BMJ Open

Neighbourhood deprivation, fetal growth and adverse pregnancy outcomes: the Generation R Study.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-049075
Article Type:	Original research
Date Submitted by the Author:	14-Jan-2021

Complete List of Authors:	Gootjes, Dionne; Erasmus MC, Department of Obstetrics and Gynaecology, Division of Obstetrics and Prenatal Medicine; Erasmus MC, Generation R Study Group Posthumus, Anke G; Erasmus MC, Department of Obstetrics and Gynaecology, Division of Obstetrics and Prenatal Medicine; Erasmus MC, Generation R Study Group Jaddoe, Vincent; Erasmus MC, Department of Paediatrics; Erasmus MC, Generation R Study Group Steegers, E.A.P.; Erasmus MC, Department of Obstetrics and Gynaecology, Division of Obstetrics and Prenatal Medicine; Erasmus MC, Generation R Study Group

Keywords:	SOCIAL MEDICINE, PUBLIC HEALTH, PREVENTIVE MEDICINE, Ultrasonography < OBSTETRICS, Prenatal diagnosis < OBSTETRICS, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Neighbourhood deprivation, fetal growth and adverse pregnancy outcomes: the Generation R Study.

D.V. Gootjes[1,3], A.G. Posthumus[1,3], V.W.V Jaddoe[2,3], E.A.P. Steegers[1,3]

[1]Department of Obstetrics and Gynaecology, Division of Obstetrics and Prenatal Medicine, [2]Department of Paediatrics, [3]Generation R Study Group, all: Erasmus University Medical Centre, Rotterdam, The Netherlands.

The authors declare no conflict of interest.

Corresponding author

Correspondence to Dionne V. Gootjes

Wytemaweg 80, 3015 CN Rotterdam

d.gootjes@erasmusmc.nl

Telephone: +3110 703 04 52 | +316 307 252 47

Key words: fetal, neighborhood/place, deprivation, pregnancy, socio-economic

Word count: 3661

Abstract

Objectives: To study the associations between neighbourhood deprivation and fetal growth, including growth in the first trimester, and adverse pregnancy outcomes.

Design: Prospective cohort study.

Setting: The Netherlands, Rotterdam.

Participants: 8617 live singleton births from the Generation R cohort study.

Interventions: Living in a deprived neighbourhood.

Outcome measures: Fetal growth, including growth in the first trimester, and adverse pregnancy outcomes (small-for-gestational age (SGA) and preterm birth (PTB)).

Results: Neighbourhood deprivation was not associated with first trimester growth. However, a higher neighbourhood status score (less deprivation), was associated with increased fetal growth in the second and third trimester (e.g. estimated fetal weight (adjusted regression coefficient 0.04 (95% CI 0.02 ; 0.06). Less deprivation was also associated with a decreased risk of SGA (aOR 0.91 (95% CI 0.86 ; 0.97)) and PTB (aOR 0.89 (95% CI 0.82 ; 0.96)).

Conclusions: We found an association between neighbourhood deprivation and fetal growth in the second and third trimester pregnancy, but not with first trimester growth. Neighbourhood deprivation is associated with adverse pregnancy outcomes. The associations remained after adjustment for individual level risk factors. This supports the hypothesis that living in a deprived neighbourhood acts as an independent risk factor for fetal growth and adverse pregnancy outcomes, above and beyond individual risk factors.

Article Summary

Strengths and limitations of this study

- This study investigated the association between neighbourhood deprivation and fetal growth and adverse pregnancy outcomes.
- This study is performed within in a large, multi-ethnic cohort.
- The Generation R study population is not completely representative of the Dutch population.
- Associations were adjusted for a wide range of relevant individual level risk factors, which allows the isolation of a neighbourhood specific effect best as possible.

Introduction

A low individual socioeconomic status (SES) is associated with adverse health outcomes.(1) Additionally, there is accumulating evidence that the socioeconomic status of the neighbourhood in which a person lives is also associated with health outcomes.(2) This is also the case for pregnancy: both individual SES and living in a deprived neighbourhood are acknowledged risk factors for adverse pregnancy outcomes.(3-5)

Recent evidence shows that other factors, such as maternal nutrition and lifestyle, already affect pregnancy from the first trimester of pregnancy onwards.(6) Gaining a better understanding of modifiable factors that influence pregnancy from the earliest phase onwards is important. First, since impaired development during the first trimester of pregnancy is associated with adverse pregnancy outcomes.(6) Second, in line with the DOHaD-paradigm (Developmental Origin of Health and Disease), impaired development in pregnancy and adverse pregnancy outcomes are associated with an increased risk of non-communicable diseases in adult life like cardiovascular disease.(7) If impaired early fetal development could be prevented or recognized, this would enable the prevention of both short-term and long-term adverse outcomes.

Living in a deprived neighbourhood is known to be a risk factor for adverse pregnancy outcomes. It is however unknown whether this potentially modifiable factor is also associated with early fetal development. Therefore, the aim of this study was to investigate the associations between neighbourhood deprivation, fetal growth including growth in the first trimester, and adverse pregnancy outcomes.

Methods

Design

This study was embedded in the Generation R Study, a population-based prospective cohort study.(8) Pregnant women living in the area of Rotterdam, the Netherlands, with an expected delivery date between April 2002 and January 2006, were invited to participate in this study. We excluded the following pregnancies: twin pregnancies, terminated pregnancies, intra-uterine deaths and pregnancies without information on area of residence or ultrasound data (**Figure 1**). The study protocol was approved by the Medical Ethical Committee of Erasmus Medical Centre, Rotterdam (MEC 198.782/ 2001/31). Written informed consent was obtained from all participants.

Patient and public involvement statement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Neighbourhood deprivation

We used area-based status scores as a proxy for neighbourhood deprivation, which were made available by the Netherlands Institute for Social Research.(9) The scores are matched on four-digit postcodes and are based on mean household income, proportion of population with low income, proportion of population with low educational level, and proportion of population without paid work. The scores are determined every 4 years, and a more negative score represents a lower socioeconomic status. The status scores used in this study were calculated in 2002 and 2006. The correlations between the status scores in 2002 and 2006 were very high: r = 0.97. To assign the status scores in the best possible way, pregnancies in 2002 and 2003 were allocated with the status score of 2002. For pregnancies in 2005 and 2006, the status score of 2006 was assigned. For pregnancies in 2004, the average score of 2002 and 2006 was assigned.

Pregnancy dating

Gestational age is the most important determinant of fetal growth, so precise dating of the pregnancy is important. It has long been assumed that embryonic growth in the first trimester of pregnancy is universal. This is the rationale behind the current practice of pregnancy dating using the CRL, if the gestational age is less than 12 weeks and 5 days and the CRL measurement is smaller than 65 mm.(10) However, study findings suggest that first trimester growth is not uniform.(11) Therefore, in our analyses with CRL measurements as the outcome of interest, pregnancy dating was not based on the CRL, but on the known and reliable last menstrual period (LMP) in case of a regular menstrual cycle (28 ± 4 days).(6) All other cases were excluded for that particular analyses of CRL. The LMP was obtained from the referral letter and confirmed at enrolment. Additional information on regularity and cycle duration was obtained through questionnaires. When the gestational age was more than 12 weeks and 5 days, or the biparietal diameter (BPD) was larger than 23 mm, pregnancy dating was performed using the BPD.

Growth parameters

Ultrasound assessments were carried out during visits to one of the research centres, and took place in early- (median 13.2 weeks of gestation), mid- (median 20.5 weeks of gestation) and late (median 30.3 weeks of gestation) pregnancy. Growth parameters included the crown-rump length (CRL), head circumference (HC), femur length (FL), abdominal circumference (AC), estimated fetal weight (EFW) and birthweight. EFW was calculated using the Hadlock formula with parameters AC, HC and FL (in cm): EFW = 10^(1.326 – 0.00326*AC*FL + 0.0107*HC + 0.0438*AC + 0.158*FL) (**Supplemental 2. First trimester and fetal growth, measurement guidelines**).(12) Gestational age adjusted standard deviation scores (SDS) were constructed for all growth measurements.(13) The SDS for birthweight were constructed using growth standards from Niklasson et al., which were adjusted for gestational age at the time of birth and sex of the neonate.(14) Measurements were performed using uniform ultrasound procedures and were executed with the Aloka® model SSD-1700 (Tokyo, Japan) or the ATL-Philips Model HDI 5000 (Seattle, WA, USA).

Adverse pregnancy outcomes

Preterm birth (PTB) was defined as a gestational age of <37 weeks at delivery. Small size for gestational age (SGA) at birth was defined as a sex and gestational age adjusted birth weight below the 10^{th} percentile (<-1.40 SDS) in the study cohort.

Covariates

Information on maternal age, education level, ethnicity, and maternal folic acid supplement use was obtained at enrolment.(8) Ethnicity of participating mothers was defined according to the classification of Statistics Netherlands, and was categorized into Dutch and other Western (European, American, and Oceanian); Turkish and Moroccan; African (Cape Verdean, other African, Surinamese-

Creole, and Dutch Antillean); and Asian (Indonesian, other Asian, and Surinamese-Hindu) according to the largest ethnic groups in our study population and similarities in skin colour and cultural background. In sensitivity analyses, the following classification was used: Dutch, European, Turkish, Moroccan, African, Dutch Antillean, Cape Verdean, Indonesian, Surinamese-Creole, Surinamese-Hindu, Surinamese-unspecified, American Western, American non Western, Asia Western, Asia non Western and Oceanian.(8) Information about smoking, alcohol consumption, and caffeine intake was assessed by questionnaires in each trimester. Maternal pre-pregnancy body mass index was calculated from the reported height (cm) and weight (kg) in the questionnaires. Information about pregnancy complications, mode of delivery and childhood sex, gestational age, and weight and length at birth was obtained from medical records.(13, 14) Complications in a previous pregnancy were defined as: gestational diabetes, pre-eclampsia, thrombosis in arm or leg, pulmonary embolism, solutio placentae, premature rupture of membranes, contractions before 37 weeks of pregnancy or pregnancy induced hypertension. We selected potential confounding variables based on their associations with the outcomes of interest, in order to isolate a neighbourhood specific effect.

Statistical analysis

First, we examined differences between quartiles of neighbourhood deprivation for maternal characteristics, first trimester growth and fetal growth and adverse pregnancy outcomes. Second, we examined the associations of neighbourhood deprivation with fetal growth patterns using unbalanced repeated measurement regression models.(15) We included neighbourhood deprivation in these models as intercept and as interaction term with gestational age to estimate fetal growth rates over time.(15) Third, we assessed the associations of neighbourhood deprivation with the risks of adverse pregnancy outcomes using multiple logistic regression models. In the basic model, the crude association between neighbourhood deprivation and the outcomes of interest were investigated. The adjusted model was adjusted for maternal age, maternal educational level, smoking, alcohol use, folic acid supplement use, ethnicity, parity, pre-pregnancy BMI and fetal sex. We tested interaction between neighbourhood deprivation and complications in previous pregnancy in the regression models. Fourth, we examined the associations of neighbourhood deprivation with fetal growth in gestational-age-adjusted SDS in each pregnancy period using linear regression models with the same adjustment models.

We performed several sensitivity analyses: in the first, we performed multilevel regression analysis in order to adjust for potential clustering between the different neighbourhoods. In the second, we repeated the analyses with all 1614 available CRL measurements, compared to the analyses with only CRL measurements below the 12 weeks of gestational age (GA).(6, 16) A third sensitivity analysis was performed to determine to which extent the inclusion of pregnancies with an impaired fetal development due to placental dysfunction influenced our results. Therefore we performed analyses excluding SGA born babies. Fourth, analyses were additionally adjusted for the household income and complications in a previous pregnancy. Fifth, we repeated the analyses with the different classification of ethnicity, described in the 'Covariates' section. Lastly, we explored the associations in the dataset only including the first born (i.e. excluding siblings). We used multiple imputation for missing values of covariates according to Markov Chain Monte Carlo method (details given in **Supplemental 1**).(17) The percentage of missing data was <10%, except for smoking (12.7%), alcohol use (13.8%) and folic acid supplement use (25.9%). Five imputed datasets were created and pooled for analyses. A sensitivity analysis was performed to observe differences in observed and expected values of confounders before and after imputation. Tests for trend were based on regression models with neighbourhood deprivation as a continuous variable. We checked whether the regression models were linear using scatterplots of the dependent variable plotted against the independent variable.(18) Residuals were normally distributed as assessed by visual inspection of a normal probability plot. We tested for multicollinearity using the tolerance statistic. As tolerance was >0.20 for all variables in our models, there were no problems of multicollinearity. The repeated measurement analysis was performed using the Statistical Analysis System version 9.3 (SAS, Institute Inc., Cary, NC, USA), including the Proc Mixed module for unbalanced repeated measurements. All other analyses were performed using the Statistical Package of Social Sciences version 21.0 for Windows (IBM Corp., Armonk, NY, USA).

Results

A total of 8976 pregnancies were included in the Generation R study. In total, we included 8617 pregnancies for analyses (**Figure 1**). **Table 1** depicts the baseline characteristics of both the total study population and the population stratified according to the quartiles of neighbourhood deprivation. Women in the total study population were on average 29.6 years old with a median BMI of 22.8 kg/m^2. Stratification of the population in deprivation quartiles revealed that 2170 women (25.2%) lived in a neighbourhood with the most deprivation, i.e. lowest status score, and 2149 (24.9%) lived in the least deprived neighbourhoods, i.e. the highest status score. When comparing women in the most deprived neighbourhoods to those in the least deprived neighbourhoods, less women were highly educated (23.7% vs. 62.8% (p<0.001)), more women continued smoking in pregnancy (22.3% vs. 11.9% (p<0.001)) and less women used any folic acid supplements (20.0% vs. 49.7% respectively (p<0.001)) (**Table 1**). In **Supplemental Table 1** the fetal growth parameters and adverse pregnancy outcomes stratified by quartile of neighbourhood deprivation are presented. Overall, growth parameters are smaller in the most deprived neighbourhoods compared to the least deprived neighbourhoods (e.g. -0.07 SD vs. 0.15 SD, EFW in the third trimester of pregnancy, respectively).

Neighbourhood deprivation and fetal growth

Figure 2 gives the results of the longitudinal analyses on the association between quartiles of neighbourhood deprivation and fetal head circumference, length, and weight growth patterns from mid-pregnancy onwards. It shows that compared to the least deprived neighbourhoods, in the more deprived neighbourhoods fetal head circumferences, length and weight are smaller (for all measures, the gestational age dependent effect of neighbourhood deprivation on fetal growth was significant value<0.05). Regression coefficients for gestational age-independent and gestational age-dependent effects are given in **Supplemental Table 2.**

The associations of neighbourhood deprivation with first trimester and second and third trimester fetal growth based on regular linear regression models are given in **Supplemental Figure 1.** In both the basic and adjusted analyses, a positive association between neighbourhood deprivation and AC was present (difference in AC in the adjusted model, 0.03 SDS [95% CI 0.01, 0.05, P-value 0.002] per 1 unit increase in neighbourhood status score). In the third trimester of pregnancy a positive association was found for the HC, AC and EFW (adjusted model difference of 0.04 SDS [95% CI 0.02, 0.05, P-value <0.001], 0.04 SDS [95% CI 0.03, 0.06, P-value <0.001] and 0.04 SDS [95% CI 0.03, 0.06, P-value <0.001] per 1 unit increase in neighbourhood status score, respectively). Overall, there is a dose-response like association between neighbourhood deprivation and fetal growth, with stronger associations in the most deprived neighbourhoods compared to the least deprived neighbourhoods.

Effect modification analyses showed significant interaction between neighbourhood deprivation and complications in previous pregnancies for PTB (**Supplemental Table 3**). The associations between neighbourhood deprivation and fetal growth and adverse pregnancy outcomes were non-significant in the group with a complication in a previous pregnancy (e.g. HC in late pregnancy attenuates from 0.06 SDS [95%CI 0.05 , 0.08, P-value <0.001] to 0.03 SDS [95%CI -0.05 , 0.11, P-value 0.50] per 1 unit increase in neighbourhood status score) (**Supplemental Table 4**).

Neighbourhood deprivation and adverse pregnancy outcomes

Results of the regression analysis between neighbourhood deprivation and adverse pregnancy outcomes are presented in **Table 2**. Living in a more affluent neighbourhood was inversely associated with the risk of delivering a SGA neonate (adjusted model, OR 0.91 [95% CI 0.86, 0.97, P-value 0.01], independent of maternal sociodemographic or lifestyle factors. Moreover, it was inversely and independently associated with the risk of PTB (adjusted model, OR 0.89 [95% CI 0.82, 0.96, P-value 0.01]. The adverse pregnancy outcomes were most prevalent in the neighbourhood with the lowest deprivation status compared to the neighbourhood with the highest social status (SGA: 12.2% vs. 7.1%, PTB: 5.9% vs. 3.8%) (**Supplemental Table 1**).

Sensitivity analyses

The first sensitivity analyses revealed largely similar associations after performing multilevel analyses (**Supplemental Table 5**). Second, the results of the associations between neighbourhood deprivation and CRL did not change after including all CRL measurements, in comparison to only the CRL measurements below 12 weeks GA (**Supplemental Table 5**). The third sensitivity analyses excluding SGA pregnancies did attenuate the results (**Supplemental Table 6**). Results also did not materially change after all other sensitivity analyses (data not shown). No major differences were observed in confounders before and after multiple imputation (**Supplemental Table 7**) and there were similar results when confounders were not imputed (data not shown).

Discussion

Main findings

We observed that living in a more deprived neighbourhood is associated with decreased fetal growth in the second and third trimester of pregnancy, and with higher odds of small for gestational age birth and preterm birth. Several pathways may explain the disadvantageous effects of living in a deprived neighbourhood on pregnancy.(19) First, it is proposed to be due to the accumulation of risk factors at the individual level.(5) Examples are smoking and inadequate nutrition and lifestyle behaviours.(20) Neighbourhood deprivation then acts as a proxy for the increased prevalence of risk factors within the deprived neighbourhoods. Our findings are substantiated by earlier studies within the Generation R birth cohort, that demonstrate that living in a deprived neighbourhood is accompanied by the accumulation of individual level risk factors. These in turn were associated with adverse pregnancy outcomes.(5) However, we observe that even after correction for the individual level risk factors, the association between neighbourhood deprivation and impaired development and adverse pregnancy outcomes remained, emphasizing an isolated role for neighbourhood deprivation as a risk factor for pregnancy. The associations between neighbourhood deprivation and fetal growth and adverse pregnancy outcomes attenuated to non-significance in the population affected by a complication in a previous pregnancy. These complications, and the maternal constitution for the development of it, may thus outweigh the contribution of neighbourhood deprivation in the associations with fetal growth and adverse pregnancy outcomes. This may be due to the fact that past complications in pregnancy are strongly associated with both neighbourhood deprivation and fetal growth and adverse pregnancy outcomes.(21). A second pathway which may explain the disadvantageous effects of living in a deprived neighbourhood on adverse pregnancy outcomes is attributed to the lack of or suboptimal access to facilities such as the possibility to purchase healthy food nearby.(22) Third, living in a deprived neighbourhood is acknowledged as a source of chronic stress, and thereby acts as an independent risk factor for adverse health outcomes.(19, 23) Stress is associated with increased cortisol levels, and both prolonged or repeated cortisol exposure increases the risk for impaired physical health.(24) Also with regard to pregnancy, stress is demonstrated to be harmful. M since maternal stress during pregnancy is associated with preterm birth, lower birthweight and the onset of preeclampsia and gestational diabetes.(25, 26)

Our data demonstrates that the associations between neighbourhood deprivation and fetal growth become stronger over the course of pregnancy. This may be due to the fact that there are different mechanisms by which external factors -such as environmental, nutritional and lifestyle factors- affect the developing fetus over the different trimesters of pregnancy. In the first trimester of pregnancy the embryo depends on the uterine glands and yolk sac for the provision of nutrients, while in the subsequent periods of pregnancy there is an exchange of nutrients between the maternal and fetal circulations across the placenta.(27) The more isolated source of nutrition in the first trimester compared to the second and third trimester of pregnancy may decrease the sensitivity of first trimester embryonic growth to external influences.

A previous study of our group, observed a negative association between neighbourhood deprivation and first trimester growth. The larger embryos in deprived neighbourhoods were hypothesized to be explained by strong unmeasured intrinsic and extrinsic factors, such as mental stressors.(28) The difference in direction of effects between that study and our current findings, may be due to the different source populations; the first study was conducted in a tertiary-hospital based cohort, while the present study is performed within a population-based cohort.

Strengths and limitations

Strengths of this study include the large number of participants and the availability of extensive data which allowed us to adjust for a large number of potential confounders. Its population-based design in a multi-ethnic population results in a good representation of the residents of the city of Rotterdam. The presence of both residents from deprived and more affluent neighbourhoods in the study population allowed us to investigate the effect of this exposure extensively. The choice of the neighbourhood deprivation indicator is another strength of this study. To classify the degree of neighbourhood deprivation often composite indexes are used, which take factors into account such as the percentage of educated or employed residents, and income of residents within a specific neighbourhood.(29) We selected the status scores of the Netherlands Institute for Social Research, because this index is comparable with international indices such as the Index of Multiple Deprivation and the Jarman score.(30, 31) The status scores are a continuous measure, which allows more accurate analyses compared to a dichotomous measure. Another strength of the study was that missing data of covariates was handled by applying multiple imputations. In comparison with complete-case analyses (which was conducted as a sensitivity analysis), this technique maintains the statistical power of the analyses. Lastly, we chose not to adjust for nutritional factors other than alcohol intake and folic acid supplement use, since alcohol intake and folic acid supplement use are strongly correlated with other lifestyle and nutritional habits.(32, 33)

Some limitations of this study also merit discussion. First, we adjusted the analyses for individual factors, to isolate a neighbourhood specific effect. However, we cannot rule out the presence of residual confounding caused by other individual factors that are strongly associated with fetal growth. Next, possible misclassification of neighbourhood deprivation may have occurred if women moved during pregnancy to a neighbourhood with a different status score from the one they moved out of. However, social mobility in pregnancy is limited and if women move, they generally tend to move to a neighbourhood with a comparable deprivation status.(34) Third, the power of the analyses on CRL are lower due to the availability of only one CRL measurement, instead of a repeated assessment of the CRL. A last disadvantage is that participants of cohort studies, even those in more deprived neighbourhoods, generally have a higher level of health awareness and are generally more healthy compared to those who do not participate.(8) This may reduce the generalizability of our findings to the general population.

Future perspectives

In future studies, a potential power issue due to the small measurement differences in first trimester growth measurements may be prevented by using larger study sample sizes. Moreover more accurate measures of early fetal growth with higher quality ultrasound could increase the variability of the measurements which enables detection of very small differences. Additionally, animal studies may help unravel the underlying mechanisms through which neighbourhood deprivation affect pregnancy. For instance, by further investigating how maternal stress affects placental nutrient transport.

In the Netherlands, in both the prenatal and postnatal setting, screening for non-medical risk factors is starting to become part of daily medical practice.(35, 36) This allows early interventions in order to prevent developmental problems of children in later life. However, we propose a shift of attention towards an earlier window of opportunity: the preconception period and first trimester of pregnancy. This periconception period provides the opportunity to optimize the conditions of pregnancy and thereby decrease the risks of adverse outcomes and all their long-term consequences.(37) For example, based on an early risk assessment, a pregnant woman living in a deprived neighbourhood could be scheduled for extra ultrasounds and check-ups, and be assisted to improve modifiable lifestyle risk factors.

Additionally, it is important to create more awareness among politicians, policymakers and public health workers. They could help to embed neighbourhood deprivation in the context of health promotion, by developing and promoting targeted preventive intervention programs.(38) These programs could specifically focus on residents of deprived neighbourhoods. It is important to stimulate these residents to diminish risk factors on the individual level, for instance to quit smoking and abstain from alcohol. This could also help to narrow health inequalities between neighbourhoods and between groups of different socioeconomic status.

In conclusion, our obtained insights on the association between neighbourhood deprivation and fetal growth and prematurity emphasize the need for a comprehensive research, care and policy approach from the preconception phase onwards, to mitigate the risk of adverse pregnancy outcomes due to deprivation.

Twitter Dionne Gootjes @dvgootjes

Acknowledgements The Generation R Study is conducted by the Erasmus Medical Centre in close collaboration with the School of Law and the Faculty of Social Sciences at the Erasmus University, Rotterdam, the Municipal Health Service, Rotterdam area and the Stichting Trombosedienst and Artsenlaboratorium Rijnmond (Star-MDC), Rotterdam. We gratefully acknowledge the contribution of children and their parents, general practitioners, hospitals, midwives and pharmacies in Rotterdam.

Author Contributions All authors made a substantive contribution to the manuscript. DG analyzed the data and wrote the article. AP, VJ, and ES contributed to the design of the paper, interpretation of the data, revisions and gave input at all stages of the study. All authors have approved the final version of the manuscript.

Funding: The Generation R Study was made possible by financial support from Erasmus MC, University Medical Centre Rotterdam, the Netherlands; the Netherlands Organization for Health Research and Development; the Netherlands Organization for Scientific Research; the Ministry of Health, Welfare and Sport; and the Ministry of Youth and Families. Prof. Dr. Vincent Jaddoe received additional grants from the Netherlands Organization for Health Research and Development (grants 90700303 and 916.10159, and VIDI 016.136.361) and a Consolidator Grant from the European Research Council (ERC-2014-CoG-64916).

Competing interests: None declared.

Patient and public involvement: Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication: Not required.

Ethics approval The study has been approved by the Medical Ethical Committee of the Erasmus Medical Centre in Rotterdam on December 17th 2001 (MEC 198.782/2001/31). Written consent was obtained from all participants.

Data availability statement Data requests can be made to the secretariat of Generation R.

ORCID iDs

Dionne Gootjes https://orcid.org/0000-0002-9382-9031

Anke Posthumus https://orcid.org/0000-0002-4882-3474

Vincent Jaddoe https://orcid.org/0000-0003-2939-0041

374 Eric Steegers https://orcid.org/0000-0001-6658-9274

Tables and figures

Figure 1. Flowchart of the study population.

Figure 2. Associations of neighbourhood deprivation with fetal growth.

Table 1. Baseline characteristics of the study population, stratified for quartiles of the neighbourhood status score.

Table 2. Associations between the neighbourhood status score and adverse pregnancy outcomes.

Supplemental material

Supplemental Table 1. Fetal growth and adverse pregnancy outcomes in the study population, stratified for quartiles of the neighbourhood status score.

Supplemental Table 2. Regression coefficients of longitudinal associations between quartiles of neighbourhood deprivation with fetal growth patterns.

Supplemental Table 3. P-value of interaction terms (neighbourhood deprivation * parity and neighbourhood status score * complications in a previous pregnancy).

Supplemental Table 4. Associations between the neighbourhood SES and fetal growth and adverse pregnancy outcomes, split for nulliparous women, multiparous women without a complications in a previous pregnancy or multiparous women with a complications in a previous pregnancy.

Supplemental Table 5. Sensitivity analysis with all available CRL measurements in the study population.

Supplemental Table 6. Associations between the neighbourhood SES and fetal growth in a selected cohort of non-SGA pregnancies.

Supplemental Table 7. Observed and expected values of covariates.

397 **Supplemental Figure 1. Associations between the neighbourhood deprivation and fetal growth parameters.**

399 **Supplemental Figure 2. Multilevel regression analysis of associations between neighbourhood deprivation and first trimester and fetal growth measurements.**

401 **Supplemental 1. Multiple imputations for missing data of covariates**

402 **Supplemental 2. First trimester and fetal growth, measurement guidelines.**

403 **Figure 1.** Flowchart of the study population.

404

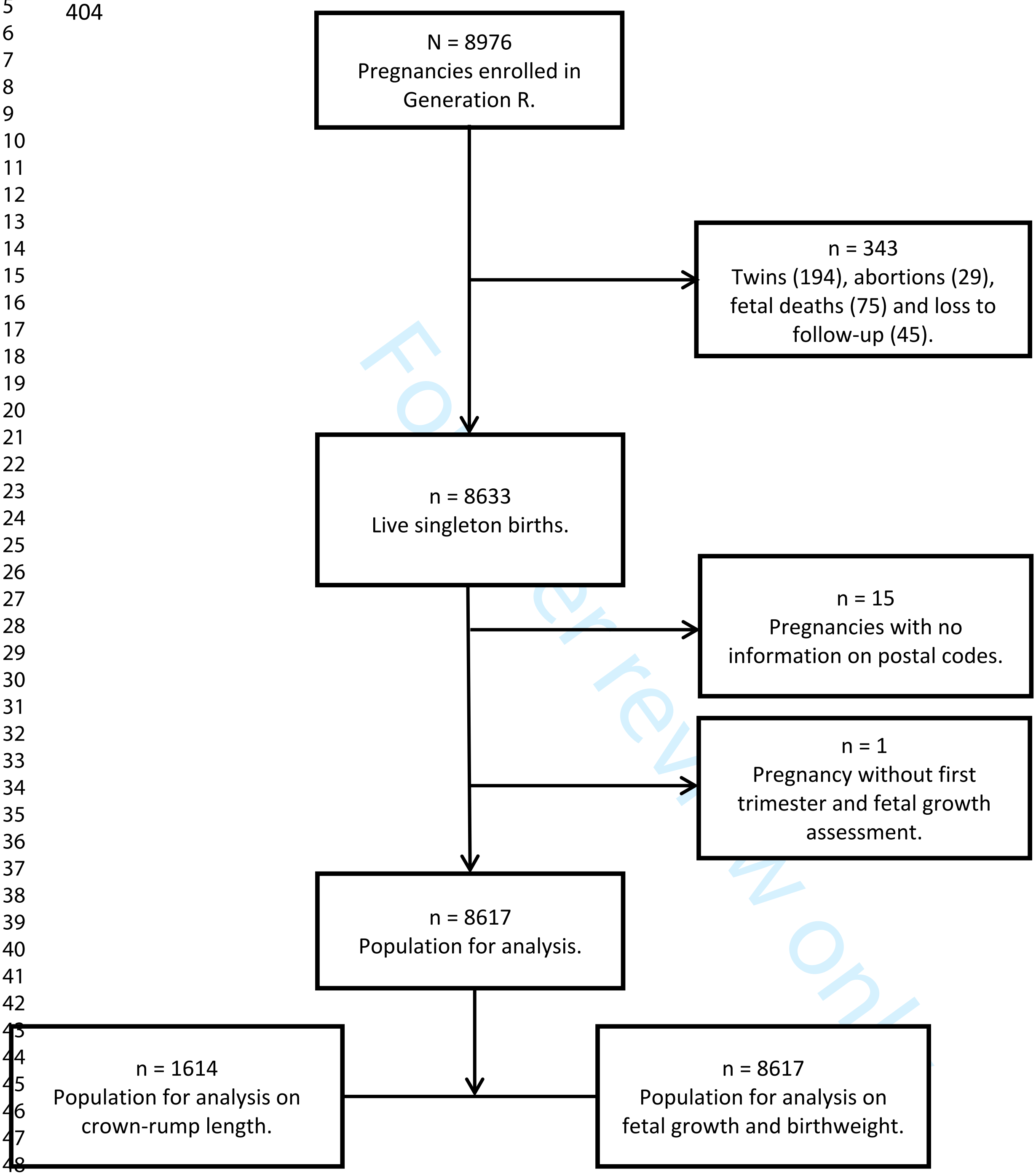


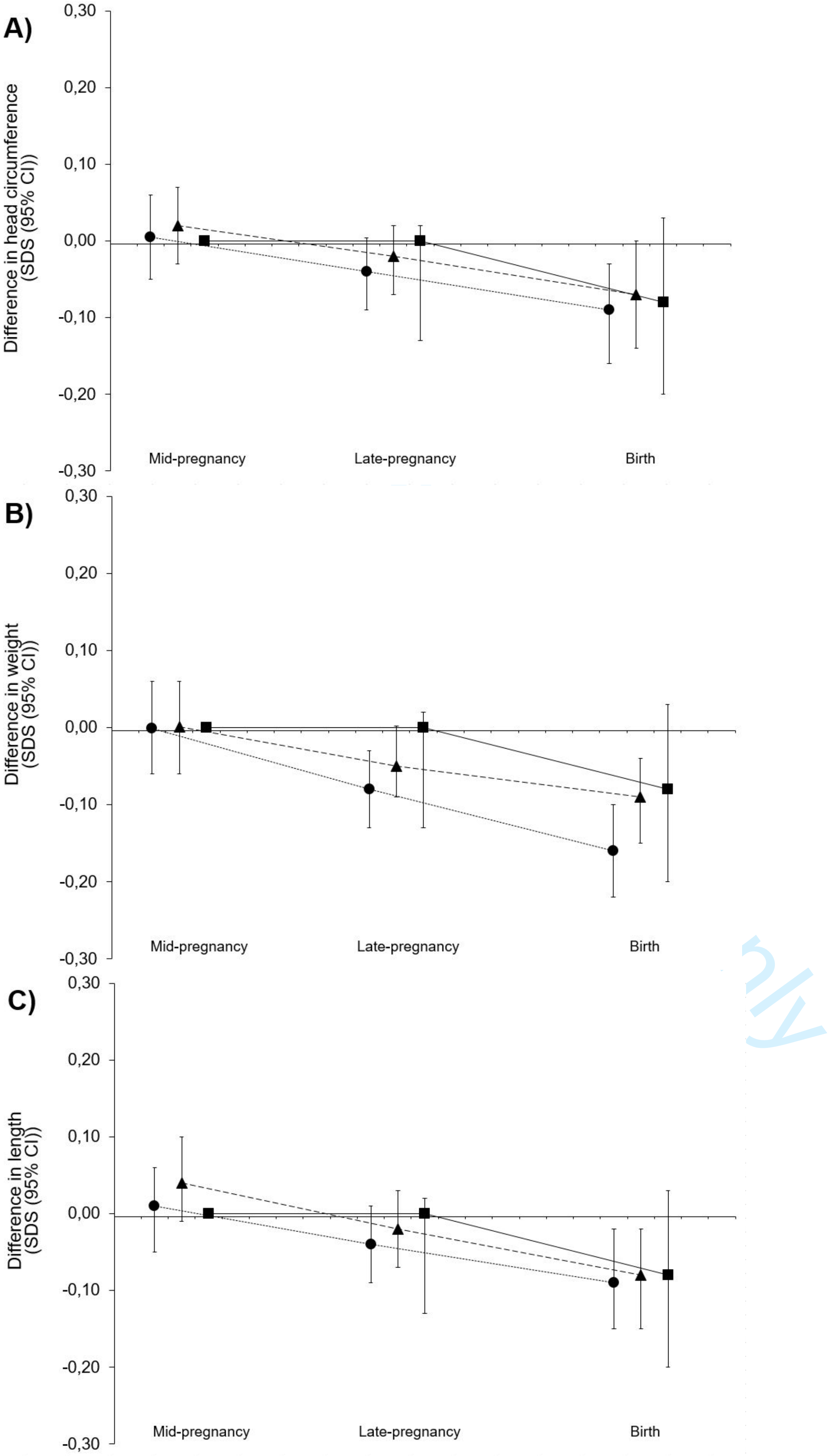
Table 1. Baseline characteristics of the study population, stratified for quartiles of neighbourhood deprivation.

Maternal characteristics	Total study population n = 8617	Lowest deprivation quartile n = 2170	Second deprivation quartile n = 2208	Third deprivation quartile n = 2090	Highest deprivation quartile n = 2149	p-value
Neighbourhood status score	-1.13 (1.39)	-2.96 (0.51)	-1.62 (0.31)	-0.51 (0.37)	0.61 (0.49)	**<0.001**
Age at intake (years)	29.6 (5.3)	28.1 (5.5)	28.7 (5.7)	30.2 (4.9)	31.6 (4.1)	**<0.001**
Pre-pregnancy body mass index (kg/m^2)	22.8 (18.4 – 32.2)	23.5 (18.0 – 33.6)	23.0 (18.1 – 32.5)	22.9 (18.2 – 32.0)	22.3 (18.5– 30.1)	**<0.001**
Parity (nulliparous)	4796 (55.7)	1090 (50.2)	1273 (57.7)	1227 (58.7)	1205 (56.1)	**<0.001**
Educational level						**<0.001**
Lower/no	1101 (12.8%)	503 (23.2)	366 (16.5)	179 (8.5)	52 (2.4)	
Middle	4060 (47.1)	1153 (53.1)	1152 (52.2)	1007 (48.2)	747 (34.8)	
High	3456 (40.1)	514 (23.7)	690 (31.3)	904 (43.3)	1349 (62.8)	
Ethnicity						**<0.001**
Dutch and Western	4967 (57.6%)	636 (29.3)	1084 (49.1)	1426 (68.2)	1821 (84.7)	
Turkish and Moroccan	1464 (17.0%)	714 (32.9)	471 (21.3)	222 (10.6)	57 (2.7)	
African	1178 (13.7%)	519 (23.9)	370 (16.8)	211 (10.1)	78 (3.6)	
Asian	1008 (11.7%)	301 (13.9)	283 (12.8)	231 (11.1)	193 (9.0)	
Smoking						**<0.001**
Never smoked during pregnancy	6256 (72.6%)	1515 (69.8)	1523 (69.0)	1518 (72.6)	1700 (79.1)	
Smoked until pregnancy was known	735 (8.5%)	171 (7.9)	183 (8.3)	188 (9.0)	193 (9.0)	
Continued smoking in pregnancy	1626 (18.9%)	484 (22.3)	502 (22.7)	384 (18.4)	256 (11.9)	
Alcohol						**<0.001**
Never alcohol consumption in pregnancy	4351 (50.5%)	1436 (66.2)	1200 (54.4)	990 (47.4)	726 (33.8)	
Alcohol consumption until pregnancy was known	1149 (13.3%)	220 (10.1)	239 (10.8)	335 (16.0)	354 (16.5)	

Continued alcohol consumption in pregnancy	3117 (36.2%)	514 (23.7)	769 (34.8))	765 (36.6)	1069 (49.7)	
Folic acid supplement intake						**<0.001**
None	2751 (31.9%)	1141 (52.6)	843 (38.2)	534 (25.6)	233 (10.8)	
Start in first 10 weeks of pregnancy	2661 (30.9%)	594 (27.4)	703 (31.8)	650 (31.1)	714 (33.2)	
Start preconceptionally	3205 (37.2%)	435 (20.0)	662 (30.0)	906 (43.3)	1202 (55.9)	
Fetal sex (male)	4347 (50.4)	1063 (49.0)	1147 (51.9)	1066 (51.0)	1071 (49.8)	0.22

406 Data are represented as n (%), mean (SD) or median with the 90% range. Differences in baseline characteristics were tested using ANOVA, Kruskal-Wallis
407 tests and chi-square tests. Confounders are imputed. Non imputed percentages are valid percentages.

Figure 2. Associations of neighbourhood deprivation with fetal growth.



411 Differences in fetal growth rates for the lower three neighbourhood status score quartiles as compared
412 to the highest neighbourhood status score. Squares represent the lowest quartile of the neighbourhood
413 status score; circles represent the second quartile; and triangles the third quartile. Results are based on
414 repeated measurement regression models and reflect the differences in gestational-age-adjusted SDS
415 scores of (a) fetal head circumference, (b) weight, and (c) length growth for the three lower
416 neighbourhood status score compared to the highest neighbourhood status score (reference group
417 represented as zero line). The models were adjusted for maternal age, educational level, smoking,
418 alcohol use, folic acid supplement use, ethnicity, parity, pre-pregnancy body mass index and fetal sex.

419

Table 2. Associations between the neighbourhood status score and adverse pregnancy outcomes.

Study population **n = 8617**	**Model**	**Lowest deprivation quartile** **n = 2277**	**Second deprivation quartile** **n = 2123**	**Third deprivation quartile** **n = 2084**	**Highest deprivation quartile** **n = 2133**	**Trend**	**p-value for trend**
		β / OR (95% CI)	**β / OR (95% CI)**	**β / OR (95% CI)**		**β / OR (95% CI)**	
Small for gestational age	Basic	**1.80 (1.46 ; 2.22)**	**1.46 (1.17 ; 1.81)**	**1.31 (1.05 ; 1.64)**	*Reference*	**0.86 (0.81 ; 0.90)**	**<0.001**
	Adjusted	**1.39 (1.09 ; 1.77)**	1.14 (0.90 ; 1.44)	1.13 (0.90 ; 1.42)	*Reference*	**0.91 (0.86 ; 0.97)**	**0.003**
Preterm birth	Basic	**1.60 (1.21 ; 2.13)**	**1.76 (1.33 ; 2.32)**	**1.41 (1.05 ; 1.89)**	*Reference*	**0.88 (0.83 ; 0.95)**	**<0.001**
	Adjusted	**1.52 (1.11 ; 2.09)**	**1.65 (1.23 ; 2.22)**	1.32 (0.97 ; 1.77)	*Reference*	**0.89 (0.82 ; 0.96)**	**0.004**

Abbreviations: β: beta; OR: odds ratio. Values are odds ratios with the 95% CI of the data in SD-score and are based on logistic regression models. Basic model: by the use of SD scores it is automatically adjusted for gestational age. Adjusted model: basic model and additionally adjusted for maternal age, educational level, smoking, alcohol use, folic acid supplement use, ethnicity, parity, pre-pregnancy body mass index and fetal sex. p-for trend analysis with the neighbourhood deprivation as a continuous measure. Small size for gestational age (SGA) at birth was defined as a sex and gestational age adjusted birthweight below the 10th percentile (<-1.40 SD-score) in the study cohort. Preterm birth (PTB) was defined as a gestational age of <37 weeks at delivery.

References

1. Mackenbach JP, Cavelaars AE, Kunst AE, Groenhof F. Socioeconomic inequalities in cardiovascular disease mortality; an international study. Eur Heart J. 2000;21(14):1141-51.
2. Pickett KE, Pearl M. Multilevel analyses of neighbourhood socioeconomic context and health outcomes: a critical review. J Epidemiol Community Health. 2001;55(2):111-22.
3. Vos AA, Posthumus AG, Bonsel GJ, Steegers EA, Denktas S. Deprived neighborhoods and adverse perinatal outcome: a systematic review and meta-analysis. Acta Obstet Gynecol Scand. 2014;93(8):727-40.
4. de Graaf JP, Ravelli AC, de Haan MA, Steegers EA, Bonsel GJ. Living in deprived urban districts increases perinatal health inequalities. J Matern Fetal Neonatal Med. 2013;26(5):473-81.
5. Timmermans S, Bonsel GJ, Steegers-Theunissen RP, Mackenbach JP, Steyerberg EW, Raat H, et al. Individual accumulation of heterogeneous risks explains perinatal inequalities within deprived neighbourhoods. Eur J Epidemiol. 2011;26(2):165-80.
6. Mook-Kanamori DO, Steegers EA, Eilers PH, Raat H, Hofman A, Jaddoe VW. Risk factors and outcomes associated with first-trimester fetal growth restriction. JAMA. 2010;303(6):527-34.
7. Barker DJ. Fetal origins of coronary heart disease. BMJ. 1995;311(6998):171-4.
8. Kooijman MN, Kruithof CJ, van Duijn CM, Duijts L, Franco OH, van IMH, et al. The Generation R Study: design and cohort update 2017. Eur J Epidemiol. 2016;31(12):1243-64.
9. National Institute for Public Health and the Environment. Sociaaleconomische status 2017 [Available from: https://www.volksgezondheidenzorg.info/onderwerp/sociaaleconomische-status/regionaal-internationaal/regionaal#node-sociaaleconomische-status. .
10. Blaas HG, Eik-Nes SH, Bremnes JB. The growth of the human embryo. A longitudinal biometric assessment from 7 to 12 weeks of gestation. Ultrasound Obstet Gynecol. 1998;12(5):346-54.
11. van Uitert EM, Exalto N, Burton GJ, Willemsen SP, Koning AH, Eilers PH, et al. Human embryonic growth trajectories and associations with fetal growth and birthweight. Hum Reprod. 2013;28(7):1753-61.
12. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements--a prospective study. Am J Obstet Gynecol. 1985;151(3):333-7.
13. Verburg BO, Steegers EA, De Ridder M, Snijders RJ, Smith E, Hofman A, et al. New charts for ultrasound dating of pregnancy and assessment of fetal growth: longitudinal data from a population-based cohort study. Ultrasound Obstet Gynecol. 2008;31(4):388-96.
14. Niklasson A, Ericson A, Fryer JG, Karlberg J, Lawrence C, Karlberg P. An update of the Swedish reference standards for weight, length and head circumference at birth for given gestational age (1977-1981). Acta Paediatr Scand. 1991;80(8-9):756-62.
15. Twisk JWR. Applied Longitudinal Data Analysis for Epidemiology: A Practical Guide. 2 ed. Cambridge: Cambridge University Press; 2013.
16. Verburg BO, Mulder PG, Hofman A, Jaddoe VW, Witteman JC, Steegers EA. Intra- and interobserver reproducibility study of early fetal growth parameters. Prenat Diagn. 2008;28(4):323-31.
17. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;338:b2393.
18. DG Altman. Practical statistics for medical research. . London, UK: Chapman & Hall; 1999.
19. de Graaf JP, Steegers EA, Bonsel GJ. Inequalities in perinatal and maternal health. Curr Opin Obstet Gynecol. 2013;25(2):98-108.
20. Van Dijk MR, Borggreven NV, Willemsen SP, Koning AHJ, Steegers-Theunissen RPM, Koster MPH. Maternal Lifestyle Impairs Embryonic Growth: The Rotterdam Periconception Cohort. Reprod Sci. 2018;25(6):916-22.

21. Posthumus AG, Birnie E, van Veen MJ, Steegers EA, Bonsel GJ. An antenatal prediction model for adverse birth outcomes in an urban population: The contribution of medical and non-medical risks. Midwifery. 2016;38:78-86.
22. Agyemang C, Vrijkotte TG, Droomers M, van der Wal MF, Bonsel GJ, Stronks K. The effect of neighbourhood income and deprivation on pregnancy outcomes in Amsterdam, The Netherlands. J Epidemiol Community Health. 2009;63(9):755-60.
23. Jokela M. Does neighbourhood deprivation cause poor health? Within-individual analysis of movers in a prospective cohort study. J Epidemiol Community Health. 2015;69(9):899-904.
24. Cohen S, Janicki-Deverts D, Miller GE. Psychological stress and disease. JAMA. 2007;298(14):1685-7.
25. Vehmeijer FOL, Guxens M, Duijts L, El Marroun H. Maternal psychological distress during pregnancy and childhood health outcomes: a narrative review. J Dev Orig Health Dis. 2019;10(3):274-85.
26. Henrichs J, Schenk JJ, Roza SJ, van den Berg MP, Schmidt HG, Steegers EA, et al. Maternal psychological distress and fetal growth trajectories: the Generation R Study. Psychol Med. 2010;40(4):633-43.
27. Burton GJ, Hempstock J, Jauniaux E. Nutrition of the human fetus during the first trimester--a review. Placenta. 2001;22 Suppl A:S70-7.
28. Gootjes DV, Koster MPH, Willemsen SP, Koning AHJ, Steegers EAP, Steegers-Theunissen RPM. The Impact of Neighbourhood Deprivation on Embryonic Growth Trajectories: Rotterdam Periconception Cohort. J Clin Med. 2019;8(11).
29. Rajaratnam JK, Burke JG, O'Campo P. Maternal and child health and neighborhood context: the selection and construction of area-level variables. Health Place. 2006;12(4):547-56.
30. Noble M, Wright G, Smith G, Dibben C. Measuring Multiple Deprivation at the Small-Area Level. Environment and Planning A: Economy and Space. 2006;38(1):169-85.
31. Jarman B. Underprivileged areas: validation and distribution of scores. Br Med J (Clin Res Ed). 1984;289(6458):1587-92.
32. Kang H-G, Joo HH, Choi KD, Lee D, Moon J. Complementarity in dietary supplements and foods: are supplement users vegetable eaters? Food Nutr Res. 2017;61(1):1361769-.
33. Kirk SF, Cade JE, Barrett JH, Conner M. Diet and lifestyle characteristics associated with dietary supplement use in women. Public Health Nutr. 1999;2(1):69-73.
34. Reitsma JB, Kardaun JW, Gevers E, de Bruin A, van der Wal J, Bonsel GJ. [Possibilities for anonymous follow-up studies of patients in Dutch national medical registrations using the Municipal Population Register: a pilot study]

Mogelijkheden voor anoniem follow-uponderzoek van patienten in landelijke medische registraties met behulp van de Gemeentelijke Basisadministratie: een pilotonderzoek. Ned Tijdschr Geneeskd. 2003;147(46):2286-90.
35. Waelput AJM, Sijpkens MK, Lagendijk J, van Minde MRC, Raat H, Ernst-Smelt HE, et al. Geographical differences in perinatal health and child welfare in the Netherlands: rationale for the healthy pregnancy 4 all-2 program. BMC Pregnancy Childbirth. 2017;17(1):254.
36. Lagendijk J, Vos AA, Bertens LCM, Denktas S, Bonsel GJ, Steyerberg EW, et al. Antenatal non-medical risk assessment and care pathways to improve pregnancy outcomes: a cluster randomised controlled trial. Eur J Epidemiol. 2018;33(6):579-89.
37. Steegers EAP, Barker ME, Steegers-Theunissen RPM, Williams MA. Societal Valorisation of New Knowledge to Improve Perinatal Health: Time to Act. Paediatric and perinatal epidemiology. 2016;30(2):201-4.
38. van Voorst SF, Vos AA, de Jong-Potjer LC, Waelput AJM, Steegers EAP, Denktas S. Effectiveness of general preconception care accompanied by a recruitment approach: protocol of a community-based cohort study (the Healthy Pregnancy 4 All study). BMJ open. 2015;5(3):e006284-e.

1 ## Supplemental data

2 **Supplemental Table 1**. Fetal growth and adverse pregnancy outcomes in the study population, stratified for quartiles of neighbourhood deprivation.

	n	Study population n = 8617	n	Lowest deprivation quartile n = 2170	n	Second deprivation quartile n = 2208	n	Third deprivation quartile n = 2090	n	Highest deprivation quartile n = 2149	p-value[1]	p-value[2]
Early pregnancy												
CRL	1614	-0.05 (1.06)	287	0.03 (1.05)	362	-0.01 (1.07)	418	-0.01 (0.95)	547	0.07 (0.87)	0.81	0.63
HC	5646	-0.27 (1.39)	1359	-0.04 (0.99)	1440	-0.04 (1.04)	1361	-0.04 (1.10)	1486	-0.09 (1.06)	0.36	0.20
FL	4682	0.61 (0.88)	1162	-0.08 (0.99)	1233	-0.18 (1.00)	1107	-0.04 (0.98)	1180	-0.10 (1.00)	0.18	0.74
Mid pregnancy												
HC	8035	-0.02 (1.02)	1972	-0.06 (1.03)	2049	-0.04 (1.05)	1973	-0.01 (1.02)	2041	0.03 (0.98)	**0.047**	**0.01**
FL	8058	0.03 (1.03)	1985	0.06 (1.07)	2046	0.06 (1.08)	1970	0.04 (1.02)	2057	-0.01 (0.97)	0.12	**0.03**
AC	8052	0.01 (1.01)	1977	-0.04 (1.02)	2050	-0.04 (1.02)	1971	0.02 (1.00)	2054	0.11 (0.98)	**<0.001**	**<0.001**
EFW	8016	-0.10 (1.01)	1975	-0.12 (1.02)	2035	-0.12 (1.04)	1957	-0.09 (1.00)	2049	-0.06 (0.97)	0.22	0.08
Late pregnancy												
HC	8163	0.01 (1.00)	2029	-0.08 (1.00)	2067	-0.09 (1.02)	1984	0.06 (1.00)	2083	0.17 (0.96)	**<0.001**	**<0.001**
FL	8234	-0.01 (1.00)	2049	-0.04 (1.00)	2083	-0.01 (1.05)	2005	0.004 (1.00)	2097	0.02 (0.97)	0.28	0.06
AC	8212	0.01 (1.01)	2042	-0.10 (1.01)	2076	-0.07 (1.04)	1995	0.04 (1.01)	2099	0.14 (0.97)	**<0.001**	**<0.001**
EFW	8201	0.03 (1.02)	2042	-0.06 (1.01)	2073	-0.02 (1.04)	1993	0.07 (1.00)	2093	0.15 (1.00)	**<0.001**	**<0.001**

Birth												
Small for gestational age	824	854 (9.9%)	261	261 (12.2%)	220	225 (10.1%)	190	190 (9.2%)	153	153 (7.1%)	**<0.001**	**<0.001**
Preterm birth	460	460 (5.3%)	128	128 (5.9%)	142	142 (6.4%)	109	109 (5.2%)	81	81 (3.8%)	**0.001**	**0.001**

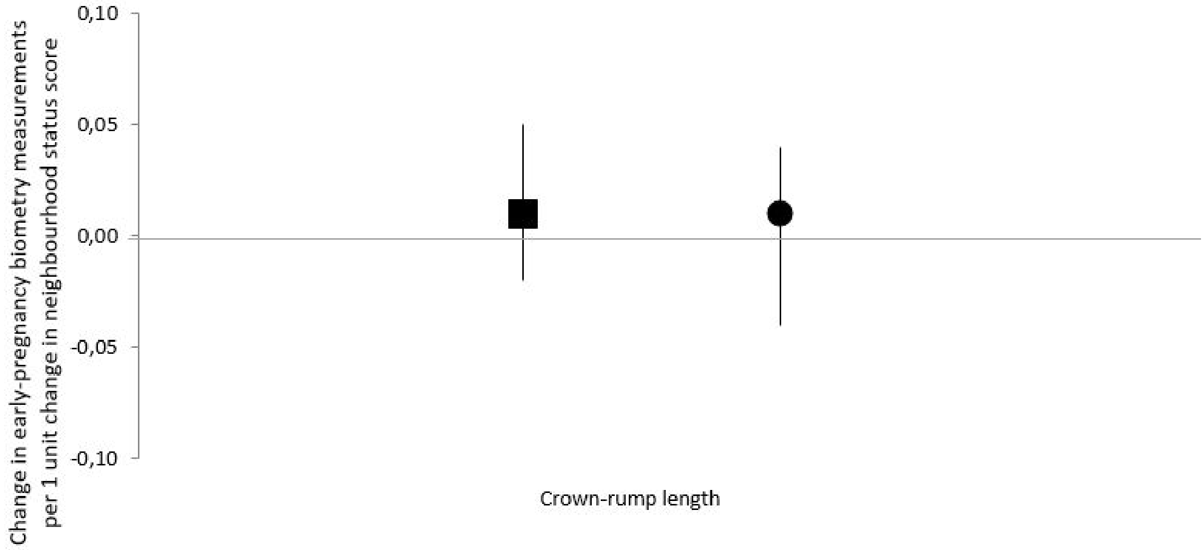
Abbreviations: SD: standard deviation. HC: head circumference. FL: femur length. AC: abdominal circumference. EFW: estimated fetal weight. Values represent data in SD-score, mean (SD) or n (%).[1] Differences between groups were evaluated using one-way-ANOVA-tests for continuous variables and Chi-square tests for proportions. [2]Differences in growth parameters between the lowest and highest neighbourhood status score groups were tested were evaluated using Student's t-tests. Percentages are valid percentages.

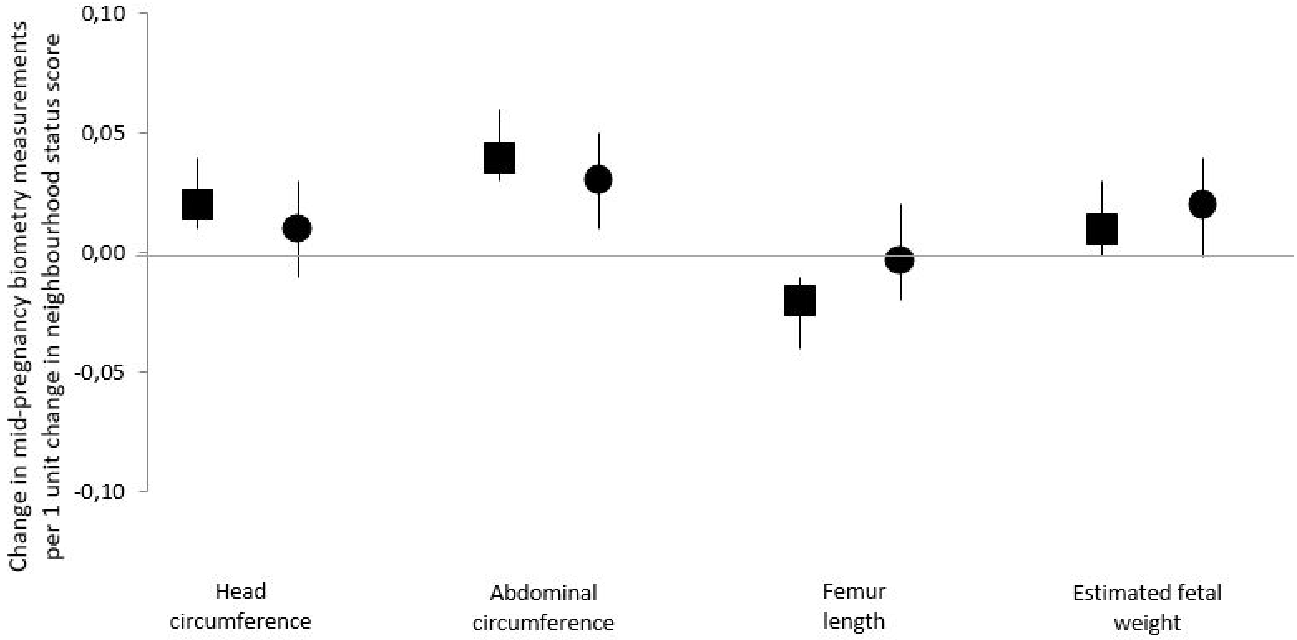
Supplemental Table 2. Regression coefficients of longitudinal associations between quartiles of neighbourhood deprivation with fetal growth patterns.

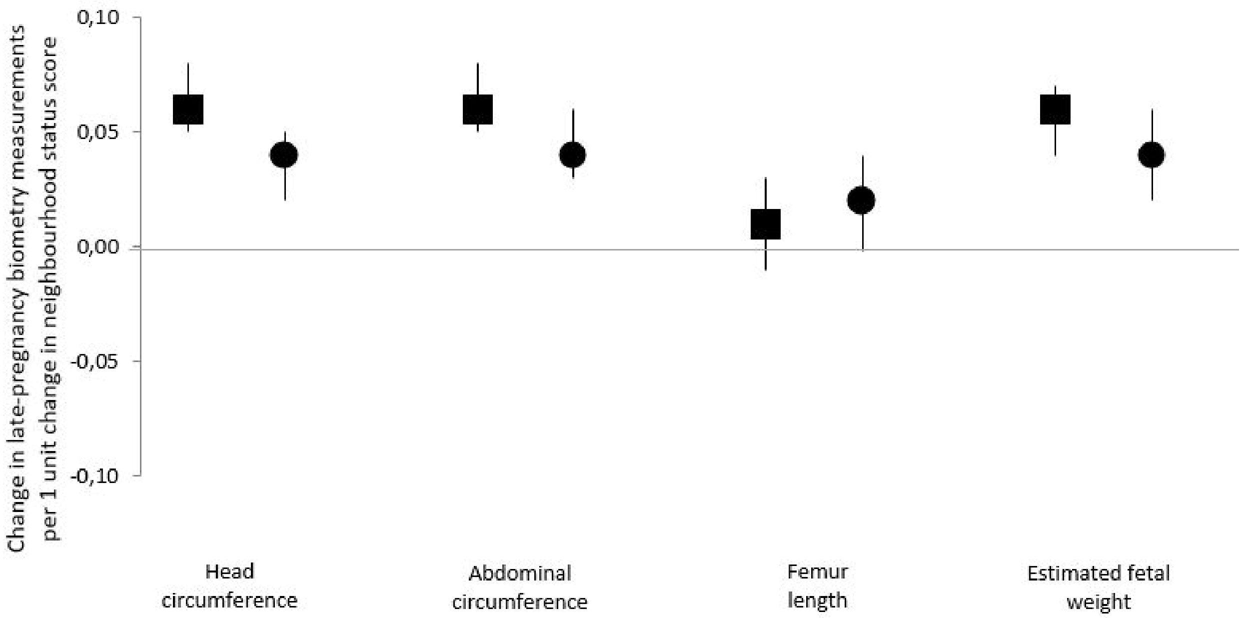
	Intercept Head circumference (SDS)	Slope Head circumference (SDS)	Intercept Length (SDS)	Slope Length (SDS)	Intercept Weight (SDS)	Slope Weight (SDS)
Neighbourhood deprivation						
Quartile 1	**0.225 (0.122; 0.328)**	**-0.010 (-0.013; -0.006)**	**0.270 (0.167; 0.373)**	**-0.012 (-0.016; -0.010)**	**0.229 (0.115; 0.3441)**	**-0.011 (-0.015; -0.008)**
Quartile 2	**0.104 (0.004; 0.204)**	**-0.005 (-0.008; -0.001)**	**0.103 (0.003; 0.203)**	**-0.005 (-0.008; -0.001)**	**0.155 (0.043; 0.268)**	**-0.008 (-0.011; -0.005)**
Quartile 3	**0.109 (0.009; 0.208)**	**-0.004 (-0.008; -0.001)**	**0.170 (0.071; 0.270)**	**-0.006 (-0.010; -0.003)**	0.095 (-0.018; 0.208)	**-0.005 (-0.008; -0.001)**
Quartile 4	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.

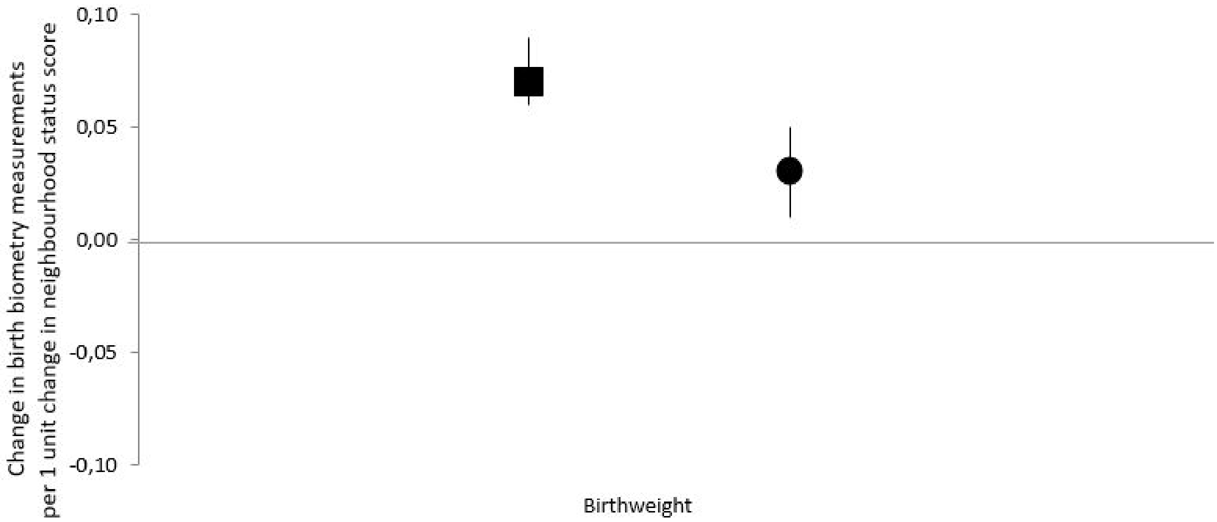
Values are regression coefficients obtained from linear repeated measurement models and reflect the (gestational) age independent differences (intercepts) and the gestational age dependent differences (slopes: change in growth characteristics SDS per week per quartile of the neighbourhood deprivation score, compared with the highest quartile of the neighbourhood deprivation score as the reference group, adjusted for maternal age, educational level, smoking, alcohol use, folic acid supplement use, ethnicity, parity, pre-pregnancy body mass index and fetal sex.)

Supplemental Figure 1. Associations between neighbourhood deprivation with first trimester and fetal growth measurements.









Data are SDS values (95% CI) from linear regression models that reflect the differences in growth characteristics in SDS's in early pregnancy, mid-pregnancy late pregnancy and birth, per 1 unit change in neighbourhood status score. Analyses with crown–rump length were based on subgroup analyses (n = 1614). Estimates are from multiple imputed data. Squares show basic model; circles show the adjusted model: basic model and additionally adjusted for maternal age, educational level, smoking, alcohol use, folic acid supplement use, ethnicity, parity, pre-pregnancy body mass index and fetal sex.

Supplemental Table 3. P-value of interaction terms (neighbourhood deprivation * parity and neighbourhood deprivation * complications in a previous pregnancy).

Study population n = 8617		
	Parity	**Complications in a previous pregnancy**
	p-value for trend	**p-value for trend**
Early pregnancy		
CRL	0.44	0.36
HC	0.25	0.24
FL	0.52	0.91
Mid pregnancy		
HC	0.15	0.20
FL	0.13	0.20
AC	0.73	0.81
EFW	0.27	0.34
Late pregnancy		
HC	0.64	0.62
FL	0.58	0.51
AC	0.66	0.88
EFW	0.82	0.99
Birth		
SGA	0.95	0.85
PTB	0.17	**0.03**

Abbreviations: β: beta; CRL: crown-rump length; HC: head circumference; FL: femur length; AC: abdominal circumference; EFW: estimated fetal weight. Values are based on the adjusted linear and logistic regression models.

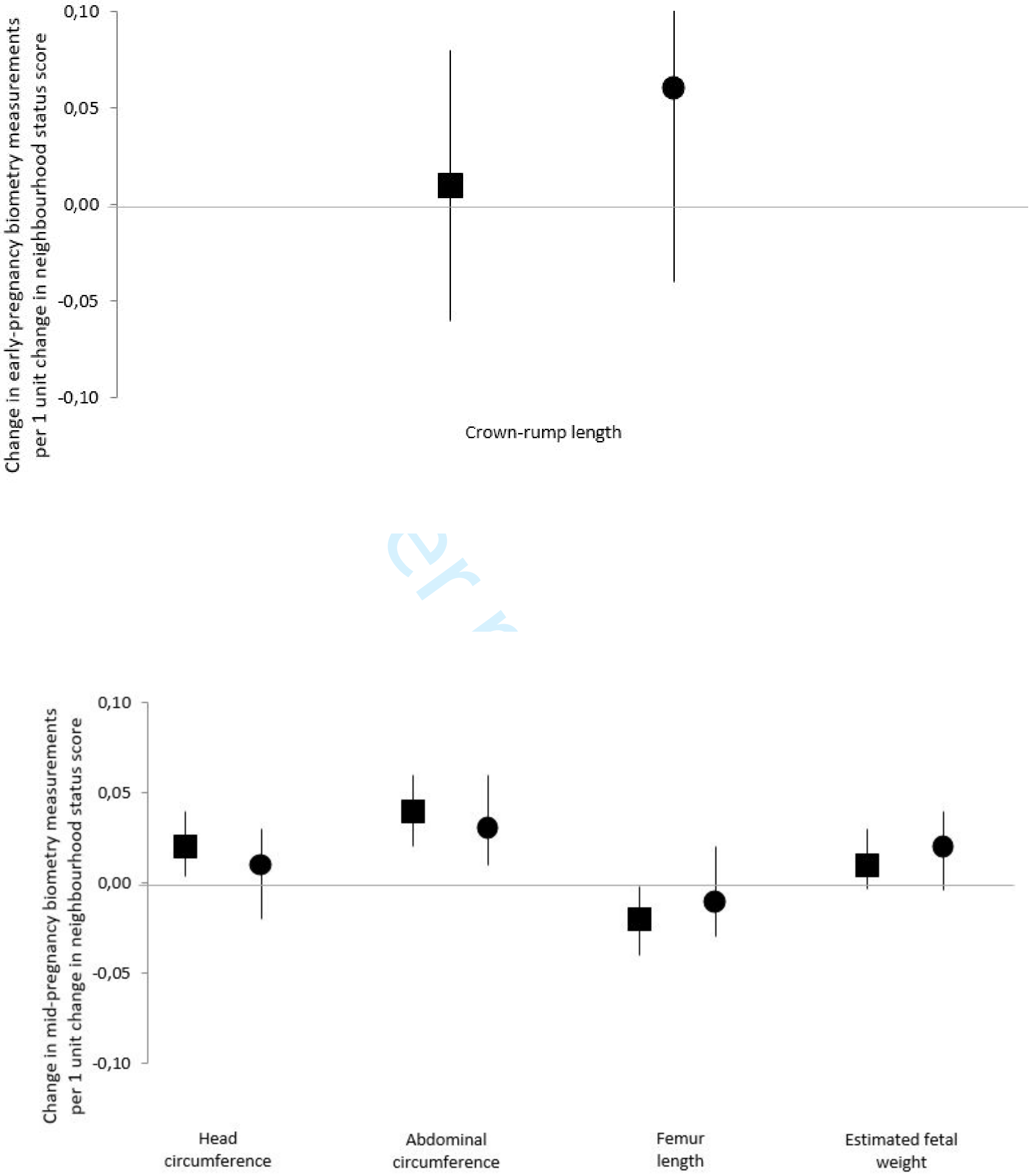
Supplemental Table 4. Associations between the neighbourhood status score and fetal growth and adverse pregnancy outcomes, split for nulliparous women, multiparous women without a complications in a previous pregnancy or multiparous women with a complications in a previous pregnancy.

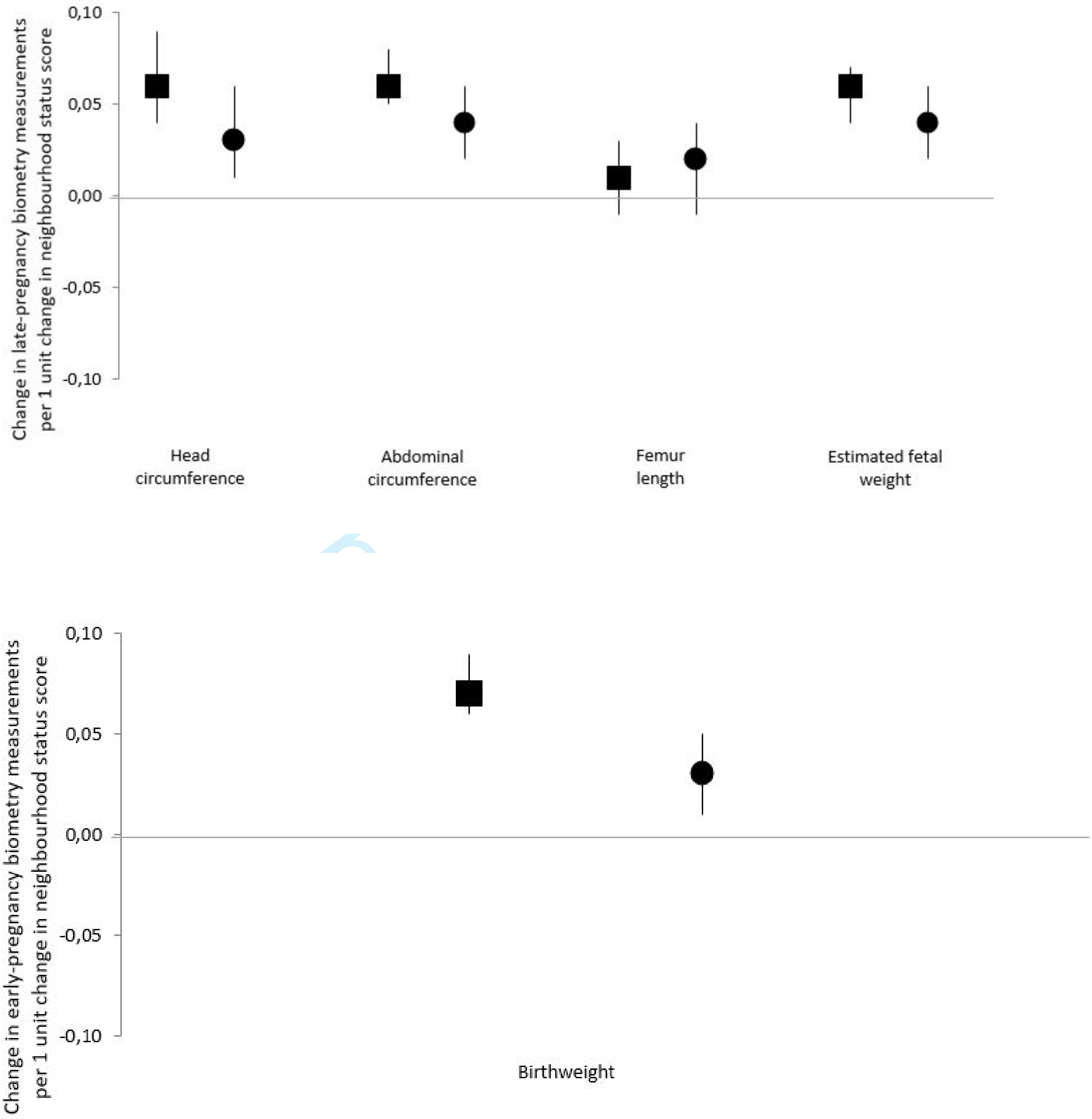
Study population n = 8617	**Nulliparous N = 4739**		**Multiparous, no complications previous pregnancy N = 3166**		**Multiparous, complications previous pregnancy N = 606**	
	Trend		**Trend**		**Trend**	
	β/OR (95% CI)	**p-value for trend**	**β/OR (95% CI)**	**p-value for trend**	**β/OR (95% CI)**	**p-value for trend**
Early pregnancy						
CRL	0.02 (-0.04 ; 0.08)	0.42	-0.01 (-0.10 ; 0.07)	0.74	0.02 (-0.19 ; 0.22)	0.88
HC	0.004 (-0.03 ; 0.04)	0.84	-0.01 (-0.05 ; 0.04)	0.73	-0.04 (-0.15 ; 0.07)	0.45
FL	0.03 (-0.01 ; 0.07)	0.09	0.04 (-0.01 ; 0.09)	0.09	-0.04 (-0.15 ; 0.07)	0.50
Mid pregnancy						
HC	0.02 (-0.02 ; 0.05)	0.32	0.02 (-0.02 ; 0.06)	0.30	**-0.11 (-0.19 ; -0.03)**	**0.01**
FL	0.01 (-0.02 ; 0.04)	0.66	-0.01 (-0.05 ; 0.03)	0.59	-0.06 (-0.15 ; 0.02)	0.14
AC	**0.03 (0.002 ; 0.06)**	**0.03**	**0.05 (0.01 ; 0.09)**	**0.01**	-0.02 (-0.11 ; 0.07)	0.66
EFW	0.02 (-0.01 ; 0.05)	0.12	0.03 (-0.01 ; 0.07)	0.18	-0.04 (-0.13 ; 0.04)	0.32
Late pregnancy						
HC	**0.04 (0.01 ; 0.07)**	**0.004**	0.03 (-0.003 ; 0.07)	0.07	0.03 (-0.05 ; 0.11)	0.50
FL	0.02 (-0.01 ; 0.05)	0.10	-0.003 (-0.04 ; 0.03)	0.89	0.03 (-0.05 ; 0.11)	0.45

AC	**0.03 (0.002 ; 0.06)**	**0.04**	**0.04 (0.01 ; 0.08)**	**0.03**	0.07 (-0.01 ; 0.16)	0.10
EFW	**0.03 (0.01 ; 0.06)**	**0.02**	**0.04 (0.001 ; 0.08)**	**0.048**	0.07 (-0.02 ; 0.16)	0.11
Birth						
SGA	**0.90 (0.82 ; 0.99)**	**0.03**	0.96 (0.82 ; 1.12)	0.60	0.88 (0.63 ; 1.23)	0.46
PTB	0.91 (0.81 ; 1.03)	0.15	**0.73 (0.58 ; 0.93)**	**0.01**	0.89 (0.66 ; 1.21)	0.46

Abbreviations: β: beta; CRL: crown-rump length; HC: head circumference; FL: femur length; AC: abdominal circumference; EFW: estimated fetal weight. Values are regression coefficients with the 95% CI of the data in SD-score and are based on adjusted linear and logistic regression models. Adjusted model: adjusted for maternal age, educational level, smoking, alcohol use, folic acid supplement use, ethnicity, parity, pre-pregnancy body mass index and fetal sex. p-for trend analysis with the neighbourhood deprivation as a continuous measure.

Supplemental Figure 2. Multilevel regression analysis of associations between the neighbourhood deprivation and first trimester and fetal growth measurements.





Data are SDS values (95% CI) from multilevel analyses and reflect the differences in growth characteristics in SDS's in early pregnancy, mid-pregnancy late pregnancy and birth, per 1 unit change in neighbourhood status score. Analyses with crown–rump length were based on subgroup analyses (n = 1614). Estimates are from multiple imputed data. Squares show basic model. Circles show adjusted model: basic model and additionally adjusted for maternal age, educational level, smoking, alcohol use, folic acid supplement use, ethnicity, parity, pre-pregnancy body mass index and fetal sex.

Supplemental Table 5. Sensitivity analysis with all available CRL measurements in the study population.

a. All CRL measurement in the study population, stratified for quartiles of the neighbourhood status score.

	n	**Study population n = 8617**	**n**	**Lowest deprivation quartile n = 2277**	**n**	**Second deprivation quartile n = 2123**	**n**	**Third deprivation quartile n = 2084**	**n**	**Highest deprivation quartile n = 2133**	**p-value[1]**	**Mean difference (95% CI)[2]**	**p-value[2]**
CRL	1614		287	0.03 (1.05)	362	-0.01 (1.07)	418	-0.01 (0.95)	547	0.07 (0.87)	0.56	-0.03 (-0.17 ; 0.10)	0.61

b. All CRL measurement in the study population and the associations between quartiles of the neighbourhood status score.

	n	**Model**	**Lowest deprivation quartile n = 300**	**Second deprivation quartile n = 373**	**Third deprivation quartile n = 399**	**Highest deprivation quartile n = 542**	**Trend**	**p-value for trend**
			β (95% CI)	**β (95% CI)**	**β (95% CI)**		**β (95% CI)**	
CRL	1614	Basic	-0.03 (-0.17 ; 0.10)	-0.08 (-0.21 ; 0.05)	-0.08 (-0.20 ; 0.05)	*Reference*	0.01 (-0.02 ; 0.05)	0.48
		Adjusted	0.02 (-0.15 ; 0.16)	-0.04 (-0.17 ; 0.10)	-0.06 (-0.19 ; 0.06)	*Reference*	0.004 (-0.04 ; 0.04)	0.85

c. All CRL measurement in the study population and the associations between quartiles of the neighbourhood status score. Complete case analysis.

	n	Model	Lowest deprivation quartile n = 2268	Second deprivation quartile n = 2118	Third deprivation quartile n = 2081	Highest deprivation quartile n = 2131	Trend	p-value for trend
			β (95% CI)	**β (95% CI)**	**β (95% CI)**		**β (95% CI)**	
CRL	1143	Adjusted	-0.06 (-0.23 ; 0.12)	0.02 (-0.14 ; 0.17)	-0.06 (-0.21 ; 0.09)	*Reference*	0.01 (-0.04 ; 0.05)	0.80

d. The association between the neighbourhood deprivation status score and all CRL measurement in the study population in a selected cohort of non-SGA pregnancies.

	n	Model	Lowest deprivation quartile n = 2268	Second deprivation quartile n = 2118	Third deprivation quartile n = 2081	Highest deprivation quartile n = 2131	Trend	p-value for trend
			β (95% CI)	**β (95% CI)**	**β (95% CI)**		**β (95% CI)**	
CRL	434	Basic	0.05 (-0.26 ; 0.35)	0.10 (-0.17 ; 0.37)	-0.05 (-0.31 ; 0.21)	*Reference*	-0.01 (-0.09 ; 0.06)	0.73
		Adjusted	0.07 (-0.30 ; 0.43)	0.09 (-0.19 ; 0.38)	-0.06 (-0.33 ; 0.21)	*Reference*	-0.02 (-0.11 ; 0.08)	0.75

Abbreviations: β: beta; CRL: crown-rump length. Values are regression coefficients with the 95% CI of the data in SD-score and are based on linear regression models. Basic model: by the use of SD scores it is automatically adjusted for gestational age. Fully adjusted model: basic model and additionally adjusted for maternal age, educational level, smoking, alcohol use, folic acid supplement use, ethnicity, parity, pre-pregnancy body mass index and fetal sex. p-for trend analysis with the neighbourhood deprivation as a continuous measure. [1] Differences between groups were evaluated using one-way-ANOVA-tests for continuous variables. [2]Differences in growth parameters between the lowest and highest neighbourhood status score groups were tested were evaluated using Student's t-tests.

Supplemental Table 6. Associations between the neighbourhood status score and fetal growth in a selected cohort of non-SGA pregnancies.

Study population n = 7710	Model	Lowest deprivation quartile n = 2268	Second deprivation quartile n = 2118	Third deprivation quartile n = 2081	Highest deprivation quartile n = 2131	Trend	
		β (95% CI)	**β (95% CI)**	**β (95% CI)**		**β (95% CI)**	**p-value for trend**
Early pregnancy							
CRL	Basic	0.05 (-0.26 ; 0.35)	0.10 (-0.17 ; 0.37)	-0.05 (-0.31 ; 0.21)	*Reference*	-0.01 (-0.09 ; 0.06)	0.73
	Adjusted	0.07 (-0.30 ; 0.43)	0.09 (-0.19 ; 0.38)	-0.06 (-0.33 ; 0.21)	*Reference*	-0.02 (-0.11 ; 0.08)	0.75
HC	Basic	**-0.38 (-0.71 ; -0.04)**	**-0.37 (-0.69 ; -0.06)**	-0.07 (-0.37 ; 0.23)	*Reference*	**0.12 (0.04 ; 0.21)**	**0.004**
	Adjusted	-0.22 (-0.60 ; 0.17)	-0.32 (-0.65 ; 0.01)	-0.06 (-0.36 ; 0.25)	*Reference*	0.09 (-0.01 ; 0.19)	0.09
FL	Basic	-0.19 (-0.53 ; 0.15)	**-0.33 (-0.63 ; -0.03)**	-0.11 (-0.40 ; 0.18)	*Reference*	0.08 (-0.002 ; 0.16)	0.06
	Adjusted	-0.24 (-0.66 ; 0.18)	**-0.36 (-0.69 ; -0.03)**	-0.13 (-0.44 ; 0.18)	*Reference*	0.10 (-0.01 ; 0.20)	0.07
Mid pregnancy							
HC	Basic	**-0.07 (-0.13 ; -0.001)**	-0.05 (-0.12 ; 0.01)	-0.03 (-0.10 ; 0.04)	*Reference*	**0.02 (0.003 ; 0.04)**	**0.02**
	Adjusted	-0.02 (-0.10 ; 0.05)	-0.03 (-0.09 ; 0.04)	-0.02 (-0.09 ; 0.05)	*Reference*	0.01 (-0.01 ; 0.03)	0.40
FL	Basic	**0.10 (0.045 ; 0.17)**	**0.10 (0.03 ; 0.16)**	**0.08 (0.01 ; 0.15)**	*Reference*	**-0.02 (-0.05 ; -0.01)**	**0.001**
	Adjusted	0.02 (-0.05 ; 0.10)	0.05 (-0.03 ; 0.11)	0.04 (-0.03 ; 0.11)	*Reference*	-0.01 (-0.03 ; 0.01)	0.42
AC	Basic	**-0.12 (-0.18 ; -0.05)**	**-0.13 (-0.20 ; -0.07)**	**-0.07 (-0.13 ; -0.01)**	*Reference*	**0.04 (0.02 ; 0.05)**	**<0.001**

	Adjusted	**-0.09 (-0.16 ; -0.01)**	**-0.11 (-0.18 ; -0.04)**	-0.06 (-0.12 ; 0.01)	*Reference*	**0.03 (0.01 ; 0.05)**	**0.01**
EFW	Basic	-0.03 (-0.08 ; 0.05)	-0.03 (-0.09 ; 0.04)	0.001 (-0.07 ; 0.06)	*Reference*	0.01 (-0.01 ; 0.02)	0.77
	Adjusted	-0.04 (-0.12 ; 0.03)	-0.04 (-0.11 ; 0.03)	-0.01 (-0.08 ; 0.05)	*Reference*	0.01 (-0.01 ; 0.03)	0.19
Late pregnancy							
HC	Basic	**-0.22 (-0.29 ; -0.16)**	**-0.24 (-0.31 ; -0.18)**	**-0.09 (-0.16 ; -0.03)**	*Reference*	**0.06 (0.04 ; 0.08)**	**<0.001**
	Adjusted	**-0.13 (-0.20 ; -0.06)**	**-0.18 (-0.24 ; -0.11)**	**-0.06 (-0.12 ; -0.001)**	*Reference*	**0.03 (0.01 ; 0.05)**	**<0.001**
FL	Basic	-0.02 (-0.09 ; 0.04)	0.01 (-0.05 ; 0.07)	0.01 (-0.05 ; 0.08)	*Reference*	0.001 (-0.02 ; 0.02)	0.90
	Adjusted	**-0.08 (-0.15 ; -0.01)**	-0.01 (-0.08 ; 0.05)	-0.01 (-0.07 ; 0.06)	*Reference*	0.01 (-0.01 ; 0.03)	0.20
AC	Basic	**-0.20 (-0.27 ; -0.14)**	**-0.18 (-0.24 ; -0.12)**	**-0.07 (-0.13 ; -0.01)**	*Reference*	**0.06 (0.04 ; 0.07)**	**<0.001**
	Adjusted	**-0.15 (-0.22 ; -0.08)**	**-0.13 (-0.19 ; -0.06)**	-0.05 (-0.12 ; 0.01)	*Reference*	**0.04 (0.02 ; 0.06)**	**0.02**
EFW	Basic	**-0.18 (-0.20 ; -0.12)**	**-0.14 (-0.20 ; -0.08)**	-0.05 (-0.11 ; 0.01)	*Reference*	**0.05 (0.03 ; 0.06)**	**<0.001**
	Adjusted	**-0.16 (-0.23 ; -0.08)**	**-0.11 (-0.17 ; -0.04)**	-0.05 (-0.11 ; 0.02)	*Reference*	**0.04 (0.02 ; 0.06)**	**<0.001**

92 Abbreviations: SGA: small for gestational age, HC: head circumference, FL: femur length, AC: abdominal circumference, EFW: estimated fetal weight.
93 Values are regression coefficients with the 95% CI of the data in SD-score and are based on linear regression models. Basic model: by the use of SD scores it
94 is automatically adjusted for gestational age. Fully adjusted model: basic model and additionally adjusted for maternal age, educational level, smoking, alcohol
95 use, folic acid supplement use, ethnicity, parity, pre-pregnancy body mass index and fetal sex. p-for trend analysis with the neighbourhood deprivation as a
96 continuous measure.

Supplemental Table 7. Observed and expected values of covariates.

Maternal characteristics	**Observed**	**Expected**
Age at intake (years)	29.6 (5.3)	29.6 (5.3)
Prepregnancy body mass index (kg/m^2)	22.8 (18.4 – 32.2)	22.6 (18.6 – 32.4)
Parity (nulliparous)	4796 (55.7)	4739 (55.7)
Fetal sex (boy)	4347 (50.4)	4346 (50.4)
Educational level		
Lower/no education	1101 (12.8)	916 (11.7)
Middle	4060 (47.1)	3638 (46.4)
High	3456 (40.1)	3282 (41.9)
Ethnicity		
Dutch and Western	4967 (57.6)	4793 (58.8)
Turkish and Moroccan	1464 (17.0)	1330 (16.3)
African	1178 (13.7)	1076 (13.2)
Asian	1008 (11.7)	946 (11.6)
Smoking		
Never smoked during pregnancy	6256 (72.6)	5472 (72.8)
Smoked until pregnancy was known	735 (8.5)	644 (8.6)
Continued smoking in pregnancy	1626 (18.9)	1403 (18.7)
Alcohol		
Never alcohol consumption in pregnancy	4351 (50.5)	3692 (49.8)
Alcohol consumption until pregnancy was known	1149 (13.3)	999 (13.5)
Continued alcohol consumption in pregnancy	3117 (36.2)	2728 (36.8)
Folic acid supplement use		
None	2751 (31.9)	1877 (29.4)
Start in first 10 weeks of pregnancy	2661 (30.9)	1981 (31.1)
Start preconceptional	3205 (37.2)	2518 (39.5)

Data are represented as n (%), mean (SD) or median with the 90% range. Percentages 'expected' displayed as valid percentages.

Supplemental 1. Multiple imputations for missing data of covariates.

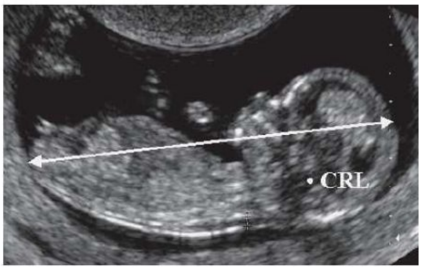
We imputed missing data of the covariates using multiple imputations (17). The percentages of missing values for the confounders within the population for analysis were lower than 20%. For the multiple imputation, we the Markov chain Monte Carlo approach. In the imputation model, we included all confounders, plus maternal age, ethnicity, parity and prepregnancy BMI. Furthermore, we additionally added the studied determinants and outcomes in the imputation model as prediction variables only; they were not imputed themselves. Five imputed datasets were created and analyzed together.

Supplemental 2. First trimester and fetal growth, measurement guidelines.

CRL: crown-rump length (39)

CRL is measured as the largest dimension of embryo, excluding the yolk sac and extremities. A midline sagittal section of the whole embryo or fetus should be obtained, ideally with the embryo or fetus oriented horizontally on the screen. An image should be magnified sufficiently to fill most of the width of the ultrasound screen, so that the measurement line between crown and rump is at about 90◦ to the ultrasound beam.

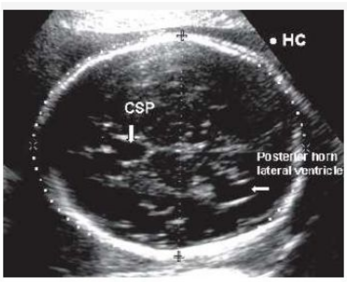
Caliper placement: measure the fetus in a neutral position (i.e. neither flexed nor hyperextended). The end points of crown and rump should be defined clearly.



HC: Head circumference (40)

As described for the BPD, ensuring that the circumference placement markers correspond to the technique described on the reference chart.

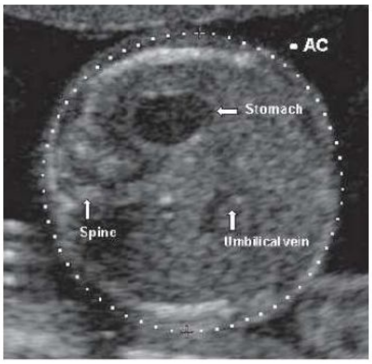
Caliper placement: If the ultrasound equipment has ellipse measurement capacity, then the HC can be measured directly by placing the ellipse around the outside of the skull bone echoes.



AC: abdominal circumference (40)

- Transverse section of the fetal abdomen (as circular as possible);
- umbilical vein at the level of the portal sinus;
- stomach bubble visualized;
- kidneys should not be visible.

Caliper placement: The AC is measured at the outer surface of the skin line, either directly with ellipse calipers or calculated from linear measurements made perpendicular to each other, usually the anteroposterior abdominal diameter and transverse abdominal diameter.



FL: femur length (40)

The FL is imaged optimally with both ends of the ossified metaphysis clearly visible. The longest axis of the ossified diaphysis is measured. The same technique as that used to establish the reference chart should be used with regard to the angle between the femur and the insonating ultrasound beams. An angle of insonation between 45◦ and 90◦ is typical.

Caliper placement: Each caliper is placed at the ends of the ossified diaphysis without including the distal femoral epiphysis if it is visible

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1

Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	#4	Present key elements of study design early in the paper	4, 5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4, 5
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	4, 5
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	4 ,5
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5, 6
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than	4, 5, 6

		one group. Give information separately for for exposed and unexposed groups if applicable.	
Bias	#9	Describe any efforts to address potential sources of bias	5, 6, 8
Study size	#10	Explain how the study size was arrived at	4, 5
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7, 8
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	
6, 8			
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	7, 8
Statistical methods	#12c	Explain how missing data were addressed	7, 8
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	7, 8
Statistical methods	#12e	Describe any sensitivity analyses	
7, 8			

Results

Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility,	9

		confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	
Participants	#13b	Give reasons for non-participation at each stage	9
Participants	#13c	Consider use of a flow diagram	
9			
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	9
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	
9			
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	
9			
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	
9, 10			
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence	9, 10

		interval). Make clear which confounders were adjusted for and why they were included	
Main results	#16b	Report category boundaries when continuous variables were categorized	9, 10
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
9, 10			
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10, 11
Discussion			
Key results	#18	Summarise key results with reference to study objectives	11
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	12, 13
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	13, 14
Generalisability	#21	Discuss the generalisability (external validity) of the study results	13
Other Information			

Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

BMJ Open

The association between neighbourhood deprivation, fetal growth, small-for-gestational age and preterm birth: a population-based prospective cohort study.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-049075.R1
Article Type:	Original research
Date Submitted by the Author:	25-Sep-2021
Complete List of Authors:	Gootjes, Dionne; Erasmus MC, Department of Obstetrics and Gynaecology, Division of Obstetrics and Prenatal Medicine; Erasmus MC, Generation R Study Group Posthumus, Anke G; Erasmus MC, Department of Obstetrics and Gynaecology, Division of Obstetrics and Prenatal Medicine; Erasmus MC, Generation R Study Group Jaddoe, Vincent; Erasmus MC, Department of Paediatrics; Erasmus MC, Generation R Study Group Steegers, E.A.P.; Erasmus MC, Department of Obstetrics and Gynaecology, Division of Obstetrics and Prenatal Medicine; Erasmus MC, Generation R Study Group
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Epidemiology, Obstetrics and gynaecology, Public health
Keywords:	SOCIAL MEDICINE, PUBLIC HEALTH, PREVENTIVE MEDICINE, Ultrasonography < OBSTETRICS, Prenatal diagnosis < OBSTETRICS, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

The association between neighbourhood deprivation, fetal growth, small-for-gestational age and preterm birth: a population-based prospective cohort study.

D.V. Gootjes[1,3], A.G. Posthumus[1,3], V.W.V Jaddoe[2,3], E.A.P. Steegers[1,3]

[1]Department of Obstetrics and Gynaecology, Division of Obstetrics and Prenatal Medicine, [2]Department of Paediatrics, [3]Generation R Study Group, all: Erasmus University Medical Centre, Rotterdam, The Netherlands.

The authors declare no conflict of interest.

Corresponding author

Correspondence to Dionne V. Gootjes

Wytemaweg 80, 3015 CN Rotterdam

d.gootjes@erasmusmc.nl

Telephone: +3110 703 04 52 | +316 307 252 47

Key words: fetal, neighborhood/place, deprivation, pregnancy, socio-economic

Word count: 4362

Abstract

Objectives: To study the associations between neighbourhood deprivation and fetal growth, including growth in the first trimester, and adverse pregnancy outcomes.

Design: Prospective cohort study.

Setting: The Netherlands, Rotterdam.

Participants: 8617 live singleton births from the Generation R cohort study.

Exposition: Living in a deprived neighbourhood.

Main outcome measures: Fetal growth trajectories of head circumference, weight and length.

Secondary outcomes measures: Small-for-gestational age (SGA) and preterm birth (PTB)).

Results: Neighbourhood deprivation was not associated with first trimester growth. However, a higher neighbourhood status score (less deprivation), was associated with increased fetal growth in the second and third trimester (e.g. estimated fetal weight (adjusted regression coefficient 0.04 (95% CI 0.02 ; 0.06). Less deprivation was also associated with a decreased odd of SGA (aOR 0.91 (95% CI 0.86 ; 0.97, p-value 0.01)) and PTB (aOR 0.89 (95% CI 0.82 ; 0.96, p-value 0.01)).

Conclusions: We found an association between neighbourhood deprivation and fetal growth in the second and third trimester pregnancy, but not with first trimester growth. Less neighbourhood deprivation is associated with lower odds of adverse pregnancy outcomes. The associations remained after adjustment for individual level risk factors. This supports the hypothesis that living in a deprived neighbourhood acts as an independent risk factor for fetal growth and adverse pregnancy outcomes, above and beyond individual risk factors.

Article Summary

Strengths and limitations of this study

- This study is performed within in a large, multi-ethnic cohort.
- The Generation R study population is not completely representative of the Dutch population.
- Associations were adjusted for a wide range of relevant individual level risk factors, which allows the isolation of a neighbourhood specific effect best as possible.

Introduction

A low individual socioeconomic status (SES) is associated with adverse health outcomes.(1) Additionally, there is accumulating evidence that the socioeconomic status of the neighbourhood in which a person lives is also associated with health outcomes.(2) This is also the case for pregnancy: both individual SES and living in a deprived neighbourhood are acknowledged risk factors for adverse pregnancy outcomes.(3-5)

Recent evidence shows that other factors, such as maternal nutrition and lifestyle, already affect pregnancy from the first trimester of pregnancy onwards.(6-9) Gaining a better understanding of modifiable factors that influence pregnancy from the earliest phase onwards is important. First, since impaired development during the first trimester of pregnancy is associated with adverse pregnancy outcomes.(6) Second, in line with the DOHaD-paradigm (Developmental Origin of Health and Disease), impaired development in pregnancy and adverse pregnancy outcomes are associated with an increased risk of non-communicable diseases in adult life like cardiovascular disease.(10) If impaired early fetal development could be prevented or recognized, this would enable the prevention of both short-term and long-term adverse outcomes.

Living in a deprived neighbourhood is known to be a risk factor for adverse health outcomes, above and beyond the association with individual risk factors such as inadequate nutrition and lifestyle behaviors. Living in a deprived neighbourhood may lead to exposure to a suboptimal environment, with higher rates of air pollution, less access to facilities such as a green environment to walk in, less health care facilities close, and little possibility to purchase healthy food nearby. Lastly, living in a deprived neighbourhood is acknowledged as a source of chronic stress, which is associated with increased cortisol levels, and thereby acts as an independent risk factor for adverse health outcomes.(11, 12) It is however unknown whether living in a deprived neighbourhood is also associated with adverse pregnancy outcomes and (early) fetal development. Therefore, the aim of this study was to investigate the associations between neighbourhood deprivation, fetal growth including growth in the first trimester, and adverse pregnancy outcomes.

Methods

Design

This study was embedded in the Generation R (Rotterdam) Study, a population-based prospective cohort study.(13) Pregnant women living in the area of Rotterdam, the Netherlands, with an expected delivery date between April 2002 and January 2006, were invited to participate in this study. The 9778 mothers enrolled in the study gave birth to 9749 live born children. Of these mothers, 91% (n=8879) were prenatally enrolled in the study, giving birth to 8976 children. Our aim was to investigate growth trajectories and outcomes of ongoing singleton pregnancies. We excluded the following pregnancies: twin pregnancies, terminated pregnancies, intra-uterine deaths and pregnancies without information on area of residence or ultrasound data (**Figure 1**). The study protocol was approved by the Medical Ethical Committee of Erasmus Medical Centre, Rotterdam (MEC 198.782/ 2001/31). Written informed consent was obtained from all participants.

Patient and public involvement statement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Materials

Neighbourhood deprivation

We used area-based status scores as a proxy for neighbourhood deprivation, which were made available by the Netherlands Institute for Social Research.(14) The scores are matched on four-digit postcodes and are based on mean household income, proportion of population with low income, proportion of population with low educational level, and proportion of population without paid work. The scores are determined every 4 years, and a more negative score represents a lower socioeconomic status. The status scores used in this study were calculated in 2002 and 2006. The correlations between the status scores in 2002 and 2006 were very high: r = 0.97. To assign the status scores in the best possible way, pregnancies in 2002 and 2003 were allocated with the status score of 2002. For pregnancies in 2005 and 2006, the status score of 2006 was assigned. For pregnancies in 2004, the average score of 2002 and 2006 was assigned.

Pregnancy dating

Gestational age is the most important determinant of fetal growth, so precise dating of the pregnancy is important. It has long been assumed that embryonic growth in the first trimester of pregnancy is universal. This is the rationale behind the current practice of pregnancy dating using the crown-rump length (CRL), if the gestational age is less than 12 weeks and 5 days and the CRL measurement is smaller than 65 mm.(15) However, study findings suggest that first trimester growth is not uniform.(16) Therefore, in our analyses with CRL measurements as the outcome of interest, pregnancy dating was not based on the CRL, but on the known and reliable last menstrual period (LMP) in case of a regular menstrual cycle (28 ± 4 days).(6) All other cases were excluded for that particular analyses of CRL. The LMP was obtained from the referral letter and confirmed at enrolment. Additional information on regularity and cycle duration was obtained through questionnaires. When the gestational age was more than 12 weeks and 5 days, or the biparietal diameter (BPD) was larger than 23 mm, pregnancy dating was performed using the BPD.

Growth parameters and adverse pregnancy outcomes

The aim of the study was to focus on fetal outcomes, in terms of growth and development. The selected outcomes were carefully chosen from the ‘Big 4 conditions’, which are specifically defined conditions that precede perinatal mortality in 85 % of all cases, namely: small for gestational age (birth weight < 10th percentile for gestational age), preterm birth (birth < 37 weeks of gestation), congenital disorders, and/or low Apgar score (<7 after 5 min).(17, 18) Due to the low numbers of cases with congenital disorders within the Generation R population, and susceptibility for Apgar score to be affected by the course of delivery which may confound the effect of neighbourhood deprivation during pregnancy, we selected the other 2 major morbidity factors as outcome for this study.

Ultrasound assessments were carried out during visits to one of the research centres, and took place in early- (median 13.2 weeks of gestation), mid- (median 20.5 weeks of gestation) and late (median 30.3 weeks of gestation) pregnancy. Growth parameters included the CRL, head circumference (HC), femur length (FL), abdominal circumference (AC), estimated fetal weight (EFW) and birthweight. EFW was calculated using the Hadlock formula with parameters AC, HC and FL (in cm): EFW = 10^(1.326 – 0.00326*AC*FL + 0.0107*HC + 0.0438*AC + 0.158*FL) (**Supplemental 1. First trimester and fetal growth, measurement guidelines**).(19) Gestational age adjusted standard deviation scores (SDS) were constructed for all growth measurements.(20) The SDS for birthweight were constructed using growth standards from Niklasson et al., which were adjusted for gestational age at the time of birth and sex of the neonate.(21) Measurements were performed using uniform ultrasound procedures and were executed with the Aloka® model SSD-1700 (Tokyo, Japan) or the ATL-Philips Model HDI 5000 (Seattle, WA, USA). Reproducibility of these measurements was assessed and described previously.(22, 23)

Small size for gestational age (SGA) at birth was defined as a sex and gestational age adjusted birth weight below the 10^{th} percentile (<-1.40 SDS) in the study cohort. Preterm birth (PTB) was defined as a gestational age of <37 weeks at delivery.

Covariates

Information on maternal age, education level, ethnicity, and maternal folic acid supplement use was obtained at enrolment.(13) All study materials such as questionnaires, newsletters, website, and information folders are available in three languages (Dutch, English, and Turkish). Furthermore, staff from different ethnic backgrounds was available and verbally translated these materials into Arabic, French and Portuguese. As such, the study staff was able to communicate with all participants.

Ethnicity of participating mothers was defined according to the classification of Statistics Netherlands, and was categorized into Dutch and other Western (European, American, and Oceanian); Turkish and Moroccan; African (Cape Verdean, other African, Surinamese-Creole, and Dutch Antillean); and Asian (Indonesian, other Asian, and Surinamese-Hindu) according to the largest ethnic groups in our study population and similarities in skin colour and cultural background. In sensitivity analyses, the following classification was used: Dutch, European, Turkish, Moroccan, African, Dutch Antillean, Cape Verdean, Indonesian, Surinamese-Creole, Surinamese-Hindu, Surinamese-unspecified, American Western, American non Western, Asia Western, Asia non Western and Oceanian.(13) Information about smoking, alcohol consumption, and caffeine intake was assessed by questionnaires in each trimester. Maternal pre-pregnancy body mass index was calculated from the reported height (cm) and weight (kg) in the questionnaires. Information about pregnancy complications, mode of delivery and childhood sex, gestational age, and weight and length at birth was obtained from medical records.(20, 21) Complications in a previous pregnancy were defined as: gestational diabetes, pre-eclampsia, thrombosis in arm or leg, pulmonary embolism, solutio placentae, premature rupture of membranes, contractions before 37 weeks of pregnancy or pregnancy induced hypertension. We selected potential confounding variables based on their associations with the outcomes of interest, in order to isolate a neighbourhood specific effect.

Statistical analysis

First, we examined differences between quartiles of neighbourhood deprivation for maternal characteristics, first trimester growth and fetal growth and adverse pregnancy outcomes. Second, we examined the associations of neighbourhood deprivation with fetal growth patterns using unbalanced repeated measurement regression models.(24) We included neighbourhood deprivation in these models as intercept and as interaction term with gestational age to estimate fetal growth rates over time.(24) Third, we assessed the associations of neighbourhood deprivation with the risks of adverse pregnancy outcomes using multiple logistic regression models. In the basic model, the crude association between neighbourhood deprivation and the outcomes of interest were investigated. The adjusted model was adjusted for maternal age, maternal educational level, smoking, alcohol use, folic acid supplement use, ethnicity, parity, pre-pregnancy BMI and fetal sex. We tested interaction between neighbourhood deprivation and complications in previous pregnancy in the regression models. Fourth, we examined the associations of neighbourhood deprivation with fetal growth in gestational-age-adjusted SDS in each pregnancy period using linear regression models with the same adjustment models. We performed several sensitivity analyses: in the first, we performed multilevel regression analysis in order to adjust for potential clustering between the different neighbourhoods. In the second, we repeated the analyses with all 1614 available CRL measurements, compared to the analyses with only CRL measurements below the 12 weeks of gestational age (GA).(6, 22) A third sensitivity analysis was performed to determine to which extent the inclusion of pregnancies with an impaired fetal development due to placental dysfunction influenced our results. Therefore we performed analyses excluding SGA born babies. Fourth, analyses were additionally adjusted for the household income. Also, we repeated the analyses with the different classification of ethnicity, described in the 'Covariates' section. Lastly, we checked whether the presence of maternal hypertensive disorders affected the analyses on SGA.

Our main outcome was the fetal growth, in terms of head circumference, length and weight. Post-hoc power for 0.1 SD difference in fetal growth with an alpha of 0.05 for a study group of 8000 (this study population 8617) participants is 99.4%. We used multiple imputation for missing values of covariates according to Markov Chain Monte Carlo method (details given in **Supplemental 2**).(25) The percentage of missing data was <10%, except for smoking (12.7%), alcohol use (13.8%) and folic acid supplement use (25.9%). Five imputed datasets were created and pooled for analyses. A sensitivity analysis was performed to observe differences in observed and expected values of confounders before and after imputation. Tests for trend were based on regression models with neighbourhood deprivation as a continuous variable. We checked whether the regression models were linear using scatterplots of the dependent variable plotted against the independent variable.(26) Residuals were normally distributed as assessed by visual inspection of a normal probability plot. We tested for multicollinearity using the tolerance statistic. As tolerance was >0.20 for all variables in our models, there were no problems of multicollinearity. The repeated measurement analysis was performed using the Statistical Analysis System version 9.3 (SAS, Institute Inc., Cary, NC, USA), including the Proc Mixed module for unbalanced repeated measurements. All other analyses were performed using the Statistical Package of Social Sciences version 21.0 for Windows (IBM Corp., Armonk, NY, USA).

Results

A total of 8976 pregnancies were included in the Generation R study. In total, we included 8617 pregnancies for analyses (**Figure 1**). **Table 1** depicts the baseline characteristics of both the total study population and the population stratified according to the quartiles of neighbourhood deprivation. Women in the total study population were on average 29.6 years old with a median BMI of 22.8 kg/m^2. Stratification of the population in deprivation quartiles revealed that 2170 women (25.2%)

lived in a neighbourhood with the most deprivation, i.e. lowest status score, and 2149 (24.9%) lived in the least deprived neighbourhoods, i.e. the highest status score. When comparing women in the most deprived neighbourhoods to those in the least deprived neighbourhoods, less women were highly educated (23.7% vs. 62.8% (p<0.001)), more women continued smoking in pregnancy (22.3% vs. 11.9% (p<0.001)) and less women used any folic acid supplements (20.0% vs. 49.7% respectively (p<0.001)) (**Table 1**). In **Supplemental Table 1** the fetal growth parameters and adverse pregnancy outcomes stratified by quartile of neighbourhood deprivation are presented. Overall, growth parameters are smaller in the most deprived neighbourhoods compared to the least deprived neighbourhoods (e.g. -0.07 SD vs. 0.15 SD, EFW in the third trimester of pregnancy, respectively).

Neighbourhood deprivation and fetal growth

Figure 2 gives the results of the longitudinal analyses on the association between quartiles of neighbourhood deprivation and fetal head circumference, length, and weight growth patterns from mid-pregnancy onwards. It shows that compared to the least deprived neighbourhoods, in the more deprived neighbourhoods fetal head circumferences, length and weight are smaller (for all measures, the gestational age dependent effect of neighbourhood deprivation on fetal growth was significant value<0.05). Regression coefficients for gestational age-independent and gestational age-dependent effects are given in **Supplemental Table 2.**

The associations of neighbourhood deprivation with first trimester and second and third trimester fetal growth based on regular linear regression models are given in **Supplemental Figure 1.** In both the basic and adjusted analyses, a positive association between neighbourhood deprivation and AC was present (difference in AC in the adjusted model, 0.03 SDS [95% CI 0.01, 0.05, P-value 0.002] per 1 unit increase in neighbourhood status score). In the third trimester of pregnancy a positive association was found for the HC, AC and EFW (adjusted model difference of 0.04 SDS [95% CI 0.02, 0.05, P-value <0.001], 0.04 SDS [95% CI 0.03, 0.06, P-value <0.001] and 0.04 SDS [95% CI 0.03, 0.06, P-value <0.001] per 1 unit increase in neighbourhood status score, respectively). Overall, there is a dose-response like association between neighbourhood deprivation and fetal growth, with stronger associations in the most deprived neighbourhoods compared to the least deprived neighbourhoods.

Effect modification analyses showed significant interaction between neighbourhood deprivation and complications in previous pregnancies for PTB (**Supplemental Table 3**). The associations between neighbourhood deprivation and fetal growth and adverse pregnancy outcomes were non-significant in the group with a complication in a previous pregnancy (e.g. HC in late pregnancy attenuates from 0.06 SDS [95%CI 0.05 , 0.08, P-value <0.001] to 0.03 SDS [95%CI -0.05 , 0.11, P-value 0.50] per 1 unit increase in neighbourhood status score) (**Supplemental Table 4**).

Neighbourhood deprivation and adverse pregnancy outcomes

Results of the regression analysis between neighbourhood deprivation and adverse pregnancy outcomes are presented in **Table 2**. Living in a more affluent neighbourhood was inversely associated with the odds of delivering a SGA neonate (adjusted model, OR 0.91 [95% CI 0.86, 0.97, P-value 0.01], independent of maternal sociodemographic or lifestyle factors. Moreover, it was inversely and independently associated with the odds of PTB (adjusted model, OR 0.89 [95% CI 0.82, 0.96, P-value 0.01]. The adverse pregnancy outcomes were most prevalent in the neighbourhood with the lowest deprivation status compared to the neighbourhood with the highest social status (SGA: 12.2% vs. 7.1%, PTB: 5.9% vs. 3.8%) (**Supplemental Table 1**).

Sensitivity analyses

The first sensitivity analyses revealed largely similar associations after performing multilevel analyses (**Supplemental Figure 2**). Second, the results of the associations between neighbourhood deprivation and CRL did not change after including all CRL measurements, in comparison to only the CRL measurements below 12 weeks GA (**Supplemental Table 5**). The third sensitivity analyses excluding SGA pregnancies did attenuate the results (**Supplemental Table 6**).). Results also did not materially change after other sensitivity analyses in which we additionally adjusted for the household income or adjusted with a different classification of ethnicity (**Supplemental Table 7 and 8**). Results did not materially change for SGA analyses, when adjusting for maternal hypertension in pregnancy (**Supplemental Table 9**). No major differences were observed in confounders before and after multiple imputation (**Supplemental Table 10**).

Discussion

Main findings

We observed that living in a more deprived neighbourhood is associated with decreased fetal growth in the second and third trimester of pregnancy, and with higher odds of small for gestational age birth and preterm birth.

Strengths and limitations

Strengths of this study include the large number of participants and the availability of extensive data which allowed us to adjust for a large number of potential confounders. Its population-based design in a multi-ethnic population results in a good representation of the residents of the city of Rotterdam. The presence of both residents from deprived and more affluent neighbourhoods in the study population allowed us to investigate the effect of this exposure extensively. The choice of the neighbourhood deprivation indicator is another strength of this study. To classify the degree of neighbourhood deprivation, often composite indexes are used which take factors into account such as the percentage of educated or employed residents, and income of residents within a specific neighbourhood.(27) We selected the status scores of the Netherlands Institute for Social Research, because this index is comparable with international indices such as the Index of Multiple Deprivation and the Jarman score.(28, 29) The status scores are a continuous measure, which allows more accurate analyses compared to a dichotomous measure. Another strength of the study was that missing data of covariates was handled by applying multiple imputations. In comparison with complete-case analyses (which was conducted as a sensitivity analysis), this technique maintains the statistical power of the analyses.

Some limitations of this study also merit discussion. First, this data with regard to residency and pregnancy are over 15 years old, since the Generation R study is an ongoing birth cohort. The methods of measuring fetal growth are according to standardized measurement methods, that are being used still. No doubt, there is the possibility that the status of different neighbourhoods are changed until now. However, no large differences are to be expected. Additionally, both exposure data (neighbourhood deprivation) and outcome data (fetal growth and pregnancy outcomes) are determined in short succession. Second, we did not use nutritional data from semi quantitative self-administrated food frequency questionnaires, since this FFQ is only validated pregnant women with Dutch ethnic background, which would have diminished the power and external validity of the study. We chose not to adjust for nutritional factors other than alcohol intake and folic acid supplement use, since alcohol intake and folic acid supplement use are strongly correlated with other lifestyle and nutritional habits.(30, 31) Third, we adjusted the analyses for individual factors, to isolate a neighbourhood specific effect. However, we cannot rule out the presence of residual confounding caused by other individual factors that are strongly associated with fetal growth. Next, possible misclassification of neighbourhood deprivation may have occurred if women moved during pregnancy to a neighbourhood with a different status score from the one they moved out of. However, social mobility in pregnancy is limited and if women move, they generally tend to move to a neighbourhood with a comparable deprivation status.(32) Also, income of undeclared work is not taken into account in the area based classification of neighbourhood status scores, while 13% of Dutch residents do or did any form of undeclared work.(33)

Sixth, the power of the analyses on CRL are lower due to the availability of only one CRL measurement, instead of a repeated assessment of the CRL. A last disadvantage is that participants of cohort studies, even those in more deprived neighbourhoods, generally have a higher level of health awareness and are generally more healthy compared to those who do not participate.(13) This may reduce the generalizability of our findings to the general population.

Several pathways may explain the disadvantageous effects of living in a deprived neighbourhood on pregnancy.(34) First, it is proposed to be due to the accumulation of risk factors at the individual level.(5) Examples are smoking and inadequate nutrition and lifestyle behaviours.(9) Neighbourhood deprivation then acts as a proxy for the increased prevalence of risk factors within the deprived neighbourhoods. Our findings are substantiated by earlier studies within the Generation R birth cohort, that demonstrate that living in a deprived neighbourhood is accompanied by the accumulation of individual level risk factors. These in turn were associated with adverse pregnancy outcomes.(5) However, we observe that even after correction for the individual level risk factors, the association between neighbourhood deprivation and impaired development and adverse pregnancy outcomes remained, emphasizing an isolated role for neighbourhood deprivation as a risk factor for pregnancy. The associations between neighbourhood deprivation and fetal growth and adverse pregnancy outcomes attenuated to non-significance in the population affected by a complication in a previous pregnancy. These complications, and the maternal constitution for the development of it, may thus outweigh the contribution of neighbourhood deprivation in the associations with fetal growth and adverse pregnancy outcomes. This may be due to the fact that past complications in pregnancy are strongly associated with both neighbourhood deprivation and fetal growth and adverse pregnancy outcomes.(35). A second pathway which may explain the disadvantageous effects of living in a deprived neighbourhood on adverse pregnancy outcomes is attributed to the lack of or suboptimal access to facilities such as the possibility to purchase healthy food nearby.(36) Third, living in a deprived neighbourhood is acknowledged as a source of chronic stress, and thereby acts as an independent risk factor for adverse health outcomes.(34, 37) Stress is associated with increased cortisol levels, and both prolonged or repeated cortisol exposure increases the risk for impaired physical health.(38) Also with regard to pregnancy, stress is demonstrated to be harmful since maternal stress during pregnancy is associated with preterm birth, lower birthweight and the onset of preeclampsia and gestational diabetes.(12, 39)

Our data demonstrates that the associations between neighbourhood deprivation and fetal growth become stronger over the course of pregnancy. This may be due to the fact that there are different mechanisms by which external factors -such as environmental, nutritional and lifestyle factors- affect the developing fetus over the different trimesters of pregnancy. In the first trimester of pregnancy the embryo depends on the uterine glands and yolk sac for the provision of nutrients, while in the subsequent periods of pregnancy there is an exchange of nutrients between the maternal and fetal circulations across the placenta.(40) The more isolated source of nutrition in the first trimester compared to the second and third trimester of pregnancy may decrease the sensitivity of first trimester embryonic growth to external influences.

A previous study of our group, observed a negative association between neighbourhood deprivation and first trimester growth. The larger embryos in deprived neighbourhoods were hypothesized to be explained by strong unmeasured intrinsic and extrinsic factors, such as mental stressors.(41) The difference in direction of effects between that study and our current findings, may be due to the different source populations; the first study was conducted in a tertiary-hospital based cohort, while the present study is performed within a population-based cohort.

Future perspectives

In future studies, a potential power issue due to the small measurement differences in first trimester growth measurements may be prevented by using larger study sample sizes. Moreover more accurate measures of early fetal growth with higher quality ultrasound could increase the variability of the measurements which enables detection of very small differences. Additionally, animal studies may help unravel the underlying mechanisms through which neighbourhood deprivation affect pregnancy. For instance, by further investigating how maternal stress affects placental nutrient transport. Moreover, additional research on the pathways between neighbourhood deprivation and fetal growth and pregnancy outcomes could be performed.

Although the magnitude of our findings is somewhat small, the results of this study suggest an isolated risk for living in a deprived neighbourhood. This emphasizes the importance of policies that promote healthier neighbourhoods. This could be achieved by targeted population-level interventions. A review has demonstrated many area-based initiatives that have been implemented in deprived areas across Western-Europe already.(42) Initiatives may consist of interventions that aim to tackle the various problems in deprived areas, with regard to the psychical (more walkable neighbourhoods, increasing green environments, reducing air pollution and the reduction of litter.) and social domain (lowering crime rates, vandalism).(43) Small effects of these interventions may be expected in terms of differences in fetal growth and birthweight. Though some very small individual effects may still have clinical and public health relevance, e.g. when they affect a large segment of the population, or when a small effect has long term implications, as is the case with birthweight.

In the Netherlands, in both the prenatal and postnatal setting, screening for non-medical risk factors is starting to become part of daily medical practice.(44, 45) This allows early interventions in order to prevent developmental problems of children in later life. However, we propose a shift of attention towards an earlier window of opportunity: the preconception period and first trimester of pregnancy. This periconception period provides the opportunity to optimize the conditions of pregnancy and thereby decrease the risks of adverse outcomes and all their long-term consequences.(46)

Additionally, it is important to create more awareness among politicians, policymakers and public health workers. They could help to embed neighbourhood deprivation in the context of health promotion, by developing and promoting targeted preventive intervention programs.(47) These programs could specifically focus on residents of deprived neighbourhoods. It is important to stimulate these residents to diminish risk factors on the individual level, for instance to quit smoking and abstain from alcohol. This could also help to narrow health inequalities between neighbourhoods and between groups of different socioeconomic status.

Conclusion

In conclusion, we observed a negative association between neighbourhood deprivation, fetal growth and prematurity. This emphasizes the need for a comprehensive research, care and policy approach from the preconception phase onwards, to mitigate the risk of adverse pregnancy outcomes due to deprivation.

Twitter Dionne Gootjes @dvgootjes

Acknowledgements The Generation R Study is conducted by the Erasmus Medical Centre in close collaboration with the School of Law and the Faculty of Social Sciences at the Erasmus University, Rotterdam, the Municipal Health Service, Rotterdam area and the Stichting Trombosedienst and Artsenlaboratorium Rijnmond (Star-MDC), Rotterdam. We gratefully acknowledge the contribution of children and their parents, general practitioners, hospitals, midwives and pharmacies in Rotterdam.

Author Contributions All authors made a substantive contribution to the manuscript. DG analyzed the data and wrote the article. AP, VJ, and ES contributed to the design of the paper, interpretation of the data, revisions and gave input at all stages of the study. All authors have approved the final version of the manuscript.

Funding: The Generation R Study was made possible by financial support from Erasmus MC, University Medical Centre Rotterdam, the Netherlands; the Netherlands Organization for Health Research and Development; the Netherlands Organization for Scientific Research; the Ministry of Health, Welfare and Sport; and the Ministry of Youth and Families. Prof. Dr. Vincent Jaddoe received additional grants from the Netherlands Organization for Health Research and Development (grants 90700303 and 916.10159, and VIDI 016.136.361) and a Consolidator Grant from the European Research Council (ERC-2014-CoG-64916).

Competing interests: None declared.

Patient and public involvement: This research was done without patient involvement.

Patient consent for publication: Not required.

Ethics approval The study has been approved by the Medical Ethical Committee of the Erasmus Medical Centre in Rotterdam on December 17th 2001 (MEC 198.782/2001/31). Written consent was obtained from all participants.

Data availability statement Data requests can be made to the secretariat of Generation R.

ORCID iDs

Dionne Gootjes https://orcid.org/0000-0002-9382-9031

Anke Posthumus https://orcid.org/0000-0002-4882-3474

Vincent Jaddoe https://orcid.org/0000-0003-2939-0041

Eric Steegers https://orcid.org/0000-0001-6658-9274

Tables and figures

Figure 1. Flowchart of the study population.

Figure 2. Associations of neighbourhood deprivation with fetal growth.

Table 1. Baseline characteristics of the study population, stratified for quartiles of the neighbourhood status score.

Table 2. Associations between the neighbourhood status score and adverse pregnancy outcomes.

427 # Supplemental material

428 **Supplemental Table 1. Fetal growth and adverse pregnancy outcomes in the study population,**
429 **stratified for quartiles of the neighbourhood status score.**

430 **Supplemental Table 2. Regression coefficients of longitudinal associations between quartiles of**
431 **neighbourhood deprivation with fetal growth patterns.**

432 **Supplemental Table 3. P-value of interaction terms (neighbourhood deprivation * parity and**
433 **neighbourhood status score * complications in a previous pregnancy).**

434 **Supplemental Table 4. Associations between the neighbourhood SES and fetal growth and**
435 **adverse pregnancy outcomes, split for nulliparous women, multiparous women without a**
436 **complications in a previous pregnancy or multiparous women with a complications in a previous**
437 **pregnancy.**

438 **Supplemental Table 5. Sensitivity analysis with all available CRL measurements in the study**
439 **population.**

440 **Supplemental Table 6. Associations between the neighbourhood SES and fetal growth in a**
441 **selected cohort of non-SGA pregnancies.**

442 **Supplemental Table 7. Associations between the neighbourhood status score and fetal growth,**
443 **additionally adjusted for household income.**

444 **Supplemental Table 8. Associations between the neighbourhood status score and fetal growth,**
445 **adjusted for different classification of ethnicity.**

446 **Supplemental Table 9.** Associations between the neighbourhood status score and SGA pregnancies,
447 adjusted for maternal hypertension.

448 **Supplemental Table 10. Observed and expected values of covariates.**

---

449 **Supplemental Figure 1. Associations between the neighbourhood deprivation and fetal growth**
450 **parameters.**

Supplemental Figure 2. Multilevel regression analysis of associations between neighbourhood deprivation and first trimester and fetal growth measurements.

Supplemental 1. First trimester and fetal growth, measurement guidelines.

Supplemental 2. Multiple imputations for missing data of covariates

Table 1. Baseline characteristics of the study population, stratified for quartiles of neighbourhood deprivation.

Maternal characteristics	**Total study population n = 8617**	**Lowest deprivation quartile n = 2170**	**Second deprivation quartile n = 2208**	**Third deprivation quartile n = 2090**	**Highest deprivation quartile n = 2149**	**p-value**
Neighbourhood status score	-1.13 (1.39)	-2.96 (0.51)	-1.62 (0.31)	-0.51 (0.37)	0.61 (0.49)	**<0.001**
Age at intake	29.6 (5.3)	28.1 (5.5)	28.7 (5.7)	30.2 (4.9)	31.6 (4.1)	**<0.001**
≤18 years	83 (1.0%)	33 (1.5 %)	35 (1.6%)	12 (0.6%)	3 (0.1%)	
>18 and ≤35 years	7256 (84.2%)	1888 (87.0%)	1867 (84.6%)	1760 (84.2%)	1741 (81.0%)	
>35 years	1278 (14.8%)	249 (11.5%)	306 (13.8%)	318 (15.2%)	405 (18.9%)	
Pre-pregnancy body mass index	22.8 (18.4 – 32.2)	23.5 (18.0 – 33.6)	23.0 (18.1 – 32.5)	22.9 (18.2 – 32.0)	22.3 (18.5–30.1)	**<0.001**
≤18.5 kg/m^2	492 (5.7%)	122 (5.6%)	139 (6.3%)	118 (5.6%)	112 (5.2%)	
>18.5 and ≤25 kg/m^2	5436 (63.0%)	1233 (56.8%)	1343 (60.8%)	1315 (62.9%)	1546 (71.9%)	
>25 kg/m^2	2689 (31.3%)	815 (37.6%)	726 (32.9%)	657 (31.4%)	491 (22.8%)	
Parity (nulliparous)	4796 (55.7)	1090 (50.2)	1273 (57.7)	1227 (58.7)	1205 (56.1)	**<0.001**
Educational level						**<0.001**
Lower/no	1101 (12.8%)	503 (23.2)	366 (16.5)	179 (8.5)	52 (2.4)	
Middle	4060 (47.1)	1153 (53.1)	1152 (52.2)	1007 (48.2)	747 (34.8)	
High	3456 (40.1)	514 (23.7)	690 (31.3)	904 (43.3)	1349 (62.8)	
Ethnicity						**<0.001**
Dutch and Western	4967 (57.6%)	636 (29.3)	1084 (49.1)	1426 (68.2)	1821 (84.7)	
Turkish and Moroccan	1464 (17.0%)	714 (32.9)	471 (21.3)	222 (10.6)	57 (2.7)	
African	1178 (13.7%)	519 (23.9)	370 (16.8)	211 (10.1)	78 (3.6)	
Asian	1008 (11.7%)	301 (13.9)	283 (12.8)	231 (11.1)	193 (9.0)	
Smoking						**<0.001**
Never smoked during pregnancy	6256 (72.6%)	1515 (69.8)	1523 (69.0)	1518 (72.6)	1700 (79.1)	
Smoked until pregnancy was known	735 (8.5%)	171 (7.9)	183 (8.3)	188 (9.0)	193 (9.0)	
Continued smoking in pregnancy	1626 (18.9%)	484 (22.3)	502 (22.7)	384 (18.4)	256 (11.9)	
Alcohol						**<0.001**
Never alcohol consumption in						

pregnancy	4351 (50.5%)	1436 (66.2)	1200 (54.4)	990 (47.4)	726 (33.8)	
Alcohol consumption until pregnancy was known	1149 (13.3%)	220 (10.1)	239 (10.8)	335 (16.0)	354 (16.5)	
Continued alcohol consumption in pregnancy	3117 (36.2%)	514 (23.7)	769 (34.8))	765 (36.6)	1069 (49.7)	
Folic acid supplement intake						**<0.001**
None	2751 (31.9%)	1141 (52.6)	843 (38.2)	534 (25.6)	233 (10.8)	
Start in first 10 weeks of pregnancy	2661 (30.9%)	594 (27.4)	703 (31.8)	650 (31.1)	714 (33.2)	
Start preconceptionally	3205 (37.2%)	435 (20.0)	662 (30.0)	906 (43.3)	1202 (55.9)	
Hypertension						0.11
Pregnancy induced hypertension	311 (3.6%)	69 (3.2%)	80 (3.6%)	74 (3.5%)	88 (4.1%)	
Pre-eclampsia	142 (1.6%)	54 (2.5%)	36 (1.6%)	29 (1.4%)	23 (1.1%)	
HELLP	29 (0.3%)	4 (0.2%)	9 (0.4%)	8 (0.4%)	8 (0.4%)	
Gestational diabetes	89 (1.0%)	21 (1.0%)	32 (1.4%)	24 (1.1%)	12 (0.6%)	**0.03**
Birth weight						**<0.01**
≤2500 grams	431 (5.0%)	118 (5.4%)	135 (6.1%)	110 (5.3%	68 (3.2%)	
>2500 grams and ≤4000 grams	7017 (81.4%)	1815 (83.6%)	1786 (80.9%)	1683 (80.5%	1733 (80.6%)	
>4000 grams	1169 (13.6%)	237 (11.0%)	287 (13.0%)	297 (14.2%)	348 (16.2%)	
Gestational age at delivery						**0.01**
<37 weeks gestational age	492 (5.7%)	134 (6.2%)	152 (6.9%)	117 (5.6%)	89 (4.1%)	
.37-42 weeks gestational age	7697 (89.3%)	1937 (89.3%)	1947 (88.2%)	1859 (88.9%)	1954 (90.9)	
>42 weeks gestational age	428 (5.0%)	99 (4.5%)	109 (4.9%)	114 (5.5%)	106 (5.0%)	
Complications in a previous pregnancy	606 (7.0%)	153 (7.1%)	149 (6.7%)	132 (6.3%)	172 (8.0%)	0.13
Fetal sex (male)	4347 (50.4)	1063 (49.0)	1147 (51.9)	1066 (51.0)	1071 (49.8)	0.22

Data are represented as n (%), mean (SD) or median with the 90% range. Differences in baseline characteristics were tested using ANOVA, Kruskal-Wallis tests and chi-square tests. Confounders are imputed. Non imputed percentages are valid percentages.

Table 2. Associations between the neighbourhood status score and adverse pregnancy outcomes.

Study population n = 8617	**Model**	**Lowest deprivation quartile n = 2277**		**Second deprivation quartile n = 2123**		**Third deprivation quartile n = 2084**		**Highest deprivation quartile n = 2133**	
			β / OR (95% CI)		**β / OR (95% CI)**		**β / OR (95% CI)**		
Small for gestational age	Basic	**261 (11.5%)**	**1.80 (1.46 ; 2.22)**	**220 (10.4%)**	**1.46 (1.17 ; 1.81)**	**190 (9.1%)**	**1.31 (1.05 ; 1.64)**	**153 (7.2%)**	*Reference*
	Adjusted		**1.39 (1.09 ; 1.77)**		1.14 (0.90 ; 1.44)		1.13 (0.90 ; 1.42)		*Reference*
Preterm birth	Basic	**129 (5.6%)**	**1.60 (1.21 ; 2.13)**	**142 (6.7%)**	**1.76 (1.33 ; 2.32)**	**109 (5.2%)**	**1.41 (1.05 ; 1.89)**	**81 (3.8%)**	*Reference*
	Adjusted		**1.52 (1.11 ; 2.09)**		**1.65 (1.23 ; 2.22)**		1.32 (0.97 ; 1.77)		*Reference*

Abbreviations: β: beta; OR: odds ratio. Values are odds ratios with the 95% CI of the data in SD-score and are based on logistic regression models. Basic model: by the use of SD scores it is automatically adjusted for gestational age. Adjusted model: basic model and additionally adjusted for maternal age, educational level, smoking, alcohol use, folic acid supplement use, ethnicity, parity, pre-pregnancy body mass index and fetal sex. p-for trend analysis with the neighbourhood deprivation as a continuous measure. Small size for gestational age (SGA) at birth was defined as a sex and gestational age adjusted birthweight below the 10th percentile (<-1.40 SD-score) in the study cohort. Preterm birth (PTB) was defined as a gestational age of <37 weeks at delivery.

References

1. Mackenbach JP, Cavelaars AE, Kunst AE, Groenhof F. Socioeconomic inequalities in cardiovascular disease mortality; an international study. Eur Heart J. 2000;21(14):1141-51.

2. Pickett KE, Pearl M. Multilevel analyses of neighbourhood socioeconomic context and health outcomes: a critical review. J Epidemiol Community Health. 2001;55(2):111-22.

3. Vos AA, Posthumus AG, Bonsel GJ, Steegers EA, Denktas S. Deprived neighborhoods and adverse perinatal outcome: a systematic review and meta-analysis. Acta Obstet Gynecol Scand. 2014;93(8):727-40.

4. de Graaf JP, Ravelli AC, de Haan MA, Steegers EA, Bonsel GJ. Living in deprived urban districts increases perinatal health inequalities. J Matern Fetal Neonatal Med. 2013;26(5):473-81.

5. Timmermans S, Bonsel GJ, Steegers-Theunissen RP, Mackenbach JP, Steyerberg EW, Raat H, et al. Individual accumulation of heterogeneous risks explains perinatal inequalities within deprived neighbourhoods. Eur J Epidemiol. 2011;26(2):165-80.

6. Mook-Kanamori DO, Steegers EA, Eilers PH, Raat H, Hofman A, Jaddoe VW. Risk factors and outcomes associated with first-trimester fetal growth restriction. JAMA. 2010;303(6):527-34.

7. Ashworth CJ, Toma LM, Hunter MG. Nutritional effects on oocyte and embryo development in mammals: implications for reproductive efficiency and environmental sustainability. Philos Trans R Soc Lond B Biol Sci. 2009;364(1534):3351-61.

8. Cetin I, Berti C, Calabrese S. Role of micronutrients in the periconceptional period. Hum Reprod Update. 2010;16(1):80-95.

9. Van Dijk MR, Borggreven NV, Willemsen SP, Koning AHJ, Steegers-Theunissen RPM, Koster MPH. Maternal Lifestyle Impairs Embryonic Growth: The Rotterdam Periconception Cohort. Reprod Sci. 2018;25(6):916-22.

10. Barker DJ. Fetal origins of coronary heart disease. BMJ. 1995;311(6998):171-4.

11. Rutter DR, Quine L. Inequalities in pregnancy outcome: a review of psychosocial and behavioural mediators. Soc Sci Med. 1990;30(5):553-68.

12. Vehmeijer FOL, Guxens M, Duijts L, El Marroun H. Maternal psychological distress during pregnancy and childhood health outcomes: a narrative review. J Dev Orig Health Dis. 2019;10(3):274-85.

13. Kooijman MN, Kruithof CJ, van Duijn CM, Duijts L, Franco OH, van IMH, et al. The Generation R Study: design and cohort update 2017. Eur J Epidemiol. 2016;31(12):1243-64.

14. National Institute for Public Health and the Environment. Sociaaleconomische status 2017 [Available from: https://www.volksgezondheidenzorg.info/onderwerp/sociaaleconomische-status/regionaal-internationaal/regionaal#node-sociaaleconomische-status. .

15. Blaas HG, Eik-Nes SH, Bremnes JB. The growth of the human embryo. A longitudinal biometric assessment from 7 to 12 weeks of gestation. Ultrasound Obstet Gynecol. 1998;12(5):346-54.

16. van Uitert EM, Exalto N, Burton GJ, Willemsen SP, Koning AH, Eilers PH, et al. Human embryonic growth trajectories and associations with fetal growth and birthweight. Hum Reprod. 2013;28(7):1753-61.

17. van der Kooy J, Poeran J, de Graaf JP, Birnie E, Denktas S, Steegers EAP, et al. Planned home compared with planned hospital births in the Netherlands: intrapartum and early neonatal death in low-risk pregnancies. Obstet Gynecol. 2011;118(5):1037-46.

18. Poeran J, Borsboom GJ, de Graaf JP, Birnie E, Steegers EA, Bonsel GJ. Population attributable risks of patient, child and organizational risk factors for perinatal mortality in hospital births. Matern Child Health J. 2015;19(4):764-75.

19. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements--a prospective study. Am J Obstet Gynecol. 1985;151(3):333-7.

20. Verburg BO, Steegers EA, De Ridder M, Snijders RJ, Smith E, Hofman A, et al. New charts for ultrasound dating of pregnancy and assessment of fetal growth: longitudinal data from a population-based cohort study. Ultrasound Obstet Gynecol. 2008;31(4):388-96.
21. Niklasson A, Ericson A, Fryer JG, Karlberg J, Lawrence C, Karlberg P. An update of the Swedish reference standards for weight, length and head circumference at birth for given gestational age (1977-1981). Acta Paediatr Scand. 1991;80(8-9):756-62.
22. Verburg BO, Mulder PG, Hofman A, Jaddoe VW, Witteman JC, Steegers EA. Intra- and interobserver reproducibility study of early fetal growth parameters. Prenat Diagn. 2008;28(4):323-31.
23. Gaillard R, de Ridder MA, Verburg BO, Witteman JC, Mackenbach JP, Moll HA, et al. Individually customised fetal weight charts derived from ultrasound measurements: the Generation R Study. Eur J Epidemiol. 2011;26(12):919-26.
24. Twisk JWR. Applied Longitudinal Data Analysis for Epidemiology: A Practical Guide. 2 ed. Cambridge: Cambridge University Press; 2013.
25. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;338:b2393.
26. DG Altman. Practical statistics for medical research. . London, UK: Chapman & Hall; 1999.
27. Rajaratnam JK, Burke JG, O'Campo P. Maternal and child health and neighborhood context: the selection and construction of area-level variables. Health Place. 2006;12(4):547-56.
28. Noble M, Wright G, Smith G, Dibben C. Measuring Multiple Deprivation at the Small-Area Level. Environment and Planning A: Economy and Space. 2006;38(1):169-85.
29. Jarman B. Underprivileged areas: validation and distribution of scores. Br Med J (Clin Res Ed). 1984;289(6458):1587-92.
30. Kang H-G, Joo HH, Choi KD, Lee D, Moon J. Complementarity in dietary supplements and foods: are supplement users vegetable eaters? Food Nutr Res. 2017;61(1):1361769-.
31. Kirk SF, Cade JE, Barrett JH, Conner M. Diet and lifestyle characteristics associated with dietary supplement use in women. Public Health Nutr. 1999;2(1):69-73.
32. Reitsma JB, Kardaun JW, Gevers E, de Bruin A, van der Wal J, Bonsel GJ. [Possibilities for anonymous follow-up studies of patients in Dutch national medical registrations using the Municipal Population Register: a pilot study]

Mogelijkheden voor anoniem follow-uponderzoek van patienten in landelijke medische registraties met behulp van de Gemeentelijke Basisadministratie: een pilotonderzoek. Ned Tijdschr Geneeskd. 2003;147(46):2286-90.
33. Winden de M, Zuurbier. Een onderzoek naar zwartwerk onder uitkeringsgerechtigden en de totale bevolking in 2010. Voorburg/Heerlen.: 2011.
34. de Graaf JP, Steegers EA, Bonsel GJ. Inequalities in perinatal and maternal health. Curr Opin Obstet Gynecol. 2013;25(2):98-108.
35. Posthumus AG, Birnie E, van Veen MJ, Steegers EA, Bonsel GJ. An antenatal prediction model for adverse birth outcomes in an urban population: The contribution of medical and non-medical risks. Midwifery. 2016;38:78-86.
36. Agyemang C, Vrijkotte TG, Droomers M, van der Wal MF, Bonsel GJ, Stronks K. The effect of neighbourhood income and deprivation on pregnancy outcomes in Amsterdam, The Netherlands. J Epidemiol Community Health. 2009;63(9):755-60.
37. Jokela M. Does neighbourhood deprivation cause poor health? Within-individual analysis of movers in a prospective cohort study. J Epidemiol Community Health. 2015;69(9):899-904.
38. Cohen S, Janicki-Deverts D, Miller GE. Psychological stress and disease. JAMA. 2007;298(14):1685-7.
39. Henrichs J, Schenk JJ, Roza SJ, van den Berg MP, Schmidt HG, Steegers EA, et al. Maternal psychological distress and fetal growth trajectories: the Generation R Study. Psychol Med. 2010;40(4):633-43.

40. Burton GJ, Hempstock J, Jauniaux E. Nutrition of the human fetus during the first trimester--a review. Placenta. 2001;22 Suppl A:S70-7.
41. Gootjes DV, Koster MPH, Willemsen SP, Koning AHJ, Steegers EAP, Steegers-Theunissen RPM. The Impact of Neighbourhood Deprivation on Embryonic Growth Trajectories: Rotterdam Periconception Cohort. J Clin Med. 2019;8(11).
42. Atkinson. Urban Design and Planning. Volume 161 2008. p. 115-22.
43. Kramer D, Harting J, Kunst AE. Understanding the impact of area-based interventions on area safety in deprived areas: realist evaluation of a neighbour nuisance intervention in Arnhem, the Netherlands. BMC Public Health. 2016;16:291.
44. Waelput AJM, Sijpkens MK, Lagendijk J, van Minde MRC, Raat H, Ernst-Smelt HE, et al. Geographical differences in perinatal health and child welfare in the Netherlands: rationale for the healthy pregnancy 4 all-2 program. BMC Pregnancy Childbirth. 2017;17(1):254.
45. Lagendijk J, Vos AA, Bertens LCM, Denktas S, Bonsel GJ, Steyerberg EW, et al. Antenatal non-medical risk assessment and care pathways to improve pregnancy outcomes: a cluster randomised controlled trial. Eur J Epidemiol. 2018;33(6):579-89.
46. Steegers EAP, Barker ME, Steegers-Theunissen RPM, Williams MA. Societal Valorisation of New Knowledge to Improve Perinatal Health: Time to Act. Paediatric and perinatal epidemiology. 2016;30(2):201-4.
47. van Voorst SF, Vos AA, de Jong-Potjer LC, Waelput AJM, Steegers EAP, Denktas S. Effectiveness of general preconception care accompanied by a recruitment approach: protocol of a community-based cohort study (the Healthy Pregnancy 4 All study). BMJ open. 2015;5(3):e006284-e.

1 **Figure 1.** Flowchart of the study population.

2

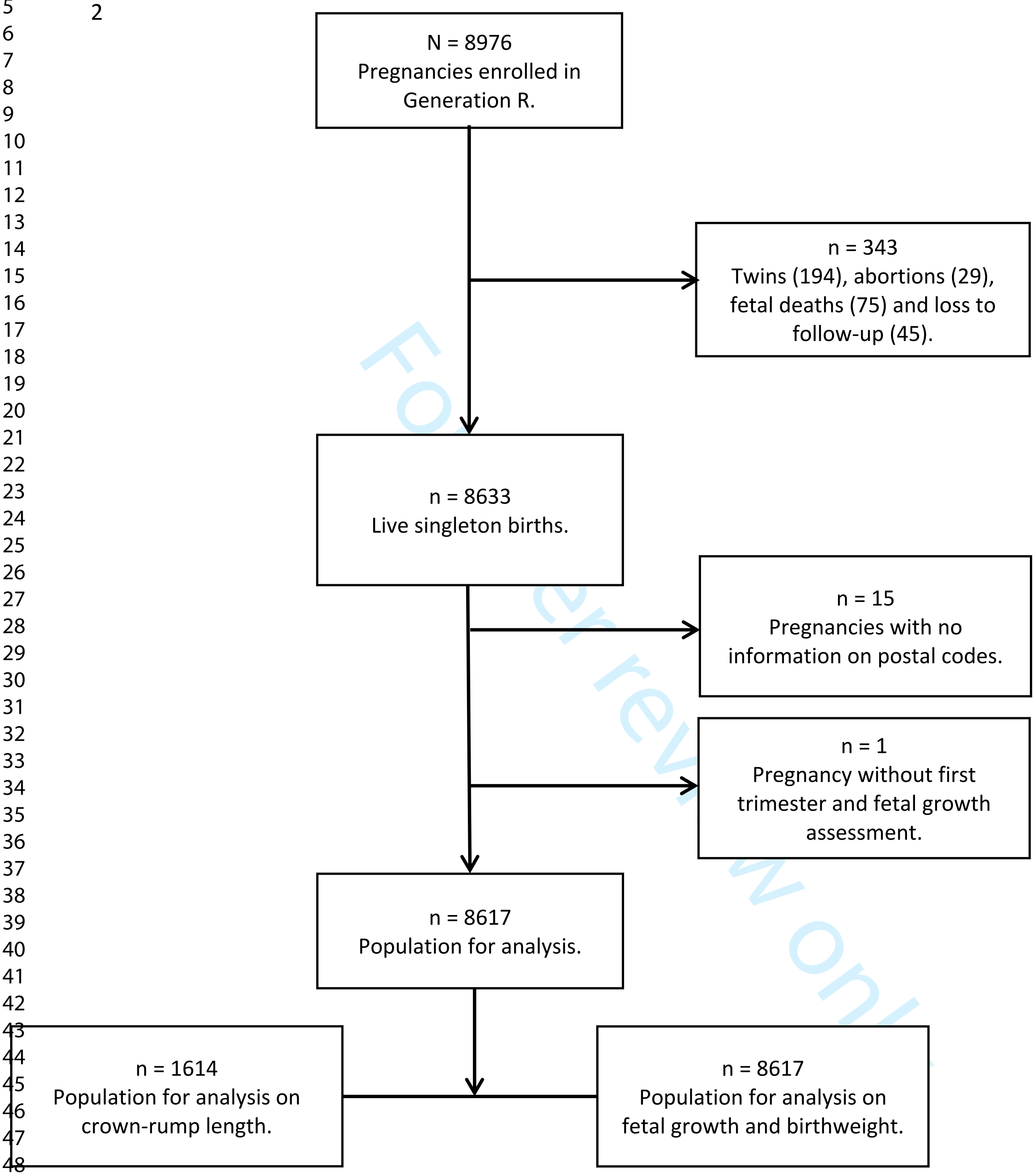
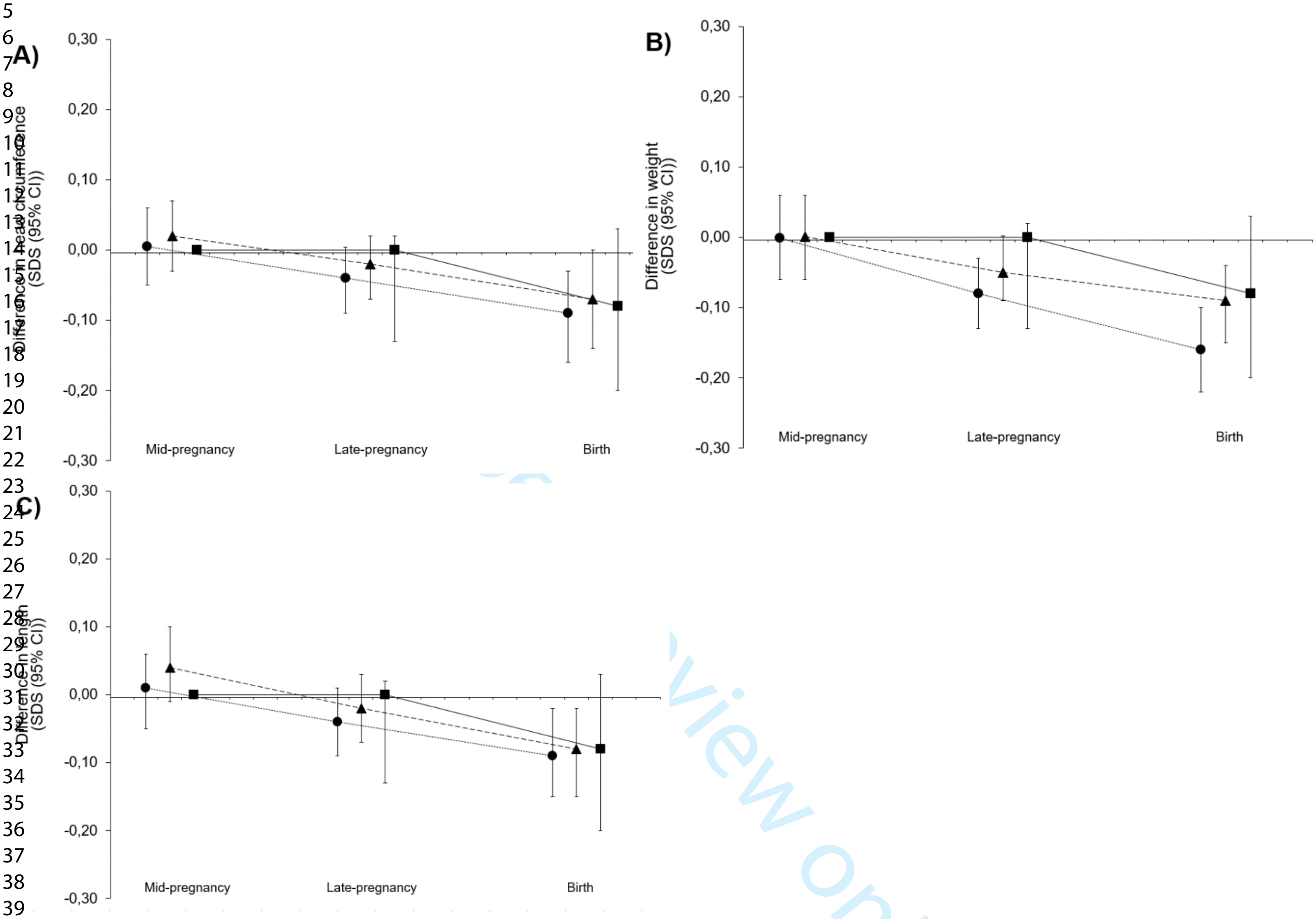


Figure 2. Associations of neighbourhood deprivation with fetal growth.



Differences in fetal growth rates for the lower three neighbourhood status score quartiles as compared to the highest neighbourhood status score. Squares represent the lowest quartile of the neighbourhood status score; circles represent the second quartile; and triangles the third quartile. Results are based on repeated measurement regression models and reflect the differences in gestational-age-adjusted SDS scores of (a) fetal head circumference, (b) weight, and (c) length growth for the three lower neighbourhood status score compared to the highest neighbourhood status score (reference group represented as zero line). The models were adjusted for maternal age, educational level, smoking, alcohol use, folic acid supplement use, ethnicity, parity, pre-pregnancy body mass index and fetal sex.

Supplemental data

Supplemental Table 1. Fetal growth and adverse pregnancy outcomes in the study population, stratified for quartiles of neighbourhood deprivation.

	n	Study population n = 8617	n	Lowest deprivation quartile n = 2170	n	Second deprivation quartile n = 2208	n	Third deprivation quartile n = 2090	n	Highest deprivation quartile n = 2149	p-value[1]	p-value[2]
Early pregnancy												
CRL	1614	-0.05 (1.06)	287	0.03 (1.05)	362	-0.01 (1.07)	418	-0.01 (0.95)	547	0.07 (0.87)	0.81	0.63
HC	5646	-0.27 (1.39)	1359	-0.04 (0.99)	1440	-0.04 (1.04)	1361	-0.04 (1.10)	1486	-0.09 (1.06)	0.36	0.20
FL	4682	0.61 (0.88)	1162	-0.08 (0.99)	1233	-0.18 (1.00)	1107	-0.04 (0.98)	1180	-0.10 (1.00)	0.18	0.74
Mid pregnancy												
HC	8035	-0.02 (1.02)	1972	-0.06 (1.03)	2049	-0.04 (1.05)	1973	-0.01 (1.02)	2041	0.03 (0.98)	**0.047**	**0.01**
FL	8058	0.03 (1.03)	1985	0.06 (1.07)	2046	0.06 (1.08)	1970	0.04 (1.02)	2057	-0.01 (0.97)	0.12	**0.03**
AC	8052	0.01 (1.01)	1977	-0.04 (1.02)	2050	-0.04 (1.02)	1971	0.02 (1.00)	2054	0.11 (0.98)	**<0.001**	**<0.001**
EFW	8016	-0.10 (1.01)	1975	-0.12 (1.02)	2035	-0.12 (1.04)	1957	-0.09 (1.00)	2049	-0.06 (0.97)	0.22	0.08
Late pregnancy												
HC	8163	0.01 (1.00)	2029	-0.08 (1.00)	2067	-0.09 (1.02)	1984	0.06 (1.00)	2083	0.17 (0.96)	**<0.001**	**<0.001**
FL	8234	-0.01 (1.00)	2049	-0.04 (1.00)	2083	-0.01 (1.05)	2005	0.004 (1.00)	2097	0.02 (0.97)	0.28	0.06
AC	8212	0.01 (1.01)	2042	-0.10 (1.01)	2076	-0.07 (1.04)	1995	0.04 (1.01)	2099	0.14 (0.97)	**<0.001**	**<0.001**
EFW	8201	0.03 (1.02)	2042	-0.06 (1.01)	2073	-0.02 (1.04)	1993	0.07 (1.00)	2093	0.15 (1.00)	**<0.001**	**<0.001**

Birth												
Small for gestational age	824	854 (9.9%)	261	261 (12.2%)	220	225 (10.1%)	190	190 (9.2%)	153	153 (7.1%)	**<0.001**	**<0.001**
Preterm birth	460	460 (5.3%)	128	128 (5.9%)	142	142 (6.4%)	109	109 (5.2%)	81	81 (3.8%)	**0.001**	**0.001**

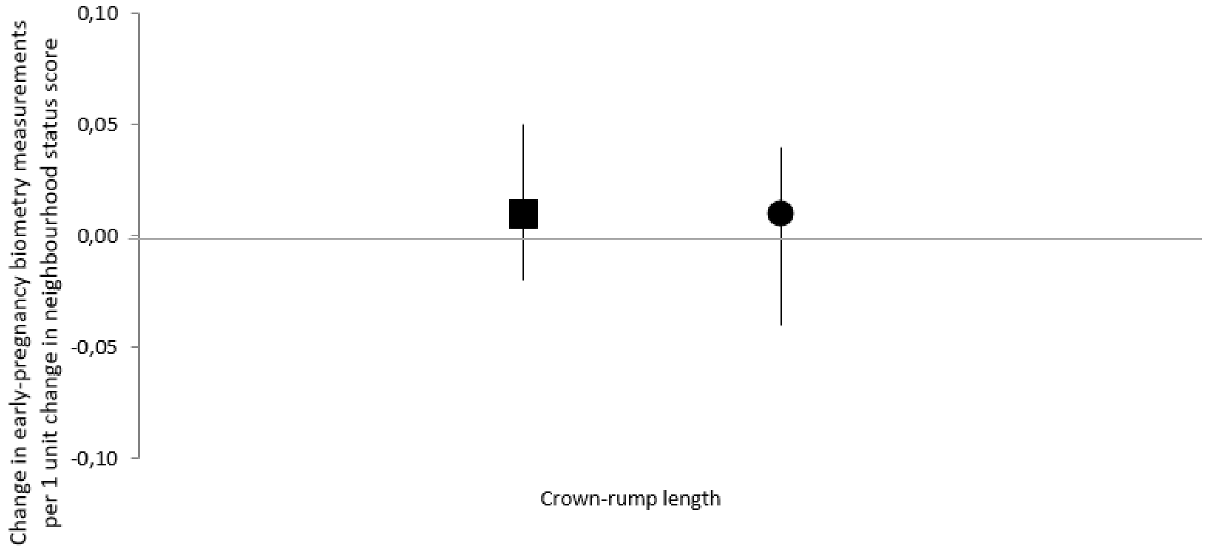
Abbreviations: SD: standard deviation. HC: head circumference. FL: femur length. AC: abdominal circumference. EFW: estimated fetal weight. Values represent data in SD-score, mean (SD) or n (%).[1] Differences between groups were evaluated using one-way-ANOVA-tests for continuous variables and Chi-square tests for proportions. [2]Differences in growth parameters between the lowest and highest neighbourhood status score groups were tested were evaluated using Student's t-tests. Percentages are valid percentages.

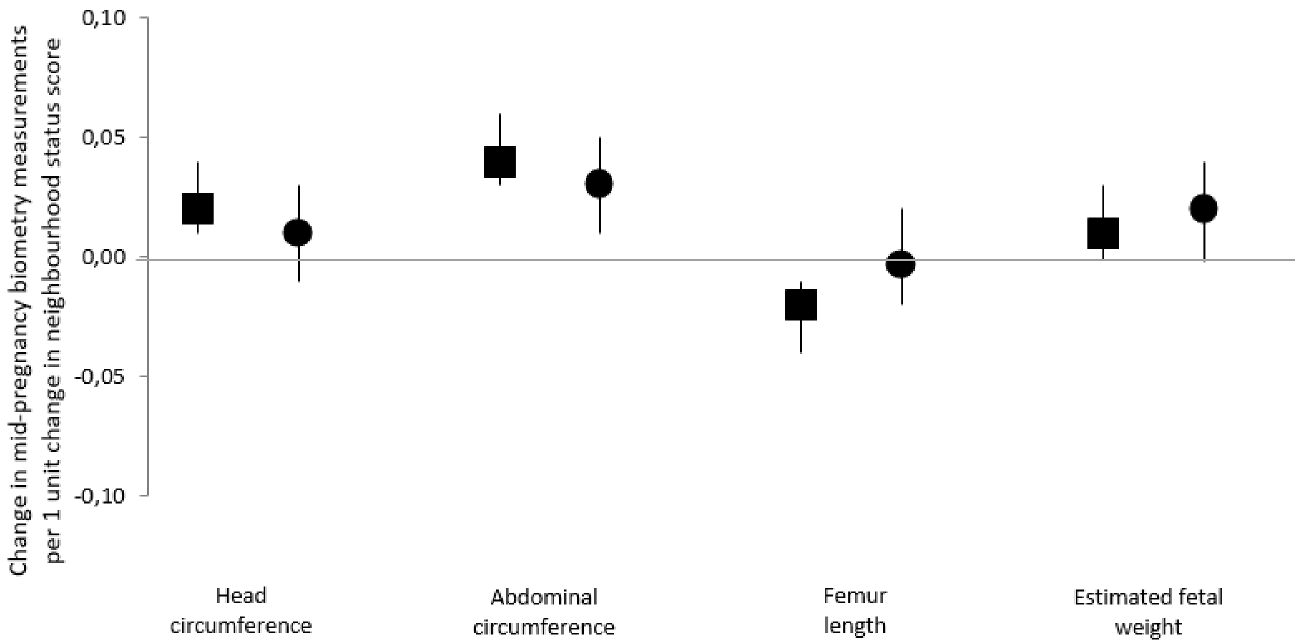
Supplemental Table 2. Regression coefficients of longitudinal associations between quartiles of neighbourhood deprivation with fetal growth patterns.

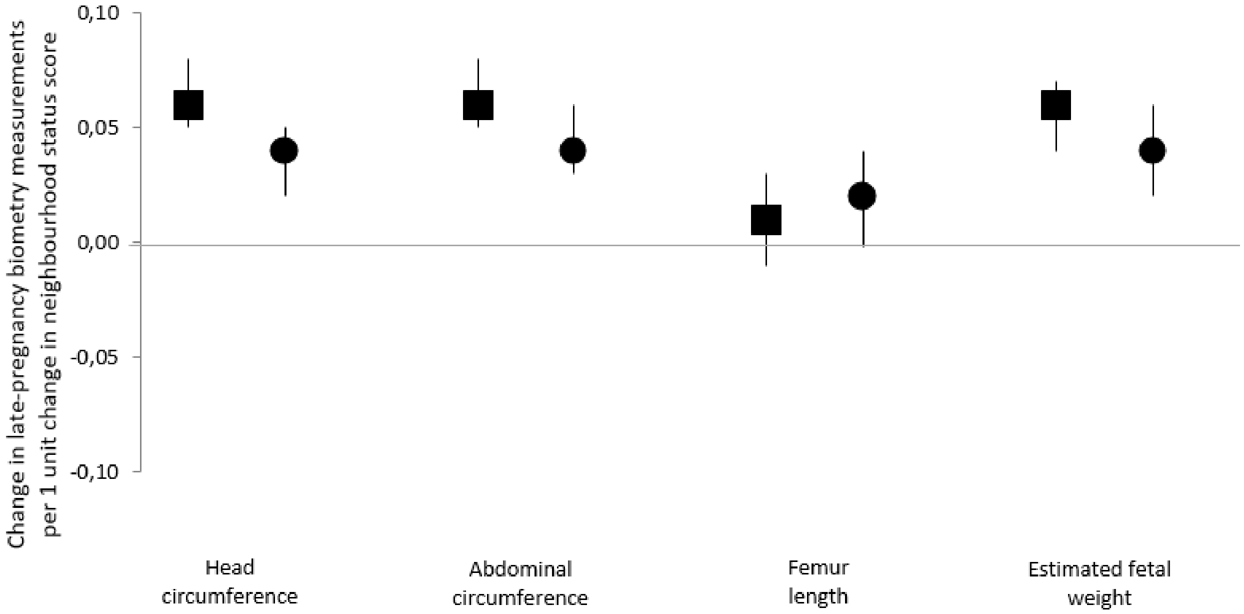
	Intercept Head circumference (SDS)	Slope Head circumference (SDS)	Intercept Length (SDS)	Slope Length (SDS)	Intercept Weight (SDS)	Slope Weight (SDS)
Neighbourhood deprivation						
Quartile 1	**0.225 (0.122; 0.328)**	**-0.010 (-0.013; -0.006)**	**0.270 (0.167; 0.373)**	**-0.012 (-0.016; -0.010)**	**0.229 (0.115; 0.3441)**	**-0.011 (-0.015; -0.008)**
Quartile 2	**0.104 (0.004; 0.204)**	**-0.005 (-0.008; -0.001)**	**0.103 (0.003; 0.203)**	**-0.005 (-0.008; -0.001)**	**0.155 (0.043; 0.268)**	**-0.008 (-0.011; -0.005)**
Quartile 3	**0.109 (0.009; 0.208)**	**-0.004 (-0.008; -0.001)**	**0.170 (0.071; 0.270)**	**-0.006 (-0.010; -0.003)**	0.095 (-0.018; 0.208)	**-0.005 (-0.008; -0.001)**
Quartile 4	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.

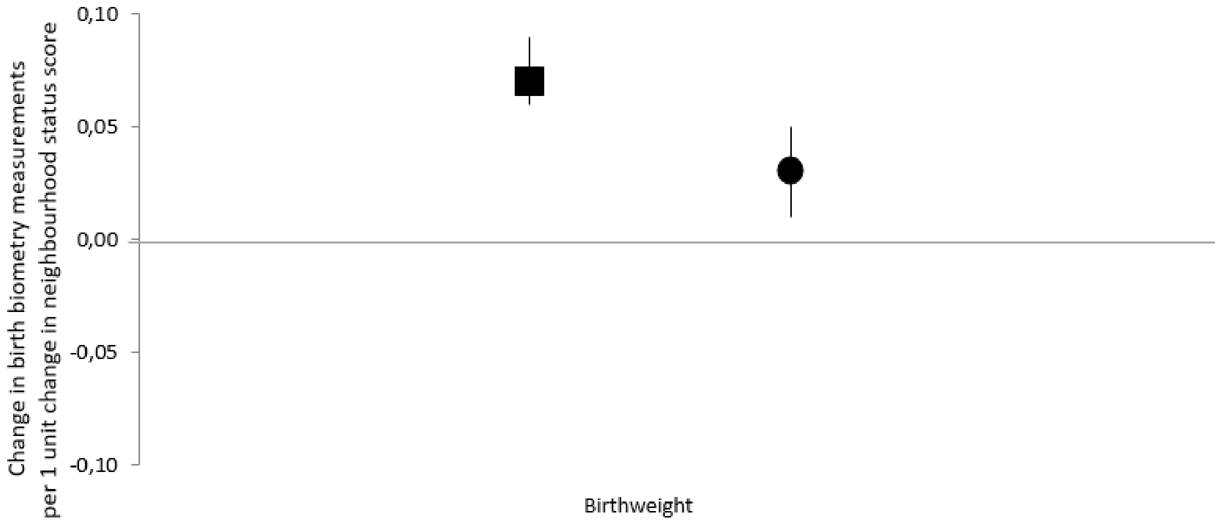
Values are regression coefficients obtained from linear repeated measurement models and reflect the (gestational) age independent differences (intercepts) and the gestational age dependent differences (slopes: change in growth characteristics SDS per week per quartile of the neighbourhood deprivation score, compared with the highest quartile of the neighbourhood deprivation score as the reference group, adjusted for maternal age, educational level, smoking, alcohol use, folic acid supplement use, ethnicity, parity, pre-pregnancy body mass index and fetal sex.)

Supplemental Figure 1. Associations between neighbourhood deprivation with first trimester and fetal growth measurements.









Data are SDS values (95% CI) from linear regression models that reflect the differences in growth characteristics in SDS's in early pregnancy, mid-pregnancy late pregnancy and birth, per 1 unit change in neighbourhood status score. Analyses with crown–rump length were based on subgroup analyses (n = 1614). Estimates are from multiple imputed data. Squares show basic model; circles show the adjusted model: basic model and additionally adjusted for maternal age, educational level, smoking, alcohol use, folic acid supplement use, ethnicity, parity, pre-pregnancy body mass index and fetal sex.

Supplemental Table 3. P-value of interaction terms (neighbourhood deprivation * parity and neighbourhood deprivation * complications in a previous pregnancy).

Study population **n = 8617**		
	Parity	**Complications in a previous pregnancy**
	p-value for trend	**p-value for trend**
Early pregnancy		
CRL	0.44	0.36
HC	0.25	0.24
FL	0.52	0.91
Mid pregnancy		
HC	0.15	0.20
FL	0.13	0.20
AC	0.73	0.81
EFW	0.27	0.34
Late pregnancy		
HC	0.64	0.62
FL	0.58	0.51
AC	0.66	0.88
EFW	0.82	0.99
Birth		
SGA	0.95	0.85
PTB	0.17	**0.03**

Abbreviations: β: beta; CRL: crown-rump length; HC: head circumference; FL: femur length; AC: abdominal circumference; EFW: estimated fetal weight. Values are based on the adjusted linear and logistic regression models.

30 **Supplemental Table 4.** Associations between the neighbourhood status score and fetal growth and adverse pregnancy outcomes, split for nulliparous women,
31 multiparous women without a complications in a previous pregnancy or multiparous women with a complications in a previous pregnancy.

Study population n = 8617	**Nulliparous N = 4739**		**Multiparous, no complications previous pregnancy N = 3166**		**Multiparous, complications previous pregnancy N = 606**	
	Trend		**Trend**		**Trend**	
	β/OR (95% CI)	**p-value for trend**	**β/OR (95% CI)**	**p-value for trend**	**β/OR (95% CI)**	**p-value for trend**
Early pregnancy						
CRL	0.02 (-0.04 ; 0.08)	0.42	-0.01 (-0.10 ; 0.07)	0.74	0.02 (-0.19 ; 0.22)	0.88
HC	0.004 (-0.03 ; 0.04)	0.84	-0.01 (-0.05 ; 0.04)	0.73	-0.04 (-0.15 ; 0.07)	0.45
FL	0.03 (-0.01 ; 0.07)	0.09	0.04 (-0.01 ; 0.09)	0.09	-0.04 (-0.15 ; 0.07)	0.50
Mid pregnancy						
HC	0.02 (-0.02 ; 0.05)	0.32	0.02 (-0.02 ; 0.06)	0.30	**-0.11 (-0.19 ; -0.03)**	**0.01**
FL	0.01 (-0.02 ; 0.04)	0.66	-0.01 (-0.05 ; 0.03)	0.59	-0.06 (-0.15 ; 0.02)	0.14
AC	**0.03 (0.002 ; 0.06)**	**0.03**	**0.05 (0.01 ; 0.09)**	**0.01**	-0.02 (-0.11 ; 0.07)	0.66
EFW	0.02 (-0.01 ; 0.05)	0.12	0.03 (-0.01 ; 0.07)	0.18	-0.04 (-0.13 ; 0.04)	0.32
Late pregnancy						
HC	**0.04 (0.01 ; 0.07)**	**0.004**	0.03 (-0.003 ; 0.07)	0.07	0.03 (-0.05 ; 0.11)	0.50
FL	0.02 (-0.01 ; 0.05)	0.10	-0.003 (-0.04 ; 0.03)	0.89	0.03 (-0.05 ; 0.11)	0.45

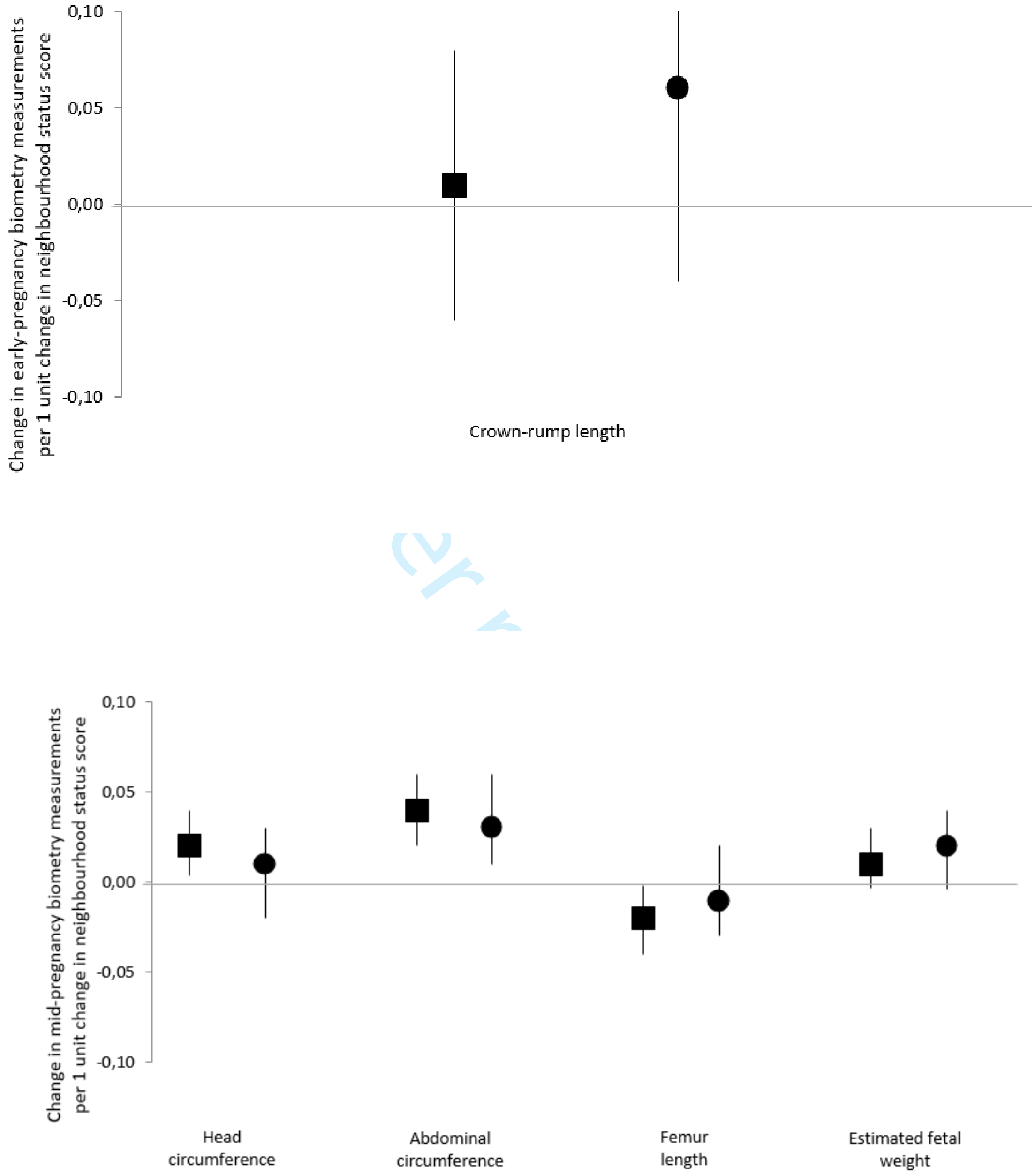
AC	**0.03 (0.002 ; 0.06)**	**0.04**	**0.04 (0.01 ; 0.08)**	**0.03**	0.07 (-0.01 ; 0.16)	0.10
EFW	**0.03 (0.01 ; 0.06)**	**0.02**	**0.04 (0.001 ; 0.08)**	**0.048**	0.07 (-0.02 ; 0.16)	0.11
Birth						
SGA	**0.90 (0.82 ; 0.99)**	**0.03**	0.96 (0.82 ; 1.12)	0.60	0.88 (0.63 ; 1.23)	0.46
PTB	0.91 (0.81 ; 1.03)	0.15	**0.73 (0.58 ; 0.93)**	**0.01**	0.89 (0.66 ; 1.21)	0.46

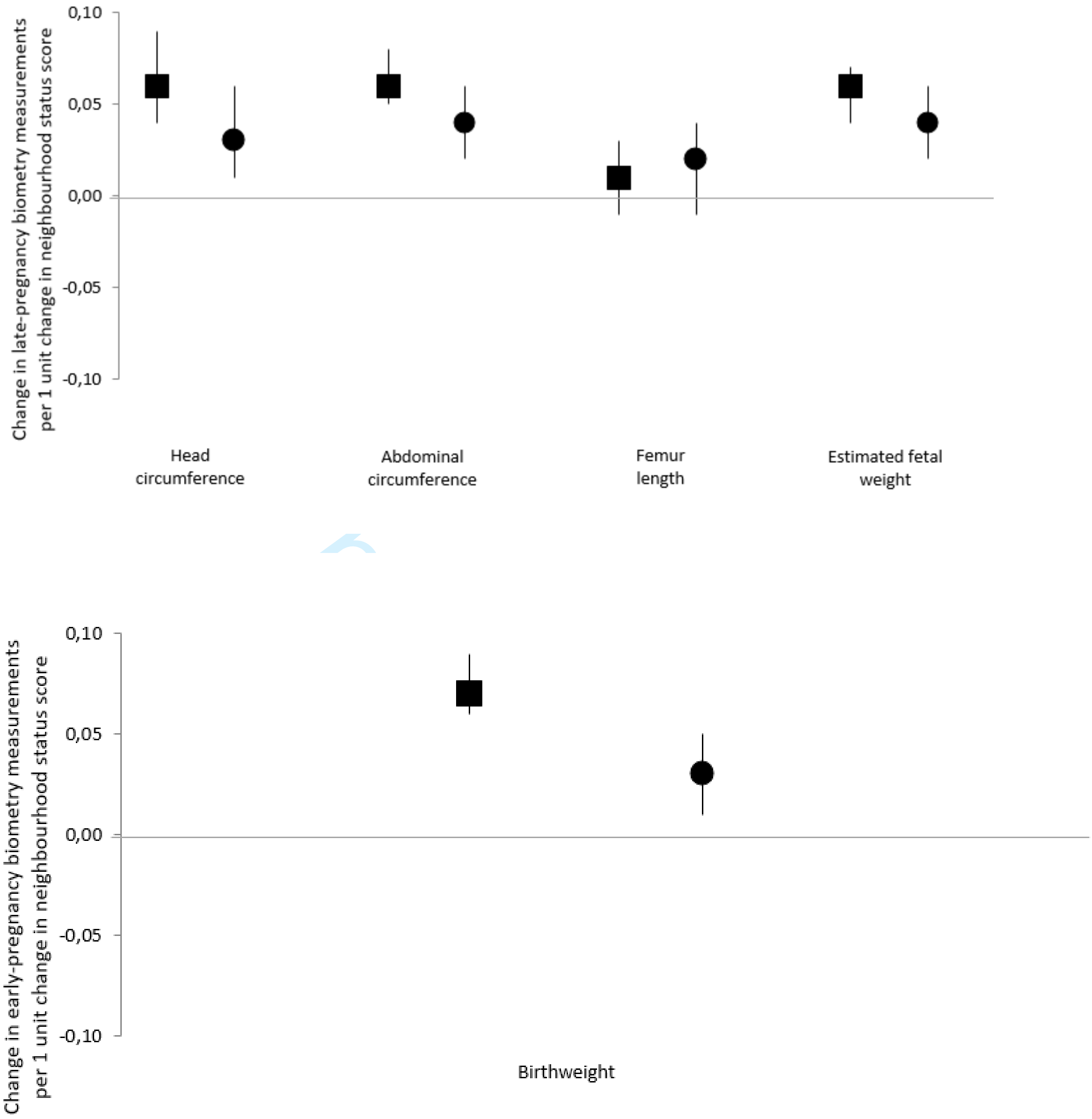
Abbreviations: β: beta; CRL: crown-rump length; HC: head circumference; FL: femur length; AC: abdominal circumference; EFW: estimated fetal weight.

Values are regression coefficients with the 95% CI of the data in SD-score and are based on adjusted linear and logistic regression models. Adjusted model: adjusted for maternal age, educational level, smoking, alcohol use, folic acid supplement use, ethnicity, parity, pre-pregnancy body mass index and fetal sex.

p-for trend analysis with the neighbourhood deprivation as a continuous measure.

Supplemental Figure 2. Multilevel regression analysis of associations between the neighbourhood deprivation and first trimester and fetal growth measurements.





Data are SDS values (95% CI) from multilevel analyses and reflect the differences in growth characteristics in SDS's in early pregnancy, mid-pregnancy late pregnancy and birth, per 1 unit change in neighbourhood status score. Analyses with crown–rump length were based on subgroup analyses (n = 1614). Estimates are from multiple imputed data. Squares show basic model. Circles show adjusted model: basic model and additionally adjusted for maternal age, educational level, smoking, alcohol use, folic acid supplement use, ethnicity, parity, pre-pregnancy body mass index and fetal sex.

Supplemental Table 5. Sensitivity analysis with all available CRL measurements in the study population.

a. All CRL measurement in the study population, stratified for quartiles of the neighbourhood status score.

	n	Study population n = 8617	n	Lowest deprivation quartile n = 2277	n	Second deprivation quartile n = 2123	n	Third deprivation quartile n = 2084	n	Highest deprivation quartile n = 2133	p-value[1]	Mean difference (95% CI)[2]	p-value[2]
CRL	1614		287	0.03 (1.05)	362	-0.01 (1.07)	418	-0.01 (0.95)	547	0.07 (0.87)	0.56	-0.03 (-0.17 ; 0.10)	0.61

b. All CRL measurement in the study population and the associations between quartiles of the neighbourhood status score.

	n	Model	Lowest deprivation quartile n = 300	Second deprivation quartile n = 373	Third deprivation quartile n = 399	Highest deprivation quartile n = 542	Trend	p-value for trend
			β (95% CI)	**β (95% CI)**	**β (95% CI)**		**β (95% CI)**	
CRL	1614	Basic	-0.03 (-0.17 ; 0.10)	-0.08 (-0.21 ; 0.05)	-0.08 (-0.20 ; 0.05)	*Reference*	0.01 (-0.02 ; 0.05)	0.48
		Adjusted	0.02 (-0.15 ; 0.16)	-0.04 (-0.17 ; 0.10)	-0.06 (-0.19 ; 0.06)	*Reference*	0.004 (-0.04 ; 0.04)	0.85

c. All CRL measurement in the study population and the associations between quartiles of the neighbourhood status score. Complete case analysis.

	n	Model	Lowest deprivation quartile n = 2268	Second deprivation quartile n = 2118	Third deprivation quartile n = 2081	Highest deprivation quartile n = 2131	Trend	p-value for trend
			β (95% CI)	β (95% CI)	β (95% CI)		β (95% CI)	
CRL	1143	Adjusted	-0.06 (-0.23 ; 0.12)	0.02 (-0.14 ; 0.17)	-0.06 (-0.21 ; 0.09)	*Reference*	0.01 (-0.04 ; 0.05)	0.80

d. The association between the neighbourhood deprivation status score and all CRL measurement in the study population in a selected cohort of non-SGA pregnancies.

	n	Model	Lowest deprivation quartile n = 2268	Second deprivation quartile n = 2118	Third deprivation quartile n = 2081	Highest deprivation quartile n = 2131	Trend	p-value for trend
			β (95% CI)	β (95% CI)	β (95% CI)		β (95% CI)	
CRL	434	Basic	0.05 (-0.26 ; 0.35)	0.10 (-0.17 ; 0.37)	-0.05 (-0.31 ; 0.21)	*Reference*	-0.01 (-0.09 ; 0.06)	0.73
		Adjusted	0.07 (-0.30 ; 0.43)	0.09 (-0.19 ; 0.38)	-0.06 (-0.33 ; 0.21)	*Reference*	-0.02 (-0.11 ; 0.08)	0.75

Abbreviations: β: beta; CRL: crown-rump length. Values are regression coefficients with the 95% CI of the data in SD-score and are based on linear regression models. Basic model: by the use of SD scores it is automatically adjusted for gestational age. Fully adjusted model: basic model and additionally adjusted for maternal age, educational level, smoking, alcohol use, folic acid supplement use, ethnicity, parity, pre-pregnancy body mass index and fetal sex. p-for trend analysis with the neighbourhood deprivation as a continuous measure. [1] Differences between groups were evaluated using one-way-ANOVA-tests for continuous variables. [2]Differences in growth parameters between the lowest and highest neighbourhood status score groups were tested were evaluated using Student's t-tests.

Supplemental Table 6. Associations between the neighbourhood status score and fetal growth in a selected cohort of non-SGA pregnancies.

Study population **n = 7710**	**Model**	**Lowest deprivation quartile** **n = 2268**	**Second deprivation quartile** **n = 2118**	**Third deprivation quartile** **n = 2081**	**Highest deprivation quartile** **n = 2131**	**Trend**	
		β (95% CI)	**β (95% CI)**	**β (95% CI)**		**β (95% CI)**	**p-value for trend**
Early pregnancy							
CRL	Basic	0.05 (-0.26 ; 0.35)	0.10 (-0.17 ; 0.37)	-0.05 (-0.31 ; 0.21)	*Reference*	-0.01 (-0.09 ; 0.06)	0.73
	Adjusted	0.07 (-0.30 ; 0.43)	0.09 (-0.19 ; 0.38)	-0.06 (-0.33 ; 0.21)	*Reference*	-0.02 (-0.11 ; 0.08)	0.75
HC	Basic	**-0.38 (-0.71 ; -0.04)**	**-0.37 (-0.69 ; -0.06)**	-0.07 (-0.37 ; 0.23)	*Reference*	**0.12 (0.04 ; 0.21)**	**0.004**
	Adjusted	-0.22 (-0.60 ; 0.17)	-0.32 (-0.65 ; 0.01)	-0.06 (-0.36 ; 0.25)	*Reference*	0.09 (-0.01 ; 0.19)	0.09
FL	Basic	-0.19 (-0.53 ; 0.15)	**-0.33 (-0.63 ; -0.03)**	-0.11 (-0.40 ; 0.18)	*Reference*	0.08 (-0.002 ; 0.16)	0.06
	Adjusted	-0.24 (-0.66 ; 0.18)	**-0.36 (-0.69 ; -0.03)**	-0.13 (-0.44 ; 0.18)	*Reference*	0.10 (-0.01 ; 0.20)	0.07
Mid pregnancy							
HC	Basic	**-0.07 (-0.13 ; -0.001)**	-0.05 (-0.12 ; 0.01)	-0.03 (-0.10 ; 0.04)	*Reference*	**0.02 (0.003 ; 0.04)**	**0.02**
	Adjusted	-0.02 (-0.10 ; 0.05)	-0.03 (-0.09 ; 0.04)	-0.02 (-0.09 ; 0.05)	*Reference*	0.01 (-0.01 ; 0.03)	0.40
FL	Basic	**0.10 (0.045 ; 0.17)**	**0.10 (0.03 ; 0.16)**	**0.08 (0.01 ; 0.15)**	*Reference*	**-0.02 (-0.05 ; -0.01)**	**0.001**
	Adjusted	0.02 (-0.05 ; 0.10)	0.05 (-0.03 ; 0.11)	0.04 (-0.03 ; 0.11)	*Reference*	-0.01 (-0.03 ; 0.01)	0.42
AC	Basic	**-0.12 (-0.18 ; -0.05)**	**-0.13 (-0.20 ; -0.07)**	**-0.07 (-0.13 ; -0.01)**	*Reference*	**0.04 (0.02 ; 0.05)**	**<0.001**

	Adjusted	**-0.09 (-0.16 ; -0.01)**	**-0.11 (-0.18 ; -0.04)**	-0.06 (-0.12 ; 0.01)	*Reference*	**0.03 (0.01 ; 0.05)**	**0.01**
EFW	Basic	-0.03 (-0.08 ; 0.05)	-0.03 (-0.09 ; 0.04)	0.001 (-0.07 ; 0.06)	*Reference*	0.01 (-0.01 ; 0.02)	0.77
	Adjusted	-0.04 (-0.12 ; 0.03)	-0.04 (-0.11 ; 0.03)	-0.01 (-0.08 ; 0.05)	*Reference*	0.01 (-0.01 ; 0.03)	0.19
Late pregnancy							
HC	Basic	**-0.22 (-0.29 ; -0.16)**	**-0.24 (-0.31 ; -0.18)**	**-0.09 (-0.16 ; -0.03)**	*Reference*	**0.06 (0.04 ; 0.08)**	**<0.001**
	Adjusted	**-0.13 (-0.20 ; -0.06)**	**-0.18 (-0.24 ; -0.11)**	**-0.06 (-0.12 ; -0.001)**	*Reference*	**0.03 (0.01 ; 0.05)**	**<0.001**
FL	Basic	-0.02 (-0.09 ; 0.04)	0.01 (-0.05 ; 0.07)	0.01 (-0.05 ; 0.08)	*Reference*	0.001 (-0.02 ; 0.02)	0.90
	Adjusted	**-0.08 (-0.15 ; -0.01)**	-0.01 (-0.08 ; 0.05)	-0.01 (-0.07 ; 0.06)	*Reference*	0.01 (-0.01 ; 0.03)	0.20
AC	Basic	**-0.20 (-0.27 ; -0.14)**	**-0.18 (-0.24 ; -0.12)**	**-0.07 (-0.13 ; -0.01)**	*Reference*	**0.06 (0.04 ; 0.07)**	**<0.001**
	Adjusted	**-0.15 (-0.22 ; -0.08)**	**-0.13 (-0.19 ; -0.06)**	-0.05 (-0.12 ; 0.01)	*Reference*	**0.04 (0.02 ; 0.06)**	**0.02**
EFW	Basic	**-0.18 (-0.20 ; -0.12)**	**-0.14 (-0.20 ; -0.08)**	-0.05 (-0.11 ; 0.01)	*Reference*	**0.05 (0.03 ; 0.06)**	**<0.001**
	Adjusted	**-0.16 (-0.23 ; -0.08)**	**-0.11 (-0.17 ; -0.04)**	-0.05 (-0.11 ; 0.02)	*Reference*	**0.04 (0.02 ; 0.06)**	**<0.001**

Abbreviations: SGA: small for gestational age, HC: head circumference, FL: femur length, AC: abdominal circumference, EFW: estimated fetal weight. Values are regression coefficients with the 95% CI of the data in SD-score and are based on linear regression models. Basic model: by the use of SD scores it is automatically adjusted for gestational age. Fully adjusted model: basic model and additionally adjusted for maternal age, educational level, smoking, alcohol use, folic acid supplement use, ethnicity, parity, pre-pregnancy body mass index and fetal sex. p-for trend analysis with the neighbourhood deprivation as a continuous measure.

97 **Supplemental Table 7.** Associations between the neighbourhood status score and foetal growth, additionally adjusted for household income.

Study population n = 8617	n	Model	Lowest SES quartile n = 2170	Second SES quartile n = 2208	Third SES quartile n = 2090	Highest SES quartile n = 2149	Trend	p-value for trend
			β (95% CI)	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	
Early pregnancy								
CRL	1614	Basic	-0.03 (-0.17 ; 0.10)	-0.08 (-0.21 ; 0.05)	-0.08 (-0.20 ; 0.05)	*Reference*	0.01 (-0.02 ; 0.05)	0.48
		Adjusted	0.002 (-0.15 ; 0.16)	-0.04 (-0.17 ; 0.10)	-0.06 (-0.19 ; 0.06)	*Reference*	0.02 (-0.02 ; 0.07)	0.30
HC	5646	Basic	0.05 (-0.03 ; 0.13)	0.05 (-0.03 ; 0.13)	0.05 (-0.02 ; 0.13)	*Reference*	-0.01 (-0.03 ; 0.01)	0.44
		Adjusted	0.02 (-0.06 ; 0.11)	0.04 (-0.04 ; 0.12)	0.05 (-0.03 ; 0.13)	*Reference*	0.004 (-0.02 ; 0.03)	0.75
FL	4682	Basic	0.01 (-0.07 ; 0.09)	**-0.09 (-0.17 ; -0.01)**	0.06 (-0.02 ; 0.14)	*Reference*	0.01 (-0.01 ; 0.03)	0.44
		Adjusted	-0.09 (-0.18 ; 0.003)	**-0.16 (-0.24 ; -0.07)**	0.01 (-0.06 ; 0.10)	*Reference*	**0.03 (0.002; 0.06)**	**0.04**
Mid pregnancy								
HC	8035	Basic	**-0.08 (-0.15 ; -0.02)**	**-0.07 (-0.13 ; -0.01)**	-0.04 (-0.10 ; 0.03)	*Reference*	**0.02 (0.01 ; 0.04)**	**0.01**
		Adjusted	-0.02 (-0.09 ; 0.05)	-0.03 (-0.10 ; 0.03)	-0.02 (-0.08 ; 0.04)	*Reference*	0.02 (-0.01 ; 0.04)	0.18
FL	8058	Basic	**0.07 (0.01 ; 0.14)**	**0.06 (0.001 ; 0.13)**	0.05 (-0.01 ; 0.12)	*Reference*	**-0.02 (-0.04 ; -0.01)**	**0.01**
		Adjusted	-0.01 (-0.08 ; 0.07)	0.02 (-0.05 ; 0.09)	0.02 (-0.05 ; 0.08)	*Reference*	0.003 (-0.02 ; 0.02)	0.80

AC	8052	Basic	**-0.15 (-0.21 ; -0.09)**	**-0.15 (-0.21 ; -0.09)**	**-0.09 (-0.15 ; -0.03)**	*Reference*	**0.04 (0.03 ; 0.06)**	**<0.001**
		Adjusted	**-0.10 (-0.17 ; -0.03)**	**-0.11 (-0.18 ; -0.05)**	**-0.07 (-0.13 ; -0.01)**	*Reference*	**0.03 (0.01 ; 0.05)**	**0.01**
EFW	8016	Basic	-0.06 (-0.12 ; 0.01)	-0.06 (-0.12 ; 0.003)	-0.03 (-0.09 ; 0.03)	*Reference*	0.01 (-0.001 ; 0.03)	0.08
		Adjusted	-0.06 (-0.14 ; 0.01)	-0.06 (-0.13 ; 0.01)	-0.03 (-0.10 ; 0.03)	*Reference*	0.02 (-0.003 ; 0.04)	0.09
Late pregnancy								
HC	8163	Basic	**-0.24 (-0.31 ; -0.18)**	**-0.25 (-0.31 ; -0.19)**	**-0.11 (-0.17 ; -0.05)**	*Reference*	**0.06 (0.05 ; 0.08)**	**<0.001**
		Adjusted	**-0.14 (-0.21 ; -0.08)**	**-0.17 (-0.24 ; -0.11)**	**-0.07 (-0.14 ; -0.01)**	*Reference*	**0.04 (0.02 ; 0.06)**	**0.001**
FL	8234	Basic	-0.06 (-0.12 ; 0.003)	-0.03 (-0.09 ; 0.03)	-0.02 (-0.08 ; 0.05)	*Reference*	0.01 (-0.01 ; 0.03)	0.21
		Adjusted	**-0.10 (-0.17 ; -0.02)**	-0.04 (-0.10 ; 0.03)	-0.03 (-0.09 ; 0.04)	*Reference*	0.02 (-0.01 ; 0.04)	0.16
AC	8212	Basic	**-0.24 (-0.30 ; -0.18)**	**-0.21 (-0.27 ; -0.15)**	**-0.10 (-0.16 ; -0.04)**	*Reference*	**0.06 (0.05 ; 0.08)**	**<0.001**
		Adjusted	**-0.16 (-0.23 ; -0.09)**	**-0.13 (-0.20 ; -0.07)**	**-0.07 (-0.13 ; -0.01)**	*Reference*	**0.03 (0.01 ; 0.05)**	**0.002**
EFW	8201	Basic	**-0.22 (-0.28 ; -0.16)**	**-0.18 (-0.24 ; -0.11)**	**-0.09 (-0.15 ; -0.02)**	*Reference*	**0.06 (0.04 ; 0.07)**	**<0.001**
		Adjusted	**-0.17 (-0.25 ; -0.10)**	**-0.12 (-0.19 ; -0.06)**	**-0.07 (-0.13 ; -0.01)**	*Reference*	**0.03 (0.01 ; 0.06)**	**0.001**

Abbreviations: HC: head circumference, FL: femur length, AC: abdominal circumference, EFW: estimated fetal weight. Values are regression coefficients with the 95% CI of the data in SD-score and are based on linear regression models. Basic model: by the use of SD scores it is automatically adjusted for gestational age. Fully adjusted model: basic model and additionally adjusted for maternal age, educational level, smoking, alcohol use, folic acid supplement use, ethnicity, parity, pre-pregnancy body mass index, fetal sex and household income. p-for trend analysis with the neighbourhood deprivation as a continuous measure.

Supplemental Table 8. Associations between the neighbourhood status score and foetal growth, adjusted for different classification of ethnicity.

Study population n = 8617	**n**	**Model**	**Lowest SES quartile n = 2170**	**Second SES quartile n = 2208**	**Third SES quartile n = 2090**	**Highest SES quartile n = 2149**	**Trend**	**p-value for trend**
			β (95% CI)	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	
Early pregnancy								
CRL	1614	Basic	-0.03 (-0.17 ; 0.10)	-0.08 (-0.21 ; 0.05)	-0.08 (-0.20 ; 0.05)	*Reference*	0.01 (-0.02 ; 0.05)	0.48
		Adjusted	0.002 (-0.15 ; 0.16)	-0.04 (-0.17 ; 0.10)	-0.06 (-0.19 ; 0.06)	*Reference*	0.01 (-0.03 ; 0.05)	0.73
HC	5646	Basic	0.05 (-0.03 ; 0.13)	0.05 (-0.03 ; 0.13)	0.05 (-0.02 ; 0.13)	*Reference*	-0.01 (-0.03 ; 0.01)	0.44
		Adjusted	0.02 (-0.06 ; 0.11)	0.04 (-0.04 ; 0.12)	0.05 (-0.03 ; 0.13)	*Reference*	0.002 (-0.02 ; 0.03)	0.90
FL	4682	Basic	0.01 (-0.07 ; 0.09)	**-0.09 (-0.17 ; -0.01)**	0.06 (-0.02 ; 0.14)	*Reference*	0.01 (-0.01 ; 0.03)	0.44
		Adjusted	-0.09 (-0.18 ; 0.003)	**-0.16 (-0.24 ; -0.07)**	0.01 (-0.06 ; 0.10)	*Reference*	**0.04 (0.01; 0.06)**	**0.003**
Mid pregnancy								
HC	8035	Basic	**-0.08 (-0.15 ; -0.02)**	**-0.07 (-0.13 ; -0.01)**	-0.04 (-0.10 ; 0.03)	*Reference*	**0.02 (0.01 ; 0.04)**	**0.01**
		Adjusted	-0.02 (-0.09 ; 0.05)	-0.03 (-0.10 ; 0.03)	-0.02 (-0.08 ; 0.04)	*Reference*	0.01 (-0.01 ; 0.02)	0.57
FL	8058	Basic	**0.07 (0.01 ; 0.14)**	**0.06 (0.001 ; 0.13)**	0.05 (-0.01 ; 0.12)	*Reference*	**-0.02 (-0.04 ; -0.01)**	**0.01**
		Adjusted	-0.01 (-0.08 ; 0.07)	0.02 (-0.05 ; 0.09)	0.02 (-0.05 ; 0.08)	*Reference*	-0.004 (-0.02 ; 0.02)	0.69

AC	8052	Basic	**-0.15 (-0.21 ; -0.09)**	**-0.15 (-0.21 ; -0.09)**	**-0.09 (-0.15 ; -0.03)**	*Reference*	**0.04 (0.03 ; 0.06)**	**<0.001**
		Adjusted	**-0.10 (-0.17 ; -0.03)**	**-0.11 (-0.18 ; -0.05)**	**-0.07 (-0.13 ; -0.01)**	*Reference*	**0.03 (0.01 ; 0.05)**	**0.01**
EFW	8016	Basic	-0.06 (-0.12 ; 0.01)	-0.06 (-0.12 ; 0.003)	-0.03 (-0.09 ; 0.03)	*Reference*	0.01 (-0.001 ; 0.03)	0.08
		Adjusted	-0.06 (-0.14 ; 0.01)	-0.06 (-0.13 ; 0.01)	-0.03 (-0.10 ; 0.03)	*Reference*	0.02 (-0.004 ; 0.03)	0.13
Late pregnancy								
HC	8163	Basic	**-0.24 (-0.31 ; -0.18)**	**-0.25 (-0.31 ; -0.19)**	**-0.11 (-0.17 ; -0.05)**	*Reference*	**0.06 (0.05 ; 0.08)**	**<0.001**
		Adjusted	**-0.14 (-0.21 ; -0.08)**	**-0.17 (-0.24 ; -0.11)**	**-0.07 (-0.14 ; -0.01)**	*Reference*	**0.03 (0.02 ; 0.05)**	**<0.001**
FL	8234	Basic	-0.06 (-0.12 ; 0.003)	-0.03 (-0.09 ; 0.03)	-0.02 (-0.08 ; 0.05)	*Reference*	0.01 (-0.01 ; 0.03)	0.21
		Adjusted	**-0.10 (-0.17 ; -0.02)**	-0.04 (-0.10 ; 0.03)	-0.03 (-0.09 ; 0.04)	*Reference*	0.02 (-0.002 ; 0.04)	0.08
AC	8212	Basic	**-0.24 (-0.30 ; -0.18)**	**-0.21 (-0.27 ; -0.15)**	**-0.10 (-0.16 ; -0.04)**	*Reference*	**0.06 (0.05 ; 0.08)**	**<0.001**
		Adjusted	**-0.16 (-0.23 ; -0.09)**	**-0.13 (-0.20 ; -0.07)**	**-0.07 (-0.13 ; -0.01)**	*Reference*	**0.04 (0.02 ; 0.06)**	**<0.001**
EFW	8201	Basic	**-0.22 (-0.28 ; -0.16)**	**-0.18 (-0.24 ; -0.11)**	**-0.09 (-0.15 ; -0.02)**	*Reference*	**0.06 (0.04 ; 0.07)**	**<0.001**
		Adjusted	**-0.17 (-0.25 ; -0.10)**	**-0.12 (-0.19 ; -0.06)**	**-0.07 (-0.13 ; -0.01)**	*Reference*	**0.04 (0.02 ; 0.06)**	**<0.001**

Abbreviations: HC: head circumference, FL: femur length, AC: abdominal circumference, EFW: estimated fetal weight. Values are regression coefficients with the 95% CI of the data in SD-score and are based on linear regression models. Basic model: by the use of SD scores it is automatically adjusted for gestational age. Fully adjusted model: basic model and additionally adjusted for maternal age, educational level, smoking, alcohol use, folic acid supplement use, ethnicity, parity, pre-pregnancy body mass index and fetal sex. p-for trend analysis with the neighbourhood deprivation as a continuous measure.

Supplemental Table 9. Associations between the neighbourhood status score and SGA pregnancies, adjusted for maternal hypertension.

Study population n = 8617	Model	Lowest deprivation quartile n = 1190		Second deprivation quartile n = 1068		Third deprivation quartile n = 1273		Highest deprivation quartile n = 1653	Trend	p-value for trend
		OR (95% CI)		OR (95% CI)		OR (95% CI)			OR (95% CI)	
Small for gestational age	Adjusted	**1.39 (1.09 ; 1.77)**	**0.01**	1.15 (0.91 ; 1.46)	0.24	1.13 (0.89 ; 1.43)	*0.31*	*Reference*	**0.91 (0.85 ; 0.97)**	**0.004**

Abbreviations: β: beta; OR: odds ratio. Values are odds ratios with the 95% CI of the data in SD-score and are based on logistic regression models. Adjusted model: basic model and additionally adjusted for maternal age, educational level, smoking, alcohol use, folic acid supplement use, ethnicity, parity, pre-pregnancy body mass index, fetal sex, and additionally for maternal hypertension.. P-for trend analysis with the neighbourhood deprivation as a continuous measure. Small size for gestational age (SGA) at birth was defined as a sex and gestational age adjusted birthweight below the 10th percentile (<-1.40 SD-score) in the study cohort.

Supplemental Table 10. Observed and expected values of covariates.

Maternal characteristics	**Observed**	**Expected**
Age at intake (years)	29.6 (5.3)	29.6 (5.3)
Prepregnancy body mass index (kg/m^2)	22.8 (18.4 – 32.2)	22.6 (18.6 – 32.4)
Parity (nulliparous)	4796 (55.7)	4739 (55.7)
Fetal sex (boy)	4347 (50.4)	4346 (50.4)
Educational level		
Lower/no education	1101 (12.8)	916 (11.7)
Middle	4060 (47.1)	3638 (46.4)
High	3456 (40.1)	3282 (41.9)
Ethnicity		
Dutch and Western	4967 (57.6)	4793 (58.8)
Turkish and Moroccan	1464 (17.0)	1330 (16.3)
African	1178 (13.7)	1076 (13.2)
Asian	1008 (11.7)	946 (11.6)
Smoking		
Never smoked during pregnancy	6256 (72.6)	5472 (72.8)
Smoked until pregnancy was known	735 (8.5)	644 (8.6)
Continued smoking in pregnancy	1626 (18.9)	1403 (18.7)
Alcohol		
Never alcohol consumption in pregnancy	4351 (50.5)	3692 (49.8)
Alcohol consumption until pregnancy was known	1149 (13.3)	999 (13.5)
Continued alcohol consumption in pregnancy	3117 (36.2)	2728 (36.8)
Folic acid supplement use		
None	2751 (31.9)	1877 (29.4)
Start in first 10 weeks of pregnancy	2661 (30.9)	1981 (31.1)
Start preconceptional	3205 (37.2)	2518 (39.5)

Data are represented as n (%), mean (SD) or median with the 90% range. Percentages ‘expected’ displayed as valid percentages.

Supplemental 1. First trimester and fetal growth, measurement guidelines.

CRL: crown-rump length (39)

CRL is measured as the largest dimension of embryo, excluding the yolk sac and extremities. A midline sagittal section of the whole embryo or fetus should be obtained, ideally with the embryo or fetus oriented horizontally on the screen. An image should be magnified sufficiently to fill most of the width of the ultrasound screen, so that the measurement line between crown and rump is at about 90◦ to the ultrasound beam.

Caliper placement: measure the fetus in a neutral position (i.e. neither flexed nor hyperextended). The end points of crown and rump should be defined clearly.

HC: Head circumference (40)

As described for the BPD, ensuring that the circumference placement markers correspond to the technique described on the reference chart.

Caliper placement: If the ultrasound equipment has ellipse measurement capacity, then the HC can be measured directly by placing the ellipse around the outside of the skull bone echoes.

AC: abdominal circumference (40)

- Transverse section of the fetal abdomen (as circular as possible);
- umbilical vein at the level of the portal sinus;
- stomach bubble visualized;
- kidneys should not be visible.

Caliper placement: The AC is measured at the outer surface of the skin line, either directly with ellipse calipers or calculated from linear measurements made perpendicular to each other, usually the anteroposterior abdominal diameter and transverse abdominal diameter.

FL: femur length (40)

The FL is imaged optimally with both ends of the ossified metaphysis clearly visible. The longest axis of the ossified diaphysis is measured. The same technique as that used to establish the reference chart should be used with regard to the angle between the femur and the insonating ultrasound beams. An angle of insonation between 45◦ and 90◦ is typical.

Caliper placement: Each caliper is placed at the ends of the ossified diaphysis without including the distal femoral epiphysis if it is visible

Supplemental 2. Multiple imputations for missing data of covariates.

We imputed missing data of the covariates using multiple imputations (17). The percentages of missing values for the confounders within the population for analysis were lower than 20%. For the multiple imputation, we the Markov chain Monte Carlo approach. In the imputation model, we included all confounders, plus maternal age, ethnicity, parity and prepregnancy BMI. Furthermore, we additionally added the studied determinants and outcomes in the imputation model as prediction variables only; they were not imputed themselves. Five imputed datasets were created and analyzed together.

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study’s design with a commonly used term in the title or the abstract	1

Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	#4	Present key elements of study design early in the paper	4, 5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4, 5
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	4, 5
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	4 ,5
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5, 6
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than	4, 5, 6

		one group. Give information separately for for exposed and unexposed groups if applicable.	
Bias	#9	Describe any efforts to address potential sources of bias	5, 6, 8
Study size	#10	Explain how the study size was arrived at	4, 5
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7, 8
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	
6, 8			
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	7, 8
Statistical methods	#12c	Explain how missing data were addressed	7, 8
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	7, 8
Statistical methods	#12e	Describe any sensitivity analyses	
7, 8			
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility,	9

		confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	
Participants	#13b	Give reasons for non-participation at each stage	9
Participants	#13c	Consider use of a flow diagram	
9			
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	9
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	
9			
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	
9			
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	
9, 10			
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence	9, 10

		interval). Make clear which confounders were adjusted for and why they were included	
Main results	#16b	Report category boundaries when continuous variables were categorized	9, 10
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
9, 10			
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10, 11
Discussion			
Key results	#18	Summarise key results with reference to study objectives	11
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	12, 13
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	13, 14
Generalisability	#21	Discuss the generalisability (external validity) of the study results	13
Other Information			

Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

 This checklist was completed on 14. January 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai