0.41,0.25)	0.25 (-0.09,0.59)	0.40 (-0.02,0.83)
Model 1+ smoking in pregnancy, birth weight & gestational age	Reference	-0.01 (-0.32,0.30)	0.42 (0.09,0.75)	0.72 (0.30,1.14)
Model 1+ maternal and paternal height	Reference	-0.01 (-0.31,0.28)	0.49 (0.19,0.80)	1.11 (0.72,1.50)
Model 1+ breastfeeding duration	Reference	-0.09 (-0.41,0.24)	0.24 (-0.11,0.59)	0.38 (-0.06,0.82
Model 1+ day-care attendance 24 months	Reference	-0.12 (-0.45,0.22)	0.19 (-0.17,0.54)	0.30 (-0.16,0.75)
Full model [4]	Reference	-0.04 (-0.33,0.25)	0.42 (0.09,0.74)	1.00 (0.57,1.43)
Full model [4] + BMI at 25 months	Reference	-0.05 (-0.34,0.24)	0.40 (0.07,0.72)	0.99 (0.57,1.42)
Full model [4] + change in BMI 2-6 months	Reference	-0.04 (-0.33,0.26)	0.42 (0.09,0.74)	1.00 (0.57,1.42)
Full model [4] + change in BMI 6-14 months	Reference	-0.01 (-0.30,0.28)	0.46 (0.14,0.79)	1.03 (0.61,1.46)
Full model [4] + change in BMI 14-25 months	Reference	-0.06 (-0.34,0.23)	0.40 (0.06,0.70)	1.01 (0.59,1.43)

* Values are differences in centimeters (with 95% CI) and derived from linear regression analyses performed on the data after applying multiple imputation.

Model 1: adjusted only for child age at measurement.

[1] Adjusted for child age at measurement, smoking in pregnancy, birth weight & gestational age, maternal and paternal height, and breastfeeding at 2 months.

[2] Adjusted for child age at measurement, smoking in pregnancy, birth weight & gestational age, maternal and paternal height, breastfeeding duration, and day-care attendance at 6 months

[3] Adjusted for child age at measurement, smoking in pregnancy, birth weight & gestational age, maternal and paternal height, breastfeeding duration, and day-care attendance at 12 months

[4] Adjusted for child age at measurement, smoking in pregnancy, birth weight & gestational age, maternal and paternal height, breastfeeding duration, and day-care attendance at 24 months

While at 6 months there were no differences in height between educational subgroups, adjustment for smoking during pregnancy, birth weight and gestational duration unmasked a taller height in the lowest educational subgroup compared with the highest (difference: 0.43 cm; 95% CI: 0.16,0.69). Adjustment for maternal and paternal height had the same effect (difference: 0.51 cm; 95% CI: 0.24,0.78).

By 14 months, children of mothers with a low educational level were 0.40 cm taller (95% CI: 0.08,0.72) than those of mothers with a high level. This difference became even stronger after adjustment for smoking during pregnancy, birth weight and gestational duration, and after adjustment for maternal and paternal height. In contrast, adjustment for breastfeeding, but more in particular adjustment for day-care attendance explained part of the taller height. In the full model, children in the lowest educational subgroup were still significantly taller than those in the highest educational subgroup (difference: 0.60 cm; 95% CI: 0.26,0.94). We found comparable results at 25 months of age; children in the lowest educational subgroup were then 1.01 cm taller (95% CI: 0.59,1.43) in the full model.

Adding BMI or change in BMI to the full models had no effect on the effect estimates.

DISCUSSION

Our study showed that compared with children of mothers with a high education, those of mothers with a low education were shorter at the age of 2 months. However, their height deficit was overcompensated by a faster linear growth between 1 and 18 months of age. By 14 months, children in the lowest educational subgroup were even taller than those in the highest educational subgroup.

Socioeconomic status and early linear growth

Previous studies have demonstrated a positive association between socioeconomic status and height in school-aged children[10-13]. Only a small number of studies investigated the association between socioeconomic status and height development in younger children[14-16]. For example, Sequin et al.[16] found that longstanding material hardship increased the risk of having a height under the tenth percentile at the age of 2.5 years, suggesting that the socioeconomic gradient in height may arise during the first years of life. In our study, height at the age of 2 months was associated with maternal educational level in the expected direction: the lower the educational level the shorter the offspring's height. An unexpected finding was the faster linear growth and the taller height from 14 months onwards associated with a low maternal education.

However, this phenomenon of a relative accelerated growth in children of low socioeconomic status has been reported once before: among infants in whom height was measured between 0 and 2 years, Herngreen et al.[15] found that children of low socioeconomic status tended to be initially shorter, but had a higher gain in height after birth compared with children of high socioeconomic status. In contrast to our study, however, socioeconomic status was no longer associated with height or height gain after allowing for other factors, i.e. ethnic descent of the parents, gestational age, birth weight, parity, maternal smoking during pregnancy, maternal age and height of the parents.

We considered different mechanisms driving the associations between a lower maternal educational level and a faster linear growth and taller height by 14 months of age.

The first is selection bias. Although the participation in The Generation R Study was relatively high (61%; 68% for participants with a Dutch ethnicity)[18, 34], there was some selection towards a study population that was relatively highly educated and more healthy[18]. For selective participation to explain our results, non-participants would have to have been more often of low socioeconomic status with children who are relatively short and grow relatively slow. This is difficult to ascertain, but selective participation is unlikely to fully explain our results. Additionally, 18% of the participants who were eligible for inclusion in our study were lost to follow-up. Compared to participants included in the present analyses, children lost to follow-up were born with a lower birth weight, and had mothers who were lower educated and who were more likely to smoke during pregnancy (data not shown). The effect of this selection on our effect estimates is difficult to predict.

Second, the relatively faster growth might be a biological response to exposure to adverse intrauterine circumstances. Children of low socioeconomic status were more likely to have mothers who smoked during pregnancy, and were smaller at birth. Postnatal catch-up growth is often seen in children born to smoking mothers or born relatively small[28, 35]. However, in our study, maternal smoking rates, birth weight and gestational age did not contribute to the explanation of the taller height in lower educational subgroups. Rather, when these variables were all set equal between educational subgroups, the difference in height became even larger.

Last, our results suggest that socioeconomic differences in feeding practices, another major determinant of early growth[25], might explain the differences in linear growth. At 14 months, part of the taller stature in the subgroup of low education was explained by a shorter breastfeeding duration in this subgroup. It is known that breastfeeding is less common in lower socioeconomic subgroups[36]. It is also known that compared to bottle-fed infants, breastfed infants grow slower in the first year of life – as is also seen in our data (data not shown) - causing

bottle-fed infants to be heavier and taller than their breastfed counterparts after the age of 6 months[25, 37]. This may be due to excessive feeding or a higher nitrogen and energy intake of formula-fed infants[38 39].

The low rate of day-care attendance in children of mothers with a low education also contributed to their taller height. This was because in our data day-care attendance was associated with a slower linear growth (data not shown). We found no previous studies that investigated the specific effect of day-care attendance on early growth to support this finding. Frequent infections or a lower risk of overfeeding might underlie this association seen between day-care attendance and growth[27, 39].

After taking all covariates into account, children in the lowest educational subgroup were about 1 cm taller than those in the highest educational subgroup. This is likely to be explained by other growth-stimulating factors that were not available for this study, such as total amount of energy intake. This merits further investigation.

Methodological considerations

Although there are other measures of socioeconomic status, including income level and occupational class[40], we selected maternal educational level as a main indicator for two reasons: first educational level not only partly reflects material resources because it structures occupation and income, it also reflects non-economic and social characteristics of the mother, such as knowledge with respect to health behavior, feeding practices and health of their children[40 41]. Second, educational level has been shown to be the most consistent socioeconomic predictor of health[42].

We restricted our analyses to the subgroup with mothers of Dutch ethnicity. About 18% of the children had a father with a non-Dutch ethnicity, causing some heterogeneity in the study population. However, we repeated the analyses in the subgroup of children of whom both parents had a Dutch ethnicity and found comparable results.

Caution should be taken when generalizing our findings. The phenomenon of accelerated linear growth during early childhood in children of low socioeconomic status, and in particular the overcompensation of their initial height deficit, may be specific to affluent Western populations with increasing availability of inexpensive, energy-dense food. Our findings are probably not generalizable to low or middle-low income countries, where low socioeconomic status is generally associated with a lack of resources for adequate nutrition.

Conclusions

This study in children from a Western European country does not support the hypothesis that the shorter adult height associated with a low socioeconomic status can be attributed to a slower linear growth in the first two years of life. Our work suggests that, while at the onset of their growth trajectory children of low socioeconomic status are shorter than their counterparts of high socioeconomic status, they show a relative accelerated linear growth until the18th month of life, leading to an overcompensation of their height deficit. The long-term consequences of this phenomenon for their height and health may be a topic of future research[43]. Our data suggest that this period of accelerated growth velocity is followed by a relative deceleration. Further follow-up is necessary to study how socioeconomic status affects growth after the second year of life, and how this relates to the socioeconomic inequalities in adult height and health.

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Chapter 8

Social disadvantage and upper respiratory tract infections in early childhood; contribution of prenatal factors

Based on: Silva LM, Labout JAM, Moll HA, Steegers EAP, Jaddoe VWV, Hofman A, Mackenbach JP, Raat H. Social disadvantage and upper respiratory tract infections in early childhood; contribution of prenatal factors.

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ABSTRACT

Objective: To examine 1) the association of maternal educational level as indicator of socioeconomic status (SES) with susceptibility to upper respiratory tract infections (URTI) in the offspring, and 2) to what extent prenatal or perinatal circumstances, independently of postnatal circumstances, explain this association.

Methods: We used data from 5554 children and their mothers participating in a population-based cohort study in Rotterdam, the Netherlands. Maternal educational level was categorized into high, mid-high, mid-low and low level. Using questionnaires, parents reported on the incidence of URTI between 0 and 6 months of age, between 7 and 12 months, and between 13 and 24 months.

Results: At all ages, there was an inverse relationship between maternal educational level and the risk for URTI. In the second year of life, toddlers of mothers with a low educational level had a 70% (OR: 1.70; 95% CI: 1.26,2.30) higher susceptibility to URTI than toddlers of mothers with a high level, after adjustment for confounders and factors related to exposure to infectious agents. The prenatal factors that substantially contributed to this increased susceptibility, independent of postnatal factors, were prenatal financial difficulties and prenatal psychiatric symptoms.

Conclusions: Toddlers of low SES are more susceptible to URTI than toddlers of high SES. Independently of postnatal circumstances, part of this increased susceptibility is due to adverse intrauterine circumstances, in particular prenatal exposure to maternal psychosocial stressors.

INTRODUCTION

The effect of socioeconomic status (SES) on children's health is well-recognized: children from families with a low SES generally have poorer health than those from families with a high SES. This socioeconomic gradient has been demonstrated for different dimensions of child health, including mortality[1], general health status[2 3], mental health[4], and specific diseases such as infectious diseases[5 6]. Recent evidence suggests that socioeconomic differences in health become larger as children get older, and that they may contribute to the origins of health differences in adult life[2]. This underlines the importance of research on the nature of socioeconomic differences in health in early life.

Despite previous efforts to explain the mechanisms underlying the socioeconomic gradient in child health[2 3 7], these mechanisms remain poorly understood. On the basis of the 'fetal origins' hypothesis[8], which highlights the importance of experiences in the womb for health later in life, researchers' attention has shifted to the possible role of the intrauterine environment in explaining the socioeconomic gradient in child health. Recently, Dowd investigated the role of maternal health status and health behaviors during pregnancy and early infancy in the explanation of the relationship between family income and overall health status of 3-year old children; these factors did not contribute to the explanation[3]. However, the role of measures of the child's prenatal and perinatal health, such as birth weight or gestational age at birth, was not explored in this study. Furthermore, information on prenatal psychosocial factors, which have been implicated in explaining socioeconomic inequalities in adult health[9], was not available.

The present study was conducted to examine socioeconomic inequalities in health among toddlers up to 2 years of age, and the extent to which prenatal or perinatal circumstances, independent of postnatal circumstances, contribute to these inequalities. The outcome of interest was upper respiratory tract infections (URTI), the most frequent diseases in early childhood that can affect the quality of life of both the children and their families[10]. Using maternal educational level as a measure of SES, we estimated socioeconomic inequalities in 'susceptibility' to URTI by controlling for any differences in exposure to infectious agents[11].

METHODS

The Generation R Study

This study was embedded within The Generation R Study, a population-based prospective cohort study from fetal life until young adulthood that has previously been described in detail[12 13]. Ideally, enrollment took place in early pregnancy, but was possible until the birth of the child. All children were born between April 2002 and January 2006 and form a prenatally enrolled birth-cohort that is currently being followed-up until young adulthood. Of all eligible children in the study area, 61% participated in the study[13]. The study was conducted in accordance with the guidelines proposed in the World Medical Association Declaration of Helsinki and has been approved by the Medical Ethical Committee of the Erasmus MC, University Medical Center Rotterdam. Written consent was obtained from all participating parents.

Population for analyses

A total of 7893 mothers and their children participated in the postnatal cohort, of whom 6969 had been included prenatally. Of these 6969 participants, 6559 gave consent for receiving questionnaires postnatally. We excluded twins (n=137) from the analyses, since data were correlated. For the same reason, data from a second (n=459) or third child (n=9) of the same mother were excluded. We also excluded participants who lacked information on maternal educational level (n=400), leaving a study population of 5554 mothers and their children.

Maternal educational level

On the basis of a questionnaire during pregnancy, we established the highest education each mother had achieved, and categorized this into: 1.) high (university or higher), 2.) mid-high (higher vocational training), 3.) mid-low (more than three years of general secondary school, or intermediate vocational training completed, or first year of higher vocational training), and 4.) low education (no education, primary school, lower vocational training, intermediate general school, or three years or less of general secondary school)[14].

Upper respiratory tract infections

When the children were 6, 12 and 24 months old, we obtained information on the occurrence of URTI through postal questionnaires. Parents were asked whether their child had suffered from a serious cold, an ear infection or a throat infection in the preceding period (i.e. from 0-6 months, from 7-12 months, and from 13-24 months), and whether they had visited a physician for this

infection. When parents reported at least one of these infections, independent of whether they had visited a physician, their children were considered to have had an URTI.

Covariates

Ethnicity of the mother, age of the mother, and age of the child at which the questionnaire was completed, were considered potential confounders in the associations between educational level and URTI in early childhood; these variables may be related to both SES and to parent-reported URTI[15 16], but are not in the causal pathway[17].

The variables listed below, which are known to be associated with respiratory tract infections in childhood[5 18 19] were hypothesized to be in the pathway from family SES to susceptibility to URTI in early childhood. These so-called explanatory variables were divided into prenatal/perinatal factors and postnatal factors. Unless stated otherwise, information on these variables was obtained using questionnaires. Categories are indicated between parentheses.

Prenatal/perinatal factors

We collected information on possible sources of maternal psychosocial stress during pregnancy. These included: *single motherhood* (yes, no); financial difficulties (yes, no); presence of *psychiatric symptoms* (including depression and anxiety) as measured using the Global Severity Index (score in tertiles, the higher the worse) of the Brief Symptom Inventory[20]; presence of *long-lasting difficulties* (score in tertiles, the higher the worse) as measured using a 12 item-checklist covering financial problems, social deprivation, neighborhood problems and problems in relationships[21]; and (*poor) family functioning* as measured with the Family Assessment Device (score in tertiles, the higher the worse)[22].

In early, mid and late pregnancy, we obtained information on whether the mother *smoked during pregnancy* (no, yes).

Birth weight and *gestational age at birth* were obtained from midwife and hospital charts. For the analyses we used gestational-age adjusted standard-deviation scores for birth weight. Two months after birth, we established whether the infant had been *hospitalized in the first week after birth* (yes, no).

Postnatal factors

Presence of postnatal psychiatric symptoms in the mother (score in tertiles, the higher the worse) was established two months after birth[20]. Presence of *postnatal financial difficulties* was established at child age of 24 months.

We established whether the child was receiving *breastfeeding at the age of 6 months* (yes, no) and whether the child was *exposed to tobacco smoke* at the ages 6 and 24 months (yes, no).

The presence of older *siblings* was established at the age of 6 months of the infant. Information on *day-care attendance* was collected at the ages 6, 12 and 24 months.

Multiple imputation and statistical analyses

Because missing data on the outcome variables were not completely random (see below), complete-case-analysis was likely to introduce biased results. Imputation of outcome variables using the predictors under study minimizes this bias[23]. Therefore, we imputed missing values in the outcome variables and the covariates using 'multiple imputation[24]. Using the PROC MI procedure in SAS 9.1.3, five imputed data sets were created, in which imputations were based on the relationships between all the variables included in this study.

After multiple imputation, logistic regression analysis was used to quantify the association between educational level and the risk for URTI, adjusted for the potential confounders (model 1). The highest educational level was set as reference. Then, the factors related to exposure to infectious agents, i.e. siblings and day-care attendance, were included in the model (model 2), which we considered to reflect the differences in 'susceptibility' to URTI.

The extent to which prenatal/perinatal circumstances contributed to the explanation of socioeconomic inequalities in susceptibility to URTI was analyzed in two stages. First, each potential mediator was added separately to model 2. For each adjustment, the percentage change in OR for the educational level with an increased risk for URTI was calculated ($100x[OR_{model\ 2} - OR_{+mediator}]/[OR_{model\ 2} - 1]$). Only those variables that individually produced at least 10% change in the OR for the educational level with the highest risk were selected for the next stage.

In the second stage, the following three models were fitted:

- Model 2 + selection of prenatal/perinatal factors (= model 3)
- Model 2 + selection of postnatal factors (= model 4)
- Model 2 + selection of prenatal/perinatal and postnatal factors (= model 5)

The contribution of prenatal/perinatal factors, independently of postnatal factors was established by calculating the percentage reduction due to the inclusion of prenatal/perinatal factors to a model already containing postnatal factors (model 5 compared to model 4)[25].

We tested interaction terms between maternal educational level and covariates. There was an indication that the effect of a low education was stronger among the Turkish mothers ($p=0.0467$). However, we found this insufficient support to present the analyses stratified by each ethnic group. Results in this paper are therefore based on models including main effects only.

Statistical analyses were performed using Statistical Package of Social Sciences version 15.0 for Windows (SPSS Inc, Chicago, IL, USA) and the Statistical Analysis System (SAS) for Windows (SAS Institute Inc, USA), version 9.1.3.

RESULTS

Of the 5554 children, 25.8% of their mothers had a high educational level, and 23.1% of their mothers had a low educational level (table 8.1). Table 8.2 shows the associations of educational level with the covariates included in this study.

Parent-reports on URTI at the ages 0-6 months, 7-12 months and 13-24 months were available in respectively 61%, 74% and 75% of the study population. Compared with responders, among the group of non-responders mothers were younger, were more often in the lower educational level, were more often of non-Dutch origin, and were more often a single mother; the infants among the group of non-responders had on average a lower birth weight (data not shown). The incidences of URTI before imputation (39.1% from 0 to 6 months, 60.1% from 7 to 12 months and 70.2% from 13 to 24 months) were somewhat lower than those after imputation (43.2% from 0 to 6 months, 64.2% from 7 to 12 months and 73.2% from 13 to 24 months).

Maternal educational level and upper respiratory tract infections

At all ages, there was an inverse relationship between maternal educational level and the risk for URTI (figure 8.1). The gradient was strongest for URTI from 13 to 24 months. To save space, results of the logistic regression analyses are therefore shown for this age period only.

After adjustment for the potential confounders, children of mothers with a low educational level had a 56% higher risk for an upper respiratory tract infection compared with those of mothers with a high educational level (OR: 1.56; 95% CI: 1.16,2.11, table 8.3). After additional adjustment for presence of siblings and day-care attendance this risk was 70% higher (OR: 1.70; 95% CI: 1.26,2.30).

Individual adjustment for prenatal financial difficulties, prenatal psychiatric symptoms, and breastfeeding at 6 months attenuated the OR of 1.70 for low education by at least 10% (table 8.4); these factors were included in the next phase of the analyses.

Table 8.1 **Characteristics of the study population (n=5554)*.**

Maternal characteristics	**Percentage / Mean (standard deviation)**
Age at enrollment (years)	30.3 (5.0)
Single motherhood	12.9
Educational level	
High	25.8
Mid-high	21.3
Mid-low	29.9
Low	23.1
Ethnicity	
Dutch	53.7
Capeverdian	4.0
Moroccan	5.5
Dutch Antillean	2.6
Surinamese	8.1
Turkish	8.2
Other European	8.1
Other	9.8
Child characteristics	
Gender (% boys)	50.2
Birth weight (grams)	3425.8 (548.6)
Gestational age at birth (weeks)	40.1 (36.0,42.4)§
Breastfeeding at 6 months	29.8
Childcare attendance at 24 months	70.5
Exposure to tobacco smoke at 24 months	18.1
Presence of siblings	33.1

* Values are percentages in case of categorical variables, or means (with standard deviation) in case of continuous variables.

§ Median (with 95% range)

Data were missing on parity (n=6), single motherhood (n=59), ethnicity (n=10), household income (n=827), birth weight (n=3), gestational age at birth (n=1), breastfeeding at 6 months (737), day-care attendance at 24 months (n=1690), exposure to tobacco smoke at 24 months (n=1362), and presence of siblings (n=2149).

Table 8.2 **Associations of maternal educational level with covariates.***

	Maternal educational level				
	High	**Mid-high**	**Mid-low**	**Low**	**P for trend†**
Maternal characteristics					
Age at enrollment	32.9 (3.3)	31.5 (4.0)	29.1 (5.1)	27.8 (5.7)	<0.001
Ethnicity					
Dutch (%)	72.4	67.5	44.9	31.4	
Capeverdian (%)	0.3	1.7	5.4	8.4	
Moroccan (%)	0.6	2.8	6.6	12.1	
Dutch Antillean (%)	0.6	1.8	4.0	4.0	<0.001
Surinamese (%)	1.3	4.7	12.3	13.3	
Turkish (%)	1.3	3.4	9.4	18.6	
Other European (%)	11.7	8.7	7.3	4.5	
Other (%)	11.7	9.3	10.2	7.6	
Single motherhood (%)	3.3	6.0	16.0	26.1	<0.001
Financial difficulties (% yes)	6.0	11.0	23.6	40.9	<0.001
Prenatal psychopathology (% highest tertile)	29.6	38.8	51.7	60.6	<0.001
Prenatal family functioning (% highest tertile)	16.1	23.6	35.6	45.0	<0.001
Prenatal long lasting difficulties (% highest tertile)	23.3	35.0	41.4	44.0	<0.001
Smoking during pregnancy (% yes)	13.7	20.7	27.0	37.5	<0.001
Postnatal financial difficulties (% highest tertile)	7.3	16.6	26.5	43.5	<0.001
Postnatal psychopathology (% highest tertile)	26.9	32.5	37.4	43.2	<0.001

Table 8.2 Continued

	Maternal educational level				
	High	**Mid-high**	**Mid-low**	**Low**	**P for trend†**
Child characteristics					
Gender (% boys)	49.8	50.2	50.2	50.9	0.603
Birth weight (grams)	3515.0 (528.8)	3465.6 (548.1)	3377.6 (549.9)	3351.6 (552.5)	<0.001
Birth weight SDS	0.04 (1.0)	-0.03 (1.0)	-0.2 (1.0)	-0.2 (1.0)	<0.001
Gestational age at birth	40.3 (36.0-42.4)	40.3 (36.0-42.4)	40.1 (35.9-42.3)	40.0 (35.6-42.3)	<0.001
Hospitalization 1st week (%)	16.5	16.3	16.6	17.8	0.495
Breastfeeding at 6 months (% yes)	39.0	34.5	22.7	21.7	<0.001
Exposure to environmental tobacco smoke at 24 months (%)	7.5	12.7	22.1	38.3	<0.001
Siblings (% yes)	31.1	30.1	30.8	44.5	<0.001
Day care attendance at 24 months (% yes)	89.5	76.7	61.7	40.4	<0.001

* Values are percentages for categorical factors, or means (with standard deviations) or median (with 95% range) for continuous factors.

† p-values are for chi-squared test for trend (categorical factors), and for (linear) trend component of one-way analysis of variance or kruskall-wallis test (continuous factors).

Adjustment for the selected prenatal factors reduced the OR for low education to 1.51 (table 8.5). This implies that these factors explained 27% (model 3 compared to model 2: 1.70-1.51/0.70) of the increased susceptibility for URTI. The *independent* contribution of these factors was also 27% (1.62-1.43/0.70; model 5 compared to model 4). Together, prenatal/perinatal and postnatal factors explained 39% (1.70-1.43/0.70) of the effect of low education. The OR for low education in the final model remained statistically significant. Adjusted for all the other factors in this final model, prenatal financial difficulties, and prenatal psychiatric symptoms were positively associated, and breastfeeding at 6 months was negatively associated with the risk for URTI. To exclude that the effects of prenatal financial difficulties and psychiatric symptoms were due to correlations with postnatal financial difficulties and psychiatric symptoms, these latter factors were added to the final model; although the effects of prenatal financial difficulties and prenatal psychiatric symptoms on URTI attenuated somewhat, they remained statistically significant (data not shown).

Prenatal financial difficulties, prenatal psychiatric symptoms, and breastfeeding at 6 months were also the most important factors contributing to the observed educational

inequalities in URTI between 0 and 6 months and between 7 and 12 months of age (data not shown).

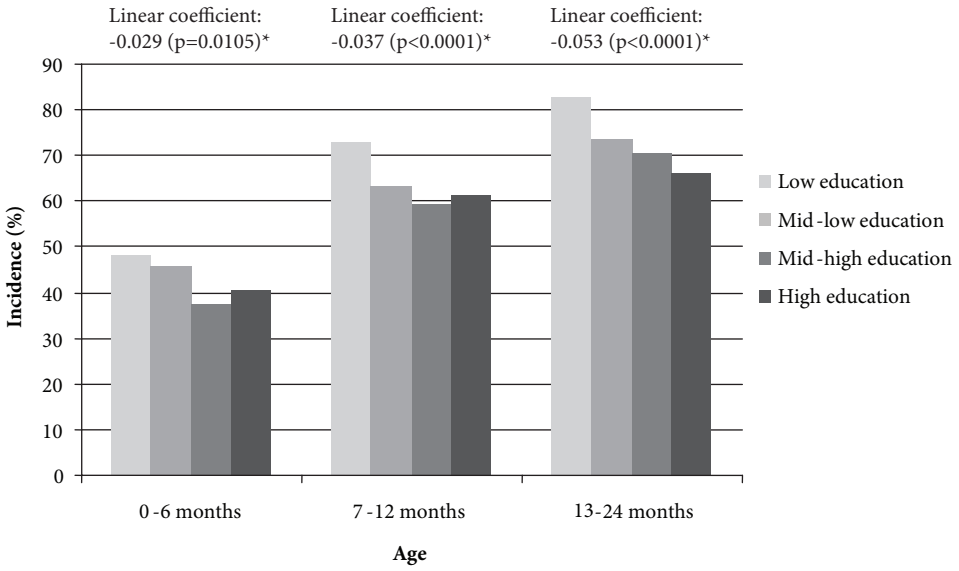

Figure 8.1 **Incidence of parent-reported upper respiratory tract infections from 0 to 6 months, from 7 to 12 months and from 13 to 24 months, stratified by maternal educational level.** * Derived from linear regression analyses where educational level was treated as a continuous variable

Table 8.3 **Logistic regression analyses: association of maternal educational level with upper respiratory tract infections between 13 and 24 months of age*.**

Socioeconomic indicator	Crude OR (model 0)	Adjusted for confounders§ (model 1)	Adjusted for confounders and exposure variables¶ (model 2)
Maternal educational level			
High	1.00	1.00	1.00
Mid-high	1.24 (1.04,1.48)	1.13 (0.95,1.29)	1.17 (0.98,1.41)
Mid-low	1.46 (1.23,1.72)	1.08 (0.90,1.29)	1.14 (0.95,1.37)
Low	2.52 (1.94,3.27)	1.56 (1.16,2.11)	1.70 (1.26,2.30)

* Values are odds ratios with associated 95% confidence intervals.

§ Potential confounders are mother's ethnicity, mother's age, and child's age at which 24-months questionnaire was completed.

¶ Exposure variables are day-care attendance at 24 months and siblings.

Table 8.4 **Change in odds ratios (OR) related to the associations of maternal educational level with upper respiratory tract infections between 13 and 24 months of age after individual adjustment for potential mediators.**

Models	OR (95%CI) ' Low education' versus ' high education'	Change*
Model 2§	1.70 (1.26,2.30)	-
Prenatal/perinatal factors		
Model 2 + single motherhood	1.66 (1.22,2.26)	-6%
Model 2 + prenatal financial difficulties	1.57 (1.16,2.12)	-19%
Model 2 + prenatal psychiatric symptoms	1.61 (1.19,2.18)	-13%
Model 2 + prenatal family functioning	1.64 (1.20,2.23)	-9%
Model 2 + prenatal long lasting difficulties	1.66 (1.22,2.25)	-6%
Model 2 + Maternal smoking during pregnancy	1.67 (1.25,2.24)	-4%
Model 2+ birth weight	1.70 (1.25,2.29)	-0%
Model 2+ gestational age at birth	1.68 (1.24,2.28)	-3%
Model 2 + hospitalisation in 1st week	1.68 (1.24,2.28)	-3%
Postnatal factors		
Model 2 + postnatal psychiatric symptoms	1.69 (1.25,2.28)	-1%
Model 2 + postnatal financial difficulties	1.66 (1.23,2.24)	-6%
Model 2 + Breastfeeding at 6 months	1.62 (1.21,2.18)	-11%
Model 2 + Exposure to environmental tobacco smoke	1.65 (1.23,2.22)	-7%

* Change in odds ratio relative to model 2 for 'low education' versus 'high education', after individual adjustment for the potential mediators ($100x[OR_{model\ 2} - OR_{model\ 2\ +mediator}]/[OR_{model\ 2} - 1]$). §Model 2: includes educational level, mother's ethnicity, mother's age, and child's age at which 24-months questionnaire was completed, day-care attendance at 24 months and siblings)

Table 8.5 **Logistic regression models fitted on the association between maternal educational level and upper respiratory tract infections between 13 and 24 months of age.***

	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)	Model 5 OR (95% CI)
Maternal education				
High (ref)	1.00	1.00	1.00	1.00
Mid-high	1.17 (0.98,1.41)	1.13 (0.95,1.35)	1.16 (0.97,1.39)	1.11 (0.93,1.34)
Mid-low	1.14 (0.95,1.37)	1.06 (0.88,1.28)	1.10 (0.97,1.39)	1.01 (0.83,1.22)
Low	1.70 (1.26,2.30)	1.51 (1.11,2.05)	1.62 (1.21,2.18)	1.43 (1.06,1.92)
Prenatal financial difficulties				
No (ref)		1.00		1.00
Yes		1.40 (1.05,1.87)		1.42 (1.06,1.89)
Prenatal psychiatric symptoms				
Lowest tertile (ref)		1.00		1.00
Middle tertile		1.26 (1.06,1.48)		1.26 (1.07,1.49)
Highest tertile		1.51 (1.28,1.78)		1.52 (1.29,1.80)
Breastfeeding at 6 months				
No (ref)			1.00	1.00
Yes			0.80 (0.69,0.93)	0.78 (0.67,0.91)

* Values are odds ratios with associated 95% confidence intervals
Model 2: Adjusted for mother's ethnicity, mother's age, and child's age at which 24-months questionnaire was completed, day-care attendance at 24 months and siblings.
Model 3: Model 2 + prenatal financial difficulties, prenatal psychiatric symptoms
Model 4: Model 2 + breastfeeding at age 6 months
Model 5: model 2 + prenatal financial difficulties, prenatal psychiatric symptoms, and breastfeeding at age 6 months

DISCUSSION

The present study indicates that toddlers of low SES, as measured by a low maternal educational level, are more susceptible to URTI than toddlers of high SES. This is in line with previous reports[5 6]. The novelty of our study lies in the demonstration that, independently of postnatal circumstances, part of this increased susceptibility was explained by adverse prenatal circumstances, in particular factors related to prenatal psychosocial stress.

In both adults and children, a low SES has been associated with a higher incidence of respiratory infections[5 6 11 26]. Theoretically, this can be attributed to an increased exposure to infectious agents, and/or to a decreased host resistance, i.e. susceptibility to infections[11]. Viral

challenge studies have provided evidence that adults of low SES are indeed more susceptible to develop URTI[11]. Our study suggests the same for toddlers. A substantial part of the increased susceptibility to these infections was explained by an increased exposure to prenatal psychosocial stressors, more specifically by prenatal financial difficulties and psychiatric symptoms in the mother. Family stress measured postnatally has previously been shown to increase children's susceptibility to infections. For example, Drummond et al.[27] found that psychosocial stress is related to recurrent URTI in children, possibly through decreased mucosal immunity. More recently, Wyman et al.[19] demonstrated that children of parents with higher levels of psychiatric symptoms in the context of family stressors had more febrile illnesses. However, while our results suggest that stress during pregnancy also has an independent effect on susceptibility to URTI in early childhood, we found no other studies that investigated such an association. It has been speculated, though, that stress during pregnancy may dampen the fetal immune system through changes in the HPA-axis[28], which supports the possibility that prenatal stress increases a child's susceptibility to infections through an intrauterine effect. Further support is provided by the observed correlation between both a low SES and depressive symptoms in the mother with higher salivary cortisol levels in children[29]. The observed effect of financial difficulties in our study concurs with results from a study by Seguin et al[30], who demonstrated that material hardship is a predictor of a range of health-related outcomes in early childhood.

While SES is strongly related to birth weight and perinatal morbidity[31 32], these factors hardly contributed to the explanation of the observed socioeconomic differences in URTI, suggesting that a low SES does not influence a child's susceptibility to these infections through its link with fetal growth and health at birth.

Methodological considerations

In this study, a major concern is the self-reported nature of the data. Parents' reports of their children's health status might be affected by their SES and by their own psychological state[33]. If mothers of lower SES and those with more psychosocial stress are more likely to consider their children as being in poor health, this might have overestimated the socioeconomic differences in URTI, as well as the contribution of psychosocial-stress factors to the explanation of these differences. However, in contrast to our results regarding URTI, preliminary analyses showed that mothers of low SES reported less asthma-related symptoms between 6 and 12 months compared with those of high SES (data not shown), a finding that concurs with previous reports[34]. This conflicts with the theory that parents of low SES report more disease. One could state that the use of data from physicians or laboratories may be a good alternative to parent

reports. However, patterns of consultation do not necessarily reflect socioeconomic variations in URTI, since the decision to seek help from a doctor is dependent on access to health care and on health behavior.

Our study was conducted in an exclusively urban population, and, although the participation rate in The Generation R Study was relatively high (61%), there was some selection towards a study population that was relatively highly educated and more healthy[13]. This limits the generalizability of our findings. Non-participation would have lead to selection bias if the associations of family SES with URTI in early childhood differed between participants and non-participants. This seems unlikely, but is difficult to ascertain. One should also take into account potential bias due to missing information on maternal educational level (6.7%). Compared with mothers with available data on their educational level, those without these data were younger, more often of non-Dutch ethnicity, were more often smokers and were more likely to have financial difficulties and a high score on psychopathology (data not shown), thus making these mothers more likely to be of low SES. URTI were also more prevalent in this subgroup (data not shown). Therefore, missing data is more likely to have resulted in an underestimation rather than an overestimation of our effect estimates. By using multiple imputation, we have minimized any bias that would have resulted from missing data on the outcome.

Although there are other measures of SES, we selected maternal educational level as main indicator, because it not only reflects material resources, but also non-economic social characteristics, such as general and health-related knowledge[35]. Nevertheless, we repeated the analyses using household income level as determinant, and found a similar inverse relationship with URTI at all ages. For example, an income of <1200 euros per month was associated with a 51% (OR 1.51; 95% CI: 1.09, 2.10) increased risk for URTI between 13 and 24 months after adjustment for confounders and presence of siblings and day-care attendance. Independent of postnatal factors, factors related to prenatal stress explained about 40% of this association (data not shown).

In conclusion, our study adds to the small body of literature concerning the contribution of early life factors to socioeconomic inequalities in child health. Although URTI are generally relatively mild, the excess in respiratory infections attributable to social disadvantage results in a higher disease burden and an impaired quality of life in children of low SES[36]. Furthermore, these infections have social implications, leading to for example more job absence and medical costs[10]. There is evidence that the increased susceptibility to respiratory infections associated with low SES in early life may persist into adulthood[26], further underlining the importance of interventions to reduce these socioeconomic inequalities early in life. Our results suggest that

a reduction may be accomplished by interventions aimed at active tracking and counselling of pregnant women exposed to psychosocial stressors.

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Part IV:

Discussion

Chapter 9

General discussion

The aim of this thesis was to contribute to a further understanding of the origins of socioeconomic inequalities in child health, in particular, of the possible role of intrauterine exposures in the genesis of these inequalities, by studying the nature, magnitude and explanation of socioeconomic inequalities in aspects of maternal, fetal and early childhood health. In this final chapter, the key findings of this thesis are discussed in the light of this aim. First, the main findings will be summarized. Then, I will give an analysis of methodological issues that should be taken into account when interpreting these findings. This is followed by an outline of possible explanations and interpretations of the findings. Finally, I will outline the implications of our results for public health policy, clinical practice, and future research.

9.1 SUMMARY OF FINDINGS

The studies presented in this thesis describe the socioeconomic inequalities in 1) maternal health outcomes during pregnancy, 2) indicators of fetal growth, and 3) early childhood health outcomes. Below, we present a summary of the main results from these studies.

Socioeconomic status and maternal health during pregnancy

Chapters 2 to 5 were dedicated to the association between maternal educational level as a measure of socioeconomic status, and the risk for several pregnancy-related diseases. We found a strong educational gradient in the risk for preeclampsia, where the lowest educational subgroup of pregnant women had a five times higher odds compared with the highest educational subgroup. Although we included a wide range of potential explanatory factors, this relationship remained largely unexplained.

The search for potential mechanisms underlying the effect of socioeconomic status on preeclampsia was continued with the study described in chapter 3. This study showed that from early pregnancy onwards, women with relatively low levels of education had higher mean blood-pressure levels than women with a high educational level. The most remarkable result, however, was that the fall in diastolic blood pressure one would normally expect in midpregnancy, was not observed in women with a low educational level. Our findings suggested that the lack of a midpregnancy fall predisposes women with a low educational level toward the development of preeclampsia.

As described in chapter 4, women with relatively low levels of education had a 30 to 50% higher risk for gestational hypertension than women with a high educational level. This increased risk was almost entirely explained by other, more proximal factors, particularly by the higher

rates of overweight and obesity, and by the relatively high blood-pressure levels at enrollment found in lower educated women. Since these factors are also known risk factors for essential hypertension[1 2], our findings suggest that the relatively high risk of gestational hypertension in women with low levels of education reflects pre-existing hypertensive tendencies in these women that are disclosed by the physiological stress of pregnancy[3].

Another pregnancy complication studied in this thesis is gestational diabetes. As shown in chapter 5, women with a low educational level were three times more likely to develop gestational diabetes as compared with women with a high level. The largest part of this increased risk was explained by relatively high rates of overweight and obesity in the lower educational subgroups.

Socioeconomic status and fetal growth

Chapter 6 of this thesis provides an assessment of the association of maternal socioeconomic status, as measured by her educational level, with fetal growth. This assessment provided three main findings. First, a low maternal educational level was associated with a progressively slower fetal growth, resulting in differences in fetal weight that were observable already from late pregnancy onwards. Second, our findings suggested that the adverse effect of low education was largest for growth of the fetal head, followed by growth of the fetal femur and abdomen. Third, while other determinants of fetal growth, in particular maternal smoking during pregnancy and maternal height, explained a large part of the educational inequalities in growth characteristics, the inequalities in fetal head circumference remained partly unexplained.

Socioeconomic status and health outcomes in early childhood

The studies described in chapters 7 and 8 provide evidence of socioeconomic inequalities in two early childhood health outcomes. The first is height and linear growth during the first two years of life. We found that, at two months of age, children of low educated mothers were shorter than their counterparts. However, contrary to what was expected, a low educational level of the mother was associated with a faster linear growth during the first 1.5 years of life as compared with a high level. By 14 months of age, children in the lowest educational subgroup had compensated their initial height deficit; at this age they were even slightly taller than children in the highest educational subgroup. While the shorter duration of breastfeeding, and, more in particular, the lower rates of day-care attendance in children in lower educational subgroups explained part of their taller height, intrauterine factors, i.e. smoking during pregnancy, birth weight and gestational age at birth, did not contribute to the explanation. On the contrary,

the positive difference in height between the lowest and the highest socioeconomic subgroup became even stronger after adjustment for these intrauterine factors.

Second, we examined the socioeconomic inequalities in upper respiratory tract infections during the first two years of life. This analysis showed an inverse relationship between maternal educational level and the child's risk for upper respiratory tract infections during the first two years of life, and this gradient seemed to increase with age. Independent of postnatal factors, prenatal financial difficulties and prenatal maternal psychiatric symptoms explained part of the increased susceptibility to these infections in children of low socioeconomic status.

9.2 METHODOLOGICAL ISSUES

The strengths and limitations of the specific studies in this thesis have been described in the previous chapters. This section is dedicated to a more general discussion of the methodological issues that should be taken into account when interpreting the results as a whole.

Study design

The Generation R Study, from which the data for this thesis were derived, had an observational prospective design. In this type of research, groups of individuals who are alike in many ways but differ by a certain characteristic, are classified according to an exposure, followed over time, and compared for a particular outcome[4].

Observational prospective studies have specific strengths and limitations.

Among the strengths are the researchers' full control over data collection – they can measure a broad set of baseline characteristics and plan frequent new measurements over time – their opportunity to assess temporal relationships between cause and effect, and the fact that the decision to participate is generally assumed to be independent of future outcomes[4]. While in most studies described in this thesis the determinant was measured before the outcome, in a few cases determinant and outcome were measured simultaneously or with a short-time interval in between. For example, in chapter 4, the first blood-pressure measurement of the mother took place around the time that her educational level was established.

There are also some limitations to this type of design: it is time-consuming, expensive and needs a lot of manpower[4]. Furthermore, it is sensitive to bias that may threaten the validity of results; these include selection bias, information bias and confounding. The extent to which our results were influenced by these types of bias will be discussed below.

Selection bias

The Generation R Study is a population-based cohort study, and its aim was to include all eligible pregnant women in a predefined area of Rotterdam. The initial participation rate, i.e. the proportion of eligible people that participated in the study, was estimated to be 61%[5-7]. Non-participation was not random; the percentage of mothers from ethnic minorities and lower educational levels among Generation R Study participants was lower than would be expected from general population figures of Rotterdam[8 9]. Furthermore, the percentages of children born preterm or with a low birth weight were relatively low. This seems to reflect a selection towards a relatively more affluent and healthy study population, and this raises concerns about potential selection bias.

Selection bias occurs when the association between determinant and outcome is different in those who participate and those who were eligible for participation, i.e. the source population. In prospective cohort studies, such bias would occur when the decision to participate is correlated with the determinant and with the outcome. Because the decision to participate in a prospective cohort study cannot be based upon future outcomes, the risk of bias due to non-participation is often considered to be small. However, this decision may be correlated with social, educational and health conditions, which in turn may correlate with risk factors for the outcome of a study[10]. Thus, it cannot be ruled out that selective non-participation influenced our results to some extent. However, a recent analysis by Nohr et al.[11] of the consequences of non-participation in a similar cohort study as The Generation R Study provided reassuring results. Nohr et al. investigated the impact of the initial selection into the Danish National Birth Cohort study, a nationwide study of 100,000 pregnant women and their offspring. The participation rate was relatively low, 30%, and like in The Generation R Study, participants were somewhat healthier than mothers in the source population. Despite this differential participation, the odds ratios for three associations between well-established risk factors and pregnancy outcomes were quite similar between participants and the source population.

Selective non-response to questionnaires and visits to the research centers, and selective loss to follow-up are probably more of a threat to our studies' internal validity than non-participation. Loss to follow-up seemed relatively low: for example, loss to follow-up during the first four postnatal years of The Generation R Study is estimated to be lower than 10%[7]. Non-response to questionnaires was the main source of missing data in our studies, in particular the studies using postnatal data. Data on covariates and outcome were more often missing in the lower socioeconomic subgroups than in the higher, and missingness was likely to be correlated with the health outcomes under study. One might assume that among the non-responders the

people of lower socioeconomic status have an even higher risk of adverse health outcomes than the responders of lower socioeconomic status. However, this may not necessarily be the case. In the studies using postnatal data, we tried to overcome the potential threats caused by selective missingness by applying multiple imputation to impute missing information on covariates, and in chapter 8 also on the outcome. In chapter 8, we observed that the total incidence of upper respiratory tract infections increased somewhat after imputation, and so did the magnitude of association between socioeconomic status and childhood upper respiratory tract infections (data not shown). Assuming that multiple imputation resulted in accurate estimates of missing data, this suggests that complete-case analyses would have led to an underestimation of the association between socioeconomic status and upper respiratory tract infections. Thus, selective non-response or loss to follow-up may have influenced the magnitude of the associations described in this thesis.

Information bias

The data that were used in our studies were assessed through parental questionnaires, medical records, ultrasound, and hands-on measurements. Self-reported data are particularly prone to misclassification[12-14]. Information on socioeconomic indicators, including educational level and household income, were all self-reported, and we cannot exclude some misclassification in these data. However, the associations presented in this thesis are biased only when misclassification of the outcome is related to the determinant or vice versa. In most of our studies, data on the outcomes were collected after establishment of indicators of socioeconomic status. Furthermore, with one exception, in our studies the outcome was either derived from medical records, or measured by research assistants, which limits the possibility of differential misclassification. The exception is the study described in chapter 8 on socioeconomic status and upper respiratory tract infections in early childhood, where both the outcome and the determinant were parent-reported. As discussed in chapter 8, this may have led to bias in our results, if mothers of lower socioeconomic status are more likely to consider their children as being in poor health.

Information on most of the risk factors that were considered potential mediators in the associations between socioeconomic status and health outcomes, such as sources of maternal psychosocial stress, maternal smoking behavior, and breastfeeding, were collected using questionnaires. Error in the measurement of such factors can bias their association with the health outcomes and with socioeconomic status, and thus may bias the contributions of these factors to the socioeconomic inequalities in these health outcomes. Although individuals

of lower socioeconomic status have been shown to be more prone to underreporting certain chronic conditions and underestimating certain traits such as height and weight[15 16], this is not a consistent phenomenon for all variables measured through self-report. A recent study among British pregnant women demonstrated that, while women generally tended to underreport smoking during pregnancy, the rates of underreporting did not differ by occupational class, education or tenure[17]. Nevertheless, the residual effects of low socioeconomic status on preeclampsia, fetal head circumference or the child's height at 14 and 25 months after full adjustment for potential confounders and mediators may at least be partly attributed to imprecise measures of these confounders and mediators.

Mediation and confounding

In all our studies, we assumed that socioeconomic status does not have a direct effect on health, but rather acts through other more proximal determinants of the health outcomes; these determinants are called 'mediators'. In the analyses, we consistently made a distinction between confounders, i.e. factors that may distort the association between socioeconomic status and health, and mediators, i.e. factors that may explain the association between socioeconomic status and health. For a factor to be confounder in such an association, it must satisfy three criteria[18 19]:

1) it must be a risk factor of the disease under study
2) it must be correlated with socioeconomic status in the study population
3) it should not be caused by socioeconomic status, or in other words it should not be an intermediate step in the causal pathway between socioeconomic status and the disease.

When a factor is a risk factor of the disease ánd is caused by socioeconomic status, it is considered to be a mediator[18 19] (see also figure 9.1).

In studying socioeconomic disparities in health, ethnicity is probably the strongest factor that might cause distortion of the apparent effect of socioeconomic status. Ethnicity satisfies the criteria for a confounder: it is usually correlated with socioeconomic status[20], it is a determinant of health during pregnancy[21-23], pregnancy outcome[24 25] and child health[26 27], and is not caused by socioeconomic status. Also, ethnicity often interacts with socioeconomic status in influencing health[22 28-32]. To avoid this type of distortion in our studies, we restricted most of our studies (chapters 2, 3, 4, 6, and 7) to participants with a Dutch ethnicity whenever preliminary analyses indicated substantial differences in the magnitude of socioeconomic inequalities across the different ethnic groups.

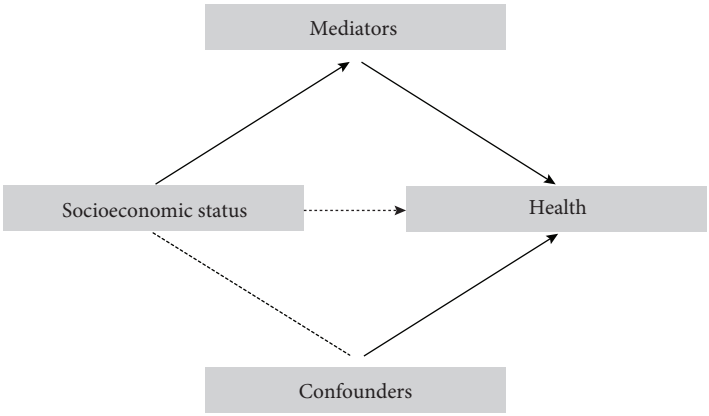

Figure 9.1 **Model representing the relationships between socioeconomic status, mediators, confounders and health.**

The choice whether to consider a factor a confounder or a mediator is based on pre-existing knowledge about social and biological determinants of disease. It is not always a straightforward one, though, and is sometimes arbitrary. Maternal age, for example, was consistently included as a confounder in our studies on socioeconomic variation in the prevalence of pregnancy related complications. We did this, because we believed that socioeconomic status is not likely to cause the age of the mother at inclusion in the study. Rather, the age of the mother partly determines the maximum educational level that can theoretically have been achieved at the time of inclusion. However, one could also argue that maternal age might act as a mediator because socioeconomic status influences the age at which women become pregnant. After all, teenage pregnancies are more common in lower socioeconomic subgroups than among higher socioeconomic subgroups[33 34].

Another source of discussion when defining a factor as a mediator is the causal relationship that is inferred between socioeconomic status and that factor. Because actual establishment of causality is only possible with experimental data, one cannot exclude the possibility that the association between socioeconomic status and the mediator is not causal. This is the case, for example for smoking, an important contributor to socioeconomic differentials in health. While in our analyses we assumed the association between socioeconomic status and smoking status during pregnancy to be (directly or indirectly) causal, this has been doubted by others. It has been argued that, because smoking patterns are generally established by age 17, they cannot be influenced by years of schooling. In stead, there may be one or more 'third

variables' that confer vulnerability to attain less education ánd to smoke[35]. However, for the explanation of socioeconomic differences in health outcomes during pregnancy, fetal growth and early childhood health, smoking initiation was not of relevance. Rather, we were interested in the contribution to these differences of smoking at time of pregnancy and thereafter. There is evidence that educational attainment has an impact on adult smoking trajectories. In a study among adults with an average age of 39 years, Gilman et al.[36] found evidence for a causal relationship between level of education and cigarette consumption, frequency of quit attempts, and likelihood of quitting, although part of the educational differences was attributable to factors shared by siblings. Moreover, a recent study on socioeconomic differences in smoking during pregnancy suggests that the socioeconomic gradient in smoking in pregnancy results from longitudinal accumulation and cross-sectional clustering of social risk exposures[37]. These findings support the inclusion of smoking during pregnancy as a potential mediator in our studies.

Assessment of mediation effects

To assess the extent to which potential mediators contributed to the observed socioeconomic differences in health outcomes, we followed the following procedure: First, we assessed the estimate of the effect of socioeconomic status on the health outcome adjusted for a set of confounders, which was considered to reflect the overall effect of socioeconomic status. Then, this estimate was compared with the estimate adjusted for the same confounders plus one or more factors hypothesized to be potential mediators. The percentage change from the first to the second estimate provided an indication of the extent to which potential mediators explained the observed effect of socioeconomic status.

The use of regression adjustment to assess mediation has been criticized, though. The assumptions necessary for this method to be valid, which include assumptions of causality, absence of unmeasured confounding of the mediating effect, and absence of unit-level interactions, are often difficult to verify[38]. Furthermore, the percentage change can be similar for different absolute changes in effect estimates. However, alternative methods, such as structural equation modelling[39], also have their drawbacks. As Kaufman et al. indicate, structural equation modelling does not seem to overcome the issues regarding causality and absence of effect modification[40]. Thus, as alternative methods have not been proven to be superior, regression adjustment still remains the most widely used approach to investigate the contribution of risk factors to socioeconomic differences in health[41-44].

Socioeconomic indicators

Socioeconomic status refers to the "social and economic factors that influence what positions individuals or groups hold within the structure of society"[45]. It is a complex and multifactorial construct. The most frequently used indicators of socioeconomic status are educational level, income level and occupational class[45 46]. In this thesis, we consistently used educational level as the main indicator of maternal socioeconomic status (see figure 9.2). This contrasts with, for example, studies from the UK and US, where occupational class and income level are more frequently used[47-51]. We believed educational level to be a useful indicator of socioeconomic status for several reasons.

First, educational level not only partly reflects maternal resources because it structures occupation and income, it also reflects non-economic social characteristics, such as literacy, problem-solving skills, prestige and general and health-related knowledge which influences health behaviour[46 52]. Second, unlike for example occupational class, a classification according to educational attainment can be applied to teenage and unemployed mothers. Third, educational level is relatively stable over time. Last, educational attainment has been reported as the facet of socioeconomic status that is more determinant of health status, particularly cardiovascular conditions[53-55]. An additional reason for using educational level in stead of, for example, income level, was that data on the latter was more often missing in the Generation R Study than the former. Focusing on income level as indicator of socioeconomic status might thus have led to a loss of power and perhaps to selection bias.

Selecting educational level as the main socioeconomic indicator also has its limitations. It does not entirely capture the material and financial aspects of socioeconomic status. Although educational level is highly correlated with occupation and income, this correlation is not one on one, meaning that low educated women may have jobs with a relatively high income, and visa versa. It is possible that education and maternal hardship differentially affect health and that these effects act through different pathways. This is illustrated by a study by Seguin et al[56], demonstrating that, independent of maternal education, longstanding maternal hardship, i.e. inadequate income to meet needs, affects a range of health-related outcomes in early childhood.

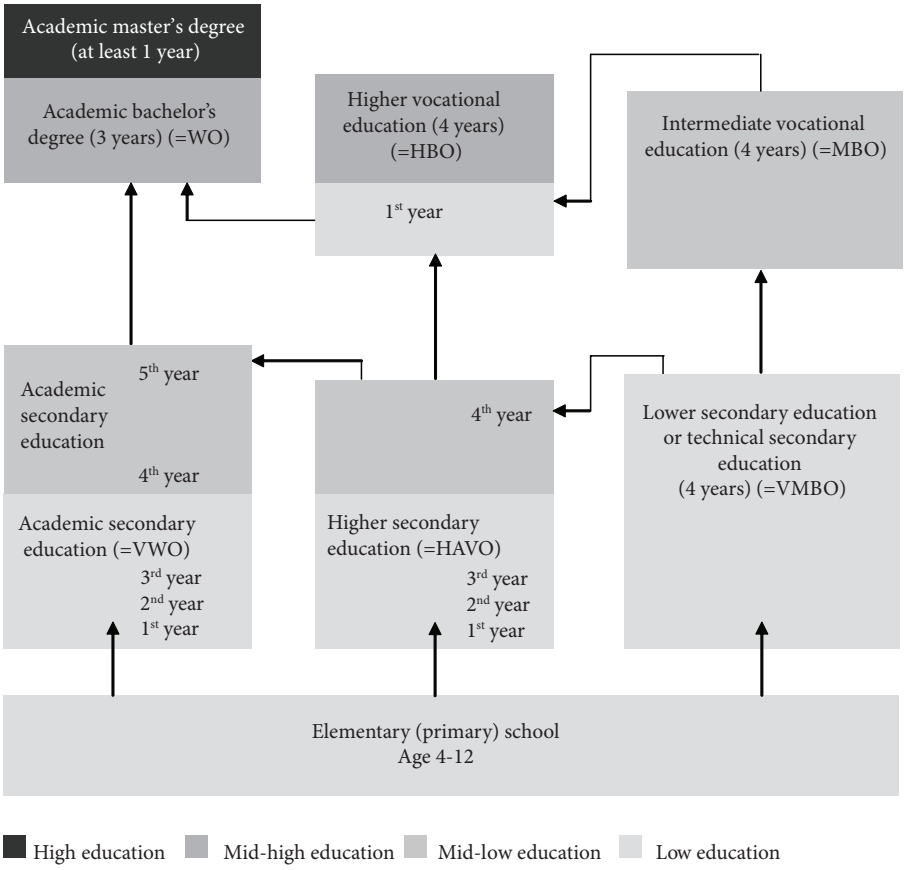

Figure 9.2 **Dutch educational system and categories as used in this thesis.** (*created by L. Van Rossem; VWO: voorbereidend wetenschappelijk onderwijs; HAVO: hoger algemeen voortgezet onderwijs; VMBO: voorbereidend middelbaar beroepsonderwijs; HBO: hoger beroepsonderwijs; WO: wetenschappelijk onderwijs).* Note: in chapter 4, five categories of education were distinguished, instead of four; elementary (primary) school represented a separate category.

External validity

When samples for observational epidemiological studies are drawn using a variety of criteria, there is always the possibility that such selection criteria might compromise generalizability. For inclusion in The Generation R Study, pregnant women had to be residents of a specific area of Rotterdam at time of delivery, and the delivery date had to be between April 2002 and January 2006. Furthermore, in many of our studies we restricted the analyses to the subgroup

with a Dutch ethnicity. Thus, the results described in this thesis may be specific to Dutch, urban populations, or even only to populations living in Rotterdam.

Previous studies have already demonstrated that the magnitude of socioeconomic inequalities and the factors contributing to these inequalities may differ between countries[57 58]. According to a recent large study on socioeconomic inequalities in health in 22 European countries[58], both absolute and relative education-related differences in mortality are relatively small in southern European populations, and relatively large in eastern and Baltic regions. The smaller inequalities in mortality in southern regions were due mainly to smaller inequalities in the rate of death from cardiovascular disease. In addition, this study showed that, while education-related inequalities in smoking are relatively large in northern, western, and continental regions, these inequalities are relatively small among men living in southern regions. What's more, among women from southern European regions, even reverse inequalities in smoking were found, meaning that smoking rates are higher in subgroups of high education than in those of low education. Given these findings, it is possible that for example socioeconomic inequalities in hypertensive disorders of pregnancy are smaller or even absent in southern European countries, or that in these countries smoking during pregnancy has a limited contribution to socioeconomic inequalities in fetal growth.

Thus, caution should be taken when generalizing the results of this thesis to other populations, as the magnitude of socioeconomic inequalities in health as well as the pathways underlying these inequalities are not necessarily the same. Particularly in low or middle-low income countries, the situation may be completely different. This is most likely the case for our findings on socioeconomic inequalities in early linear growth (chapter 7). There were indications that overfeeding was partly behind the relative accelerated growth in children of low socioeconomic status. This is probably specific to wealthy populations with increasing availability of inexpensive, energy-dense food. It is unlikely that the same phenomenon will be found in poor countries, where low socioeconomic status is generally associated with a lack of resources for adequate nutrition.

9.3 INTERPRETATION OF FINDINGS

Socioeconomic status and maternal health during pregnancy

As mentioned in the Introduction, socioeconomic conditions affect child health[30 47 59-63], and this effect is present already at birth, as illustrated by for example socioeconomic inequalities in birth weight[50 64 65]. Child health may be influenced by socioeconomic status from fetal

life onwards through multiple pathways. One hypothesized pathway is through an effect on mother's physical health during pregnancy.

It is known that maternal health at time of pregnancy, both mental and physical, is of substantial influence on health and development of her unborn child[66-69]. Regarding maternal physical health, previous studies have demonstrated the effects of general measures of health as well as specific diseases during pregnancy[67 68 70]. For example, it has been found that women with poor or very poor health at the time of pregnancy, as assessed by an obstetrician at the first antenatal care visit, are at increased risk of hypertension during pregnancy, of delivering preterm, and of having a lower birth weight infant[67]. Regarding the more specific diseases, much attention has been paid to the impact of hypertensive disorders of pregnancy and gestational diabetes[1 68 70-76]. Globally, hypertensive disorders of pregnancy, in particular preeclampsia, are leading causes of maternal and perinatal mortality and morbidity[76-79]. Preeclampsia, for instance, is associated with a two to three times increased risk for fetal death, and a three to four times increased risk for preterm delivery or a small- for-gestational-age infant[68 70 73]. Gestational diabetes also has risks for the fetus; these include macrosomia, birth trauma such as brachial plexus injury or clavicular fracture, and neonatal metabolic problems including hypoglycaemia[80].

Evidence suggests that poor maternal physical health also has longterm health consequences for the offspring. Poor health of the mother at the time of pregnancy has been associated with a shorter stature and lower weight in childhood as well as with adult cardiovascular health problems[67]. Furthermore, children who were exposed in utero to hypertensive disorders are more likely to have a delayed neurological development in infancy[81], higher blood pressure levels and impaired glucose metabolism during childhood and adolescence[75 82-84]. Children intrauterinely exposed to diabetes are at increased risk for later development of the metabolic syndrome and type 2 diabetes[80 85].

On the basis of these findings, one could postulate that indicators of maternal health might be involved in the pathway between socioeconomic status and offspring health. For indicators of maternal health to be in this pathway, they must be strongly associated with maternal socioeconomic status. This thesis investigated the effect of socioeconomic status on specific maternal health outcomes: hypertensive disorders of pregnancy, blood pressure and gestational diabetes. We found marked socioeconomic differences in these outcomes, where the lower socioeconomic subgroups of pregnant women were consistently worse off as compared with the higher socioeconomic subgroups.

Taken together, the results indicate that women of low socioeconomic status seem to have lower chances of completing a healthy pregnancy. Our analyses not only showed that mothers with a low educational level are more likely to develop pregnancy-related complications, they also showed that these women have unfavourable risk profiles. With some exceptions, factors that are known to increase the risk for adverse pregnancy outcomes were more prevalent among pregnant women of low socioeconomic status than among those with high socioeconomic status. These factors include sources of psychosocial stress such as financial difficulties and psychiatric symptoms, smoking during pregnancy, illegal drug use, physically demanding working conditions, overweight and obesity, and pre-existing chronic conditions[66 86-91].

The increased susceptibility to hypertensive pregnancy complications among socioeconomically disadvantaged women also has implications for their own cardiovascular health. There is substantial evidence that women with a history of preeclampsia or gestational hypertension have a two to three times higher risk for hypertension, ischemic heart disease, and premature cardiovascular death, compared with women who had normotensive pregnancies[92-95]. Furthermore, hypertensive pregnancy complications and cardiovascular disease share risk factors as well as underlying metabolic abnormalities, suggesting similarities in etiology[96 97]. On the basis of these observations, hypertensive disorders of pregnancy have been proposed to be "early manifestations" of underlying cardiovascular risk and therefore "risk markers of potential future cardiovascular disease in women"[93 97]. One of the mechanisms believed to represent the link between hypertensive disorders of pregnancy and cardiovascular disease is the presence of endothelial dysfunction prior to pregnancy[98-101]. Endothelial dysfunction is a known risk factor for hypertension and cardiovascular disease[102 103], and has been shown to precede the development of preeclampsia[101 104]. In women who develop preeclampsia, endothelial dysfunction is believed to lead to intravascular coagulation, loss of fluid from the intravascular space and increased sensitivity to vasopressors[100]. The latter results in a failure of normal cardiovascular adaptations to pregnancy that are needed to create a high-flow-low-resistance state[101 105 106]. This failure is reflected in the lack of the midpregnancy fall in blood pressure seen in preeclamptic patients[106]. The lack of the physiological midpregnancy fall in diastolic blood pressure seen in women of low socioeconomic status led us to hypothesize that endothelial dysfunction, developed over the life course of women of low socioeconomic status, might underlie their susceptibility to both hypertensive disorders of pregnancy and future cardiovascular disease.

Together, the relatively high blood-pressure levels, the lack of the physiological midpregnancy fall in diastolic blood pressure, and the increased risk of developing hypertensive

pregnancy disorders in women of low socioeconomic status as compared with women of high socioeconomic status, suggest an underlying increased cardiovascular risk in these women that is manifested during pregnancy. This is compatible with the well-known socioeconomic gradient in cardiovascular morbidity and mortality among adult women[41 107 108].

Socioeconomic status and fetal and early postnatal growth

Growth is a fundamental and integral marker of health and well-being in children[109]. Normal growth is an indicator of health, whereas abnormal growth may indicate illness, malnutrition, or something awry in the child's environment. Intrauterine growth is particularly vulnerable to adverse circumstances, and intrauterine life is considered a critical period during which adverse stimuli may have lifelong consequences for health[110-113].

Previous studies have consistently shown low socioeconomic status to be associated with a lower birth weight[50 64 65], suggesting that socioeconomic disadvantage is related to relative growth retardation of the fetus. Chapter 6 of this thesis provides the first longitudinal assessment of the effect of an individual-level socioeconomic indicator (i.e. maternal educational level) on fetal growth characteristics. Not only did this assessment confirm that a low socioeconomic status impairs fetal growth, it also provided more insight in the magnitude, nature and explanation of this effect.

First, our results indicated that the adverse effect of a low socioeconomic status on fetal growth was not constant over time, but increased as pregnancy progressed, both in absolute and relative terms. This suggests that the adverse effects of socioeconomic disadvantage are not limited to one specific period of fetal development, but act during the whole course of pregnancy. Furthermore, our study was the first to demonstrate that socioeconomic differences in fetal body weight can be traced back to the 30th week of gestation, meaning that the adverse effect of socioeconomic disadvantage manifests itself at least as early as the last trimester of pregnancy. The most interesting finding was that, compared with growth of fetal femur and abdomen, growth of the fetal head seemed most sensitive to the effect of low socioeconomic status.

Fetal growth is regulated by genomic and environmental mechanisms, including somatotrophic mechanisms, uteroplacental and fetoplacental vascular development, and placental transport mechanisms[114]. Operating through these mechanisms, various maternal, fetal and placental factors may impair fetal growth[115], and might contribute to the explanation of the observed socioeconomic inequalities in fetal growth. We investigated the extent to which a number of maternal factors, i.e. maternal height, pre-pregnancy BMI, smoking during

pregnancy, single motherhood, whether the pregnancy was planned and financial difficulties, could explain the slower fetal growth in subgroups with a low socioeconomic status. These factors, in particular maternal smoking and maternal height, explained a large part. The detrimental effects of smoking during pregnancy on intrauterine growth have been well recognized[86 116 117], and is believed to be due to an impairment of utero-placental circulation as a result of the vasoconstricting effect of nicotine[86 118-120]. The interpretation of the role of maternal height in explaining socioeconomic inequalities in fetal growth is somewhat more complex. Maternal attained height results from a complex interaction of genetic, social, and environmental influences. The contribution of maternal height to socioeconomic inequalities in fetal growth may therefore represent common genetic factors between mother and fetus, as well as transgenerational effects of adverse environmental exposures accumulated over maternal life course[121].

Even after taking all the above-mentioned maternal factors into account, a significant effect of low socioeconomic status on fetal head circumferences remained, suggesting that still other factors are involved in this relationship. Since maternal head circumference is a strong predictor of neonatal head circumference[68], this would be the most obvious factor explaining the residual effect of low socioeconomic status. Other candidates are nutritional or psychosocial factors[122 123].

Since fetal growth is an important predictor of perinatal, infant, child, and also of subsequent adult health[110-113 124], the observed effects of socioeconomic status on fetal growth may not only represent the genesis of socioeconomic inequalities in birth size, they may also represent the genesis of health inequalities during childhood and adulthood. For example, given the link between fetal growth and adult cardiovascular disease[110], the higher morbidity and mortality from cardiovascular disease seen in lower socioeconomic subgroups may partly originate from the fetal period. The finding that socioeconomic disadvantage particularly impairs fetal head growth has more specific implications. Because head circumference is considered an indicator of brain mass[125], and is associated with cognitive functioning and academic achievements[111 126], our finding might have consequences for later cognitive abilities, educational attainment and job performance for the offspring of low-educated mothers, thereby perpetuating the cycle between educational level, growth, and health.

The investigation of the association of socioeconomic status with growth was continued in chapter 7, which focused on offspring height and linear growth during the first two years of life.

It is known that infants that are relatively growth retarded in utero tend to catch up after birth[127-129]. The results described in chapter 7 were in line with this phenomenon. The relative growth delay that infants of low socioeconomic status had suffered during fetal life in comparison with infants of high socioeconomic status was still observable at the age of 2 months: infants of low socioeconomic status were shorter than their peers of high socioeconomic status, and this could be attributed to prenatal circumstances, i.e. their higher rates of intrauterine smoke exposure, and their lower birth weight and gestational duration. However, until about 18 months of age, infants of low socioeconomic status had a faster linear growth velocity compared with children of high socioeconomic status, eventually leading to a taller height at the age of 14 months. This phenomenon of a relative accelerated growth in children of low socioeconomic status has been reported once before in a Dutch study conducted by Herngreen et al. in the 1990s[30]. In 1900 infants, Herngreen et al. found that while infants of low educated mothers were initially shorter, they had a higher gain in height between birth and 24 months compared with children of high-educated mothers. Nevertheless, our findings contrast with most of the available literature on this topic. As in adults, previous studies on socioeconomic inequalities in height in children aged 2 years and older have shown low socioeconomic status to be associated with a shorter height [30 56 130-134]. This contrast casts doubt on the generalizability of our results. As previously discussed, our results may be specific to affluent populations, or even more specific, to the Dutch population, which is characterized by higher breastfeeding rates and higher rates of day-care attendance in children from higher socioeconomic subgroups. Nevertheless, extrapolation of the linear growth curves suggested that the relative accelerated growth in the first 1.5 years seen in children of low socioeconomic status is followed by a relative deceleration. (See figure 9.3) Although speculative, we believe that persistence of this deceleration would lead children of low socioeconomic status to eventually attain a shorter height than their counterparts of high socioeconomic status, which would better fit the current literature.

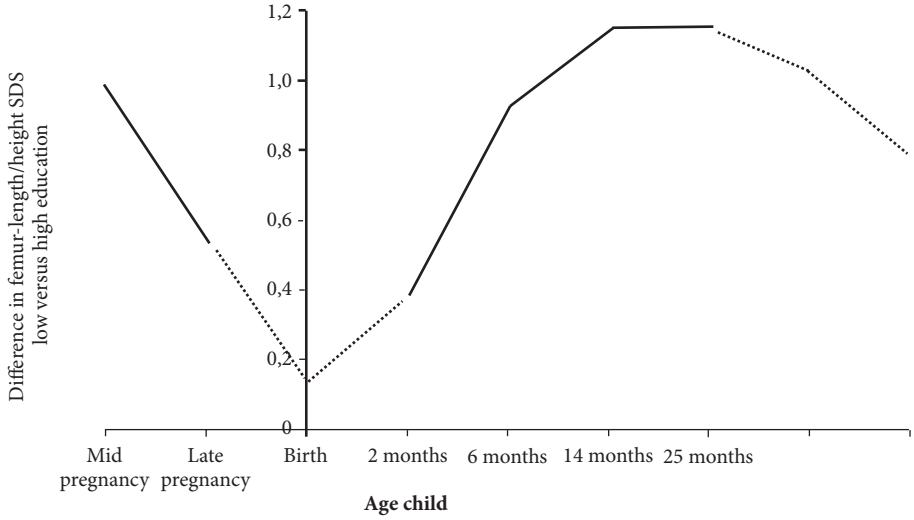

Figure 9.3 **Overview of association between maternal education and offspring growth from fetal life until early childhood.** The values in this figure are derived from results from chapters 6 and 7, and represent femur length SDS if before birth and height SDS if after birth. The value at birth is an estimation based on extrapolation of results from chapter 6. Values after the age of 25 months are an estimation based on extrapolation of results from chapter 7.

An important question to consider is: is the observed acceleration in linear growth in lower socioeconomic subgroups beneficial to them? It seems to be, at least on the short term. Due to this acceleration in growth, infants of low socioeconomic status were able to compensate their initial height deficit. However, there is reason to believe that, in the long run, the accelerated growth might have adverse health consequences. Population-based studies as well as studies in subjects born preterm or small for gestational age, have shown that accelerated growth during childhood, both in weight and in height, is associated with later cardiovascular disease and its risk factors, including insulin insensitivity, obesity and higher blood pressure[135-142]. These effects were independent, of size at birth, suggesting that accelerated growth rather than intrauterine growth retardation adversely program later cardiovascular outcomes, shifting the focus away from the so-called "fetal origins hypothesis" of cardiovascular disease to an "accelerated postnatal growth hypothesis"[141 142]. Given these latest insights, one may speculate that the relative growth retardation in utero, followed by the relative growth acceleration in early childhood observed in children of lower socioeconomic status might lead to an increased

propensity to later obesity, metabolic syndrome and cardiovascular disease. Such a hypothesis would fit the well-known socioeconomic gradient in cardiovascular disease and its risk factors[107 108 143 144].

Socioeconomic status and upper respiratory tract infections in early childhood

As shown in chapter 8, a low socioeconomic status of the mother was associated with a higher susceptibility in her offspring for upper respiratory tract infections during the first two years of life. While there was no evidence that the effect of low socioeconomic status acted through its link with fetal growth or health at birth, our data suggested that the effect was partly mediated by intrauterine exposure to psychosocial stressors.

For prenatal psychosocial stress to be a true mediator in the above association, prenatal psychosocial stress must be a direct or indirect risk factor for upper respiratory tract infections. While previous studies have shown an association between postnatal psychosocial stress and infections in childhood[145 146], studies showing the same for prenatal psychosocial stress are lacking. However, available research in this field has led to speculations that stress during pregnancy may lead to imbalance of the fetal immune system through changes in the hypothalamic-pituitary-adrenal (HPA) system and cortisol levels[147]. Furthermore, researchers have described a correlation between both a low socioeconomic status and depressive symptoms in the mother with higher salivary cortisol levels in children[148]. Although until now, it is not clear how signals of maternal stress may reach the fetus, researchers have postulated several mechanisms through which maternal stress might lead to overproduction and hypersecretion of fetal cortisol[123]. One of these mechanisms postulates that maternal cortisol that is released in response to stress passes the placenta and enters the fetal circulation. Another postulates that maternal cortisol stimulates the release of placental corticotrophin-releasing hormone, which in turn stimulates the HPA axis of the fetus, leading to an increase in fetal cortisol levels.

Nonetheless, until future studies confirm an association between prenatal exposure to stress and risk for respiratory infections, one must be careful with interpreting our results. It is possible that the observed association between prenatal stress and upper respiratory tract infections is not a causal one. Because both the presence of stressors and the occurrence of upper respiratory tract infections were reported by the same person, this association might be driven by response bias.

To what extent can socioeconomic inequalities in early childhood health be explained by intrauterine exposures?

For two early childhood health outcomes, i.e. height/linear growth and susceptibility to upper respiratory tract infections during the first two years of life, an answer to this last study question can be directly derived from the analyses in this thesis. While intrauterine exposures largely explained the shorter height seen at 2 months of age in children of low socioeconomic status as compared with children of high socioeconomic status, they could not explain the taller height during the second year of life in children of low socioeconomic status. Regarding upper respiratory tract infections, about one quarter of the increased susceptibility to these infections in children of low socioeconomic status was explained by prenatal factors. Thus, the contribution of intrauterine exposures to the explanation of socioeconomic inequalities in the two early childhood health outcomes discussed in this thesis was relatively limited. Postnatal factors appeared to be more important in explaining the observed inequalities, in particular regarding the inequalities in linear growth during early childhood.

There are a few possible explanations for the limited contribution of intrauterine circumstances to socioeconomic inequalities in the studied early childhood health outcomes.

The first is that these outcomes are poor proxies for the true health status of young children. In other words, they do not capture all dimensions of early childhood health, and other dimensions, such as mental health, cognition or cardiovascular health may be more vulnerable to the consequences of poor intrauterine health associated with a low socioeconomic status[149-153]. The results from this thesis allow us to hypothesize on the contribution of some intrauterine factors to socioeconomic inequalities in other dimensions of childhood health. In this thesis, an overview is provided of the relationship of socioeconomic status of women at the time of pregnancy with various intrauterine factors: material factors (e.g. financial difficulties), psychosocial factors (e.g. long-lasting difficulties, psychopathology), health-related behaviors (e.g. smoking and alcohol consumption during pregnancy), biological factors (i.e. blood pressure during pregnancy), pregnancy-related diseases (i.e. preeclampsia, gestational hypertension and gestational diabetes) and fetal growth. The extent to which these factors might contribute to socioeconomic inequalities in other child health outcomes than studied here will depend on their etiologic fraction for the health outcome of interest[154 155]. The etiologic fraction of a factor for a certain outcome depends both on the relative risk and its prevalence in the population of interest. It follows that if a mediator is only weakly associated with the outcome, or if the mediator has a low prevalence in the study population, then the contribution of that mediator to the explanation of socioeconomic inequalities in the health outcome will be limited[154 155].

When we consider the potential contribution of pregnancy-related diseases to the origins of socioeconomic inequalities in health of the offspring, we must conclude that this contribution is probably limited. This is because the prevalence of preeclampsia, gestational hypertension and gestational diabetes in our study population was relatively low: 1.5%, 5.5% and 1% respectively. Other prenatal factors described in this thesis are likely to have larger contributions to inequalities in child health. The most important example of such a factor is maternal smoking during pregnancy. In developed countries, smoking has been shown to be one of the leading causes of disease burden[156]. Although the adverse health effects of smoking during pregnancy are thought to be common knowledge, still 15-37% of women smoke while pregnant[157-159]. Within the Generation R cohort, 7-8% of the women smoked until they knew they were pregnant, while about 17% continued to smoke after the pregnancy was known. Strikingly, women of low socioeconomic status were about eight times more likely than women of high socioeconomic status to continue to smoke during pregnancy. Prenatal smoke exposure has a wide range of effects on multiple dimensions of child health. Not only is it a major cause of low birth weight, reduced head size at birth and preterm birth, it also increases the risk for Sudden Infant Death Syndrome and persisting reduced lung function, probably reflecting underdevelopment of lungs and airways[86 116 117 160 161]. Prenatal smoke exposure has also been associated with respiratory infections and asthma in childhood, with childhood overweight, and with a number of neurodevelopmental and behavioral problems, such as reduced general intellectual ability and attention deficit and hyperactivity disorder[149 150 160 162]. Childhood obesity and behavioral problems are health outcomes that show socioeconomic inequalities[61 163 164], and prenatal smoke exposure is likely to explain part of these inequalities.

A second possible explanation for the limited contribution of intrauterine circumstances to socioeconomic inequalities in the studied early childhood health outcomes, is that the health effects of poor intrauterine circumstances associated with socioeconomic disadvantage are not manifested until after the second year of life. The effects of poor intrauterine circumstances might be latent effects, or adverse exposures might have to first accumulate over time from fetal life onwards to cause a lower health status later in life[165]. This phenomenon of a delayed manifestation might apply to health outcomes such as obesity, the metabolic syndrome and cardiovascular disease. As previously discussed, the finding that a low socioeconomic status is associated with a relative growth retardation in utero, and a relative growth acceleration in early childhood might underlie the development of the socioeconomic gradient in above disorders.

The results from this thesis might also indicate that the health disadvantage that children of low socioeconomic status suffer before they are born actually has little direct

consequences for their health during childhood. This would be in line with the few previous studies on this topic. Case, Lubotsky and Paxon found that health of children aged 0 to17 years was positively related to household income[47]. They established this relationship for parental assessed health status of the child as well as for specific health conditions, such as digestive disorders, heart conditions, asthma, and sinusitis. Using >1 week hospital admission after birth and/or a very low birth weight (<3.5 pounds) as indicators of poor health at birth, Case et al. found that health at birth did not account for the relationship between income and health. In a more recent study[59], it was investigated whether maternal health status and health behaviors during pregnancy and early infancy, including maternal smoking, drinking, and vitamin use during pregnancy, breastfeeding and secondhand smoke exposure after birth, could explain the relationship between family income and overall health status of 3-year old children. These factors did not contribute to the explanation.

9.4 IMPLICATIONS

Socioeconomic inequalities in health form one of the greatest social injustices in the world. As evidence of the robustness of these inequalities have accumulated over the years, tackling these inequalities have become a public health priority. Because changing ones socioeconomic status is difficult, interventions aimed at reducing socioeconomic health inequalities should focus on the modifiable risk factors that contribute to these inequalities. Thus, tackling socioeconomic inequalities in health requires knowledge of the mechanisms underlying them. Furthermore, a reduction in the socioeconomic health gap will only be accomplished if people of low socioeconomic status benefit more from these interventions than those of high socioeconomic status.

This thesis shows marked socioeconomic inequalities in maternal health outcomes during pregnancy, fetal growth, and health outcomes during early childhood. In this section I will give my view on how a reduction in the above mentioned inequalities could be accomplished.

Of all the studied risk factors, the higher rates of overweight and obesity in subgroups of women of lower socioeconomic status were recognized as the most important contributor to their higher risk of preeclampsia, gestational hypertension and gestational diabetes. It follows that interventions aimed at reducing the burden of overweight in women of reproductive age, with special focus on those of lower socioeconomic status, has the highest potential of reducing the inequalities in, as well as the overall prevalences of the above mentioned pregnancy-related diseases. Since excess energy intake and a lack of physical activity are major determinants of

overweight, these are the most obvious targets for interventions.

Another major target for intervention suggested by this thesis is smoking during pregnancy. This was the most important contributor to the socioeconomic inequalities in fetal growth and in height at the age of 2 months. Since smoking is also a major risk factor for cardiovascular disease and lung cancer[166 167], cessation of smoking will not only decrease the risk to the fetus, it is also likely to improve the overall health and physical wellbeing of the mother. A number of interventions aimed at smoking cessation in pregnancy have been developed (e.g. brief counselling, pregnancy-specific educational printed materials, behavioural therapy, pharmacotherapy), and successful smoking cessation in pregnancy has been shown to prevent about 20% of low birth-weight births, and about 15% of preterm deliveries[168]. Currently, brief counselling by the prenatal caregiver is the safest and most effective intervention in pregnant women[169]. An office-based cessation counselling session of 5 to 15 minutes with a trained provider is associated with a smoking cessation rate of 5% to 10% in pregnant women[168 170]. When pregnancy-specific educational printed materials is provided in addition to brief counselling, the rate of smoking cessation is doubled to approximately 20%. Financial incentives and competitions have been proposed as an adjunct to counselling to encourage recruitment in smoking cessation programs, reinforce behaviour changes, and reward success[171 172]. Financial rewards can be especially effective in persuading pregnant women of low socioeconomic status to undergo treatment, and thereby reduce their risk for adverse pregnancy outcomes. However, these practices do not seem to enhance long-term quit rates[172].

Researchers have emphasized that smoking cessation programs should be initiated even *before* conception in order to protect the developing embryo from tobacco exposure during organogenesis and to minimize other risks[173]. Assessment of risk factors such as smoking and overweight, counseling, and enrollment in intervention programs before conception are principle components of the concept 'preconception care', which has internationally been proposed to be implemented in prenatal prevention programmes[174]. Preconception care addresses risk factors that are present prior to pregnancy, and aims at improving pregnancy outcome by eliminating or altering risk factors during the preconception period, thereby optimizing the quality of fetal, newborn and infant life through primary prevention[175 176]. This thesis indicates that preconception care is especially needed in socioeconomically disadvantaged women, in whom risk factors are often clustered. The Dutch Foundation for Preconception Care was launched in 2004 to promote easy-accessible preconception consultation in the Netherlands. Currently, a pilot study is being conducted in socioeconomically disadvantaged neighbourhoods of Rotterdam. The aims of this pilot study are to increase the awareness of

availability of preconception care, to introduce structured preconception care, and to reach individuals of all ethnic and socioeconomic strata.

Pregnant women and young children of lower socioeconomic status experience more disease in their lives than their more affluent counterparts. This has implications for doctors who work with them. One could argue that doctors should give priority to patients of low socioeconomic status in the delivering of clinical care, in order to compensate for the unjust health inequalities that exist in our society. However, as Hurst states, such a recommendation would infer reverse discrimination[177]. Doctors would be compensating for social injustices that took place outside the remit of medicine, and because they are likely to have varying conceptions of what constitute unjust health inequalities, there would be a high risk of arbitrariness in their decisions.[177]

I believe the most important recommendation to be that midwives, obstetricians and paediatricians should be aware of the impact of socioeconomic disadvantage on maternal and child health. Clinicians should think of social disadvantage as a risk factor for preeclampsia, low birth weight or preterm birth in the same way that for example smoking increases the risk for heart disease[178]. They should also be aware that adverse social circumstances, biological risk factors, and diseases tend to cluster in patients of low socioeconomic status, and that these might interfere with the treatment of the primary disorder for which the patients are cared. We therefore recommend the assessment of socioeconomic factors in individual consultations. For example, pediatricians should know which parents of young children are unsupported, socially isolated, or have financial difficulties[179], so that families can be referred for additional counseling whenever needed.

9.5 DIRECTIONS FOR FUTURE RESEARCH

While the studies in this thesis contribute to our knowledge of the effects of socioeconomic status on maternal and child health, they also raise new questions that should be addressed in future research. Here we summarize the most important recommendations for future research.

First, the present thesis had a number of methodological limitations that will need to be addressed. Future studies on socioeconomic inequalities in maternal and child health should make efforts to minimize selective response and selective loss to follow-up in order to minimize bias. Furthermore, these studies should minimize the use of self-reported data on the health outcomes of interest. For example, our study of socioeconomic inequalities in upper respiratory tract infections in young children needs replication using more objective measures of the outcome, such as registrations of doctor-diagnosed respiratory infections.

Second, some of our findings need replication. These include the apparent effect of intrauterine exposure to maternal stressors on susceptibility to upper respiratory tract infections in early childhood. More in particular, the finding that children of low socioeconomic status have a taller height than children of high socioeconomic status in their second year of life, should be confirmed in other populations.

Third, the strong association between a low maternal socioeconomic status and her risk for preeclampsia remained largely unexplained, despite the inclusion of a wide range of known risk factors for preeclampsia. Since preeclampsia is a leading cause of maternal and perinatal morbidity and mortality[76 180], reducing the observed socioeconomic inequalities in this disorder is important. However, this requires further study of the mechanisms underlying the association between socioeconomic status and preeclampsia. Results from chapter 3 suggest that endothelial dysfunction in women of lower socioeconomic status might be one of the mechanisms. This might be confirmed in future studies on the association of socioeconomic status and objective measures of endothelial function, e.g. flow-mediated vasodilatation[181].

Equally so, we were unable to explain the relative faster linear growth in children of low socioeconomic status compared with those of high socioeconomic status. We expect that socioeconomic differences in diet and energy intake play an important role in the explanation, and recommend that researchers conduct a detailed study of nutrition and energy intake from birth onwards in relation to socioeconomic status, and relate this to growth in early life.

Last, our rather surprising results regarding socioeconomic status and early linear growth emphasizes the need for further follow-up of our study population in order to establish how socioeconomic status affects growth after the second year of life, how this relates to the socioeconomic inequalities in adult height, and how the relative acceleration in early linear growth observed in disadvantaged subgroups relates to later development of obesity, the metabolic syndrome and cardiovascular disease.

CONCLUSIONS

Several conclusions can be drawn from our findings.

First, women of low socioeconomic status have lower chances of completing a healthy pregnancy: they display more risk factors, such as psychosocial stress, smoking during pregnancy, and obesity, and are more likely to develop preeclampsia, gestational hypertension and gestational diabetes, which may negatively affect fetal, perinatal and long-term health of the offspring. Our findings also have implications for these womens' cardiovascular health, as they suggest an underlying increased cardiovascular risk that is manifested during pregnancy.

Second, we can conclude that fetal and early postnatal health is affected by mother's socioeconomic status. Offspring of women of low socioeconomic status grow more slowly in utero, grow faster in height during early childhood, and are more susceptible to upper respiratory tract infections compared with offspring of women of high socioeconomic status.

Last, our studies showed some evidence for a contribution of intrauterine exposures to the explanation of socioeconomic inequalities in height and linear growth, and upper respiratory tract infections in early childhood, although this contribution was relatively limited.

Future research may shed more light on the contribution of intrauterine exposures to socioeconomic inequalities in other early childhood health outcomes, as well as in inequalities in child health at later ages.

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SUMMARY

Socioeconomic inequalities in health are a major public health concern. In all European countries with available data, morbidity and mortality has been shown to be higher in lower socioeconomic subgroups compared with higher socioeconomic subgroups. Our understanding of the explanations of socioeconomic health inequalities has progressed. Any causal effect of low socioeconomic status on health is likely to act through more specific health determinants that are unequally distributed across socioeconomic groups, such as material factors, psychosocial factors, and health-related behaviours. However, despite increases in knowledge, the exact mechanisms underlying socioeconomic health inequalities are not completely clear. Researchers have proposed to adopt the so-called 'life-course perspective' in the search for explanations of socioeconomic health inequalities, which postulates that at least part of these inequalities is a result of socioeconomic conditions in an earlier stage in life.

Early life socioeconomic circumstances also affect health during childhood. Children living in socioeconomic disadvantage generally have worse health than their advantaged peers. Despite increases in research on the impact of socioeconomic status on child health, some issues are not completely clear. First, compared with school-aged children, relatively little is known about the nature and magnitude of the socioeconomic gradient in health of infants and toddlers. Second, the mechanisms underlying the socioeconomic gradient in child health are not fully understood. On the basis of the 'fetal-origins' hypothesis, researchers' attention has shifted to the possible role of intrauterine exposures in the explanation of the socioeconomic gradient in child health. Research findings indicate that a low socioeconomic status at the time of pregnancy is associated with circumstances that negatively influence the course of pregnancy, intrauterine growth, and delivery, which in turn may have consequences for later health of the offspring. This led us to hypothesize that the impact of adverse socioeconomic circumstances at time of pregnancy creates vulnerabilities in the offspring, that might result in an increased risk for adverse health outcomes in childhood, and, later, in adulthood.

The aim of this thesis was to contribute to a further understanding of the origins of socioeconomic inequalities in child health, and of the possible role of intrauterine effects of socioeconomic circumstances in the genesis of these inequalities. The following specific research questions were formulated:

1a) Are there socioeconomic inequalities in maternal health during pregnancy that may affect fetal, perinatal and long-term health of the offspring?

1b) How can these inequalities be explained?

2a) Are there socioeconomic inequalities in fetal and/or perinatal health?
2b) How can these inequalities be explained?

3a) Are there socioeconomic inequalities in early childhood health?
3b) To what extent can these inequalities be explained by intrauterine exposures of the child?

All studies in this thesis were conducted within the framework of The Generation R Study, a prospective population-based cohort study from fetal life until young adulthood, conducted in Rotterdam, the Netherlands.

In chapters 2 to 5 we studied the association between maternal educational level as a measure of socioeconomic status, and the risk for several pregnancy-related conditions. **Chapter 2** shows that a strong educational gradient exists in the risk for preeclampsia, where the lowest educational subgroup of pregnant women had a five times higher odds compared with the highest educational subgroup. Although we included a wide range of potential explanatory factors, this relationship remained largely unexplained.

The search for potential mechanisms underlying the effect of socioeconomic status on preeclampsia was continued with the study described in **chapter 3**. This study showed that from early pregnancy onwards, women with relatively low levels of education had higher mean blood-pressure levels than women with a high educational level. The most remarkable result, however, was that the fall in diastolic blood pressure one would normally expect in midpregnancy, was not observed in women with a low educational level. Our findings also suggested that the lack of a midpregnancy fall predisposes women with a low educational level toward the development of preeclampsia. The midpregnancy fall in blood pressure is a physiological phenomenon that is triggered by a decrease in total peripheral vascular resistance through vasodilatation in order to achieve a high-flow-low-resistance state. The lack of such a fall suggests endothelial dysfunction. Therefore, we hypothesized that women of low socioeconomic status have a latent endothelial dysfunction, which is manifested during pregnancy and which may partly explain their increased susceptibility to preeclampsia.

As described in **chapter 4**, women with relatively low levels of education had a 30 to 50% higher risk for gestational hypertension than women with a high educational level. This increased risk was almost entirely explained by other, more proximal factors, particularly by the higher rates of overweight and obesity, and by the relatively high blood-pressure levels at enrollment found in lower educated women. Since these factors are also known risk factors for essential

hypertension, our findings suggest that the relatively high risk of gestational hypertension in women with low levels of education reflects pre-existing hypertensive tendencies in these women that are disclosed by the physiological stress of pregnancy.

Another pregnancy complication studied in this thesis is gestational diabetes. As shown in **chapter 5**, women with a low educational level were three times more likely to develop gestational diabetes as compared with women with a high level. The largest part of this increased risk was explained by relatively high rates of overweight and obesity in the lower educational subgroups. Since a hyperglycemic intrauterine environment has been implicated in the pathogenesis of type 2 diabetes later in life, socioeconomic inequalities in gestational diabetes may contribute to the maintenance of the increased burden of type 2 diabetes in lower socioeconomic subgroups.

Chapter 6 of this thesis provides an assessment of the association of maternal socioeconomic status, as measured by her educational level, with fetal growth. This assessment provided three main findings. First, a low maternal educational level was associated with a progressively slower fetal growth, resulting in differences in fetal weight that were observable already from late pregnancy onwards. Second, our findings suggested that the adverse effect of low education was largest for growth of the fetal head, followed by growth of the fetal femur and abdomen. Third, while other determinants of fetal growth, in particular maternal smoking during pregnancy and maternal height, explained a large part of the educational inequalities in growth characteristics, the inequalities in fetal head circumference remained partly unexplained.

Chapter 7 describes the association of socioeconomic status with height and linear growth during the first two years of life. We found that, at two months of age, children of low educated mothers were shorter than their counterparts. However, contrary to what was expected, a low educational level of the mother was associated with a faster linear growth during the first 1.5 years of life as compared with a high level. By 14 months of age, children in the lowest educational subgroup had compensated their initial height deficit; at this age they were even slightly taller than children in the highest educational subgroup. While the shorter duration of breastfeeding, and, more in particular, the lower rates of day-care attendance in children in lower educational subgroups explained part of their taller height, intrauterine factors, i.e. smoking during pregnancy, birth weight and gestational age at birth, did not contribute to the explanation. On the contrary, the positive difference in height between the lowest and the highest socioeconomic subgroup became even stronger after adjustment for these intrauterine factors. After taking all covariates into account, children in the lowest educational subgroup were still about 1 cm taller than those in the highest educational subgroup. This is likely to be explained by other growth-stimulating factors that were not available for this study, such as total

amount of energy intake. This merits further investigation.

In **chapter 8**, we examined the socioeconomic inequalities in upper respiratory tract infections during the first two years of life. This analysis showed an inverse relationship between maternal educational level and the child's susceptibility to upper respiratory tract infections during the first two years of life, and this gradient seemed to increase with age. Independent of postnatal factors, prenatal financial difficulties and prenatal maternal psychiatric symptoms explained 27% of the increased susceptibility to these infections in children of low socioeconomic status.

Chapter 9 provides a general discussion of the main findings, as well as an analysis of important methodological issues, an outline of implications of our results for public health policy and clinical practice, and suggestions for future research.

Several conclusions can be drawn from our findings.

First, women of low socioeconomic status have lower chances of completing a healthy pregnancy: they display more risk factors, such as psychosocial stress, smoking during pregnancy, and obesity, and are more likely to develop preeclampsia, gestational hypertension and gestational diabetes, which may negatively affect fetal, perinatal and long-term health of the offspring. Our findings also have implications for these womens' cardiovascular health, as they suggest an underlying increased cardiovascular risk that is manifested during pregnancy.

Second, we can conclude that fetal and early postnatal health is affected by mothers' socioeconomic status. Offspring of women of low socioeconomic status grow more slowly in utero, grow faster in height during early childhood, and are more susceptible to upper respiratory tract infections compared with offspring of women of high socioeconomic status.

Last, our studies showed some evidence for a contribution of intrauterine exposures to the explanation of socioeconomic inequalities in height and linear growth, and upper respiratory tract infections in early childhood, although this contribution was relatively limited.

Future research may shed more light on the contribution of intrauterine exposures to socioeconomic inequalities in other early childhood health outcomes, as well as in inequalities in child health at later ages.

SAMENVATTING

Sociaal-economische gezondheidsverschillen vormen een groot maatschappelijk probleem. In alle Europese landen met beschikbare gegevens is aangetoond dat subgroepen met een lage sociaal-economische status een hogere mortaliteit en morbiditeit hebben dan subgroepen met een hoge sociaal-economische status. Onze kennis over de oorzaak van sociaal-economische gezondheidsverschillen is de afgelopen decennia flink toegenomen. Het effect van een lage sociaal-economische status op de gezondheid loopt zeer waarschijnlijk via andere, meer proximale determinanten van gezondheid die ongelijk verdeeld zijn over de verschillende sociaal-economische subgroepen, zoals materiële factoren, psychosociale factoren en gezondheidsgerelateerde gedragingen. Echter, de exacte mechanismen die ten grondslag liggen aan sociaal-economische verschillen in gezondheid zijn nog niet helemaal helder. Wetenschappers hebben voorgesteld om het zogenaamde 'levensloop perspectief' aan te nemen in de zoektocht naar verklaringen voor sociaal-economische gezondheidsverschillen. Volgens dit perspectief zou een deel van deze verschillen veroorzaakt worden door sociaal-economische omstandigheden eerder in het leven.

Sociaal-economische omstandigheden in het vroege leven hebben ook effect op de gezondheid van kinderen. Kinderen die onder ongunstige sociaal-economische omstandigheden leven hebben een slechtere gezondheid dan hun leeftijdsgenoten die onder gunstige sociaal-economische omstandigheden leven. Hoewel er afgelopen jaren steeds meer onderzoek is verricht naar het effect van sociaal-economische status op gezondheid van kinderen, blijven sommige aspecten onduidelijk. Ten eerste is er relatief weinig onderzoek gedaan naar de aard en omvang van sociaal-economische gezondheidsverschillen bij baby's en peuters. Ten tweede zijn de mechanismen die ten grondslag liggen aan sociaal-economische verschillen in gezondheid bij jonge kinderen niet helemaal bekend. Aan de hand van de 'foetale origine' hypothese, die het belang van omstandigheden in de baarmoeder voor de latere gezondheid benadrukt, is de aandacht van onderzoekers verschoven naar de mogelijke rol van intra-uteriene blootstellingen in het verklaren van de sociaal-economische gradiënt in de gezondheid van kinderen. Onderzoek heeft immers reeds aangetoond dat een lage sociaal-economische status ten tijde van de zwangerschap gerelateerd is aan omstandigheden die een ongunstige invloed hebben op het beloop van de zwangerschap, intra-uteriene groei en bevalling, wat op de lange termijn negatieve gevolgen kan hebben voor de gezondheid van het kind. Dit bracht ons tot de hypothese dat de impact van ongunstige sociaal-economische omstandigheden tijdens de zwangerschap leidt tot een verhoogde gevoeligheid in het ongeboren kind voor het later ontwikkelen van gezondheidsproblemen.

Het doel van dit proefschrift was om bij te dragen aan de kennis over het ontstaan van sociaal-economische gezondheidsverschillen bij kinderen, en over de rol van intra-uteriene effecten van sociaal-economische omstandigheden in het ontstaan van deze verschillen. De volgende onderzoeksvragen werden geformuleerd:

1a) Zijn er sociaal-economische verschillen in gezondheid van de moeder tijdens de zwangerschap die van invloed kunnen zijn op de foetale, perinatale en latere gezondheid van het kind?
1b) Hoe kunnen deze verschillen worden verklaard?

2a) Zijn er sociaal-economische verschillen in foetale en/of perinatale gezondheid?
2b) Hoe kunnen deze verschillen worden verklaard?

3a) Zijn er sociaal-economische verschillen in gezondheid op de jonge kinderleeftijd?
3b) 3In hoeverre worden deze verschillen verklaard door intra-uteriene blootstellingen van het kind?

Alle in dit proefschrift beschreven studies waren ingebed in het Generation R Onderzoek, een prospectieve, populatie-gebaseerde studie vanaf de foetale periode tot aan de jong-volwassen leeftijd, welke wordt uitgevoerd in Rotterdam, Nederland.

In hoofdstukken 2 tot en met 5 hebben we de relatie bestudeerd tussen opleidingsniveau van moeder (als maat voor haar sociaal-economische status), en het risico op een aantal zwangerschapsgerelateerde aandoeningen. **Hoofdstuk 2** laat een sterke gradiënt zien naar opleidingsniveau in het risico op preeclampsie, waarbij zwangere vrouwen met het laagste opleidingsniveau een vijf maal verhoogd risico hadden dan vrouwen met het hoogste opleidingsniveau. Hoewel we een groot aantal mogelijk verklarende factoren hebben meegenomen in de analyses, bleef de bovenstaande associatie grotendeels onverklaard.

De zoektocht naar andere mogelijke verklaringen voor de relatie tussen sociaal-economische status en preeclampsia werd voortgezet in **hoofdstuk 3**. Met deze studie werd aangetoond dat al vanaf het eerste zwangerschapstrimester, vrouwen met een lager opleidingsniveau een hogere bloeddruk hadden dan vrouwen met een hoger opleidingsniveau. Echter, het meest opmerkelijke resultaat was dat de daling in diastolische bloeddruk die men normaal zou verwachten in het tweede trimester, afwezig was in moeders met een laag opleidingsniveau. Onze bevindingen suggereerden ook dat de afwezigheid van een dergelijke

daling in diastolische bloeddruk geassocieerd is met een verhoogd risico op preeclampsie bij vrouwen met een laag opleidingsniveau. De daling in bloeddruk in het tweede trimester is een fysiologisch fenomeen dat wordt geactiveerd door een afname in totale perifere vaatweerstand door vaatverwijding, om zo een hoge-flow-lage-weerstand situatie te creëren. Het ontbreken van een dergelijke daling suggereert een verminderde endotheelfunctie. Onze theorie is daarom dat vrouwen met een lage sociaal-economische status een verminderde endotheelfunctie hebben die tot uiting komt tijdens de zwangerschap en mogelijk deels hun verhoogde risico op preeclampsie verklaren.

In het onderzoek gepresenteerd in **hoofdstuk 4** vonden we dat vrouwen met een lager opleidingsniveau 30-50% meer kans hadden op het krijgen van zwangerschapshypertensie in vergelijking met vrouwen met een hoog opleidingsniveau. Dit verhoogde risico was bijna helemaal verklaard door andere risicofactoren, men name door de hogere percentages overgewicht en hogere bloeddrukken bij inclusie onder laag opgeleide vrouwen. Omdat overgewicht en een relatief verhoogde bloeddruk bekende risicofactoren zijn voor het ontwikkelen van essentiële hypertensie, suggereren onze bevindingen dat het relatief verhoogde risico op zwangerschapshypertensie bij laag opgeleide vrouwen een uiting is van pre-existente hypertensieve neigingen, die door de zwangerschap tot uiting komen.

Een andere zwangerschapscomplicatie die bestudeerd is in dit proefschrift is zwangerschapsdiabetes. Zoals beschreven in **hoofdstuk 5**, hebben vrouwen met een laag opleidingsniveau een drie maal hoger risico op het ontwikkelen van zwangerschapsdiabetes vergeleken met vrouwen met een hoog opleidingsniveau. Het grootste deel van dit verhoogde risico werd verklaard door relatief hoge percentages overgewicht in de lagere opleidingsgroepen. Omdat is aangetoond dat intra-uteriene blootstelling aan hyperglycemie een rol speelt in de pathogenese van type 2 diabetes later in het leven, zouden sociaal-economische verschillen in zwangerschapsdiabetes kunnen bijdragen aan de instandhouding van het verhoogde risico op type 2 diabetes in lagere sociaal-economische groepen.

Hoofdstuk 6 van dit proefschrift beschrijft de associatie tussen opleidingsniveaus van moeder, als maat voor haar sociaal-economische status, en foetale groei. Er waren drie belangrijke bevindingen. Ten eerste was een laag opleidingsniveau van moeder geassocieerde met een tragere foetale groei, resulterende in verschillen in foetaal gewicht die reeds in het derde zwangerschapstrimester waarneembaar waren. Ten tweede suggereerden onze bevindingen dat het negatieve effect van aan lage opleiding op foetale groei het grootst was voor groei van het hoofd, gevolgd door groei van de femur en abdomen. Ten derde, terwijl andere determinanten van foetale groei, in het bijzonder rookgedrag van de moeder tijdens de zwangerschap en lengte

van de moeder, een groot deel van de opleidingsverschillen in foetale groei verklaarden, bleven de verschillen in foetale hoofdomtrek deels onverklaard.

In **hoofdstuk 7** wordt de associatie tussen sociaal-economische status en lengte en lineaire groei tijdens de eerste 2 jaar van het leven beschreven. We vonden dat op de leeftijd 2 maanden kinderen van laag opgeleide moeders korter waren dan kinderen van hoog opgeleide moeders. Echter, tegen de verwachting in groeiden kinderen van laag opgeleide moeders gedurende de eerste 1.5 jaar met een hogere groeisnelheid dan kinderen van hoog opgeleide moeders. Op de leeftijd van 14 maanden waren kinderen van laag opgeleide moeders zelfs iets langer dan kinderen van hoog opgeleide moeders. Terwijl verschillen in borstvoeding en crèche bezoek tussen opleidingsgroepen een deel van de langere lengte verklaarden, droegen intra-uteriene factoren, waaronder roken tijdens de zwangerschap, geboortegewicht en zwangerschapsduur, niet bij aan de verklaring. In tegendeel, het verschil in lengte tussen de laagste en hoogste opleidingsgroepen werd zelfs groter na correctie voor deze intra-uteriene factoren. Na correctie voor alle covariaten, waren kinderen van laag opgeleide vrouwen nog steeds ongeveer 1 cm langer dan kinderen van hoog opgeleide moeders. Dit kan waarschijnlijk worden verklaard door andere groeistimulerende factoren die voor onze studie niet beschikbaar waren, zoals totale energie-intake. Dit moet verder onderzocht worden.

In **hoofdstuk 8** bestudeerden wij de sociaal-economische verschillen in bovenste luchtweginfecties tijdens de eerste twee levensjaren. We vonden een omgekeerde relatie tussen opleidingsniveau van de moeder en gevoeligheid voor bovenste luchtweginfecties tijdens de eerste twee levensjaren van het kind, en deze gradiënt leek toe te nemen met toenemende leeftijd van het kind. Onafhankelijk van postnatale factoren, verklaarden het hebben van prenatale financiële problemen en prenatale psychiatrische symptomen van de moeder 27% van de verhoogde gevoeligheid voor bovenste luchtweginfecties in kinderen met een lage sociaal-economische status.

Hoofdstuk 9 bestaat uit een algemene discussie van de belangrijkste bevindingen in dit proefschrift, alsook een bespreking van een aantal methodologische aspecten, een overzicht van de mogelijke implicaties van onze bevindingen, en de mogelijkheden voor toekomstig onderzoek.

Aan de hand van onze bevindingen kunnen een aantal conclusies worden getrokken.

Ten eerste: vrouwen met een lage sociaal-economische status hebben een lagere kans op het voldragen van een gezonde zwangerschap. Zij vertonen vaker risicofactoren, zoals psychosociale stress, roken tijdens de zwangerschap en overgewicht, en hebben een hogere kans op

het ontwikkelen van preeclampsie, zwangerschapshypertensie en zwangerschapsdiabetes, welke een negatieve invloed kunnen hebben op de foetale, perinatale en lange termijn gezondheid van de nakomeling. Onze bevindingen hebben ook implicaties voor de cardiovasculaire gezondheid van vrouwen van lage sociaal-economische status, omdat de bevindingen suggereren dat deze vrouwen een onderliggend verhoogd risico hebben op cardiovasculaire problemen welke tijdens de zwangerschap tot uiting komt.

Ten tweede: we kunnen concluderen dat gezondheid tijdens de foetale en vroege postnatale periode beïnvloed wordt door moeders sociaal-economische status. Vergeleken met kinderen van moeders met een hoge sociaal-economische status, groeien kinderen van moeders met een lage sociaal-economische status trager in utero, vertonen zijn een snellere lengtegroei tijdens de eerste levensjaren, en zijn zij gevoeliger voor bovenste luchtweginfecties.

Als laatste: onze studies leverden enig bewijs voor een bijdrage van intra-uteriene blootstellingen aan de verklaring van sociaal-economische verschillen in lengte en lengtegroei, en bovenste luchtweginfecties in de eerste twee levensjaren.

Toekomstig onderzoek zou meer inzicht kunnen bieden in de bijdrage van intra-uteriene blootstellingen aan sociaal-economische verschillen in andere gezondheidsuitkomsten bij jonge kinderen.

LIST OF PUBLICATIONS

Silva LM, Coolman M, Steegers EAP, Jaddoe VWV, Moll HA, Hofman A, Mackenbach JP, Raat H. Maternal educational level and risk of gestational hypertension: the Generation R Study. *J Hum Hypertension. 2008 Jul;22(7):483-92.*

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ABBREVIATIONS

AC	Abdominal circumference
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
DBP	Diastolic blood pressure
FL	Femur length
HC	Head circumference
OR	Odds ratio
Ref	Reference
SBP	Systolic blood pressure
SES	Socioeconomic status
Yrs	Years

DANKWOORD

Er staat slechts één naam op de kaft van dit proefschrift, maar dat is niet helemaal eerlijk. Vele anderen hebben, ieder op zijn/haar eigen manier, bijgedragen aan het boekje dat nu voor u ligt. Aan al deze mensen gaat mijn oprechte dank:

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PHD PORTFOLIO

Name PhD student: LM Silva	PhD period: 15 September 2005 – 1 May 2009
Erasmus MC Department: Public Health	Promotor(s): JP Mackenbach
Research School: NIHES	Supervisor: H Raat

1. PhD training

	Year	Workload (Hours/ECTS)
Research skills		
Principles of Research in Medicine and Epidemiology, NIHES	2001	1.0
Clinical Decision Analysis, NIHES	2001	1.0
Methods of Public Health Research, NIHES	2001	1.0
Data collection in Epidemiology Research, NIHES	2001	1.0
Study design, NIHES	2001	3.0
Introduction to Data-analysis, NIHES	2002	2.0
Regression Analysis, NIHES	2002	2.0
Survival Analysis, NIHES	2002	2.0
Clinical Trials, NIHES	2003	1.0
Topics in Meta-Analysis, NIHES	2003	1.0
Bayesian Analysis, NIHES	2003	1.0
Analysis of Repeated Measurements, NIHES	2003	1.0
General academic skills		
Working with SPSS for Windows, NIHES	2002	0.3
Introduction to Medical Writing, NIHES	2003	2.0
Biomedical English Writing and Communication	2008	4.0
In-depth courses		
Design, Conduct and Analysis of Multi-center Studies, NIHES	2002	0.8
Health Status Measurement, NIHES	2002	1.2
Addiction and Substance Use: Epidemiology and HSR, NIHES	2002	1.2
Epidemiology of Major Diseases and Major Determinants, NIHES	2003	2.0
Maternal and Child Health, NIHES	2003	1.2
Missing Values in Clinical Research, NIHES	2007	0.9
International courses		
Principles of Epidemiology, Harvard School of Public Health, Boston, USA	2003	4.0
Management in Health Care Organisations, Harvard School of Public Health, Boston, USA	2003	4.0
(Inter)national conferences – participation and presentations		
DOHaD 2006, 4th World Congress on Developmental Origins of Health & Disease, Utrecht, the Netherlands. Posters: *Low*	2006	0.6

maternal education is a risk factor for hypertension in late pregnancy. The Generation R Study & *Explaining the association between low maternal education and risk for gestational diabetes. The Generation R Study*.		
Retraite van de Werkgemeenschap Jeugd & Gezondheid 2006, Soesterberg, the Netherlands. Oral: *Prenataal ontstaan van sociaal-economische verschillen in gezondheid bij jonge kinderen*.	2006	0.6
Nederlands Congres voor Volksgezondheid 2008, Groningen, the Netherlands. Orals: *Lage sociaal-economische status is een risicofactor voor preeclampsie. De Generation R Studie* & *sociaal-economische verschillen in bloeddrukniveau en bloeddrukverandering tijdens de zwangerschap. De Generation R Studie*.	2008	0.6
Lustrum congres Nederlandse Vereniging voor Studie van Sociale Tandheelkunde 2008, Zwolle, the Netherlands. Keynote speaker: *De levenslange last van vroeggeboorte en prenatale groeiretardatie*.	2008	0.6
ISSHP 2008, XVI World Congress of the International Society for the Study of Hypertension in Pregnancy, Washington, United States. Poster: *No mid-pregnancy fall in diastolic blood pressure in women with a low educational level*.	2008	1.3
EAP 2008, 2nd Congress of the European Academy of Paediatrics, Nice, France. Oral: *Mother's educational level and foetal growth; the genesis of health inequalities*.	2008	1.3
Nederlandse Werkgroep Preeclampsie (Nedwep), Utrecht, the Netherlands. Oral: *No mid-pregnancy fall in diastolic blood pressure in women with a low educational level.*	2008	0.6
Seminars and workshops		
Workshop subsidie aanvragen (Training Upcoming Leaders In Paediatric Science)	2009	0.1

2. Teaching activities

	Year	Workload (Hours/ECTS)
Lecturing		
Teaching assistant for NIHES course "Maternal and Child Health"	2007	0.5

Supervising practicals and excursions	2006	0.1
Supervising practical on *study design*		
Supervising Master's theses		
Supervised Sheila Murray*: Low educational level is a risk factor of gestational diabetes; The Generation R Study*	2008	4
Other		
Supervised four medical students in writing Preventive Child Health Care assignment.	2008	0.1