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

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3 1 **Neighbourhood deprivation, fetal growth and adverse pregnancy outcomes:**
4
5 2 **the Generation R Study.**

6
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16 9 **The authors declare no conflict of interest.**

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28
29 16
30 17
31 18 **Key words:** fetal, neighborhood/place, deprivation, pregnancy, socio-economic

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35 19 **Word count:** 3661

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2
3 20 **Abstract**
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5 21 **Objectives:** To study the associations between neighbourhood deprivation and fetal growth, including
6
7 22 growth in the first trimester, and adverse pregnancy outcomes.
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10 23 **Design:** Prospective cohort study.
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13 24 **Setting:** The Netherlands, Rotterdam.
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16 25 **Participants:** 8617 live singleton births from the Generation R cohort study.
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19 26 **Interventions:** Living in a deprived neighbourhood.
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22 27 **Outcome measures:** Fetal growth, including growth in the first trimester, and adverse pregnancy
23
24 28 outcomes (small-for-gestational age (SGA) and preterm birth (PTB)).
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26

27 29 **Results:** Neighbourhood deprivation was not associated with first trimester growth. However, a higher
28
29 30 neighbourhood status score (less deprivation), was associated with increased fetal growth in the
30
31 31 second and third trimester (e.g. estimated fetal weight (adjusted regression coefficient 0.04 (95% CI
32
33 32 0.02 ; 0.06). Less deprivation was also associated with a decreased risk of SGA (aOR 0.91 (95% CI
34
35 33 0.86 ; 0.97)) and PTB (aOR 0.89 (95% CI 0.82 ; 0.96)).
36
37

38 34 **Conclusions:** We found an association between neighbourhood deprivation and fetal growth in the
39
40 35 second and third trimester pregnancy, but not with first trimester growth. Neighbourhood deprivation
41
42 36 is associated with adverse pregnancy outcomes. The associations remained after adjustment for
43
44 37 individual level risk factors. This supports the hypothesis that living in a deprived neighbourhood acts
45
46 38 as an independent risk factor for fetal growth and adverse pregnancy outcomes, above and beyond
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48 39 individual risk factors.
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3 40 **Article Summary**
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6 41 **Strengths and limitations of this study**
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- 9 42 • This study investigated the association between neighbourhood deprivation and fetal growth
10
11 43 and adverse pregnancy outcomes.
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14 44 • This study is performed within in a large, multi-ethnic cohort.
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17 45 • The Generation R study population is not completely representative of the Dutch population.
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20 46 • Associations were adjusted for a wide range of relevant individual level risk factors, which
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22 47 allows the isolation of a neighbourhood specific effect best as possible.
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48 Introduction

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

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

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

68

69 Methods

70 Design

71 This study was embedded in the Generation R Study, a population-based prospective cohort
72 study.(8) Pregnant women living in the area of Rotterdam, the Netherlands, with an expected delivery
73 date between April 2002 and January 2006, were invited to participate in this study. We excluded the

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2
3 74 following pregnancies: twin pregnancies, terminated pregnancies, intra-uterine deaths and pregnancies
4
5 75 without information on area of residence or ultrasound data (**Figure 1**). The study protocol was
6
7 76 approved by the Medical Ethical Committee of Erasmus Medical Centre, Rotterdam (MEC 198.782/
8
9 77 2001/31). Written informed consent was obtained from all participants.
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11

12 78 **Patient and public involvement statement**

13 79 This research was done without patient involvement. Patients were not invited to comment on
14
15 80 the study design and were not consulted to develop patient relevant outcomes or interpret the results.
16
17 81 Patients were not invited to contribute to the writing or editing of this document for readability or
18
19 82 accuracy.
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23 83 **Neighbourhood deprivation**

24 84 We used area-based status scores as a proxy for neighbourhood deprivation, which were made
25
26 85 available by the Netherlands Institute for Social Research.(9) The scores are matched on four-digit
27
28 86 postcodes and are based on mean household income, proportion of population with low income,
29
30 87 proportion of population with low educational level, and proportion of population without paid work.
31
32 88 The scores are determined every 4 years, and a more negative score represents a lower socioeconomic
33
34 89 status. The status scores used in this study were calculated in 2002 and 2006. The correlations between
35
36 90 the status scores in 2002 and 2006 were very high: $r = 0.97$. To assign the status scores in the best
37
38 91 possible way, pregnancies in 2002 and 2003 were allocated with the status score of 2002. For
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40 92 pregnancies in 2005 and 2006, the status score of 2006 was assigned. For pregnancies in 2004, the
41
42 93 average score of 2002 and 2006 was assigned.
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46 94 **Pregnancy dating**

47 95 Gestational age is the most important determinant of fetal growth, so precise dating of the
48
49 96 pregnancy is important. It has long been assumed that embryonic growth in the first trimester of
50
51 97 pregnancy is universal. This is the rationale behind the current practice of pregnancy dating using the
52
53 98 CRL, if the gestational age is less than 12 weeks and 5 days and the CRL measurement is smaller than
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55 99 65 mm.(10) However, study findings suggest that first trimester growth is not uniform.(11) Therefore,
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58 100 in our analyses with CRL measurements as the outcome of interest, pregnancy dating was not based
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60 101 on the CRL, but on the known and reliable last menstrual period (LMP) in case of a regular menstrual

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3 102 cycle (28 ± 4 days).(6) All other cases were excluded for that particular analyses of CRL. The LMP
4
5 103 was obtained from the referral letter and confirmed at enrolment. Additional information on regularity
6
7 104 and cycle duration was obtained through questionnaires. When the gestational age was more than 12
8
9 105 weeks and 5 days, or the biparietal diameter (BPD) was larger than 23 mm, pregnancy dating was
10
11 106 performed using the BPD.

107 **Growth parameters**

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

120 **Adverse pregnancy outcomes**

121 Preterm birth (PTB) was defined as a gestational age of <37 weeks at delivery. Small size for
122 gestational age (SGA) at birth was defined as a sex and gestational age adjusted birth weight below the
123 10th percentile (<-1.40 SDS) in the study cohort.

124 **Covariates**

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

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3 129 Creole, and Dutch Antillean); and Asian (Indonesian, other Asian, and Surinamese-Hindu) according
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5 130 to the largest ethnic groups in our study population and similarities in skin colour and cultural
6
7 131 background. In sensitivity analyses, the following classification was used: Dutch, European, Turkish,
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9 132 Moroccan, African, Dutch Antillean, Cape Verdean, Indonesian, Surinamese-Creole, Surinamese-
10
11 133 Hindu, Surinamese-unspecified, American Western, American non Western, Asia Western, Asia non
12
13 134 Western and Oceanian.(8) Information about smoking, alcohol consumption, and caffeine intake was
14
15 135 assessed by questionnaires in each trimester. Maternal pre-pregnancy body mass index was calculated
16
17 136 from the reported height (cm) and weight (kg) in the questionnaires. Information about pregnancy
18
19 137 complications, mode of delivery and childhood sex, gestational age, and weight and length at birth was
20
21 138 obtained from medical records.(13, 14) Complications in a previous pregnancy were defined as:
22
23 139 gestational diabetes, pre-eclampsia, thrombosis in arm or leg, pulmonary embolism, solutio placentae,
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25 140 premature rupture of membranes, contractions before 37 weeks of pregnancy or pregnancy induced
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27 141 hypertension. We selected potential confounding variables based on their associations with the
28
29 142 outcomes of interest, in order to isolate a neighbourhood specific effect.
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144 **Statistical analysis**

145 First, we examined differences between quartiles of neighbourhood deprivation for maternal
146 characteristics, first trimester growth and fetal growth and adverse pregnancy outcomes. Second, we
147 examined the associations of neighbourhood deprivation with fetal growth patterns using unbalanced
148 repeated measurement regression models.(15) We included neighbourhood deprivation in these
149 models as intercept and as interaction term with gestational age to estimate fetal growth rates over
150 time.(15) Third, we assessed the associations of neighbourhood deprivation with the risks of adverse
151 pregnancy outcomes using multiple logistic regression models. In the basic model, the crude
152 association between neighbourhood deprivation and the outcomes of interest were investigated. The
153 adjusted model was adjusted for maternal age, maternal educational level, smoking, alcohol use, folic
154 acid supplement use, ethnicity, parity, pre-pregnancy BMI and fetal sex. We tested interaction between
155 neighbourhood deprivation and complications in previous pregnancy in the regression models. Fourth,
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2
3 156 we examined the associations of neighbourhood deprivation with fetal growth in gestational-age-
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5 157 adjusted SDS in each pregnancy period using linear regression models with the same adjustment
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7 158 models.

9 159 We performed several sensitivity analyses: in the first, we performed multilevel regression
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11 160 analysis in order to adjust for potential clustering between the different neighbourhoods. In the second,
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13 161 we repeated the analyses with all 1614 available CRL measurements, compared to the analyses with
14
15 162 only CRL measurements below the 12 weeks of gestational age (GA).^(6, 16) A third sensitivity
16
17 163 analysis was performed to determine to which extent the inclusion of pregnancies with an impaired
18
19 164 fetal development due to placental dysfunction influenced our results. Therefore we performed
20
21 165 analyses excluding SGA born babies. Fourth, analyses were additionally adjusted for the household
22
23 166 income and complications in a previous pregnancy. Fifth, we repeated the analyses with the different
24
25 167 classification of ethnicity, described in the ‘Covariates’ section. Lastly, we explored the associations in
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27 168 the dataset only including the first born (i.e. excluding siblings). We used multiple imputation for
28
29 169 missing values of covariates according to Markov Chain Monte Carlo method (details given in
30
31 170 **Supplemental 1**).⁽¹⁷⁾ The percentage of missing data was <10%, except for smoking (12.7%),
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33 171 alcohol use (13.8%) and folic acid supplement use (25.9%). Five imputed datasets were created and
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35 172 pooled for analyses. A sensitivity analysis was performed to observe differences in observed and
36
37 173 expected values of confounders before and after imputation. Tests for trend were based on regression
38
39 174 models with neighbourhood deprivation as a continuous variable. We checked whether the regression
40
41 175 models were linear using scatterplots of the dependent variable plotted against the independent
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43 176 variable.⁽¹⁸⁾ Residuals were normally distributed as assessed by visual inspection of a normal
44
45 177 probability plot. We tested for multicollinearity using the tolerance statistic. As tolerance was >0.20
46
47 178 for all variables in our models, there were no problems of multicollinearity. The repeated measurement
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49 179 analysis was performed using the Statistical Analysis System version 9.3 (SAS, Institute Inc., Cary,
50
51 180 NC, USA), including the Proc Mixed module for unbalanced repeated measurements. All other
52
53 181 analyses were performed using the Statistical Package of Social Sciences version 21.0 for Windows
54
55 182 (IBM Corp., Armonk, NY, USA).

183 Results

184 A total of 8976 pregnancies were included in the Generation R study. In total, we included
185 8617 pregnancies for analyses (**Figure 1**). **Table 1** depicts the baseline characteristics of both the total
186 study population and the population stratified according to the quartiles of neighbourhood deprivation.
187 Women in the total study population were on average 29.6 years old with a median BMI of 22.8
188 kg/m². Stratification of the population in deprivation quartiles revealed that 2170 women (25.2%)
189 lived in a neighbourhood with the most deprivation, i.e. lowest status score, and 2149 (24.9%) lived in
190 the least deprived neighbourhoods, i.e. the highest status score. When comparing women in the most
191 deprived neighbourhoods to those in the least deprived neighbourhoods, less women were highly
192 educated (23.7% vs. 62.8% (p<0.001)), more women continued smoking in pregnancy (22.3% vs.
193 11.9% (p<0.001)) and less women used any folic acid supplements (20.0% vs. 49.7% respectively
194 (p<0.001)) (**Table 1**). In **Supplemental Table 1** the fetal growth parameters and adverse pregnancy
195 outcomes stratified by quartile of neighbourhood deprivation are presented. Overall, growth
196 parameters are smaller in the most deprived neighbourhoods compared to the least deprived
197 neighbourhoods (e.g. -0.07 SD vs. 0.15 SD, EFW in the third trimester of pregnancy, respectively).

198 Neighbourhood deprivation and fetal growth

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

206 The associations of neighbourhood deprivation with first trimester and second and third
207 trimester fetal growth based on regular linear regression models are given in **Supplemental Figure 1**.
208 In both the basic and adjusted analyses, a positive association between neighbourhood deprivation and
209 AC was present (difference in AC in the adjusted model, 0.03 SDS [95% CI 0.01, 0.05, P-value 0.002]
210 per 1 unit increase in neighbourhood status score). In the third trimester of pregnancy a positive

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3 211 association was found for the HC, AC and EFW (adjusted model difference of 0.04 SDS [95% CI
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5 212 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
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7 213 0.03, 0.06, P-value <0.001] per 1 unit increase in neighbourhood status score, respectively). Overall,
8
9 214 there is a dose-response like association between neighbourhood deprivation and fetal growth, with
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11 215 stronger associations in the most deprived neighbourhoods compared to the least deprived
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14 216 neighbourhoods.

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16 217 Effect modification analyses showed significant interaction between neighbourhood
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18 218 deprivation and complications in previous pregnancies for PTB (**Supplemental Table 3**). The
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20 219 associations between neighbourhood deprivation and fetal growth and adverse pregnancy outcomes
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22 220 were non-significant in the group with a complication in a previous pregnancy (e.g. HC in late
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24 221 pregnancy attenuates from 0.06 SDS [95%CI 0.05 , 0.08, P-value <0.001] to 0.03 SDS [95%CI -0.05 ,
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26 222 0.11, P-value 0.50] per 1 unit increase in neighbourhood status score) (**Supplemental Table 4**).

27 28 223 **Neighbourhood deprivation and adverse pregnancy outcomes**

29
30 224 Results of the regression analysis between neighbourhood deprivation and adverse pregnancy
31
32 225 outcomes are presented in **Table 2**. Living in a more affluent neighbourhood was inversely associated
33
34 226 with the risk of delivering a SGA neonate (adjusted model, OR 0.91 [95% CI 0.86, 0.97, P-value
35
36 227 0.01], independent of maternal sociodemographic or lifestyle factors. Moreover, it was inversely and
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38 228 independently associated with the risk of PTB (adjusted model, OR 0.89 [95% CI 0.82, 0.96, P-value
39
40 229 0.01]. The adverse pregnancy outcomes were most prevalent in the neighbourhood with the lowest
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42 230 deprivation status compared to the neighbourhood with the highest social status (SGA: 12.2% vs.
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44 231 7.1%, PTB: 5.9% vs. 3.8%) (**Supplemental Table 1**).

45 46 47 232 **Sensitivity analyses**

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49 233 The first sensitivity analyses revealed largely similar associations after performing multilevel
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51 234 analyses (**Supplemental Table 5**). Second, the results of the associations between neighbourhood
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53 235 deprivation and CRL did not change after including all CRL measurements, in comparison to only the
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55 236 CRL measurements below 12 weeks GA (**Supplemental Table 5**). The third sensitivity analyses
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57 237 excluding SGA pregnancies did attenuate the results (**Supplemental Table 6**). Results also did not
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59 238 materially change after all other sensitivity analyses (data not shown). No major differences were

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3 239 observed in confounders before and after multiple imputation (**Supplemental Table 7**) and there were
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5 240 similar results when confounders were not imputed (data not shown).
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9 241 **Discussion**

11 242 **Main findings**

13 243 We observed that living in a more deprived neighbourhood is associated with decreased fetal
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15 244 growth in the second and third trimester of pregnancy, and with higher odds of small for gestational
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17 245 age birth and preterm birth. Several pathways may explain the disadvantageous effects of living in a
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19 246 deprived neighbourhood on pregnancy.(19) First, it is proposed to be due to the accumulation of risk
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21 247 factors at the individual level.(5) Examples are smoking and inadequate nutrition and lifestyle
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23 248 behaviours.(20) Neighbourhood deprivation then acts as a proxy for the increased prevalence of risk
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25 249 factors within the deprived neighbourhoods. Our findings are substantiated by earlier studies within
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27 250 the Generation R birth cohort, that demonstrate that living in a deprived neighbourhood is
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29 251 accompanied by the accumulation of individual level risk factors. These in turn were associated with
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31 252 adverse pregnancy outcomes.(5) However, we observe that even after correction for the individual
32
33 253 level risk factors, the association between neighbourhood deprivation and impaired development and
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35 254 adverse pregnancy outcomes remained, emphasizing an isolated role for neighbourhood deprivation as
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37 255 a risk factor for pregnancy. The associations between neighbourhood deprivation and fetal growth and
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39 256 adverse pregnancy outcomes attenuated to non-significance in the population affected by a
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41 257 complication in a previous pregnancy. These complications, and the maternal constitution for the
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43 258 development of it, may thus outweigh the contribution of neighbourhood deprivation in the
44
45 259 associations with fetal growth and adverse pregnancy outcomes. This may be due to the fact that past
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47 260 complications in pregnancy are strongly associated with both neighbourhood deprivation and fetal
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49 261 growth and adverse pregnancy outcomes.(21). A second pathway which may explain the
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51 262 disadvantageous effects of living in a deprived neighbourhood on adverse pregnancy outcomes is
52
53 263 attributed to the lack of or suboptimal access to facilities such as the possibility to purchase healthy
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55 264 food nearby.(22) Third, living in a deprived neighbourhood is acknowledged as a source of chronic
56
57 265 stress, and thereby acts as an independent risk factor for adverse health outcomes.(19, 23) Stress is
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3 266 associated with increased cortisol levels, and both prolonged or repeated cortisol exposure increases
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5 267 the risk for impaired physical health.(24) Also with regard to pregnancy, stress is demonstrated to be
6
7 268 harmful. M since maternal stress during pregnancy is associated with preterm birth, lower birthweight
8
9 269 and the onset of preeclampsia and gestational diabetes.(25, 26)

10
11 270 Our data demonstrates that the associations between neighbourhood deprivation and fetal
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13 271 growth become stronger over the course of pregnancy. This may be due to the fact that there are
14
15 272 different mechanisms by which external factors -such as environmental, nutritional and lifestyle
16
17 273 factors- affect the developing fetus over the different trimesters of pregnancy. In the first trimester of
18
19 274 pregnancy the embryo depends on the uterine glands and yolk sac for the provision of nutrients, while
20
21 275 in the subsequent periods of pregnancy there is an exchange of nutrients between the maternal and
22
23 276 fetal circulations across the placenta.(27) The more isolated source of nutrition in the first trimester
24
25 277 compared to the second and third trimester of pregnancy may decrease the sensitivity of first trimester
26
27 278 embryonic growth to external influences.

28
29
30 279 A previous study of our group, observed a negative association between neighbourhood
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32 280 deprivation and first trimester growth. The larger embryos in deprived neighbourhoods were
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34 281 hypothesized to be explained by strong unmeasured intrinsic and extrinsic factors, such as mental
35
36 282 stressors.(28) The difference in direction of effects between that study and our current findings, may
37
38 283 be due to the different source populations; the first study was conducted in a tertiary-hospital based
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40 284 cohort, while the present study is performed within a population-based cohort.

41 42 43 44 285 **Strengths and limitations**

45 286 Strengths of this study include the large number of participants and the availability of
46
47 287 extensive data which allowed us to adjust for a large number of potential confounders. Its population-
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49 288 based design in a multi-ethnic population results in a good representation of the residents of the city of
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51 289 Rotterdam. The presence of both residents from deprived and more affluent neighbourhoods in the
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53 290 study population allowed us to investigate the effect of this exposure extensively. The choice of the
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55 291 neighbourhood deprivation indicator is another strength of this study. To classify the degree of
56
57 292 neighbourhood deprivation often composite indexes are used, which take factors into account such as
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59 293 the percentage of educated or employed residents, and income of residents within a specific

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3 294 neighbourhood.(29) We selected the status scores of the Netherlands Institute for Social Research,
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5 295 because this index is comparable with international indices such as the Index of Multiple Deprivation
6
7 296 and the Jarman score.(30, 31) The status scores are a continuous measure, which allows more accurate
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9 297 analyses compared to a dichotomous measure. Another strength of the study was that missing data of
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11 298 covariates was handled by applying multiple imputations. In comparison with complete-case analyses
12
13 299 (which was conducted as a sensitivity analysis), this technique maintains the statistical power of the
14
15 300 analyses. Lastly, we chose not to adjust for nutritional factors other than alcohol intake and folic acid
16
17 301 supplement use, since alcohol intake and folic acid supplement use are strongly correlated with other
18
19 302 lifestyle and nutritional habits.(32, 33)

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21
22 303 Some limitations of this study also merit discussion. First, we adjusted the analyses for
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24 304 individual factors, to isolate a neighbourhood specific effect. However, we cannot rule out the
25
26 305 presence of residual confounding caused by other individual factors that are strongly associated with
27
28 306 fetal growth. Next, possible misclassification of neighbourhood deprivation may have occurred if
29
30 307 women moved during pregnancy to a neighbourhood with a different status score from the one they
31
32 308 moved out of. However, social mobility in pregnancy is limited and if women move, they generally
33
34 309 tend to move to a neighbourhood with a comparable deprivation status.(34) Third, the power of the
35
36 310 analyses on CRL are lower due to the availability of only one CRL measurement, instead of a repeated
37
38 311 assessment of the CRL. A last disadvantage is that participants of cohort studies, even those in more
39
40 312 deprived neighbourhoods, generally have a higher level of health awareness and are generally more
41
42 313 healthy compared to those who do not participate.(8) This may reduce the generalizability of our
43
44 314 findings to the general population.

315 **Future perspectives**

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

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3 322 In the Netherlands, in both the prenatal and postnatal setting, screening for non-medical risk
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5 323 factors is starting to become part of daily medical practice.(35, 36) This allows early interventions in
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7 324 order to prevent developmental problems of children in later life. However, we propose a shift of
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9 325 attention towards an earlier window of opportunity: the preconception period and first trimester of
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11 326 pregnancy. This periconception period provides the opportunity to optimize the conditions of
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13 327 pregnancy and thereby decrease the risks of adverse outcomes and all their long-term
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15 328 consequences.(37) For example, based on an early risk assessment, a pregnant woman living in a
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17 329 deprived neighbourhood could be scheduled for extra ultrasounds and check-ups, and be assisted to
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19 330 improve modifiable lifestyle risk factors.

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22 331 Additionally, it is important to create more awareness among politicians, policymakers and
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24 332 public health workers. They could help to embed neighbourhood deprivation in the context of health
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26 333 promotion, by developing and promoting targeted preventive intervention programs.(38) These
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28 334 programs could specifically focus on residents of deprived neighbourhoods. It is important to stimulate
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30 335 these residents to diminish risk factors on the individual level, for instance to quit smoking and abstain
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32 336 from alcohol. This could also help to narrow health inequalities between neighbourhoods and between
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34 337 groups of different socioeconomic status.

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37 338 In conclusion, our obtained insights on the association between neighbourhood deprivation
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39 339 and fetal growth and prematurity emphasize the need for a comprehensive research, care and policy
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41 340 approach from the preconception phase onwards, to mitigate the risk of adverse pregnancy outcomes
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43 341 due to deprivation.

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3 343 **Twitter** Dionne Gootjes @dvgootjes
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13
14 350

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35

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38
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40 365 **Patient consent for publication:** Not required.
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43 366 **Ethics approval** The study has been approved by the Medical Ethical Committee of the Erasmus
44 367 Medical Centre in Rotterdam on December 17th 2001 (MEC 198.782/2001/31). Written consent was
45 368 obtained from all participants.
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48 369 **Data availability statement** Data requests can be made to the secretariat of Generation R.
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375 **Tables and figures**

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

377 **Figure 2. Associations of neighbourhood deprivation with fetal growth.**

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

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

381 **Supplemental material**

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

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

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

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

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

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

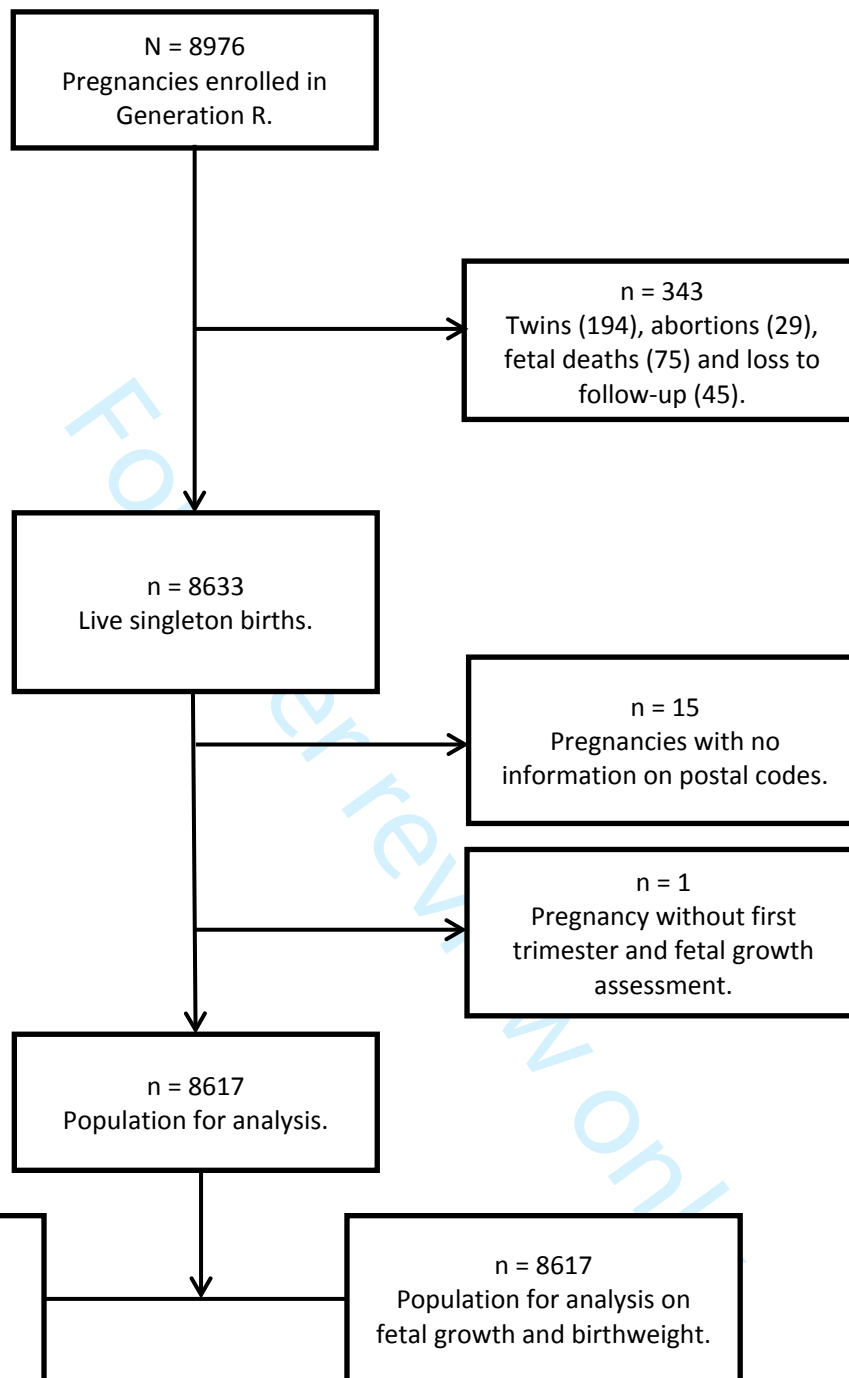
396 **Supplemental Table 7. Observed and expected values of covariates.**

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3 397 **Supplemental Figure 1. Associations between the neighbourhood deprivation and fetal growth**
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5 398 **parameters.**
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8 399 **Supplemental Figure 2. Multilevel regression analysis of associations between neighbourhood**
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10 400 **deprivation and first trimester and fetal growth measurements.**
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12 401 **Supplemental 1. Multiple imputations for missing data of covariates**
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15 402 **Supplemental 2. First trimester and fetal growth, measurement guidelines.**
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403 **Figure 1.** Flowchart of the study population.

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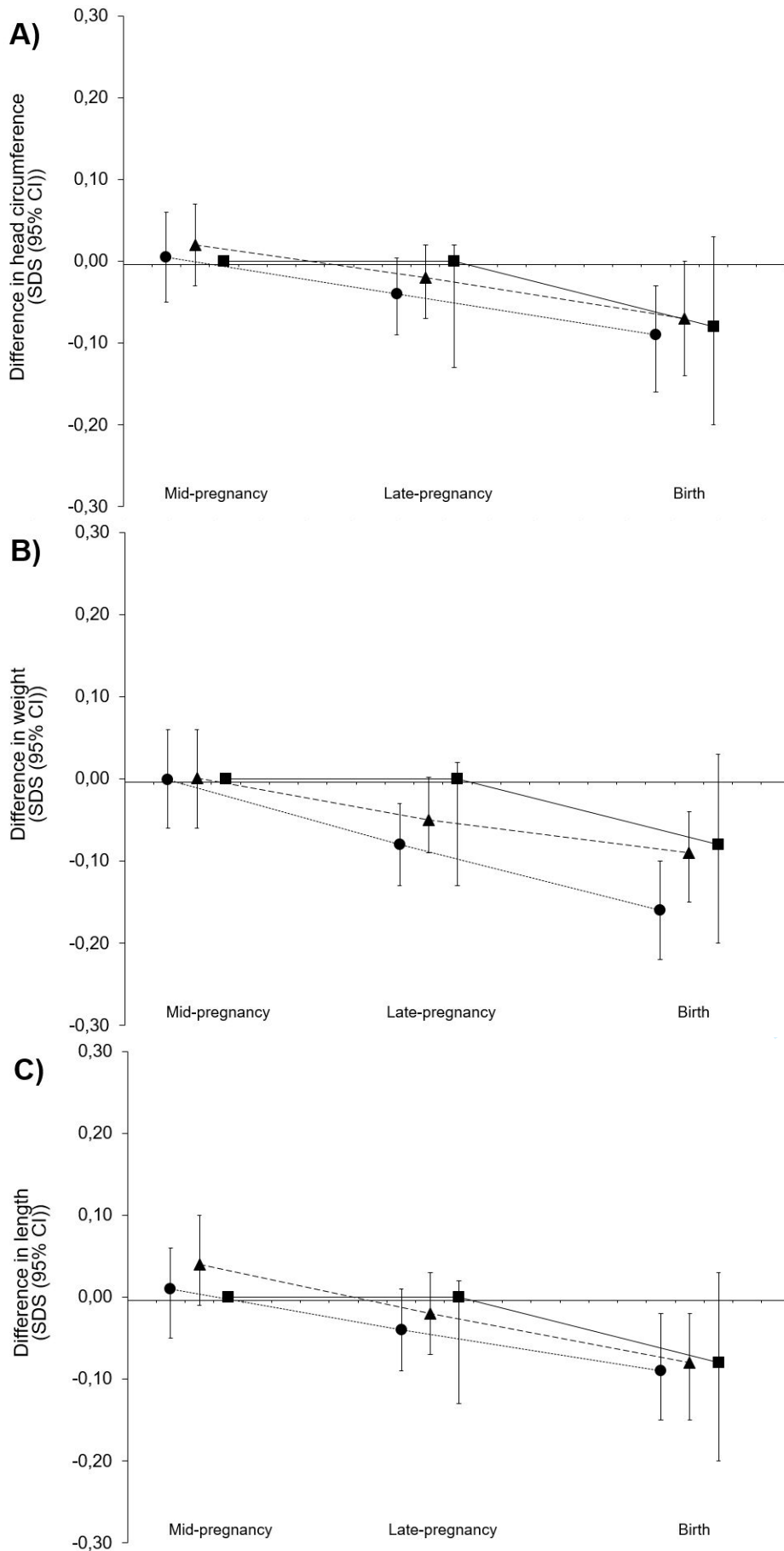
405 **Table 1.** Baseline characteristics of the study population, stratified for quartiles of neighbourhood deprivation.

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.

408 **Figure 2. Associations of neighbourhood deprivation with fetal growth.**



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3 411 Differences in fetal growth rates for the lower three neighbourhood status score quartiles as compared
4 412 to the highest neighbourhood status score. Squares represent the lowest quartile of the neighbourhood
5 413 status score; circles represent the second quartile; and triangles the third quartile. Results are based on
6 414 repeated measurement regression models and reflect the differences in gestational-age-adjusted SDS
7 415 scores of (a) fetal head circumference, (b) weight, and (c) length growth for the three lower
8 416 neighbourhood status score compared to the highest neighbourhood status score (reference group
9 417 represented as zero line). The models were adjusted for maternal age, educational level, smoking,
10 418 alcohol use, folic acid supplement use, ethnicity, parity, pre-pregnancy body mass index and fetal sex.
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420 **Table 2.** Associations between the neighbourhood status score and adverse pregnancy outcomes.

Study population	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	0.89 (0.82 ; 0.96)	0.004

421 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
 422 model: by the use of SD scores it is automatically adjusted for gestational age. Adjusted model: basic model and additionally adjusted for maternal age,
 423 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
 424 neighbourhood deprivation as a continuous measure. Small size for gestational age (SGA) at birth was defined as a sex and gestational age adjusted
 425 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.

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52 524

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

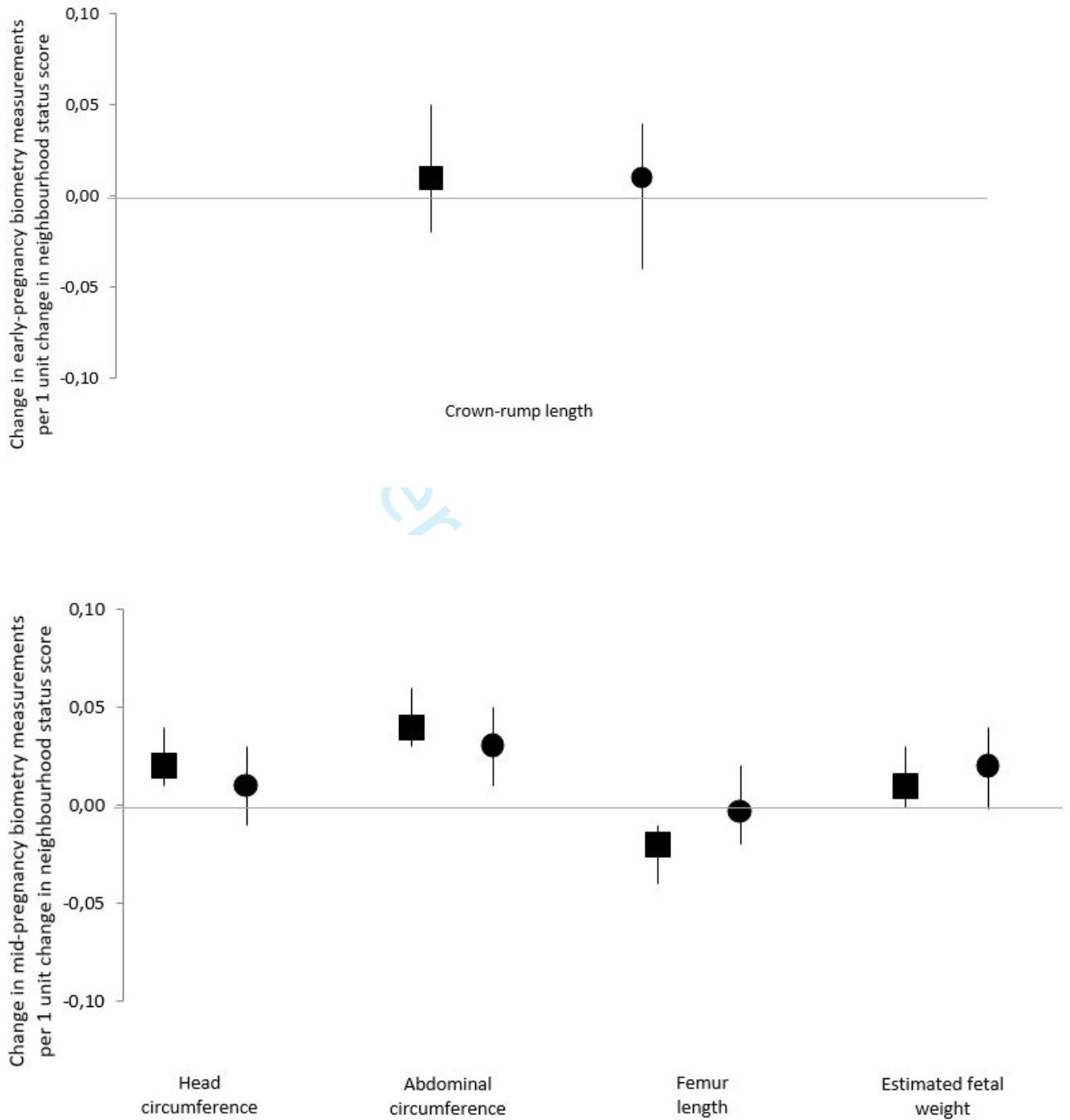
3 Abbreviations: SD: standard deviation. HC: head circumference. FL: femur length. AC: abdominal circumference. EFW: estimated fetal weight. Values
4 represent data in SD-score, mean (SD) or n (%).¹ Differences between groups were evaluated using one-way-ANOVA-tests for continuous variables and Chi-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

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

	Intercept	Slope	Intercept	Slope	Intercept	Slope
	Head circumference	Head circumference	Length	Length	Weight	Weight
	(SDS)	(SDS)	(SDS)	(SDS)	(SDS)	(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.

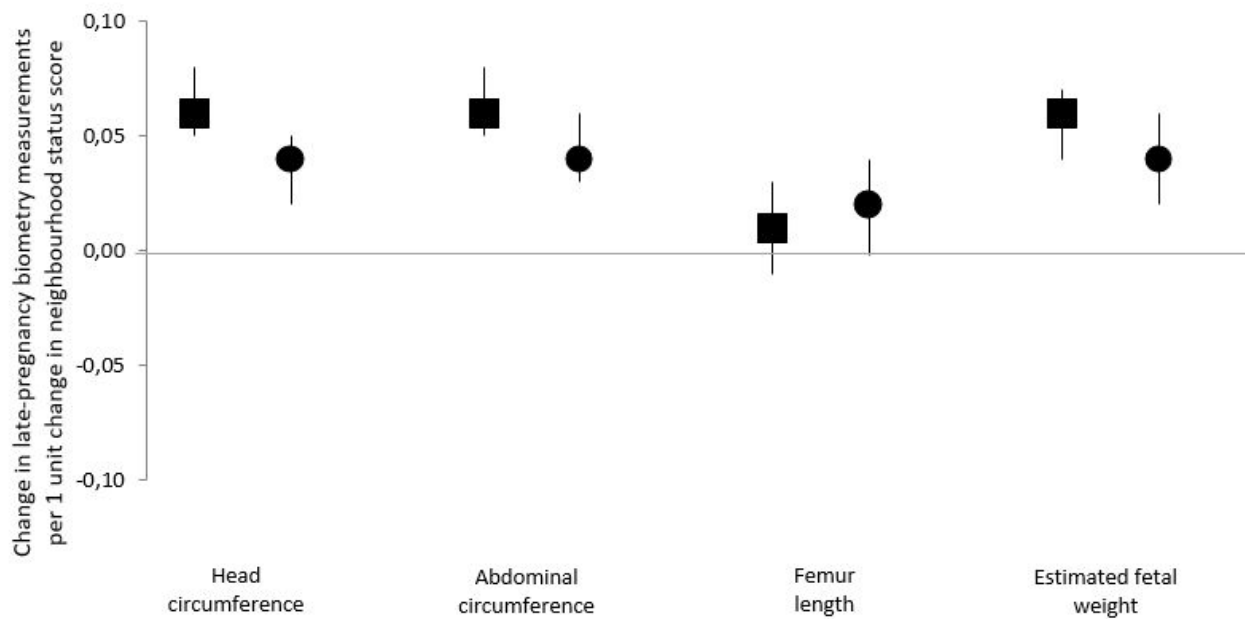
10 Values are regression coefficients obtained from linear repeated measurement models and reflect the (gestational) age independent differences (intercepts) and
 11 the gestational age dependent differences (slopes: change in growth characteristics SDS per week per quartile of the neighbourhood deprivation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

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

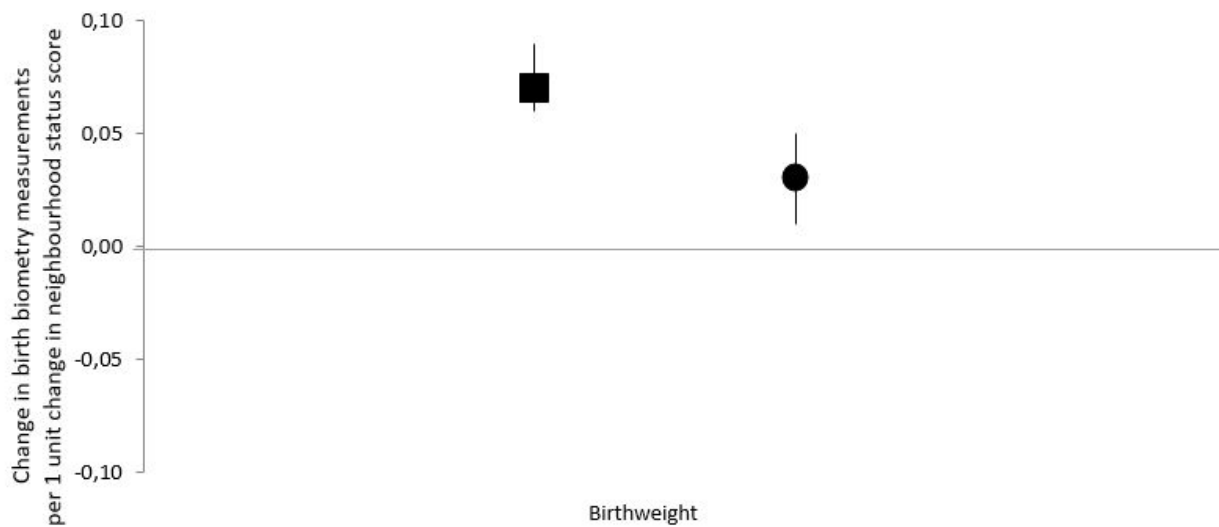


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19 Data are SDS values (95% CI) from linear regression models that reflect the differences in growth
 20 characteristics in SDS's in early pregnancy, mid-pregnancy late pregnancy and birth, per 1 unit change
 21 in neighbourhood status score. Analyses with crown-rump length were based on subgroup analyses (n
 22 = 1614). Estimates are from multiple imputed data. Squares show basic model; circles show the
 23 adjusted model: basic model and additionally adjusted for maternal age, educational level, smoking,
 24 alcohol use, folic acid supplement use, ethnicity, parity, pre-pregnancy body mass index and fetal sex.

25 **Supplemental Table 3.** P-value of interaction terms (neighbourhood deprivation * parity and
 26 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

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

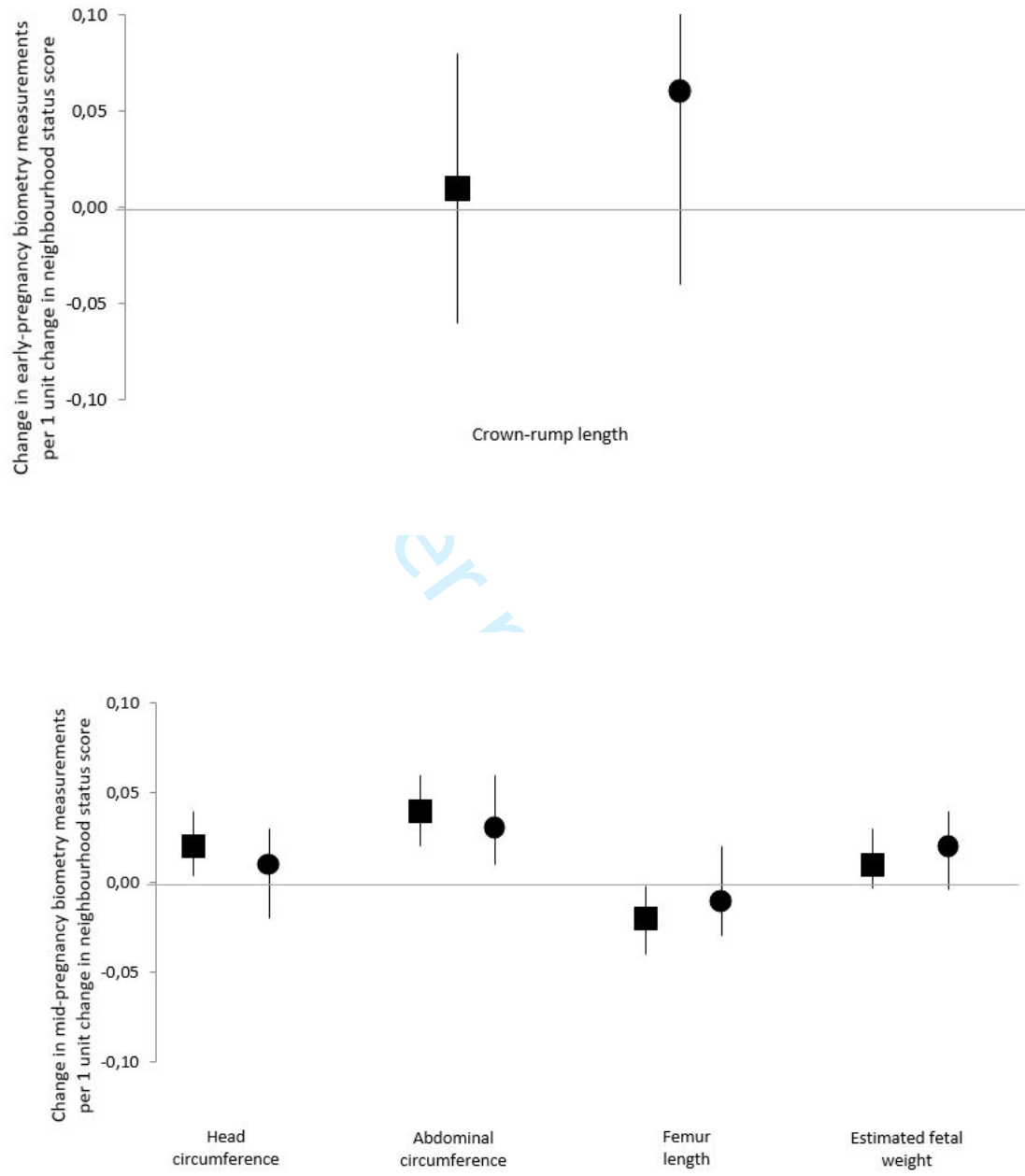
30 **Supplemental Table 4.** Associations between the neighbourhood status score and fetal growth and adverse pregnancy outcomes, split for nulliparous women,
 31 multiparous women without a complications in a previous pregnancy or multiparous women with a complications in a previous pregnancy.

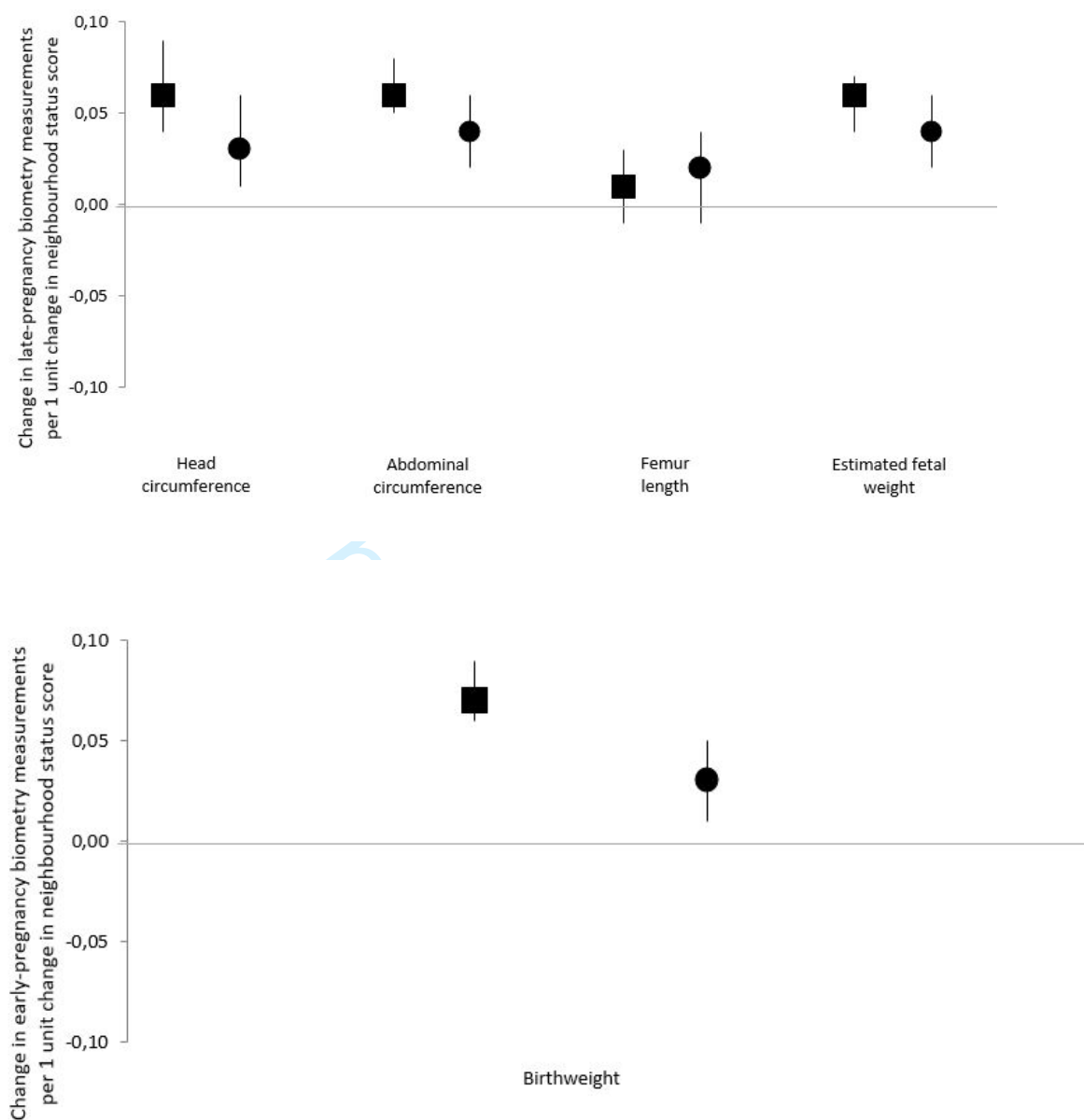
Study population	Nulliparous n = 8617		Multiparous, no complications previous pregnancy N = 3166		Multiparous, complications previous pregnancy N = 606	
	Trend		Trend		Trend	
	β /OR (95% CI)	p-value for trend	β /OR (95% CI)	p-value for trend	β /OR (95% CI)	p-value for trend
Early pregnancy						
CRL	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

32 Abbreviations: β : beta; CRL: crown-rump length; HC: head circumference; FL: femur length; AC: abdominal circumference; EFW: estimated fetal weight.
 33 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:
 34 adjusted for maternal age, educational level, smoking, alcohol use, folic acid supplement use, ethnicity, parity, pre-pregnancy body mass index and fetal sex.
 35 p-for trend analysis with the neighbourhood deprivation as a continuous measure.

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





65 Data are SDS values (95% CI) from multilevel analyses and reflect the differences in growth
 66 characteristics in SDS's in early pregnancy, mid-pregnancy late pregnancy and birth, per 1 unit change
 67 in neighbourhood status score. Analyses with crown-rump length were based on subgroup analyses (n
 68 = 1614). Estimates are from multiple imputed data. Squares show basic model. Circles show adjusted
 69 model: basic model and additionally adjusted for maternal age, educational level, smoking, alcohol
 70 use, folic acid supplement use, ethnicity, parity, pre-pregnancy body mass index and fetal sex.

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

72 **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

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77 **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

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80 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

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83 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.
84

	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

85 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
86 regression models. Basic model: by the use of SD scores it is automatically adjusted for gestational age. Fully adjusted model: basic model and additionally
87 adjusted for maternal age, educational level, smoking, alcohol use, folic acid supplement use, ethnicity, parity, pre-pregnancy body mass index and fetal sex.
88 p-for trend analysis with the neighbourhood deprivation as a continuous measure. ¹Differences between groups were evaluated using one-way-ANOVA-tests
89 for continuous variables. ²Differences in growth parameters between the lowest and highest neighbourhood status score groups were tested were evaluated
90 using Student’s t-tests.

91 **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)	<i>Reference</i>	-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)	<i>Reference</i>	-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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	-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)	<i>Reference</i>	-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)	<i>Reference</i>	0.04 (0.02 ; 0.05)	<0.001

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	Adjusted	-0.09 (-0.16 ; -0.01)	-0.11 (-0.18 ; -0.04)	-0.06 (-0.12 ; 0.01)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	0.01 (-0.01 ; 0.03)	0.19
<hr/>							
Late pregnancy							
HC	Basic	-0.22 (-0.29 ; -0.16)	-0.24 (-0.31 ; -0.18)	-0.09 (-0.16 ; -0.03)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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.** 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)

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

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3 101 **Supplemental 1.** Multiple imputations for missing data of covariates.
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5 102 We imputed missing data of the covariates using multiple imputations (17). The percentages of
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7 103 missing values for the confounders within the population for analysis were lower than 20%. For the
8
9 104 multiple imputation, we the Markov chain Monte Carlo approach. In the imputation model, we
10 105 included all confounders, plus maternal age, ethnicity, parity and prepregnancy BMI. Furthermore, we
11 106 additionally added the studied determinants and outcomes in the imputation model as prediction
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13 107 variables only; they were not imputed themselves. Five imputed datasets were created and analyzed
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15 108 together.

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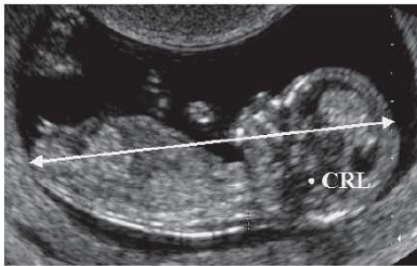
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3 **Supplemental 2.** First trimester and fetal growth, measurement guidelines.

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5 112 **CRL: crown-rump length (39)**

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7 113 CRL is measured as the largest dimension of embryo, excluding the yolk sac and extremities. A
8 114 midline sagittal section of the whole embryo or fetus should be obtained, ideally with the embryo or
9 115 fetus oriented horizontally on the screen. An image should be magnified sufficiently to fill most of the
10 116 width of the ultrasound screen, so that the measurement line between crown and rump is at about 90°
11 117 to the ultrasound beam.

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14 118 Caliper placement: measure the fetus in a neutral position (i.e. neither flexed nor hyperextended). The
15 119 end points of crown and rump should be defined clearly.



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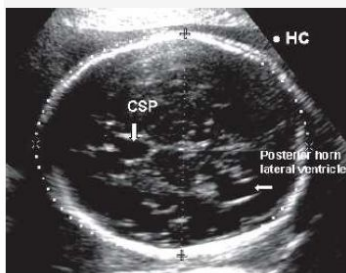
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30 123 **HC: Head circumference (40)**

31 124 As described for the BPD, ensuring that the circumference placement markers correspond to the
32 125 technique described on the reference chart.

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35 126 Caliper placement: If the ultrasound equipment has ellipse measurement capacity, then the HC can be
36 127 measured directly by placing the ellipse around the outside of the skull bone echoes.



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3 **129 AC: abdominal circumference (40)**

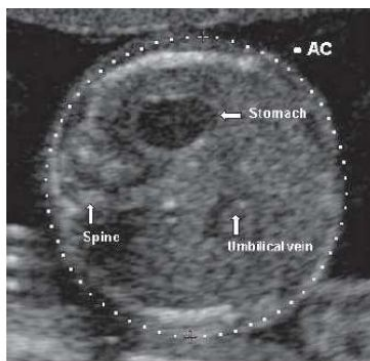
4 130 - Transverse section of the fetal abdomen (as circular as possible);

5 131 - umbilical vein at the level of the portal sinus;

6 132 - stomach bubble visualized;

7 133 - kidneys should not be visible.

8 134 Caliper placement: The AC is measured at the outer surface of the skin line, either directly with ellipse
9 135 calipers or calculated from linear measurements made perpendicular to each other, usually the
10 136 anteroposterior abdominal diameter and transverse abdominal diameter.



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30 **139 FL: femur length (40)**

31 140 The FL is imaged optimally with both ends of the ossified metaphysis clearly visible. The longest
32 141 axis of the ossified diaphysis is measured. The same technique as that used to establish the reference
33 142 chart should be used with regard to the angle between the femur and the insonating ultrasound beams.
34 143 An angle of insonation between 45° and 90° is typical.

35 144 Caliper placement: Each caliper is placed at the ends of the ossified diaphysis without including the
36 145 distal femoral epiphysis if it is visible



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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 cohort reporting guidelines, and cite them as:

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

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

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

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6	Bias	#9	Describe any efforts to address potential sources of bias 5, 6, 8
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9	Study size	#10	Explain how the study size was arrived at 4, 5
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12	Quantitative	#11	Explain how quantitative variables were handled in the 7, 8
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14	variables		analyses. If applicable, describe which groupings were
15			chosen, and why
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19	Statistical	#12a	Describe all statistical methods, including those used to
20			control for confounding
21	methods		
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25	6, 8		
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28	Statistical	#12b	Describe any methods used to examine subgroups and 7, 8
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30	methods		interactions
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33	Statistical	#12c	Explain how missing data were addressed 7, 8
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35	methods		
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39	Statistical	#12d	If applicable, explain how loss to follow-up was addressed 7, 8
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41	methods		
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44	Statistical	#12e	Describe any sensitivity analyses
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46	methods		
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53	Results		
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56	Participants	#13a	Report numbers of individuals at each stage of study—eg 9
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58			numbers potentially eligible, examined for eligibility,
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confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.

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17	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
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36	Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	
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42	Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	
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52	Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence	9, 10
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interval). Make clear which confounders were adjusted for
and why they were included

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6 Main results [#16b](#) Report category boundaries when continuous variables were 9, 10
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8 categorized
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11 Main results [#16c](#) If relevant, consider translating estimates of relative risk into
12 absolute risk for a meaningful time period
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19 Other analyses [#17](#) Report other analyses done—eg analyses of subgroups and 10, 11
20 interactions, and sensitivity analyses
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24 Discussion

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28 Key results [#18](#) Summarise key results with reference to study objectives 11
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31 Limitations [#19](#) Discuss limitations of the study, taking into account sources 12, 13
32 of potential bias or imprecision. Discuss both direction and
33 magnitude of any potential bias.
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39 Interpretation [#20](#) Give a cautious overall interpretation considering objectives, 13, 14
40 limitations, multiplicity of analyses, results from similar
41 studies, and other relevant evidence.
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46 Generalisability [#21](#) Discuss the generalisability (external validity) of the study 13
47 results
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50 Other Information

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1 Funding [#22](#) Give the source of funding and the role of the funders for the 15
2
3 present study and, if applicable, for the original study on
4
5 which the present article is based
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The association between neighbourhood deprivation, fetal growth, small-for-gestational age and preterm birth: a population-based prospective cohort study.

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3 1 **The association between neighbourhood deprivation, fetal growth, small-for-**
4 **gestational age and preterm birth: a population-based prospective cohort**
5 2 **study.**
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9 4 D.V. Gootjes^{1,3}, A.G. Posthumus^{1,3}, V.W.V Jaddoe^{2,3}, E.A.P. Steegers^{1,3}

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19 10 **The authors declare no conflict of interest.**
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2
3 21 **Abstract**
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5 22 **Objectives:** To study the associations between neighbourhood deprivation and fetal growth, including
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7 23 growth in the first trimester, and adverse pregnancy outcomes.
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10 24 **Design:** Prospective cohort study.
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13 25 **Setting:** The Netherlands, Rotterdam.
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16 26 **Participants:** 8617 live singleton births from the Generation R cohort study.
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19 27 **Exposition:** Living in a deprived neighbourhood.
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22 28 **Main outcome measures:** Fetal growth trajectories of head circumference, weight and length.
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25 29 **Secondary outcomes measures:** Small-for-gestational age (SGA) and preterm birth (PTB)).
26
27

28 30 **Results:** Neighbourhood deprivation was not associated with first trimester growth. However, a higher
29
30 31 neighbourhood status score (less deprivation), was associated with increased fetal growth in the
31
32 32 second and third trimester (e.g. estimated fetal weight (adjusted regression coefficient 0.04 (95% CI
33
34 33 0.02 ; 0.06). Less deprivation was also associated with a decreased odd of SGA (aOR 0.91 (95% CI
35
36 34 0.86 ; 0.97, p-value 0.01)) and PTB (aOR 0.89 (95% CI 0.82 ; 0.96, p-value 0.01)).
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38

39 35 **Conclusions:** We found an association between neighbourhood deprivation and fetal growth in the
40
41 36 second and third trimester pregnancy, but not with first trimester growth. Less neighbourhood
42
43 37 deprivation is associated with lower odds of adverse pregnancy outcomes. The associations remained
44
45 38 after adjustment for individual level risk factors. This supports the hypothesis that living in a deprived
46
47 39 neighbourhood acts as an independent risk factor for fetal growth and adverse pregnancy outcomes,
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49 40 above and beyond individual risk factors.
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3 41 **Article Summary**
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6 42 **Strengths and limitations of this study**
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- 9 43 • This study is performed within in a large, multi-ethnic cohort.
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12 44 • The Generation R study population is not completely representative of the Dutch population.
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15 45 • Associations were adjusted for a wide range of relevant individual level risk factors, which
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17 46 allows the isolation of a neighbourhood specific effect best as possible.
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47 Introduction

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

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

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

73 **Methods**

74 **Design**

75 This study was embedded in the Generation R (Rotterdam) Study, a population-based
76 prospective cohort study.⁽¹³⁾ Pregnant women living in the area of Rotterdam, the Netherlands, with
77 an expected delivery date between April 2002 and January 2006, were invited to participate in this
78 study. The 9778 mothers enrolled in the study gave birth to 9749 live born children. Of these mothers,
79 91% (n=8879) were prenatally enrolled in the study, giving birth to 8976 children. Our aim was to
80 investigate growth trajectories and outcomes of ongoing singleton pregnancies. We excluded the
81 following pregnancies: twin pregnancies, terminated pregnancies, intra-uterine deaths and pregnancies
82 without information on area of residence or ultrasound data (**Figure 1**). The study protocol was
83 approved by the Medical Ethical Committee of Erasmus Medical Centre, Rotterdam (MEC 198.782/
84 2001/31). Written informed consent was obtained from all participants.

85 **Patient and public involvement statement**

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

90 **Materials**

91 **Neighbourhood deprivation**

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

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3 100 pregnancies in 2005 and 2006, the status score of 2006 was assigned. For pregnancies in 2004, the
4
5 101 average score of 2002 and 2006 was assigned.
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7

8 102 **Pregnancy dating**

9 103 Gestational age is the most important determinant of fetal growth, so precise dating of the
10
11 104 pregnancy is important. It has long been assumed that embryonic growth in the first trimester of
12
13 105 pregnancy is universal. This is the rationale behind the current practice of pregnancy dating using the
14
15 106 crown-rump length (CRL), if the gestational age is less than 12 weeks and 5 days and the CRL
16
17 107 measurement is smaller than 65 mm.(15) However, study findings suggest that first trimester growth is
18
19 108 not uniform.(16) Therefore, in our analyses with CRL measurements as the outcome of interest,
20
21 109 pregnancy dating was not based on the CRL, but on the known and reliable last menstrual period
22
23 110 (LMP) in case of a regular menstrual cycle (28 ± 4 days).(6) All other cases were excluded for that
24
25 111 particular analyses of CRL. The LMP was obtained from the referral letter and confirmed at
26
27 112 enrolment. Additional information on regularity and cycle duration was obtained through
28
29 113 questionnaires. When the gestational age was more than 12 weeks and 5 days, or the biparietal
30
31 114 diameter (BPD) was larger than 23 mm, pregnancy dating was performed using the BPD.
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35 115 **Growth parameters and adverse pregnancy outcomes**

36 116 The aim of the study was to focus on fetal outcomes, in terms of growth and development. The
37
38 117 selected outcomes were carefully chosen from the 'Big 4 conditions', which are specifically defined
39
40 118 conditions that precede perinatal mortality in 85 % of all cases, namely: small for gestational age
41
42 119 (birth weight < 10th percentile for gestational age), preterm birth (birth < 37 weeks of gestation),
43
44 120 congenital disorders, and/or low Apgar score (<7 after 5 min).(17, 18) Due to the low numbers of
45
46 121 cases with congenital disorders within the Generation R population, and susceptibility for Apgar score
47
48 122 to be affected by the course of delivery which may confound the effect of neighbourhood deprivation
49
50 123 during pregnancy, we selected the other 2 major morbidity factors as outcome for this study.
51
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53 124 Ultrasound assessments were carried out during visits to one of the research centres, and took
54
55 125 place in early- (median 13.2 weeks of gestation), mid- (median 20.5 weeks of gestation) and late
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57 126 (median 30.3 weeks of gestation) pregnancy. Growth parameters included the CRL, head
58
59 127 circumference (HC), femur length (FL), abdominal circumference (AC), estimated fetal weight (EFW)
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1
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3 128 and birthweight. EFW was calculated using the Hadlock formula with parameters AC, HC and FL (in
4
5 129 cm): $EFW = 10^{(1.326 - 0.00326*AC*FL + 0.0107*HC + 0.0438*AC + 0.158*FL)}$ (**Supplemental**
6
7 130 **1. First trimester and fetal growth, measurement guidelines**).(19) Gestational age adjusted
8
9 131 standard deviation scores (SDS) were constructed for all growth measurements.(20) The SDS for
10
11 132 birthweight were constructed using growth standards from Niklasson et al., which were adjusted for
12
13 133 gestational age at the time of birth and sex of the neonate.(21) Measurements were performed using
14
15 134 uniform ultrasound procedures and were executed with the Aloka® model SSD-1700 (Tokyo, Japan)
16
17 135 or the ATL-Philips Model HDI 5000 (Seattle, WA, USA). Reproducibility of these measurements was
18
19 136 assessed and described previously.(22, 23)

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21
22 137 Small size for gestational age (SGA) at birth was defined as a sex and gestational age adjusted
23
24 138 birth weight below the 10th percentile (<-1.40 SDS) in the study cohort. Preterm birth (PTB) was
25
26 139 defined as a gestational age of <37 weeks at delivery.

29 140 **Covariates**

30 141 Information on maternal age, education level, ethnicity, and maternal folic acid supplement
31
32 142 use was obtained at enrolment.(13) All study materials such as questionnaires, newsletters, website,
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34 143 and information folders are available in three languages (Dutch, English, and Turkish). Furthermore,
35
36 144 staff from different ethnic backgrounds was available and verbally translated these materials into
37
38 145 Arabic, French and Portuguese. As such, the study staff was able to communicate with all participants.

39
40
41 146 Ethnicity of participating mothers was defined according to the classification of Statistics
42
43 147 Netherlands, and was categorized into Dutch and other Western (European, American, and Oceanian);
44
45 148 Turkish and Moroccan; African (Cape Verdean, other African, Surinamese-Creole, and Dutch
46
47 149 Antillean); and Asian (Indonesian, other Asian, and Surinamese-Hindu) according to the largest ethnic
48
49 150 groups in our study population and similarities in skin colour and cultural background. In sensitivity
50
51 151 analyses, the following classification was used: Dutch, European, Turkish, Moroccan, African, Dutch
52
53 152 Antillean, Cape Verdean, Indonesian, Surinamese-Creole, Surinamese-Hindu, Surinamese-
54
55 153 unspecified, American Western, American non Western, Asia Western, Asia non Western and
56
57 154 Oceanian.(13) Information about smoking, alcohol consumption, and caffeine intake was assessed by
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3 155 questionnaires in each trimester. Maternal pre-pregnancy body mass index was calculated from the
4
5 156 reported height (cm) and weight (kg) in the questionnaires. Information about pregnancy
6
7 157 complications, mode of delivery and childhood sex, gestational age, and weight and length at birth was
8
9 158 obtained from medical records.(20, 21) Complications in a previous pregnancy were defined as:
10
11 159 gestational diabetes, pre-eclampsia, thrombosis in arm or leg, pulmonary embolism, solutio placentae,
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13 160 premature rupture of membranes, contractions before 37 weeks of pregnancy or pregnancy induced
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15 161 hypertension. We selected potential confounding variables based on their associations with the
16
17 162 outcomes of interest, in order to isolate a neighbourhood specific effect.
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21 163 **Statistical analysis**

22 164 First, we examined differences between quartiles of neighbourhood deprivation for maternal
23
24 165 characteristics, first trimester growth and fetal growth and adverse pregnancy outcomes. Second, we
25
26 166 examined the associations of neighbourhood deprivation with fetal growth patterns using unbalanced
27
28 167 repeated measurement regression models.(24) We included neighbourhood deprivation in these
29
30 168 models as intercept and as interaction term with gestational age to estimate fetal growth rates over
31
32 169 time.(24) Third, we assessed the associations of neighbourhood deprivation with the risks of adverse
33
34 170 pregnancy outcomes using multiple logistic regression models. In the basic model, the crude
35
36 171 association between neighbourhood deprivation and the outcomes of interest were investigated. The
37
38 172 adjusted model was adjusted for maternal age, maternal educational level, smoking, alcohol use, folic
39
40 173 acid supplement use, ethnicity, parity, pre-pregnancy BMI and fetal sex. We tested interaction between
41
42 174 neighbourhood deprivation and complications in previous pregnancy in the regression models. Fourth,
43
44 175 we examined the associations of neighbourhood deprivation with fetal growth in gestational-age-
45
46 176 adjusted SDS in each pregnancy period using linear regression models with the same adjustment
47
48 177 models. We performed several sensitivity analyses: in the first, we performed multilevel regression
49
50 178 analysis in order to adjust for potential clustering between the different neighbourhoods. In the second,
51
52 179 we repeated the analyses with all 1614 available CRL measurements, compared to the analyses with
53
54 180 only CRL measurements below the 12 weeks of gestational age (GA).(6, 22) A third sensitivity
55
56 181 analysis was performed to determine to which extent the inclusion of pregnancies with an impaired
57
58 182 fetal development due to placental dysfunction influenced our results. Therefore we performed
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60

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3 183 analyses excluding SGA born babies. Fourth, analyses were additionally adjusted for the household
4
5 184 income. Also, we repeated the analyses with the different classification of ethnicity, described in the
6
7 185 ‘Covariates’ section. Lastly, we checked whether the presence of maternal hypertensive disorders
8
9 186 affected the analyses on SGA.

11 187 Our main outcome was the fetal growth, in terms of head circumference, length and weight.
12
13 188 Post-hoc power for 0.1 SD difference in fetal growth with an alpha of 0.05 for a study group of 8000
14
15 189 (this study population 8617) participants is 99.4%. We used multiple imputation for missing values of
16
17 190 covariates according to Markov Chain Monte Carlo method (details given in **Supplemental 2**).⁽²⁵⁾
18
19 191 The percentage of missing data was <10%, except for smoking (12.7%), alcohol use (13.8%) and folic
20
21 192 acid supplement use (25.9%). Five imputed datasets were created and pooled for analyses. A
22
23 193 sensitivity analysis was performed to observe differences in observed and expected values of
24
25 194 confounders before and after imputation. Tests for trend were based on regression models with
26
27 195 neighbourhood deprivation as a continuous variable. We checked whether the regression models were
28
29 196 linear using scatterplots of the dependent variable plotted against the independent variable.⁽²⁶⁾
30
31 197 Residuals were normally distributed as assessed by visual inspection of a normal probability plot. We
32
33 198 tested for multicollinearity using the tolerance statistic. As tolerance was >0.20 for all variables in our
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35 199 models, there were no problems of multicollinearity. The repeated measurement analysis was
36
37 200 performed using the Statistical Analysis System version 9.3 (SAS, Institute Inc., Cary, NC, USA),
38
39 201 including the Proc Mixed module for unbalanced repeated measurements. All other analyses were
40
41 202 performed using the Statistical Package of Social Sciences version 21.0 for Windows (IBM Corp.,
42
43 203 Armonk, NY, USA).

204 Results

51 205 A total of 8976 pregnancies were included in the Generation R study. In total, we included
52
53 206 8617 pregnancies for analyses (**Figure 1**). **Table 1** depicts the baseline characteristics of both the total
54
55 207 study population and the population stratified according to the quartiles of neighbourhood deprivation.
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57 208 Women in the total study population were on average 29.6 years old with a median BMI of 22.8
58
59 209 kg/m². Stratification of the population in deprivation quartiles revealed that 2170 women (25.2%)

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3 210 lived in a neighbourhood with the most deprivation, i.e. lowest status score, and 2149 (24.9%) lived in
4
5 211 the least deprived neighbourhoods, i.e. the highest status score. When comparing women in the most
6
7 212 deprived neighbourhoods to those in the least deprived neighbourhoods, less women were highly
8
9 213 educated (23.7% vs. 62.8% ($p<0.001$)), more women continued smoking in pregnancy (22.3% vs.
10
11 214 11.9% ($p<0.001$)) and less women used any folic acid supplements (20.0% vs. 49.7% respectively
12
13 215 ($p<0.001$)) (**Table 1**). In **Supplemental Table 1** the fetal growth parameters and adverse pregnancy
14
15 216 outcomes stratified by quartile of neighbourhood deprivation are presented. Overall, growth
16
17 217 parameters are smaller in the most deprived neighbourhoods compared to the least deprived
18
19 218 neighbourhoods (e.g. -0.07 SD vs. 0.15 SD, EFW in the third trimester of pregnancy, respectively).

219 **Neighbourhood deprivation and fetal growth**

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

227 The associations of neighbourhood deprivation with first trimester and second and third
228 trimester fetal growth based on regular linear regression models are given in **Supplemental Figure 1**.
229 In both the basic and adjusted analyses, a positive association between neighbourhood deprivation and
230 AC was present (difference in AC in the adjusted model, 0.03 SDS [95% CI 0.01, 0.05, P-value 0.002]
231 per 1 unit increase in neighbourhood status score). In the third trimester of pregnancy a positive
232 association was found for the HC, AC and EFW (adjusted model difference of 0.04 SDS [95% CI
233 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
234 0.03, 0.06, P-value <0.001] per 1 unit increase in neighbourhood status score, respectively). Overall,
235 there is a dose-response like association between neighbourhood deprivation and fetal growth, with
236 stronger associations in the most deprived neighbourhoods compared to the least deprived
237 neighbourhoods.

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3 238 Effect modification analyses showed significant interaction between neighbourhood
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5 239 deprivation and complications in previous pregnancies for PTB (**Supplemental Table 3**). The
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7 240 associations between neighbourhood deprivation and fetal growth and adverse pregnancy outcomes
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9 241 were non-significant in the group with a complication in a previous pregnancy (e.g. HC in late
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11 242 pregnancy attenuates from 0.06 SDS [95%CI 0.05 , 0.08, P-value <0.001] to 0.03 SDS [95%CI -0.05 ,
12
13 243 0.11, P-value 0.50] per 1 unit increase in neighbourhood status score) (**Supplemental Table 4**).

15 244 **Neighbourhood deprivation and adverse pregnancy outcomes**

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18 245 Results of the regression analysis between neighbourhood deprivation and adverse pregnancy
19
20 246 outcomes are presented in **Table 2**. Living in a more affluent neighbourhood was inversely associated
21
22 247 with the odds of delivering a SGA neonate (adjusted model, OR 0.91 [95% CI 0.86, 0.97, P-value
23
24 248 0.01], independent of maternal sociodemographic or lifestyle factors. Moreover, it was inversely and
25
26 249 independently associated with the odds of PTB (adjusted model, OR 0.89 [95% CI 0.82, 0.96, P-value
27
28 250 0.01]. The adverse pregnancy outcomes were most prevalent in the neighbourhood with the lowest
29
30 251 deprivation status compared to the neighbourhood with the highest social status (SGA: 12.2% vs.
31
32 252 7.1%, PTB: 5.9% vs. 3.8%) (**Supplemental Table 1**).

34 253 **Sensitivity analyses**

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36 254 The first sensitivity analyses revealed largely similar associations after performing multilevel
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38 255 analyses (**Supplemental Figure 2**). Second, the results of the associations between neighbourhood
39
40 256 deprivation and CRL did not change after including all CRL measurements, in comparison to only the
41
42 257 CRL measurements below 12 weeks GA (**Supplemental Table 5**). The third sensitivity analyses
43
44 258 excluding SGA pregnancies did attenuate the results (**Supplemental Table 6**). Results also did not
45
46 259 materially change after other sensitivity analyses in which we additionally adjusted for the household
47
48 260 income or adjusted with a different classification of ethnicity (**Supplemental Table 7 and 8**). Results
49
50 261 did not materially change for SGA analyses, when adjusting for maternal hypertension in pregnancy
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52 262 (**Supplemental Table 9**). No major differences were observed in confounders before and after
53
54 263 multiple imputation (**Supplemental Table 10**).

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265 Discussion

266 Main findings

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

270 Strengths and limitations

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

286 Some limitations of this study also merit discussion. First, this data with regard to residency
287 and pregnancy are over 15 years old, since the Generation R study is an ongoing birth cohort. The
288 methods of measuring fetal growth are according to standardized measurement methods, that are being
289 used still. No doubt, there is the possibility that the status of different neighbourhoods are changed
290 until now. However, no large differences are to be expected. Additionally, both exposure data
291 (neighbourhood deprivation) and outcome data (fetal growth and pregnancy outcomes) are determined
292 in short succession. Second, we did not use nutritional data from semi quantitative self-administrated

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3 293 food frequency questionnaires, since this FFQ is only validated pregnant women with Dutch ethnic
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5 294 background, which would have diminished the power and external validity of the study. We chose not
6
7 295 to adjust for nutritional factors other than alcohol intake and folic acid supplement use, since alcohol
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9 296 intake and folic acid supplement use are strongly correlated with other lifestyle and nutritional
10
11 297 habits.(30, 31) Third, we adjusted the analyses for individual factors, to isolate a neighbourhood
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13 298 specific effect. However, we cannot rule out the presence of residual confounding caused by other
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15 299 individual factors that are strongly associated with fetal growth. Next, possible misclassification of
16
17 300 neighbourhood deprivation may have occurred if women moved during pregnancy to a neighbourhood
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19 301 with a different status score from the one they moved out of. However, social mobility in pregnancy is
20
21 302 limited and if women move, they generally tend to move to a neighbourhood with a comparable
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23 303 deprivation status.(32) Also, income of undeclared work is not taken into account in the area based
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25 304 classification of neighbourhood status scores, while 13% of Dutch residents do or did any form of
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27 305 undeclared work.(33)

30
31 306 Sixth, the power of the analyses on CRL are lower due to the availability of only one CRL
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33 307 measurement, instead of a repeated assessment of the CRL. A last disadvantage is that participants of
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35 308 cohort studies, even those in more deprived neighbourhoods, generally have a higher level of health
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37 309 awareness and are generally more healthy compared to those who do not participate.(13) This may
38
39 310 reduce the generalizability of our findings to the general population.

40
41 311 Several pathways may explain the disadvantageous effects of living in a deprived
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43 312 neighbourhood on pregnancy.(34) First, it is proposed to be due to the accumulation of risk factors at
44
45 313 the individual level.(5) Examples are smoking and inadequate nutrition and lifestyle behaviours.(9)
46
47 314 Neighbourhood deprivation then acts as a proxy for the increased prevalence of risk factors within the
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49 315 deprived neighbourhoods. Our findings are substantiated by earlier studies within the Generation R
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51 316 birth cohort, that demonstrate that living in a deprived neighbourhood is accompanied by the
52
53 317 accumulation of individual level risk factors. These in turn were associated with adverse pregnancy
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55 318 outcomes.(5) However, we observe that even after correction for the individual level risk factors, the
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57 319 association between neighbourhood deprivation and impaired development and adverse pregnancy
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59 320 outcomes remained, emphasizing an isolated role for neighbourhood deprivation as a risk factor for

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3 321 pregnancy. The associations between neighbourhood deprivation and fetal growth and adverse
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5 322 pregnancy outcomes attenuated to non-significance in the population affected by a complication in a
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7 323 previous pregnancy. These complications, and the maternal constitution for the development of it, may
8
9 324 thus outweigh the contribution of neighbourhood deprivation in the associations with fetal growth and
10
11 325 adverse pregnancy outcomes. This may be due to the fact that past complications in pregnancy are
12
13 326 strongly associated with both neighbourhood deprivation and fetal growth and adverse pregnancy
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15 327 outcomes.(35). A second pathway which may explain the disadvantageous effects of living in a
16
17 328 deprived neighbourhood on adverse pregnancy outcomes is attributed to the lack of or suboptimal
18
19 329 access to facilities such as the possibility to purchase healthy food nearby.(36) Third, living in a
20
21 330 deprived neighbourhood is acknowledged as a source of chronic stress, and thereby acts as an
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23 331 independent risk factor for adverse health outcomes.(34, 37) Stress is associated with increased
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25 332 cortisol levels, and both prolonged or repeated cortisol exposure increases the risk for impaired
26
27 333 physical health.(38) Also with regard to pregnancy, stress is demonstrated to be harmful since
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29 334 maternal stress during pregnancy is associated with preterm birth, lower birthweight and the onset of
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31 335 preeclampsia and gestational diabetes.(12, 39)

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34 336 Our data demonstrates that the associations between neighbourhood deprivation and fetal
35
36 337 growth become stronger over the course of pregnancy. This may be due to the fact that there are
37
38 338 different mechanisms by which external factors -such as environmental, nutritional and lifestyle
39
40 339 factors- affect the developing fetus over the different trimesters of pregnancy. In the first trimester of
41
42 340 pregnancy the embryo depends on the uterine glands and yolk sac for the provision of nutrients, while
43
44 341 in the subsequent periods of pregnancy there is an exchange of nutrients between the maternal and
45
46 342 fetal circulations across the placenta.(40) The more isolated source of nutrition in the first trimester
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48 343 compared to the second and third trimester of pregnancy may decrease the sensitivity of first trimester
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50 344 embryonic growth to external influences.

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53 345 A previous study of our group, observed a negative association between neighbourhood
54
55 346 deprivation and first trimester growth. The larger embryos in deprived neighbourhoods were
56
57 347 hypothesized to be explained by strong unmeasured intrinsic and extrinsic factors, such as mental
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59 348 stressors.(41) The difference in direction of effects between that study and our current findings, may

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3 349 be due to the different source populations; the first study was conducted in a tertiary-hospital based
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5 350 cohort, while the present study is performed within a population-based cohort.
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8 351 **Future perspectives**

9 352 In future studies, a potential power issue due to the small measurement differences in first
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11 353 trimester growth measurements may be prevented by using larger study sample sizes. Moreover more
12
13 354 accurate measures of early fetal growth with higher quality ultrasound could increase the variability of
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15 355 the measurements which enables detection of very small differences. Additionally, animal studies may
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17 356 help unravel the underlying mechanisms through which neighbourhood deprivation affect pregnancy.
18
19 357 For instance, by further investigating how maternal stress affects placental nutrient transport.
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21 358 Moreover, additional research on the pathways between neighbourhood deprivation and fetal growth
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23 359 and pregnancy outcomes could be performed.
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26 360 Although the magnitude of our findings is somewhat small, the results of this study suggest an
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28 361 isolated risk for living in a deprived neighbourhood. This emphasizes the importance of policies that
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30 362 promote healthier neighbourhoods. This could be achieved by targeted population-level interventions.
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32 363 A review has demonstrated many area-based initiatives that have been implemented in deprived areas
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34 364 across Western-Europe already.(42) Initiatives may consist of interventions that aim to tackle the
35
36 365 various problems in deprived areas, with regard to the physical (more walkable neighbourhoods,
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38 366 increasing green environments, reducing air pollution and the reduction of litter.) and social domain
39
40 367 (lowering crime rates, vandalism).(43) Small effects of these interventions may be expected in terms
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42 368 of differences in fetal growth and birthweight. Though some very small individual effects may still
43
44 369 have clinical and public health relevance, e.g. when they affect a large segment of the population, or
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46 370 when a small effect has long term implications, as is the case with birthweight.
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49 371 In the Netherlands, in both the prenatal and postnatal setting, screening for non-medical risk
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51 372 factors is starting to become part of daily medical practice.(44, 45) This allows early interventions in
52
53 373 order to prevent developmental problems of children in later life. However, we propose a shift of
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55 374 attention towards an earlier window of opportunity: the preconception period and first trimester of
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57 375 pregnancy. This periconception period provides the opportunity to optimize the conditions of
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3 376 pregnancy and thereby decrease the risks of adverse outcomes and all their long-term
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5 377 consequences.(46)

6
7 378 Additionally, it is important to create more awareness among politicians, policymakers and
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9 379 public health workers. They could help to embed neighbourhood deprivation in the context of health
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11 380 promotion, by developing and promoting targeted preventive intervention programs.(47) These
12
13 381 programs could specifically focus on residents of deprived neighbourhoods. It is important to stimulate
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15 382 these residents to diminish risk factors on the individual level, for instance to quit smoking and abstain
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17 383 from alcohol. This could also help to narrow health inequalities between neighbourhoods and between
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19 384 groups of different socioeconomic status.
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24 385 **Conclusion**

25
26 386 In conclusion, we observed a negative association between neighbourhood deprivation, fetal
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28 387 growth and prematurity. This emphasizes the need for a comprehensive research, care and policy
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30 388 approach from the preconception phase onwards, to mitigate the risk of adverse pregnancy outcomes
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32 389 due to deprivation.
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17

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19
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23
24 400 the data, revisions and gave input at all stages of the study. All authors have approved the final version
25
26 401 of the manuscript.
27

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42

43
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45

46
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48

49
50 411 **Patient consent for publication:** Not required.
51

52
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54
55 413 Medical Centre in Rotterdam on December 17th 2001 (MEC 198.782/2001/31). Written consent was
56
57 414 obtained from all participants.
58

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60 415 **Data availability statement** Data requests can be made to the secretariat of Generation R.

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3 421 **Tables and figures**
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6 422 **Figure 1. Flowchart of the study population.**
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9 423 **Figure 2. Associations of neighbourhood deprivation with fetal growth.**
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12 424 **Table 1. Baseline characteristics of the study population, stratified for quartiles of the**
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14 425 **neighbourhood status score.**
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17 426 **Table 2. Associations between the neighbourhood status score and adverse pregnancy outcomes.**
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3 **427 Supplemental material**
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6 **428 Supplemental Table 1. Fetal growth and adverse pregnancy outcomes in the study population,**
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8 **429 stratified for quartiles of the neighbourhood status score.**
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11 **430 Supplemental Table 2. Regression coefficients of longitudinal associations between quartiles of**
12
13 **431 neighbourhood deprivation with fetal growth patterns.**
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16 **432 Supplemental Table 3. P-value of interaction terms (neighbourhood deprivation * parity and**
17
18 **433 neighbourhood status score * complications in a previous pregnancy).**
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21 **434 Supplemental Table 4. Associations between the neighbourhood SES and fetal growth and**
22
23 **435 adverse pregnancy outcomes, split for nulliparous women, multiparous women without a**
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25 **436 complications in a previous pregnancy or multiparous women with a complications in a previous**
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27 **437 pregnancy.**
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30 **438 Supplemental Table 5. Sensitivity analysis with all available CRL measurements in the study**
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32 **439 population.**
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35 **440 Supplemental Table 6. Associations between the neighbourhood SES and fetal growth in a**
36
37 **441 selected cohort of non-SGA pregnancies.**
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40 **442 Supplemental Table 7. Associations between the neighbourhood status score and fetal growth,**
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42 **443 additionally adjusted for household income.**
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45 **444 Supplemental Table 8. Associations between the neighbourhood status score and fetal growth,**
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47 **445 adjusted for different classification of ethnicity.**
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50 **446 Supplemental Table 9. Associations between the neighbourhood status score and SGA pregnancies,**
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52 **447 adjusted for maternal hypertension.**
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54 **448 Supplemental Table 10. Observed and expected values of covariates.**
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57 **449 Supplemental Figure 1. Associations between the neighbourhood deprivation and fetal growth**
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59 **450 parameters.**
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3 451 **Supplemental Figure 2. Multilevel regression analysis of associations between neighbourhood**
4 **deprivation and first trimester and fetal growth measurements.**

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7 453 **Supplemental 1. First trimester and fetal growth, measurement guidelines.**

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10 454 **Supplemental 2. Multiple imputations for missing data of covariates**

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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%)	1233 (56.8%)	1343 (60.8%)	118 (5.6%)	112 (5.2%)	
>18.5 and ≤25 kg/m ²	5436 (63.0%)	815 (37.6%)	726 (32.9%)	1315 (62.9%)	1546 (71.9%)	
>25 kg/m ²	2689 (31.3%)			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						

1							
2							
3	pregnancy	4351 (50.5%)	1436 (66.2)	1200 (54.4)	990 (47.4)	726 (33.8)	
4	Alcohol consumption until	1149 (13.3%)	220 (10.1)	239 (10.8)	335 (16.0)	354 (16.5)	
5	pregnancy was known	3117 (36.2%)	514 (23.7)	769 (34.8)	765 (36.6)	1069 (49.7)	
6	Continued alcohol						
7	consumption in pregnancy						
8							
9	Folic acid supplement intake						<0.001
10	None	2751 (31.9%)	1141 (52.6)	843 (38.2)	534 (25.6)	233 (10.8)	
11	Start in first 10 weeks of	2661 (30.9%)	594 (27.4)	703 (31.8)	650 (31.1)	714 (33.2)	
12	pregnancy	3205 (37.2%)	435 (20.0)	662 (30.0)	906 (43.3)	1202 (55.9)	
13	Start preconceptionally						
14	Hypertension						0.11
15	Pregnancy induced	311 (3.6%)	69 (3.2%)	80 (3.6%)	74 (3.5%)	88 (4.1%)	
16	hypertension	142 (1.6%)	54 (2.5%)	36 (1.6%)	29 (1.4%)	23 (1.1%)	
17	Pre-eclampsia	29 (0.3%)	4 (0.2%)	9 (0.4%)	8 (0.4%)	8 (0.4%)	
18	HELLP						
19	Gestational diabetes	89 (1.0%)	21 (1.0%)	32 (1.4%)	24 (1.1%)	12 (0.6%)	0.03
20	Birth weight						<0.01
21	≤2500 grams	431 (5.0%)	118 (5.4%)	135 (6.1%)	110 (5.3%)	68 (3.2%)	
22	>2500 grams and ≤4000	7017 (81.4%)	1815 (83.6%)	1786 (80.9%)	1683	1733 (80.6%)	
23	grams	1169 (13.6%)	237 (11.0%)	287 (13.0%)	(80.5%)	348 (16.2%)	
24	>4000 grams				297		
25					(14.2%)		
26	Gestational age at delivery						0.01
27	<37 weeks gestational	492 (5.7%)	134 (6.2%)	152 (6.9%)	117 (5.6%)	89 (4.1%)	
28	age	7697 (89.3%)	1937 (89.3%)	1947 (88.2%)	1859	1954 (90.9)	
29	.37-42 weeks gestational	428 (5.0%)	99 (4.5%)	109 (4.9%)	(88.9%)	106 (5.0%)	
30	age				114 (5.5%)		
31	>42 weeks gestational						
32	age						
33	Complications in a previous	606 (7.0%)	153 (7.1%)	149 (6.7%)	132 (6.3%)	172 (8.0%)	0.13
34	pregnancy						
35	Betal sex (male)	4347 (50.4)	1063 (49.0)	1147 (51.9)	1066 (51.0)	1071 (49.8)	0.22

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

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

Study population	Model	Lowest deprivation quartile	Second deprivation quartile	Third deprivation quartile	Highest deprivation quartile				
n = 8617		n = 2277	n = 2123	n = 2084	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%)	<i>Reference</i>
	Adjusted		1.39 (1.09 ; 1.77)		1.14 (0.90 ; 1.44)		1.13 (0.90 ; 1.42)		<i>Reference</i>
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%)	<i>Reference</i>
	Adjusted		1.52 (1.11 ; 2.09)		1.65 (1.23 ; 2.22)		1.32 (0.97 ; 1.77)		<i>Reference</i>

462 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
463 model: by the use of SD scores it is automatically adjusted for gestational age. Adjusted model: basic model and additionally adjusted for maternal age,
464 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
465 neighbourhood deprivation as a continuous measure. Small size for gestational age (SGA) at birth was defined as a sex and gestational age adjusted
466 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.

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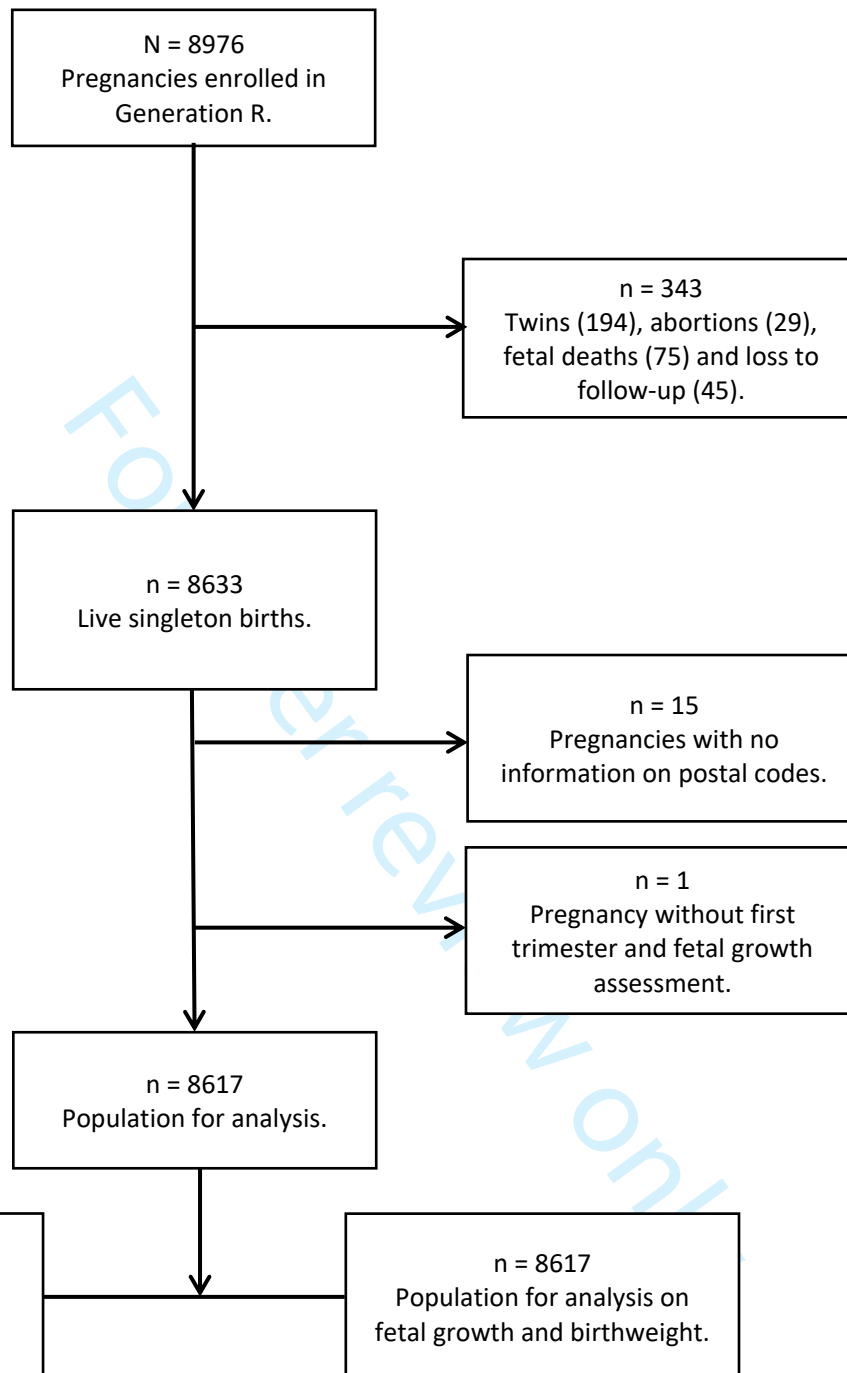
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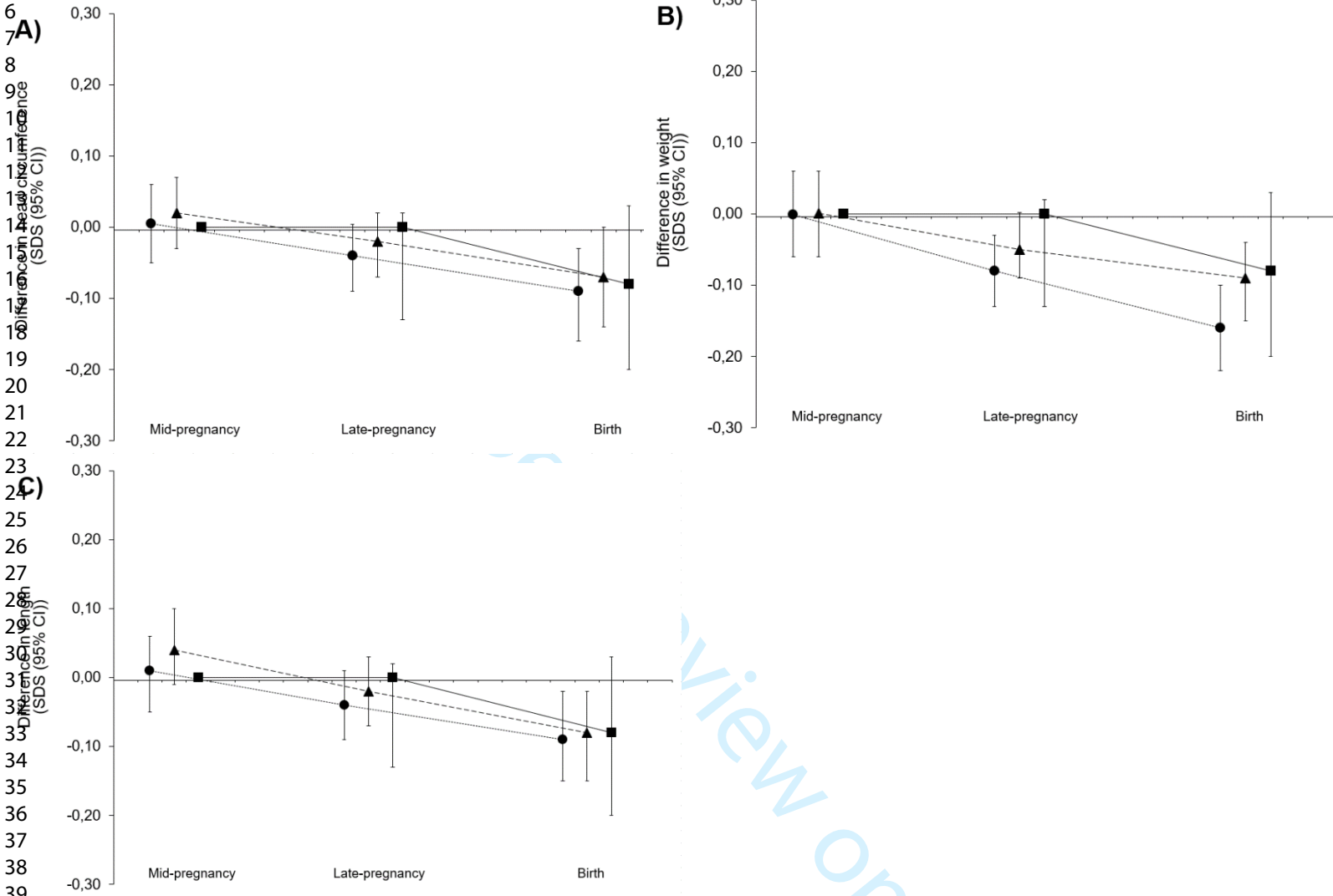
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3 **Figure 1.** Flowchart of the study population.
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Figure 2. Associations of neighbourhood deprivation with fetal growth.

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.

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

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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

3 Abbreviations: SD: standard deviation. HC: head circumference. FL: femur length. AC: abdominal circumference. EFW: estimated fetal weight. Values
4 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-
5 square tests for proportions. ²Differences in growth parameters between the lowest and highest neighbourhood status score groups were tested were evaluated
6 using Student’s t-tests. Percentages are valid percentages.

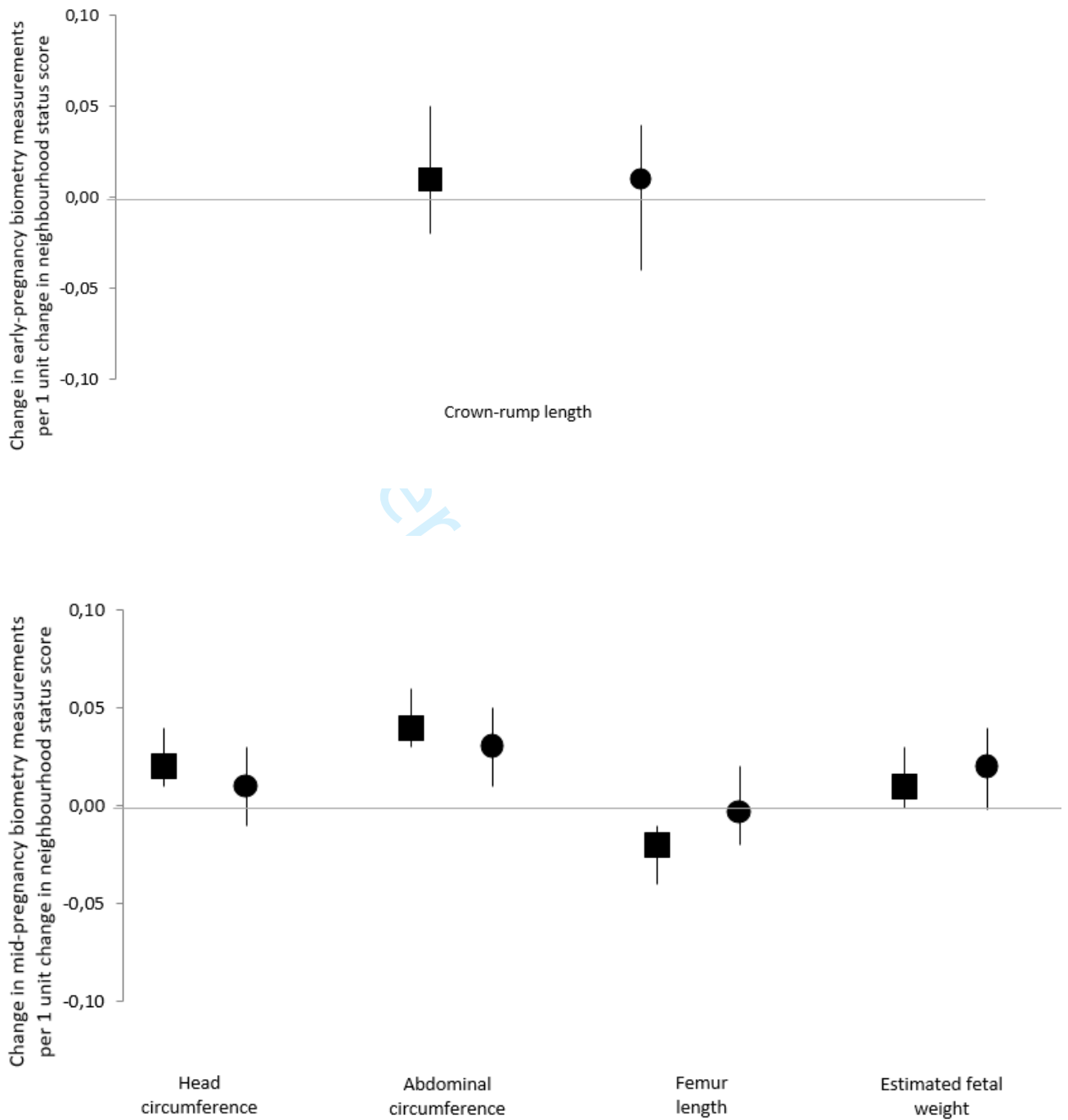
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8 **Supplemental Table 2. Regression coefficients of longitudinal associations between quartiles of neighbourhood deprivation with fetal growth**
 9 **patterns.**

	Intercept	Slope	Intercept	Slope	Intercept	Slope
	Head circumference	Head circumference	Length	Length	Weight	Weight
	(SDS)	(SDS)	(SDS)	(SDS)	(SDS)	(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.

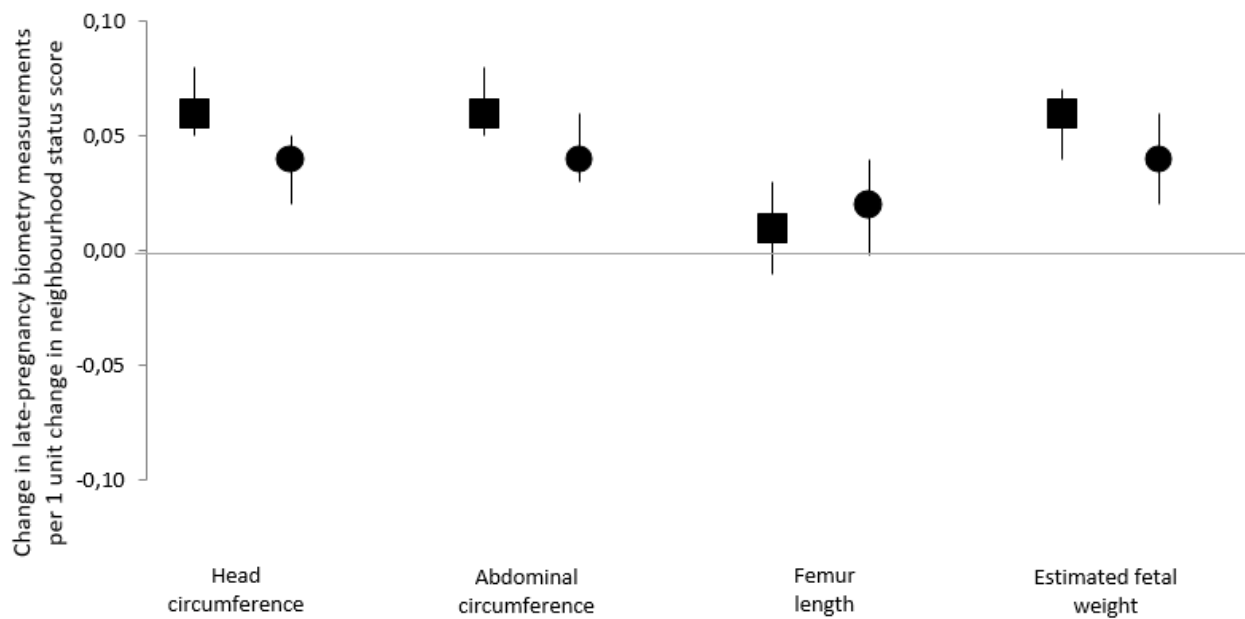
10 Values are regression coefficients obtained from linear repeated measurement models and reflect the (gestational) age independent differences (intercepts) and
 11 the gestational age dependent differences (slopes: change in growth characteristics SDS per week per quartile of the neighbourhood deprivation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

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

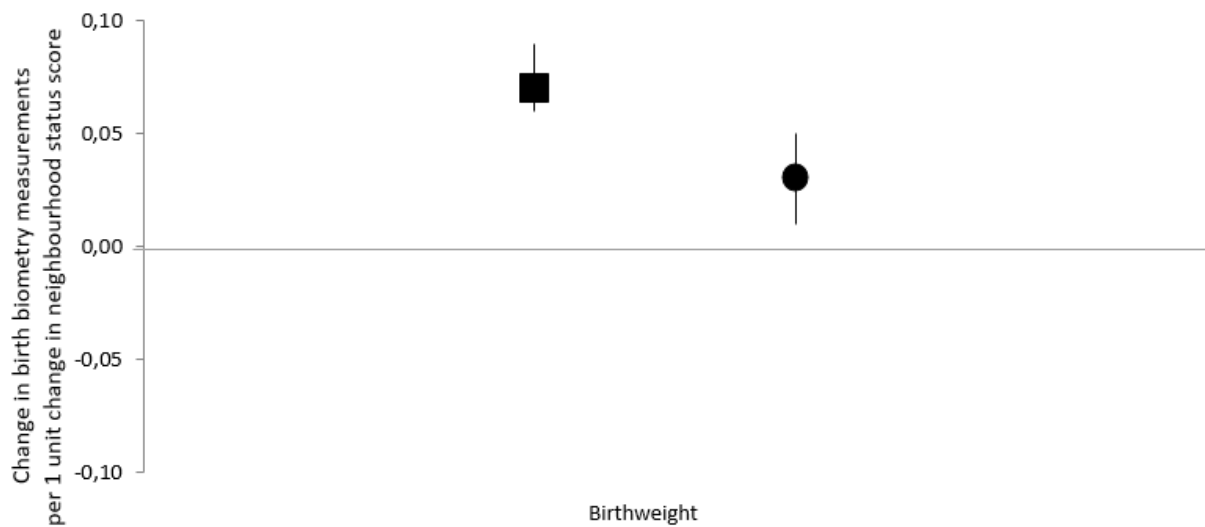


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19 Data are SDS values (95% CI) from linear regression models that reflect the differences in growth
 20 characteristics in SDS's in early pregnancy, mid-pregnancy late pregnancy and birth, per 1 unit change
 21 in neighbourhood status score. Analyses with crown-rump length were based on subgroup analyses (n
 22 = 1614). Estimates are from multiple imputed data. Squares show basic model; circles show the
 23 adjusted model: basic model and additionally adjusted for maternal age, educational level, smoking,
 24 alcohol use, folic acid supplement use, ethnicity, parity, pre-pregnancy body mass index and fetal sex.

25 **Supplemental Table 3.** P-value of interaction terms (neighbourhood deprivation * parity and
 26 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

27 Abbreviations: β : beta; CRL: crown-rump length; HC: head circumference; FL: femur length; AC:
 28 abdominal circumference; EFW: estimated fetal weight. Values are based on the adjusted linear and
 29 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	Nulliparous n = 8617		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

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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

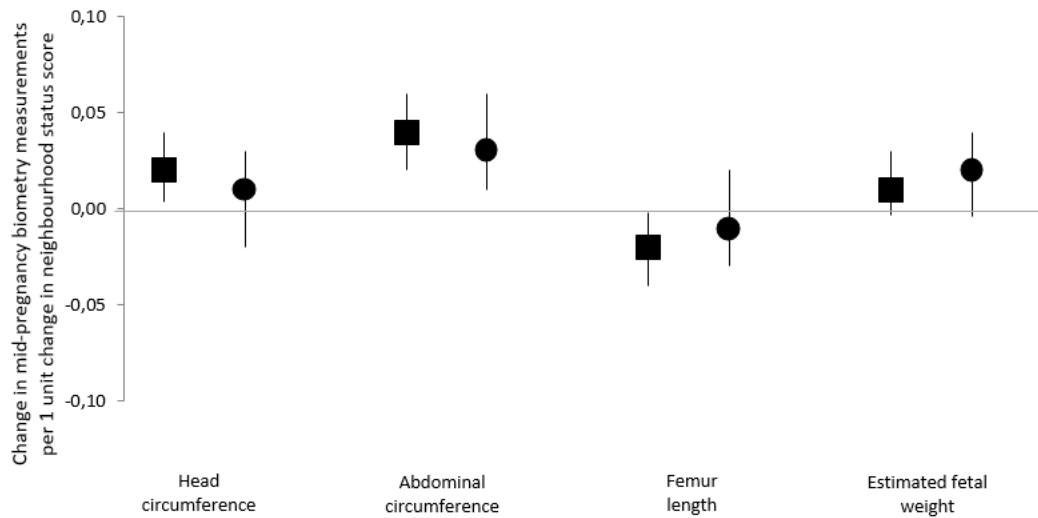
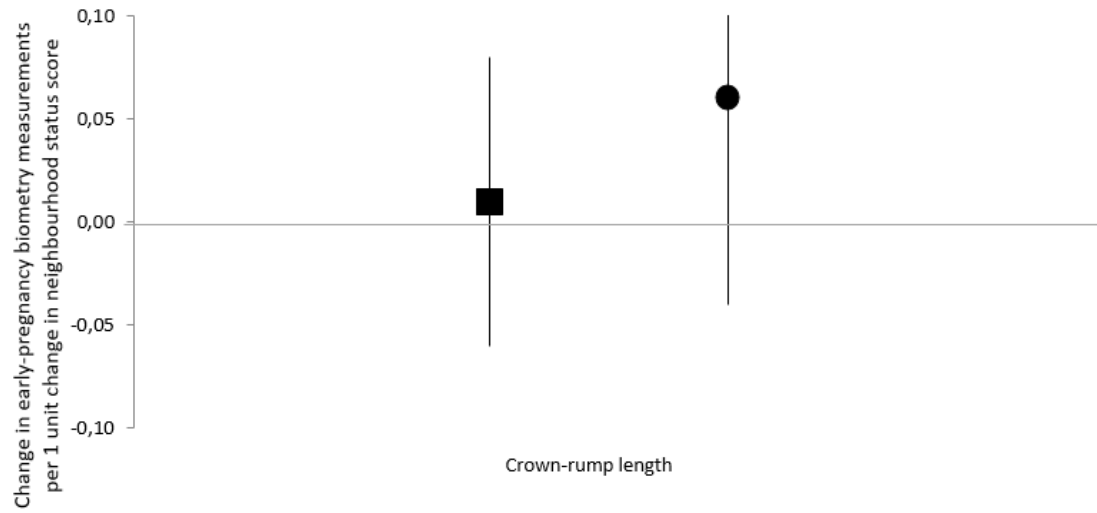
32 Abbreviations: β : beta; CRL: crown-rump length; HC: head circumference; FL: femur length; AC: abdominal circumference; EFW: estimated fetal weight.

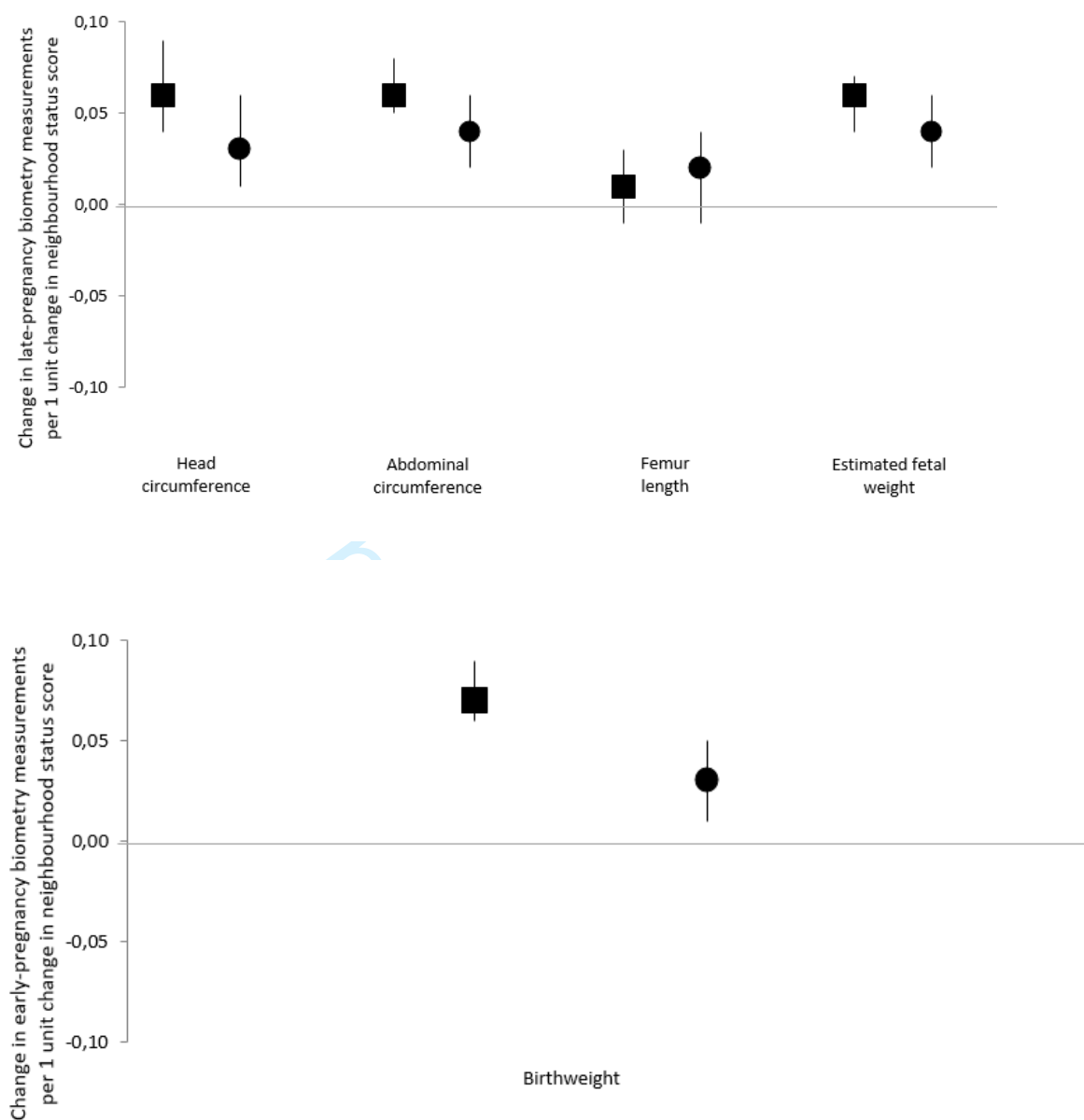
33 Values are regression coefficients with the 95% CI of the data in SD-score and are based on adjusted linear and logistic regression models. Adjusted model:

34 adjusted for maternal age, educational level, smoking, alcohol use, folic acid supplement use, ethnicity, parity, pre-pregnancy body mass index and fetal sex.

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

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





65 Data are SDS values (95% CI) from multilevel analyses and reflect the differences in growth
 66 characteristics in SDS's in early pregnancy, mid-pregnancy late pregnancy and birth, per 1 unit change
 67 in neighbourhood status score. Analyses with crown-rump length were based on subgroup analyses (n
 68 = 1614). Estimates are from multiple imputed data. Squares show basic model. Circles show adjusted
 69 model: basic model and additionally adjusted for maternal age, educational level, smoking, alcohol
 70 use, folic acid supplement use, ethnicity, parity, pre-pregnancy body mass index and fetal sex.

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

72 **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

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77 **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)	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

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80 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

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83 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.
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	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

85 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
86 regression models. Basic model: by the use of SD scores it is automatically adjusted for gestational age. Fully adjusted model: basic model and additionally
87 adjusted for maternal age, educational level, smoking, alcohol use, folic acid supplement use, ethnicity, parity, pre-pregnancy body mass index and fetal sex.
88 p-for trend analysis with the neighbourhood deprivation as a continuous measure. ¹Differences between groups were evaluated using one-way-ANOVA-tests
89 for continuous variables. ²Differences in growth parameters between the lowest and highest neighbourhood status score groups were tested were evaluated
90 using Student’s t-tests.

91 **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)	<i>Reference</i>	-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)	<i>Reference</i>	-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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	-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)	<i>Reference</i>	-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)	<i>Reference</i>	0.04 (0.02 ; 0.05)	<0.001

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	Adjusted	-0.09 (-0.16 ; -0.01)	-0.11 (-0.18 ; -0.04)	-0.06 (-0.12 ; 0.01)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	0.01 (-0.01 ; 0.03)	0.19
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Late pregnancy							
HC	Basic	-0.22 (-0.29 ; -0.16)	-0.24 (-0.31 ; -0.18)	-0.09 (-0.16 ; -0.03)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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.

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

Study population	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	-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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	-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)	<i>Reference</i>	0.003 (-0.02 ; 0.02)	0.80

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AC	8052	Basic	-0.15 (-0.21 ; -0.09)	-0.15 (-0.21 ; -0.09)	-0.09 (-0.15 ; -0.03)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	0.03 (0.01 ; 0.06)	0.001	

98 Abbreviations: HC: head circumference, FL: femur length, AC: abdominal circumference, EFW: estimated fetal weight. Values are regression coefficients
 99 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
 100 gestational age. Fully adjusted model: basic model and additionally adjusted for maternal age, educational level, smoking, alcohol use, folic acid supplement

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

Study population	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	-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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	-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)	<i>Reference</i>	-0.004 (-0.02 ; 0.02)	0.69

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AC	8052	Basic	-0.15 (-0.21 ; -0.09)	-0.15 (-0.21 ; -0.09)	-0.09 (-0.15 ; -0.03)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	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)	<i>Reference</i>	0.04 (0.02 ; 0.06)	<0.001

104 Abbreviations: HC: head circumference, FL: femur length, AC: abdominal circumference, EFW: estimated fetal weight. Values are regression coefficients
 105 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
 106 gestational age. Fully adjusted model: basic model and additionally adjusted for maternal age, educational level, smoking, alcohol use, folic acid supplement
 107 use, ethnicity, parity, pre-pregnancy body mass index and fetal sex. p-for trend analysis with the neighbourhood deprivation as a continuous measure.

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

Study population	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 (0.91 ; 1.46)	1.15 (0.89 ; 1.43)	0.24 (0.89 ; 1.43)	1.13 <i>0.31</i>	<i>Reference</i> 0.91 (0.85 ; 0.97)	0.004

109 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
110 model: basic model and additionally adjusted for maternal age, educational level, smoking, alcohol use, folic acid supplement use, ethnicity, parity, pre-
111 pregnancy body mass index, fetal sex, and additionally for maternal hypertension.. P-for trend analysis with the neighbourhood deprivation as a continuous
112 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-
113 score) in the study cohort.

115 **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)

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

117 displayed as valid percentages.

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3 118 **Supplemental 1.** First trimester and fetal growth, measurement guidelines.

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5 120 **CRL: crown-rump length (39)**

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7 121 CRL is measured as the largest dimension of embryo, excluding the yolk sac and extremities. A
8 122 midline sagittal section of the whole embryo or fetus should be obtained, ideally with the embryo or
9 123 fetus oriented horizontally on the screen. An image should be magnified sufficiently to fill most of the
10 124 width of the ultrasound screen, so that the measurement line between crown and rump is at about 90°
11 125 to the ultrasound beam.

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14 126 Caliper placement: measure the fetus in a neutral position (i.e. neither flexed nor hyperextended). The
15 127 end points of crown and rump should be defined clearly.

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18 130 **HC: Head circumference (40)**

19 131 As described for the BPD, ensuring that the circumference placement markers correspond to the
20 132 technique described on the reference chart.

21 133 Caliper placement: If the ultrasound equipment has ellipse measurement capacity, then the HC can be
22 134 measured directly by placing the ellipse around the outside of the skull bone echoes.

23 135

24 136

25 137 **AC: abdominal circumference (40)**

26 138 - Transverse section of the fetal abdomen (as circular as possible);

27 139 - umbilical vein at the level of the portal sinus;

28 140 - stomach bubble visualized;

29 141 - kidneys should not be visible.

30 142 Caliper placement: The AC is measured at the outer surface of the skin line, either directly with ellipse
31 143 calipers or calculated from linear measurements made perpendicular to each other, usually the
32 144 anteroposterior abdominal diameter and transverse abdominal diameter.

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36 148 **FL: femur length (40)**

37 149 The FL is imaged optimally with both ends of the ossified metaphysis clearly visible. The longest
38 150 axis of the ossified diaphysis is measured. The same technique as that used to establish the reference
39 151 chart should be used with regard to the angle between the femur and the insonating ultrasound beams.
40 152 An angle of insonation between 45° and 90° is typical.

41 153 Caliper placement: Each caliper is placed at the ends of the ossified diaphysis without including the
42 154 distal femoral epiphysis if it is visible

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3 156 **Supplemental 2.** Multiple imputations for missing data of covariates.
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5 157 We imputed missing data of the covariates using multiple imputations (17). The percentages of
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7 158 missing values for the confounders within the population for analysis were lower than 20%. For the
8
9 159 multiple imputation, we the Markov chain Monte Carlo approach. In the imputation model, we
10
11 160 included all confounders, plus maternal age, ethnicity, parity and prepregnancy BMI. Furthermore, we
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13 161 additionally added the studied determinants and outcomes in the imputation model as prediction
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15 162 variables only; they were not imputed themselves. Five imputed datasets were created and analyzed
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17 163 together.
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For peer review only

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 cohort reporting guidelines, and cite them as:

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

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

1	Abstract	#1b	Provide in the abstract an informative and balanced summary	2
2				
3			of what was done and what was found	
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6	Introduction			
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9				
10	Background /	#2	Explain the scientific background and rationale for the	4
11	rationale		investigation being reported	
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15	Objectives	#3	State specific objectives, including any prespecified	4
16			hypotheses	
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20	Methods			
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23	Study design	#4	Present key elements of study design early in the paper	4, 5
24				
25				
26	Setting	#5	Describe the setting, locations, and relevant dates, including	4, 5
27			periods of recruitment, exposure, follow-up, and data	
28			collection	
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34	Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of	4, 5
35			selection of participants. Describe methods of follow-up.	
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39	Eligibility criteria	#6b	For matched studies, give matching criteria and number of	4, 5
40			exposed and unexposed	
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45	Variables	#7	Clearly define all outcomes, exposures, predictors, potential	5, 6
46			confounders, and effect modifiers. Give diagnostic criteria, if	
47			applicable	
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53	Data sources /	#8	For each variable of interest give sources of data and details	4, 5, 6
54	measurement		of methods of assessment (measurement). Describe	
55			comparability of assessment methods if there is more than	
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one group. Give information separately for for exposed and unexposed groups if applicable.

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6	Bias	#9	Describe any efforts to address potential sources of bias	5, 6, 8
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9	Study size	#10	Explain how the study size was arrived at	4, 5
10				
11				
12	Quantitative	#11	Explain how quantitative variables were handled in the	7, 8
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14	variables		analyses. If applicable, describe which groupings were	
15			chosen, and why	
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19	Statistical	#12a	Describe all statistical methods, including those used to	
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21	methods		control for confounding	
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25	6, 8			
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28	Statistical	#12b	Describe any methods used to examine subgroups and	7, 8
29				
30	methods		interactions	
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33	Statistical	#12c	Explain how missing data were addressed	7, 8
34				
35	methods			
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39	Statistical	#12d	If applicable, explain how loss to follow-up was addressed	7, 8
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41	methods			
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44	Statistical	#12e	Describe any sensitivity analyses	
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46	methods			
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49	7, 8			
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52	Results			
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56	Participants	#13a	Report numbers of individuals at each stage of study—eg	9
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58			numbers potentially eligible, examined for eligibility,	
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confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.

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8	Participants	#13b	Give reasons for non-participation at each stage	9
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11	Participants	#13c	Consider use of a flow diagram	
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17	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
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27	Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	
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36	Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	
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42	Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	
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49	9, 10			
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52	Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence	9, 10
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interval). Make clear which confounders were adjusted for
and why they were included

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6 Main results [#16b](#) Report category boundaries when continuous variables were 9, 10
7
8 categorized
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11 Main results [#16c](#) If relevant, consider translating estimates of relative risk into
12 absolute risk for a meaningful time period
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16 9, 10
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20 Other analyses [#17](#) Report other analyses done—eg analyses of subgroups and 10, 11
21 interactions, and sensitivity analyses
22
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24 Discussion

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28 Key results [#18](#) Summarise key results with reference to study objectives 11
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31 Limitations [#19](#) Discuss limitations of the study, taking into account sources 12, 13
32 of potential bias or imprecision. Discuss both direction and
33 magnitude of any potential bias.
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39 Interpretation [#20](#) Give a cautious overall interpretation considering objectives, 13, 14
40 limitations, multiplicity of analyses, results from similar
41 studies, and other relevant evidence.
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46 Generalisability [#21](#) Discuss the generalisability (external validity) of the study 13
47 results
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49

50 Other Information

1 Funding [#22](#) Give the source of funding and the role of the funders for the 15
2
3 present study and, if applicable, for the original study on
4
5 which the present article is based
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